

# A simple epidemiological model for evaluating the malaria inoculation rate and the risk of infection in infants

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*A simple epidemiological model for evaluating the malaria inoculation rate and the risk of infection in infants was applied to describe the disease picture in an area of East Africa. Fairly good agreement was noted between the actual and expected curves of disease acquisition; this model could therefore be used for simulating epidemiological processes. Entomological and parasitological inoculation rates were compared by means of different approaches. As a result, it was possible to calculate the factor of proportionality defined as the proportion of anophelines having in their glands sporozoites that are actually infective.*

The planning of preventive measures against communicable diseases requires both a good knowledge of the natural course of these diseases and reliable information on the actual values of the main factors involved in the transmission process. Quantitative aspects of malaria transmission have long been studied by Ross (1), Moškovskij (2), Macdonald (3, 4), and Dietz et al. (5). The relationships between parasite, vector, and man have been expressed in mathematical systems, which have been applied in developing antimalaria strategies. However, difficulties have been encountered in using such systems owing to the inadequacy of baseline data and/or the lack of satisfactory estimates of some of the factors governing transmission of the disease (G. Gramiccia, unpublished WHO document, 1972).

The direct estimation of the rate of effective contacts—or force of infection—in holoendemic or hyperendemic situations by measuring the age-specific rate of disease acquisition requires the follow-up of a large number of susceptible newborn infants. In order to obtain cohorts of reasonable size, investigations must be carried out in large populations. Owing to financial and operational difficulties, few surveys of this kind have actually been completed, and the literature contains only limited data on the age-specific incidence rate of malaria in infants.

Estimates of certain main epidemiological parameters can also be derived from prevalence surveys of infants. Such cross-sectional surveys are easier to organize than incidence surveys are; moreover, as all infants are examined, information is obtained from larger samples. On the other hand, interpretation of the findings is more complex, as the age-specific prevalence is affected by the reversion from positivity to negativity, owing both to recovery and to limitations of the parasitological test.

Entomological surveys provide information on the activity of the vector. The man-biting rate and the sporozoite rate are essential parameters for measuring the risk to man of developing parasitaemia, the force of infection being directly proportional to the entomological inoculation rate. The factor of proportionality, called  $b$  by Macdonald (3), is defined as the proportion of anophelines having in their glands sporozoites that are actually infective; its calculation requires the simultaneous collection of entomological and parasitological data in the same area and for the same population.

The successful organization and implementation of such synchronized field surveys is a costly and technically difficult task, and this explains why so little is known of the numerical value that may be assigned to the probability that an infected bite is infective.

This paper is a modest contribution to the knowledge of quantitative aspects of the transmission of infection from vector to man as studied in a representative malarious region of East Africa.

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## MATERIAL

The parasitological and entomological data used in the analysis were collected during the preparatory phase of a WHO field trial to test a new insecticide. The project site was in Nyanza Province, Kenya, on the shores of Lake Victoria. To satisfy the requirements of the experimental design, the territory was divided into three zones: an evaluation zone with 16 500 inhabitants; a comparison zone with 5 500 inhabitants; and a barrier zone with 32 000 inhabitants. The area selected for the present study comprised only the first two of these zones, with a total population of 22 000, because only there were data collected over the one-year period preceding the start of the spraying operations in August 1973.

*Parasitology*

Blood specimens were collected from all infants (approximately 650) once every 3 months and 200 thick-blood fields on each slide were examined for the presence of malaria parasites. Table 1 gives the results of these quarterly examinations according to age, as well as the consolidated prevalence rates.

Cohorts of about 45 newborn infants were examined early each month for the presence of malaria parasites in the blood and were followed up longi-

tudinally every month until they were found to be positive. Aggregated findings and derived age-specific incidence rates are reported in Table 2 for the period September 1972–August 1973.

*Entomology*

Nocturnal biting-captures were made in selected indoor stations on about 50 human bait  $\times$  nights per month; female anophelines were counted, identified, and dissected for the presence of sporozoites. In addition, mosquitos were collected by pyrethrum spraying in about 350 huts per month and from exit-traps in about 50 huts per month. The female anophelines were not only counted, identified, and dissected for the presence of sporozoites, but were also classified according to abdominal stages, so that the density of fed females per person could be calculated and then adjusted to the human-blood index (specific to the species), thus providing, in principle, another estimate of the man-biting rate. The number of entomological observations and the calculated value of basic indices for each month are summarized in Table 3. These data were collected over a 12-month period starting in August 1972 and the detection of new malaria cases among infants began in early September of the same year; this shift was made so as to take into account, as far as possible, the dur-

Table 1. Results of quarterly blood examination of all infants, according to age

Age (in months)	1st Survey November 1972		2nd Survey February 1973		3rd Survey May 1973		4th Survey August 1973		Total		
	No. examined	No. positive	No. examined	No. positive	No. examined	No. positive	No. examined	No. positive	No. examined	No. positive	Prevalence rate (%)
0–	39	0	50	1	45	1	52	0	186	2	1.1
1–	38	3	52	4	57	7	55	12	202	26	12.9
2–	59	16	63	23	59	17	54	20	235	76	32.3
3–	69	26	42	23	59	25	40	17	210	91	43.3
4–	55	26	46	21	52	17	57	29	210	93	44.3
5–	55	32	67	41	65	27	56	40	243	140	57.6
6–	48	29	68	37	46	18	57	37	219	121	55.3
7–	48	29	71	48	50	25	50	26	219	128	58.4
8–	63	34	54	30	65	30	59	41	241	135	56.0
9–	48	31	48	31	63	34	40	25	199	121	60.8
10–	55	31	50	34	55	29	44	24	204	118	57.8
11–	50	34	55	32	46	27	54	39	205	132	64.4
Total	627	291	666	325	662	257	618	310	2 573	1 183	46.0

Table 2. Results of monthly blood examination of susceptible infants born and followed-up between September 1972 and August 1973

Age (in months)	No. of susceptible infants examined	No. of primary infections	Monthly parasite incidence rate <sup>a</sup> (%)
0-	507	12	2.4
1-	443	82	18.5
2-	320	73	22.8
3-	222	64	28.8
4-	131	33	25.2
5-	79	26	32.9
6-	39	11	28.2
7-	21	5	23.8
8-	16	3	18.8
9-	6	1	(16.7)
10-	4	2	(50.0)
11-	1	—	(—)

<sup>a</sup> Rates based on fewer than 10 observations are shown in parentheses.

ation of the incubation period when relating the incidence of the disease to mosquito activity.

Furthermore, blood meals were identified by precipitin test on 2 903 *Anopheles gambiae* and 2 577 *A. funestus* mosquitoes to determine their human-blood index. A value of 0.95 was obtained for *A. gambiae* and a value of 0.99 for *A. funestus*.

#### METHOD

By analogy with the catalytic process observed in chemistry, Muench (6) developed a simple mathematical model of infection to describe the disease picture. Under conditions of stable malaria, it can be assumed that, over the time interval considered, the infant population is exposed to a constant force of infection; <sup>a</sup> this force is measured in terms of effective contacts per susceptible child per day, no matter how complex the events leading up to these contacts may be. It is assumed, furthermore, that the evidence of effective contact is proved by blood-smear positivity for malaria parasites.

On these assumptions, the acquisition of the dis-

ease in time by a cohort of newborn infants can be described by the differential equation:

$$dy/dt = h(1-y) \quad (1)$$

where  $y$  is the fraction of the population with proved parasitaemia,  $h$  is the force of infection in terms of effective contacts per unit of time and susceptible infant, and  $t$  is the age. In this study  $t$  will be measured in days; consequently  $h$ , also called the parasitological inoculation rate, will be a daily rate.

Under the initial condition that  $y=0$  when  $t=0$ , the solution of equation (1) is:

$$y = 1 - \exp(-ht) \quad (2)$$

Infants, once found positive for parasitaemia, may show negative results at some subsequent blood examinations. This may be due either to the limited ability of the test to detect those that are positive or, to a lesser extent, to parasite clearance (recovery).

In order to express this more complex situation mathematically, it is necessary to combine the reversible catalytic curve and the catalytic curve with movable asymptote. The resulting differential equation may be written:

$$dy/dt = h(k-y) - ry \quad (3)$$

where  $r$  is the daily recovery rate and  $k$  the proportion of infected infants actually detected at the time of the parasite prevalence survey. Under the initial condition mentioned above, the solution to this equation is:

$$y = [hk/(h+r)][1 - \exp(-(h+r)t)] \quad (4)$$

Estimations of the parameters  $h$ ,  $k$ , and  $r$  are made from the actual observations as indicated below.

#### RESULTS

##### *Application of the model*

The observed data on the age-specific incidence and prevalence, in infants, of malaria detected by microscopic examination provide the necessary information to estimate the parametric values of equations (2) and (4). Good agreement between the actual incidence and prevalence patterns and the trends simulated by the simple mathematical models described in this paper validates both the underlying rationale and the numerical estimation of the constants involved in the hypotheses.

The age-specific cumulated numbers and rates of the new malaria cases detected by microscopic examination in an initial cohort of 1 000 newborn infants can be derived from the calculated monthly parasite incidence rates given in Table 2. The compu-

<sup>a</sup> When malaria is of the stable type, variations in the human parasite reservoir are small and their role in the transmission of infection can be disregarded.

Table 3. Number of entomological observations and calculated value of basic indices per month

Year and month	<i>A. gambiae</i>						<i>A. funestus</i>											
	dissection for sporozoites			biting collection			Pyrethrum-spray and exit-trap collections			dissection for sporozoites			biting collection			Pyrethrum-spray and exit-trap collections		
	No. dissected	sporozoite rate (%) (100s)	No. collected	biting rate <sup>a</sup> (ma)	No. of mosquitoes collected	density of fed mosquitoes <sup>b</sup>	No. dissected	sporozoite rate (%) (100s)	No. collected	biting rate <sup>a</sup> (ma)	No. of mosquitoes collected	density of fed mosquitoes <sup>b</sup>	No. dissected	sporozoite rate (%) (100s)	No. collected	biting rate <sup>a</sup> (ma)	No. of mosquitoes collected	density of fed mosquitoes <sup>b</sup>
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)						
1972																		
August	2 864	7.86	173	3.60	1 793	1.80	2 869	4.36	125	2.60	3 218	3.24						
September	1 201	6.08	85	2.36	734	1.15	1 910	3.66	212	5.89	1 326	2.05						
October	1 333	4.35	48	1.00	1 147	1.53	1 664	5.53	132	2.75	1 126	1.50						
November	2 917	0.86	941	22.40	4 544	6.54	1 720	1.74	265	6.31	1 490	2.13						
December	3 304	5.60	685	19.03	5 905	9.11	2 031	3.35	209	5.81	2 418	3.76						
1973																		
January	2 624	10.79	253	5.27	1 611	2.17	2 437	5.38	462	9.63	1 636	2.21						
February	1 685	9.73	137	2.85	1 098	1.70	2 262	4.82	489	10.19	1 917	2.98						
March	1 776	10.98	71	1.48	1 104	1.38	2 481	6.25	251	5.23	2 378	2.98						
April	2 310	6.67	114	2.38	1 601	1.88	2 296	3.88	155	3.23	3 207	3.79						
May	4 699	2.47	938	15.63	8 757	9.23	3 425	2.86	426	7.10	3 688	3.90						
June	3 957	4.85	489	10.19	6 037	7.62	3 385	1.54	310	6.46	6 720	8.44						
July	2 818	14.12	113	2.09	1 668	1.86	3 667	7.01	196	3.63	3 521	3.92						

<sup>a</sup> Rate per human bait per night.<sup>b</sup> Density per person per hut and per night. This figure, when multiplied by the human blood index, gives also an estimate of the human biting rate.

tational steps followed, and the results, are shown in Table 4.

Applying the technique described by Muench (6) to the observed rates given in column (5) of Table 4, the estimated value obtained for *h* (the daily force of infection per susceptible infant), was 0.0084. The equation of the simple catalytic model thus becomes:

$$y = 1 - \exp(-0.0084t) \quad (2')$$

The theoretical cumulated incidence rates calculated from this equation are given for successive age classes in column (6) of Table 4.

Both the observed and the theoretical age curves of acquisition of infection are presented in Fig. 1. The theoretical positive fraction appears to increase more rapidly than the observed fraction up to the age of 4 months and more slowly after that age. This phenomenon may well indicate that the hypothesis of a constant force of infection over age is not quite correct, the lower risk of acquiring infection observed in the first months of life probably being due to the lengthening of the pre-patent period by maternal antibodies. On the whole, however, the two lines do not deviate significantly and it can

Table 4. Observed and theoretical cumulated incidence of new malaria cases in a cohort of 1 000 newborn infants

Exact age (in months)	Observed monthly parasite incidence rate (%)	No. of susceptible infants	New malaria cases in the cohort		Cumulated age-specific incidence rate (%)	
			per month	cumulated	observed	theoretical <sup>a</sup>
	(1)	(2)	(3)	(4)	(5)	(6)
0		1 000				
	2.4		24	24	3.6 <sup>b</sup>	8.1
1		976				
	18.5		181	205	20.5	25.5
2		795				
	22.8		181	386	38.6	42.1
3		614				
	28.8		177	563	56.3	55.0
4		437				
	25.2		110	673	67.3	65.0
5		327				
	32.9		108	781	78.1	72.8
6		219				
	28.2		62	843	84.3	78.9
7		157				
	23.8		37	880	88.0	83.6
8		120				
	18.8		23	903	90.3	87.2
9		97				
	(16.7) <sup>c</sup>		16	919	91.9	90.1
10		81				

<sup>a</sup> Calculated with the equation of the simple catalytic model:  $y = 1 - \exp(-0.0084t)$ .

<sup>b</sup> Adjusted on the assumption of a 10-day incubation period.

<sup>c</sup> Based on fewer than 10 observations.

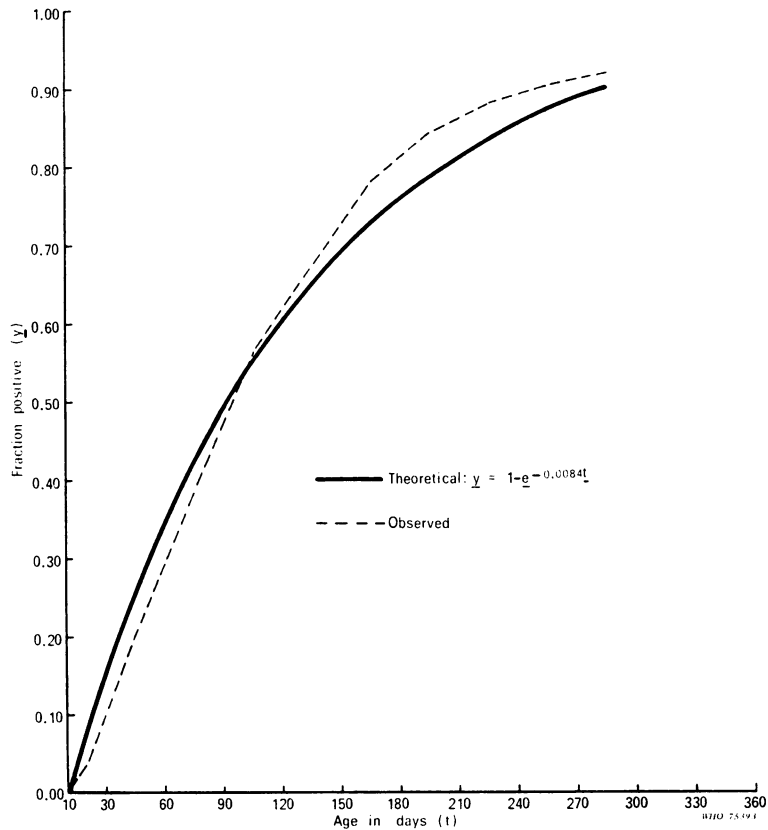


Fig. 1. Cumulated age incidence of malaria detected by microscopic examination (observed and theoretical curves).

reasonably be concluded that the model satisfactorily simulates the actual observations.

As stated on pages 510-511, infants that have been found positive for parasitaemia at a given time can show negative blood smears at subsequent examinations owing to the absence of parasites in the peripheral blood, to a parasite density so reduced that the probability of non-detection is high, or even to actual blood clearance. As a result of possible reversion from positivity to negativity, the age-specific prevalence rates of infection detected by microscopic examination, observed in the cross-sectional survey, are lower than the corresponding incidence rates (this may be confirmed by comparing Tables 1 and 2).

According to the technique of Muench (6), the combined catalytic curve was fitted to the observed prevalence rates given in the last column of Table 1. As a result, equation (4) becomes:

$$y = 0.65[1 - \exp(-0.0091t)] \quad (4')$$

In Table 5, the theoretical prevalence rates derived from this equation are compared with the rates actually observed; the corresponding age-prevalence curves are shown in Fig. 2.

As already noted in the adjustment of the incidence curve, the observed prevalence rates in younger infants are slightly lower than might have been expected. Here again, the discrepancy is probably due to the lengthening of the pre-patent period by maternal antibodies. There is, however, fairly good agreement between the two curves and, on the whole, their slight deviation does not invalidate the hypotheses made; the combined catalytic function can be taken as the mathematical expression of a satisfactory simulation model.

Equating the corresponding coefficients of formulae (4) and (4') gives:

$$\left. \begin{aligned} hk/(h+r) &= 0.65 \\ h+r &= 0.0091 \end{aligned} \right\} \quad (5)$$

Table 5. Observed and theoretical age-specific prevalence rates of parasitologically positive infants

Age in months	Prevalence rate (%)	
	observed	theoretical <sup>a</sup>
0-	1.6 <sup>b</sup>	5.7
1-	12.9	17.8
2-	32.3	29.1
3-	43.3	37.7
4-	44.3	44.3
5-	57.6	49.3
6-	55.3	53.1
7-	58.4	56.0
8-	56.0	58.2
9-	60.8	59.9
10-	57.8	61.1
11-	64.4	62.1

<sup>a</sup> Calculated with the equation of the reversible catalytic model:  $y = 0.65 [1 - \exp(-0.0091 t)]$ .  
<sup>b</sup> Adjusted on the assumption of a 10-day incubation period.

The value of the parasitological inoculation rate  $h$ , as estimated from the incidence curve, was 0.0084 effective contacts per day and per susceptible infant. After substituting this value for  $h$  in equation (5), the system is easily solved. The numerical values obtained were 0.0007 for  $r$  (the daily recovery rate per infected infant) and 0.70 for  $k$  (the proportion of infected infants actually detected at any survey). As is to be expected, the recovery rate is practically negligible in the first year of life.

*Entomological versus parasitological inoculation rate*

The data on the activity of the vector (summarized in Table 3) provide the basis for calculating the rate  $h'$  of infected-mosquito bites received per man per day; this parameter is commonly known as the daily entomological inoculation rate and is expressed by the formula:

$$h' = mas \tag{6}$$

where  $m$  is the anopheline density in relation to man,

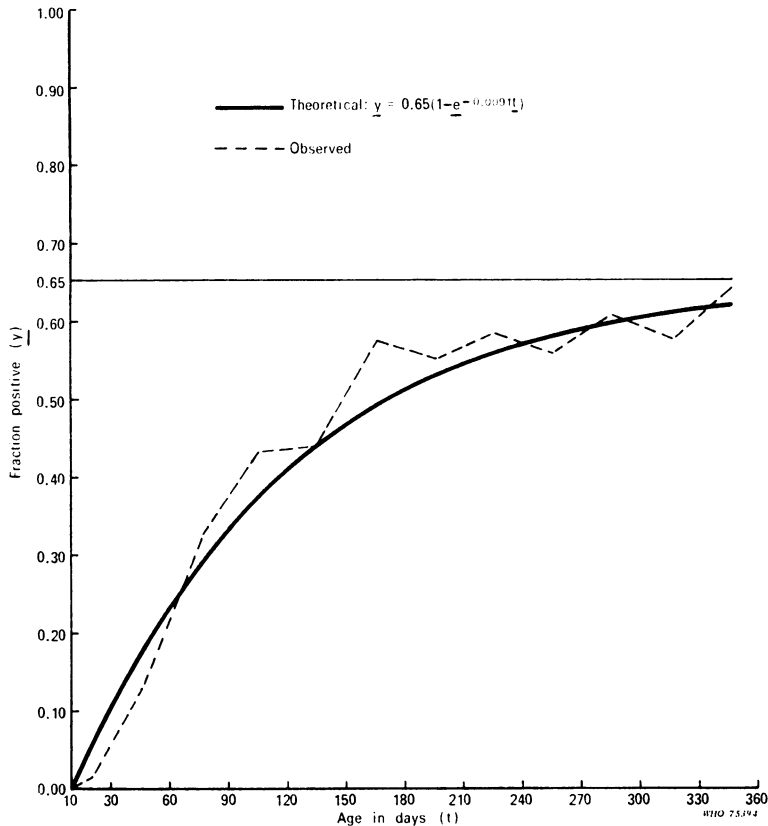


Fig. 2. Age prevalence of malaria detected by microscopic examination in infants (observed and theoretical curves).

*a* the average number of persons bitten by one mosquito in one day, and *s* the proportion of mosquitos with sporozoites in their salivary glands.

Values of *h'* calculated from the biting rates (*ma*) and the sporozoite rates (100*s*) given in Table 3 are shown for *A. gambiae* and *A. funestus*, respectively, in columns (1) and (3) of Table 6. The total inoculation rate for the two species can be seen in column (5).

Another estimate of the man-biting rate, *ma*, is obtained by multiplying the density per person of fed female mosquitos collected by pyrethrum spraying and from exit-traps by the human-blood index (0.95 for *A. gambiae* and 0.99 for *A. funestus*). Further multiplication by *s* provides another way of estimating the daily inoculation rate *h'*. Results of the computation are given in columns (2), (4), and (6) of Table 6. Seasonal variation in the two series of estimates can be appreciated from Fig. 3.

A surprisingly large difference is observed between the two estimates of the annual average rate: 0.573 for the estimate based on the man-biting rate and 0.319 for that based on the density per person of fed mosquitos (Table 6). The difference between these two rates may be partly explained by the particular techniques used to capture anophelines on human bait, which may have made the huts more

attractive than is normally the case, resulting in an inflated biting rate. A precise measurement of the man-vector contact is highly desirable and the problem deserves further research.

It is well known that not all infected bites result in infection. To link the entomological inoculation rate *h'* with the parasitological inoculation rate (or force of infection) *h*, it is necessary to know what proportion of anophelines with sporozoites in their glands are actually infective. As already mentioned, this parameter, called *b* by Macdonald (3), cannot be measured direct, but can be estimated from the formula:

$$h = bh' \tag{7}$$

when the numerical values of *h* and *h'* have been calculated concurrently in a given epidemiological situation.

When replacing in equation (7) the parasitological inoculation rate by its value and the entomological inoculation rate by its extreme values, lower and upper limits are obtained for the probability *b* as follows:

$$b_L = \frac{0.0084}{0.573} = 0.015 \text{ and } b_U = \frac{0.0084}{0.319} = 0.026$$

In other words, the percentage of infected bites that actually result in infection is estimated to be between

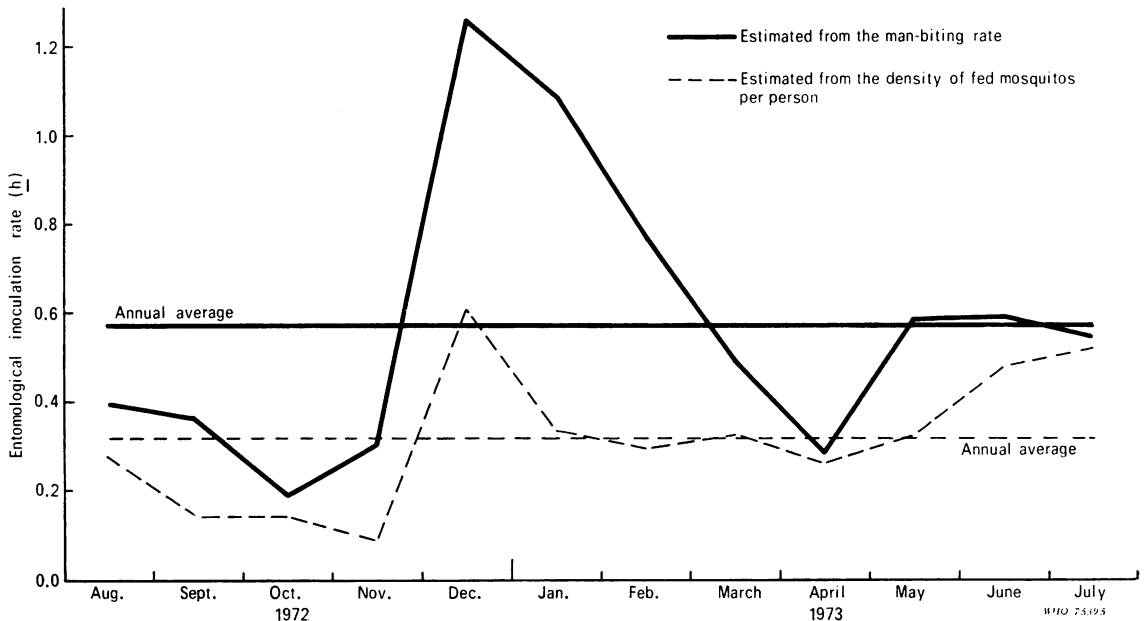


Fig. 3. Seasonal variation of the entomological inoculation rate.



1.5 and 2.6, as evidenced by the data of the present survey. This means that between 38 and 67 infected bites are needed to produce a single infection.

References to estimates of  $b$  are rare in the literature. There is, however, evidence that, in African regions where conditions of stable malaria prevail, this factor of proportionality may vary between 1% and 5%. It appeared conclusive to Macdonald (7) that in one area only about 1 in every 100 bites inflicted on infants by sporozoite-infected mosquitos resulted in the establishment of infection, whereas in another area this ratio was 1 : 20.

#### DISCUSSION

With the simple mathematical model of infection described in the present paper it was possible to reproduce satisfactorily the epidemiological pattern of malaria incidence and prevalence in infants, as observed in situations actually encountered in East Africa. It was confirmed that the recovery rate is very low during the first year of life; furthermore,

it was shown that, on the average, about one-third of infected infants were not detected by the single microscopic examination (200 thick-blood fields) made during a parasitological point prevalence survey.

The model might be used for describing actual epidemiological processes and for predicting the expected incidence of the disease in a nonimmune population when variations occur in the force of infection—either under natural conditions or under the influence of control measures. It might also be used as a basis for estimating the degree of reduction in the force of infection to be brought about by intervention measures in order to attain targets set in advance.

An attempt was made, by comparing entomological and parasitological inoculation rates, to evaluate the probability that an infected anopheline would effectively transmit the infection to a susceptible person. The estimates of the entomological inoculation rate were calculated from biting rates measured on adult human bait and from mosquito den-

Table 6. Monthly entomological inoculation rate ( $h'$ ) estimated from the observed man-biting rate and from the density of fed mosquitos per person

Year and month	<i>A. gambiae</i>		<i>A. funestus</i>		Total	
	from man-biting rate	from density of fed mosquitos <sup>a</sup>	from man-biting rate	from density of fed mosquitos <sup>b</sup>	from man-biting rate	from density of fed mosquitos
	(1)	(2)	(3)	(4)	(5)	(6)
1972						
August	0.283	0.135	0.113	0.140	0.396	0.275
September	0.143	0.067	0.216	0.074	0.359	0.141
October	0.044	0.063	0.152	0.082	0.196	0.145
November	0.193	0.053	0.110	0.037	0.303	0.090
December	1.066	0.485	0.195	0.125	1.261	0.610
1973						
January	0.569	0.222	0.518	0.118	1.087	0.340
February	0.277	0.157	0.491	0.142	0.768	0.299
March	0.163	0.144	0.327	0.184	0.490	0.328
April	0.159	0.119	0.125	0.146	0.284	0.265
May	0.386	0.217	0.203	0.110	0.589	0.327
June	0.494	0.351	0.099	0.129	0.593	0.480
July	0.295	0.250	0.254	0.272	0.549	0.522
Average	0.339	0.189	0.234	0.130	0.573	0.319

<sup>a</sup> Calculated with a human-blood index value of 0.95.

<sup>b</sup> Calculated with a human-blood index value of 0.99.

sities established for the general population. It is probable that a relatively smaller number of mosquito bites is inflicted on infants because of the reduced skin surface exposed to risk. In the con-

ditions prevailing in East Africa, the proportion of effective contacts could well be above 3%, which corresponds to fewer than 33 infected bites per new infant case.

### ACKNOWLEDGEMENTS

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### RÉSUMÉ

#### MODÈLE ÉPIDÉMIOLOGIQUE SIMPLE DESTINÉ À ÉVALUER LE TAUX D'INOCULATION DU PALUDISME ET LE RISQUE D'INFECTION CHEZ LES NOURRISSONS

Les auteurs décrivent un modèle épidémiologique très simple qui permet d'estimer le taux d'inoculation du paludisme et le risque d'infection chez les nourrissons; ce modèle décrit l'évolution dans le temps du taux d'infection en fonction du risque encouru, et reproduit d'une façon satisfaisante les variations de l'incidence et de la prévalence dans une population de nourrissons, telles qu'elles furent observées dans des situations rencontrées en Afrique orientale.

Ce modèle est utile non seulement pour simuler les événements épidémiologiques observés mais également

pour prédire l'incidence de la maladie dans une population non immune, compte tenu des variations de la force d'infection dans des conditions naturelles ou sous l'influence de mesures antipaludiques. Il pourrait permettre d'estimer le degré de réduction de la force d'infection qui serait nécessaire pour que les objectifs fixés à l'avance soient atteints.

Par différentes approches, les auteurs ont essayé d'estimer la probabilité qu'a un anophèle infecté de transmettre effectivement l'infection à des populations réceptives.

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