



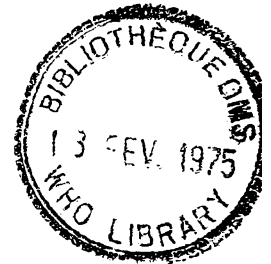
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A CRITICAL REVIEW OF THE FIELD APPLICATION OF A  
MATHEMATICAL MODEL OF MALARIA EPIDEMIOLOGY

by

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INTRODUCTION

From September 1966 to February 1969 a field research project was carried out in the north of Nigeria to assess the possibility of interrupting malaria transmission by a combination of attack measures, in an area considered representative of the northern savanna of West Africa.

The selection of attack measures, their timing and cycle of application were based on a computer simulation study of expected results, applying to Macdonald's mathematical model of malaria epidemiology (Macdonald, 1957), parameters considered to represent the characteristics of the area and the anticipated effects of the attack measures (Macdonald et al., 1967, a, b; Foll et al., 1967; Macdonald et al., 1968).

The trial area covered a population of about 52 000 people in 550 km<sup>2</sup> in the south of Kankiya District of the Katsina Emirate in the North Central State of Nigeria.

The plan of antimalaria attack consisted of:

1. Mass drug administration of a single dose treatment of chloroquine and pyrimethamine to at least 80% of the resident population every 60 days. Each mass drug administration to be completed in one month.
2. DDT house spraying to be carried out on a four-month cycle starting at the end of the dry season, each spray round to be completed in one month.

The operations were carried out between November 1966 and August 1968 (Nájera et al., 1973) and may be summarized as follows:

Eleven mass drug administrations were carried out according to plan between mid-November 1966 to mid-August 1968 with coverages varying between 78.2 and 92.4%.

During the first rainy season two spray rounds were carried out, the first from mid-June to mid-July and the second from mid-October to mid-November 1967.

The first spray round had been actually programmed for the period mid-April to mid-May but had to be postponed due to logistical difficulties. Transmission of malaria was not controlled during 1967 and, although the rainy season had been unusually late (not having

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started until after the spraying of the Central Indicator Area was completed), it was speculated that the delay in spraying might have been responsible for this failure, therefore, the project was continued for another year, but as entomological observations already indicated a duration of insecticidal effect shorter than expected, the spray cycle was reduced to two-and-a-half months.

Spraying in 1968 was carried out as planned starting in mid-April and first July.

At the end of August 1968 it was decided to discontinue the project in view of the failure to control malaria transmission.

Evaluation was based on the study of an Indicator Zone (population of about 5000), centrally located, where an attempt was made to examine a blood sample from each individual every two months at the time of mass drug administration, coverages were practically the same as with drug treatments (78.2 to 92.4% of the registered population).

Malaria in the area was predominantly caused by Plasmodium falciparum (88.5 to 99.6%, the highest values corresponding to higher transmission periods). The other parasites present were P. malariae and P. ovale.

Although there may be some doubts concerning the parasitological data considered as base-line preoperational levels, reliable postoperational data showed that malaria prevalence was reduced to very low levels during the two dry seasons but returned to high levels (higher than the recorded preoperational rates) during the main transmission seasons.

General parasite rates in the Central Indicator Zone decreased from 19.0% at the initiation of attack measures in November-December 1966 to 1.0% in May-June 1967. With the coming of the rainy season it shot up to 16.7% in July-August to reach 19.1% in November 1967. During the second year it reached a minimum of 2.0% in May-June to increase to 23.5% in July-August 1968. The comparison area showed parasite rates between 23.5 and 44.3% with seasonal variations somewhat parallel to those shown above.

It was concluded that although the marked dry season reductions in parasite rates could be attributed to the mass drug administration, this method of attack was insufficient to control transmission during the rainy season and that the expected effect from the DDT house spraying did not occur. The lack of effect of DDT was attributed to its excito-repellent effect which drove Anopheles gambiae outdoors after feeding and to its exceptionally short residual insecticidal effect on soot-covered thatch and local mud surfaces.

There were considerable discrepancies between the predictions of the model and the observations in the field. These were attributed to a combination of causes, including possible errors in the estimation of parameter values. Nevertheless, the analysis of the project development suggested also the inadequacy of the mathematical model itself and the existence of a greater number of variables than generally recognized for its application to concrete situations. We shall discuss these points in the following sections.

#### Application of the mathematical model to the Kankiya situation

It is our opinion that most of the necessary parameters to define the epidemiological situation of Kankiya in terms of the mathematical model were lacking or insufficiently known. This may apply not only to the basic epidemiological variables but also to the anticipated effects of the attack measures. Also, the expectations from the attack measures and the feasibility of perfection in their application were exaggerated. Besides that, the epidemiological situation of the area was not known with sufficient detail and the project had to be planned based on rather broad general assumptions (Foll & Pant, 1966, Foll et al., 1967; Macdonald et al., 1967a). As the project developed, more detailed observations were made and difficulties were experienced not only in ascertaining changes in the absence of sufficient base line data, but also in using the mathematical model for static descriptive purposes.

Attempts to use the project data to describe the epidemiological situation in terms of the model ran into gross discrepancies as may be illustrated by the comparison of the estimates of the basic reproduction rate,  $z_0$ , by the following methods (Table 2):

(a) from the estimated values of the inoculation rate, "h", applied to formula:  

$$z_0 = \frac{h}{r} \left( \frac{a}{-\log_e p} + \frac{1}{x_g} \right)$$
, "h" is estimated from the observed incidence in infants during

a given period, i.e. from the number of infants that, at the time of a periodical blood examination, were found positive for the first time having been examined before and found negative in every previous examination. These data are shown in Table 1. Relating this "h" to the average gametocyte rate during the period "x<sub>g</sub>", the estimates of "p" (mosquito probability of survival through one day) obtained for a period close in time, and considering "a" (man-biting habit) as 0.4 and "r" (recovery rate) as 0.025 (e.g., considering that 80% of the cases will have a gametocytaemia averaging 30 days as a result of the bi-monthly treatment and 20% will have the normal 80 days), an estimate is obtained, which is shown in Table 2 as "z<sub>0</sub>(h)". This method of estimating z<sub>0</sub> was used only in the Central Indicator Zone as it was the only one with bi-monthly longitudinal examinations of a registered population. The values obtained show a variation from 2.63 to 11.96;

(b) from entomological data where we obtain an estimate of  $\frac{z_0}{b}$  by the formula:

$$\frac{z_0}{b} = \frac{ma^2 p^n}{ax - \log_e p}$$
. In this formula, "b" is defined as, "the proportion actually

infective among sporozoite positive anophelines", and "n" is the "time required for the extrinsic cycle". The results presented in Table 2 show a variation from 5.5 to 234.4 in the sprayed area, and from 632.5 to 4250.4 in the unsprayed area. The lack of proportionality between these and the two other estimates indicates that "b" is not a single variable but a function of several variables which may vary independently;

(c) from the observed sporozoite rates by the formula:  $z_0 = \frac{p^{12}}{p^{12-L_s}}$ . It is

surprising how low are the values obtained for z<sub>0</sub> with this formula and how little they vary (see Table 2, z<sub>0</sub>(s)) in comparison with the other estimates.

An examination of Table 2 shows not only gross discrepancies between the estimates of the reproduction rate by different formulae for the same periods but also the lack of any proportionality between them. This may be due in part to the rapid variation of the entomological variables in nature and the lack of representativeness of entomological samples.

A considerable part of the discrepancies is due to deficiencies in the model. In our opinion, as stated above, "b" cannot be considered as a single variable, but as a function of the variables needed to describe the viability of the sporozoites and the immunological status of the receiving host. Furthermore, the consistency with which estimates of z<sub>0</sub> from the sporozoite rates give values very close to 1 emphasizes the fact that observed sporozoite rates are always much lower than would be expected from the observed parasitological data if the model described adequately the dynamics of malaria transmission. This discrepancy is mainly due to the fact that the actual mosquitos get their infections from a population which, due to the working of immunity, has a relatively low infectivity in comparison with that of the theoretical population of the model, in which all individuals become infective for  $\frac{1}{r}$  days (assumed value: 80 days) after each infective bite they receive throughout life. People should have become permanently infective for the rest of their lives at a very young age, when h > r, contrary to experience. In general, observed sporozoite rates are too small in relation to the estimated values of p<sup>12</sup>, giving values of z<sub>0</sub> consistently near unity. Moreover, although it seems logical to recognize the possibility of z<sub>0</sub> being less than one, under certain static conditions of eradication (with s → 0) with low receptivity, this formula gives z<sub>0</sub> = 1 for all such conditions.

TABLE 1. CALCULATION OF INCUBATION RATES FOR EACH TWO-MONTH INTER-MDA PERIOD FOR CENTRAL INDICATOR ZONE FROM INFANTS FOUND POSITIVE FOR THE FIRST TIME AT THE END OF EACH PERIOD

| Inter-MDA Period                  | III - IV   |      | IV - V     |        | V - VI     |        | VI - VII   |        | VII - VIII |         | VIII - IX  |         | IX - X     |        | X - XI     |        |
|-----------------------------------|------------|------|------------|--------|------------|--------|------------|--------|------------|---------|------------|---------|------------|--------|------------|--------|
|                                   | Orig. Neg. | Pos. | Orig. Neg. | Pos.   | Orig. Neg. | Pos.   | Orig. Neg. | Pos.   | Orig. Neg. | Pos.    | Orig. Neg. | Pos.    | Orig. Neg. | Pos.   | Orig. Neg. | Pos.   |
| 1. Tsa town                       | 5          | 0    | 11         | 0      | 17         | 1      | 19         | 1      | 17         | 0       | 20         | 0       | 17         | 1      | 20         | 1      |
| 2. Kofa town                      | 5          | 0    | 9          | 0      | 10         | 0      | 9          | 0      | 8          | 0       | 10         | 1       | 13         | 1      | 14         | 1      |
| 3. Kofa Remawa                    | 28         | 0    | 37         | 5      | 33         | 3      | 39         | 7      | 37         | 0       | 42         | 0       | 51         | 0      | 48         | 8      |
| 21. Tunkawa                       | 4          | 0    | 6          | 1      | 3          | 0      | 5          | 1      | 8          | 1       | 6          | 0       | 7          | 0      | 9          | 1      |
| 22. Kavyen Samaro                 | 1          | 0    | 2          | 0      | 2          | 0      | 2          | 0      | 2          | 0       | 2          | 0       | 2          | 0      | 3          | 1      |
| 32. Assurara                      | 50         | 0    | 56         | 11     | 56         | 6      | 48         | 8      | 46         | 2       | 50         | 3       | 47         | 0      | 53         | 13     |
| 34. Kuchin Bushiya                | 4          | 0    | 4          | 0      | 1          | 1      | 10         | 1      | 9          | 1       | 9          | 0       | 9          | 0      | 10         | 1      |
| 40. Machinjiri                    | 5          | 0    | 9          | 0      | 14         | 2      | 13         | 2      | 8          | 0       | 14         | 0       | 13         | 1      | 14         | 2      |
| 42. Tsa Outside                   | 12         | 0    | 22         | 3      | 22         | 3      | 19         | 5      | 17         | 0       | 18         | 0       | 22         | 0      | 22         | 6      |
| 46. Kyafau                        | 29         | 0    | 44         | 4      | 50         | 2      | 54         | 9      | 43         | 0       | 48         | 2       | 49         | 0      | 52         | 6      |
| 50. Dau Iya                       | 8          | 0    | 21         | 2      | 23         | 4      | 19         | 5      | 18         | 2       | 17         | 0       | 18         | 0      | 21         | 5      |
| 74. Rurjin Kalgo                  | 7          | 0    | 11         | 1      | 14         | 3      | 13         | 0      | 15         | 0       | 15         | 0       | 17         | 0      | 21         | 3      |
| 118. Kavyen Leko                  | 10         | 0    | 11         | 2      | 14         | 1      | 12         | 0      | 13         | 0       | 12         | 0       | 11         | 0      | 12         | 3      |
| TOTALS                            | 168        | 0    | 245        | 29     | 267        | 25     | 262        | 39     | 241        | 6       | 263        | 6       | 276        | 3      | 299        | 51     |
| Incidence (1 - e <sup>-ht</sup> ) |            |      |            | 0.118  |            | 0.094  |            | 0.149  |            | 0.025   |            | 0.023   |            | 0.011  |            | 0.184  |
| Inoculation rate (h)              |            |      |            | 0.0021 |            | 0.0016 |            | 0.0027 |            | 0.00042 |            | 0.00039 |            | 0.0018 |            | 0.0033 |

Orig. Neg. - Originally Negative; number of infants examined at the end of the period and which previously had been found to be negative in all examinations at least once.  
Pos. - Positive; those becoming positive, among the originally negative.

Calendar of Inter-MDA Periods: III-IV (mid-April to mid-May 1967), IV-V (mid-June to mid-July 1967), V-VI (mid-August to mid-September 1967), VI-VII (mid-October to mid-November 1967), VII-VIII (mid-December 1967 to mid-January 1968), VIII-IX (mid-February to mid-March 1968), IX-X (mid-April to mid-May 1968), X-XI (mid-June to mid-July 1968).

TABLE 2. DIFFERENT ESTIMATIONS OF THE REPRODUCTION RATES FOR PERIODS FOR WHICH CONCOMITANT OBSERVATIONS ARE AVAILABLE

| Function                      | $z_0 = \frac{h}{r} \left( \frac{a}{-\log_e p} + \frac{1}{x_g} \right)$ |  | $z_0 = \frac{p^{12}}{p^{12} - L_s}$ |                                  | $\frac{z_0^2 n}{b} = \frac{ma^2 p^n}{ax - \log_e p}$ |
|-------------------------------|--|--|-------------------------------------|----------------------------------|--|
|                               | Inoculation rate (h)   | Average gametocyte rate (x) <sub>g</sub> | Proportion parous (p <sup>4</sup> ) | Sporozoite rate (L) <sub>s</sub> |  |
| <u>Sprayed (CIZ)</u>          |  |  |                                     |                                  |  |
| Jun-Jul 1967                  | 0.0022   | 0.0075                                   | 0.561                               | 0.003                            | 1.70   |
| Aug-Sep 1967                  | 0.0015   | 0.022                                    | 0.489                               | 0.010                            | 11.22  |
| Oct-Nov 1967                  | 0.0027   | 0.046                                    | 0.540                               | -                                | 0.17   |
| Jun-Jul 1968                  | 0.0033   | 0.0405                                   | 0.585                               | -                                | 1.00   |
|                               |  |  |                                     |                                  | 61.31  |
|                               |  |  |                                     |                                  | 234.37   |
|                               |  |  |                                     |                                  | 5.51   |
|                               |  |  |                                     |                                  | 47.98  |
| <u>Unsprayed (Comparison)</u> |  |  |                                     |                                  |  |
| Jun-Jul 1967                  |  |  | 0.865                               | 0.014                            | 6.060  |
| Aug-Sep 1967                  |  |  | 0.674                               | 0.010                            | 42.830   |
| Oct-Nov 1967                  |  |  | 0.767                               | 0.059                            | 2.944  |
| Jun-Jul 1968                  |  |  | 0.750                               | 0.006                            | 5.389  |
|                               |  |  |                                     |                                  | 1002.50  |

m - the anopheline density in relation to man.  
a - the average number of men bitten by one mosquito in one day.  
b - the proportion of those anophelines with sporozoites in their glands which are actually infective.  
p - the probability of a mosquito surviving through one whole day.  
n - the time taken for completion of the extrinsic cycle.  
s - the proportion of mosquitos with sporozoites in their salivary glands.  
L<sub>s</sub> - limit of 's' when equilibrium is reached.  
h - the proportion of the population receiving inocula in one day.

x<sub>g</sub> - the proportion of people with gametocytaemia.  
r - the proportion of affected people, who have received one infective inoculum only, who revert to the uninfected state in one day.  
z - the reproduction rate, or number of secondary infections distributed by a single primary case.  
z<sub>0</sub> - the limit of 'z' as 'x' approaches zero, or basic reproduction rate.  
z<sub>0</sub>(h) - 'z<sub>0</sub>' calculated from a field estimation of 'h'.  
z<sub>0</sub>(s) - 'z<sub>0</sub>' calculated from a field estimation of 'L<sub>s</sub>'.

The Kankiya experiment and the preceding considerations justify a thorough review of the mathematical model in general, towards which we have to offer the following comments.

#### The mathematical model

This model is essentially deterministic and applicable to stable populations, where the different parameters have a value supposedly determinable. The introduction of a stochastic variable (the inoculation rate) in some of the computer applications of the model did not change its essentially deterministic nature. In real situations, especially in areas of extreme climatological conditions as in Kankiya, where the transmission is always focal with a relatively short and explosive main season, the parameters change so rapidly and widely that they cannot be built into a deterministic formula because the estimates for the different parameters in it often refer to different epidemiological situations, as it is generally impossible to carry out all the observations necessary to estimate all the parameters in the same place at the same time.

Moreover, the model itself represents the epidemiological knowledge of the early 1950's and is, therefore, relatively overloaded with entomological variables. The whole of the host-parasite relationships were not included except by assuming that after a fixed time ( $\frac{1}{r}$ ), inverse of the "recovery rate", the parasite will die in the host. Later on, it was intended to interpret these relationships as included in the variable  $b$  of the model, which was originally defined as, "the proportion of those anophelines with sporozoites in their glands which are actually infective", and, therefore, referred to the viability of the sporozoites in general and not to the host response. It is exaggerated to pretend that a value of  $b$  could be found that would be a valid representation for a given population during a certain period, of the interplay of the viability of sporozoites (with all the factors related to the parasite and the mosquito) and the immunological reaction of the host both to sporozoites, trophozoites and gametocytes, the outcome of which is not only the suppression or not of the infection but actually the implantation of infections of different durations, levels of parasitaemias and subsequent infectivity in different individuals as their level of immunity is different. (Macdonald, 1951; McGregor, 1965; Jeffery, 1966)

Macdonald's innovation, over Ross' model, of considering the possibility of superinfection is carried to the extreme of ignoring the working of immunity, except by the recognition that his formulae of the variations of parasite rates are only applicable to infants and epidemic outbreaks, and that immunity is one of the main factors responsible for the discrepancies between various estimates of the inoculation and reproduction rates. Nevertheless, these verbal descriptions are not incorporated in the mathematical model, the function of 'x' (in spite of the recognition that it is really only valid for the description of happenings in non-immunes) is incorporated into the formulation of the inoculation and reproduction rates which are used for the description of conditions of stability.

A more serious difficulty is that most of the formulae parameters cannot as yet be measured in the field with the required degree of accuracy to produce usable comparisons. The practical sampling techniques give estimates based on samples too small and biased to evaluate confidence limits to their values or to determine the area and period of which they may be considered representative.

We can make the following comments about the main parameters of the model:

"m" the mosquito density in relation to man. Although it is difficult to estimate general mosquito populations, "ma" (the man-biting rate) can be estimated in inhabited houses (Garrett-Jones, 1970).

However, the selection of the samples present considerable problems, i.e. the selection of the localities, the houses within them, the selection and location of the baits, and the timing of the observations. It is the normal practice that "capture stations" are selected in localities chosen for their accessibility throughout the year, general facilities and

cooperation of the inhabitants, and within these localities actual houses are picked on account of their high mosquito yields. It is obvious that values so obtained may be useful and practical for the estimation of changes in mosquito densities which could be attributed to seasonal or secular variations, control measures, etc., but would be far from representative of the conditions of the whole area.

"s" the sporozoite rate, can be measured directly but actual data are subject to the same undeterminable sampling errors pointed out in the preceding paragraph. Real sporozoite rates are always very much smaller than their theoretical values. Many important malaria vectors have such low sporozoite rates that any determination of their value is considered impractical.

"a" the man-biting habit, the square of which is a factor in the reproduction rate, is the product of the "biting habit" of the mosquito and the "human blood index", neither of which can be adequately estimated for whole mosquito populations in the field. There is no practical technique to determine mosquito biting habits although it is possible to make educated guesses from laboratory observations under varying conditions of humidity and temperature and field observations of the proportions of different stages of blood digestion and ovarian development, the existence or absence of gonotrophic dissociation, etc. The disproportion between the size and dispersal of mosquito populations and the resources for entomological observations makes impractical the direct observation of biting of marked released mosquitos.

The "human blood index" is measured as the proportion of blood-fed mosquitos with human blood. A worldwide study for several years has given valuable indications of the general human blood index of most vector species (Bruce-Chwatt et al., 1960, 1966). There are, nevertheless, enormous variations from sample to sample for any species. The cost of precipitin testing of mosquito bloodmeals is a very important factor in limiting the size of the measureable sample and, as a result, the determination of this factor is generally limited to a biased subsample of the already biased sample obtained for density determinations, as discussed above. It is, moreover, quite obvious that both these parameters are subject to a considerable degree of local and seasonal variation depending on environmental factors (especially humidity and temperature) which may condition the biting habit of the vector, and the changes of human/animal ratios which may influence the human blood index.

Other methods of study of vector preference for humans in comparison with other animals, offered under similar conditions, give information not translatable to a "human blood index" (Gillies, 1964, 1967).

The values given in actual applications of the model become, therefore, a matter of largely subjective estimation. To describe the same Kankiya epidemiological situation, different authors have come to the following "estimations" of "a": 0.5, i.e. the average mosquito took a bloodmeal every two days and always on man (Macdonald et al., 1968); 0.4 (Nájera et al., 1973), and 0.21 (Garrett-Jones & Shidrawi, 1969) when lower anthropophily and less frequent feeding were assumed.

"n" the length of the sporogonic cycle, is assumed to be constant for a parasite species, under the average meteorological conditions of an area. It has been shown in the laboratory to be closely dependent on temperature and is normally estimated from general data for temperature for the area and season. No assessment has been made of its variations in the field, either directly or through the assessment of the temperature variations to which the actual mosquitos are exposed in their microclimate.

"p" the probability of survival of the vector through one day, is considered as constant throughout the life of the mosquito on the grounds of observations on A. culicifacies under simili-natural conditions and some laboratory observations on A. quadrimaculatus and A. maculipennis atroparvus (Macdonald, 1952). It was concluded that the main causes of mortality for mosquitos were external hazards. It may be contended that this may not be true for A. gambiae or any other species of mosquitos well-adapted to their environment. Some of the observations, even the original ones on A. culicifacies, suggest that "p" may be lower than average in the early days of life, increasing later in mid-life, to decline rapidly at the higher ages, as is generally the case with most animal populations.

Whatever the case, even a general survival (or mortality) rate remains a very difficult parameter to estimate. There is no direct method of measurement, hence one must rely on indirect estimations, of which the more generally used is the determination of the "proportion parous" (Davidson, 1954, 1955; Garrett-Jones & Grab, 1964) and, rarely, the much more laborious determination of the physiological age composition of the population of the vector. (Detinova, 1962; Detinova & Gillies, 1964; Gillies & Wilkes, 1965; Garrett-Jones & Shidrawi, 1969; Hamon, 1963; Hamon et al., 1961).

In this estimation, the "proportion parous" considered as equal to " $p^g$ ", where "g", representing the difference between the average ages of nulliparous and parous mosquitos, is generally equated with the "oviposition interval" which in turn has been considered equivalent to the "feeding habit" and encompassed within the term "gonotrophic cycle". Field evidence of gonotrophic dissociation under various conditions of humidity and temperature and laboratory observations suggest that these assumptions are not valid in areas subject to great meteorological variations like Kankiya.

It is also obvious that the proportion parous (or, the age composition) is dependent not only on the probability of survival but also on the "birth rate" or output of breeding places (Gillies, 1954). It is a common observation that at the beginning of the rains when humidity is increasing and therefore conditions would appear to be becoming more favourable for survival, the estimated "p" drops as a consequence of the great output of young nulliparous females. The opposite occurs during the dry season.

The reliability of the estimates will be also affected if it were true that mortality varied with the age of the mosquito.

Another method of estimating "p", as the ratio of immediate to delayed sporozoite rates (Draper & Davidson, 1953; Davidson & Draper, 1953) is based on the same assumption of stability so that a division of a population into two age-groups may give an estimate of "p".

"x" the parasite or the gametocyte rate, can be measured directly although it is very difficult to relate to entomological observations. Generally, the former refers to a wide geographical area while the latter comes from spot samples on whose lack of representativeness it has been commented above. These parameters are also very largely affected by movements of population, and differences in age composition of the resident and migrant population and of the samples taken. The numbers of fields examined microscopically will naturally affect this index as well.

Macdonald's formulae do not distinguish with different symbols gametocyte and parasite rates, both being referred to as "x" and in the same way recovery rates are represented by "r" whether they refer to recovery from gametocytaemia or from parasitaemia. "x" represents the gametocyte rate in the formula: 
$$s = \frac{p^n x}{ax - \log_e p}$$

of the sporozoite rate, and in those formulae derived from it for "h", the inoculation rate, and "z<sub>0</sub>", the basic reproduction rate. In the latter, "r" appears as the recovery rate from gametocytaemia. Nevertheless, the same symbols "x" and "r" refer to parasitaemia in the formula:  $x = L - (L - x_0)e^{-rt}$ , and those related to it and in their applications to the analysis of infant parasite rates.

"r" the "recovery rate" from parasitaemia or gametocytaemia; there is no way of measuring these "r" in the field, although in our opinion some effort should be made to make determinations of the duration of parasitaemia and of gametocytaemia at least for several strains from the main geographical areas. Macdonald considers that the average duration of P. falciparum parasitaemia is 200 days and that of gametocytaemia, 80 days. These estimates (Macdonald, 1950; Macdonald & Göckel, 1964) are based on the study by Earle et al. (1939), of 76 Puerto Rican children in which he actually followed up 23 patients showing only P. falciparum infections at the first examination. Earle himself, in fact, estimates the mean duration of P. falciparum infection at 560 days. There are also well-documented series of long average durations of parasitaemia including a Panamanian strain of 279.4 ± 19.9 days (Jeffery & Eyles, 1954).

In areas where the strain will be similar to the Panamanian strain, recovery rates would be close to 0.0036. This, incidentally, will affect the prevalent criterion for interruption of transmission (WHO, 1964 & 1966) as the expected parasite rate at the end of the first year should be 27%<sup>1</sup> of the original level (instead of 16%). It is most likely that the Panamanian strain is not the most longeval one in the world and field observations show that at least one African strain of P. falciparum might be longer lived (Verdrager, 1964).

"b" the proportion of actually infective anophelines is a largely undefined parameter as mentioned above; the attempted application of the model to the Kankiya situation, suggests that this cannot be represented by a single variable, as is shown by the lack of any proportionality between estimates of "z<sub>0</sub>" and  $\frac{z_0}{b}$  for the same areas and time periods.

"z<sub>0</sub>" "the basic reproduction rate" or the limit, when  $x \rightarrow 0$ , of the reproduction rate or number of secondary infections distributed by a single primary case, is considered the most important synthetic function of all factors in malaria transmission. It is always a calculated value and its descriptive value is considerably diminished by the deficiencies in the theoretical definition and feasibility of estimation of some of the basic variables involved, as illustrated before in relation to the Kankiya experiment.

"h" "the inoculation rate" or the proportion of the population receiving inocula in one day. Also a synthetic descriptive function which could be calculated from entomological variables or more directly, from the observed incidence of malaria cases in infants, as attempted earlier from the Kankiya data (Table 1).

## DISCUSSION

There is no doubt that "most statements intended to convey precise information are capable of some mathematical development", (Bailey, 1967), and it is also obvious to us that the discussion of whether epidemiology is or not an area of applicability of mathematical methods has convincingly enough been answered in the affirmative (Bailey, 1957; Macdonald, 1957; Moskovskij, 1963, 1964, 1967). Ross' statement:

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<sup>1</sup> Deducted from the formula:  $x = e^{-rt}$  (Macdonald, 1957).

"All epidemiology, concerned as it is with the variation of disease from time to time and from place to place, must be considered mathematically, however many variables are implicated, if it is to be considered scientifically at all." (Macdonald, 1957)

may, nevertheless, be a bit exaggerated in its enthusiasm. The value of Macdonald's model of the dynamics of malaria transmission both as a landmark in mathematical epidemiology (Bruce-Chwatt, 1969b) or as an inspiration for further research and development of the theory is not a point for discussion either.

Mathematics is, nevertheless, only a way of expression and elaboration of thought, although more precise and articulate and far easier to handle than mere verbal expressions. It is therefore necessary to be extremely careful not to be affected by the "fetichism of numbers" when facing the beauty, conciseness and potentiality for elaboration of a mathematical formula, not to mention the need to avoid and recognize the more spurious usages with the purpose of impressing the unaware or vainly attempting to provide a scientific polish for conclusions hastily drawn from insufficient or inadequate observations. Unfortunately, it is not rare that the biologist suffers towards mathematical formulae the same type of uncritical faith-inducing awe which the general layman once suffered towards Latin or the printed word (Nájera, 1952).

The application of mathematics to epidemiology, as to other natural sciences, presents two levels of theoretical formulation. On the one hand, the discovery of correlation, among several measurable phenomena may lead to the postulation of hypothesis of causal relationships and their formulation in mathematical terms as empirical laws which in turn may be checked by observation and experimentation. The most important quality of these laws is the possibility of measurement of the variables involved and, therefore, the ease in their confirmation, use and modification, if further observations so suggest.

A second level is the building of an overall theory which tries to explain the inter-relations of all the partial laws and give a complete description of the dynamics of the phenomenon under consideration. Such a theory requires a certain number of intuitive assumptions (axioms) on whose general validity depends the usefulness of the theory. This is only an ordering of our knowledge and has no more claim to being an actual representation of reality than our previous knowledge could have. Comprehensive and philosophically beautiful theories are generally magnificent didactic tools and very inspiring for the research worker by keeping him aware of the general significance of his observations. Most scientific theories tend, nevertheless, to outlive their usefulness.

A serious danger of the philosophical appeal of a theory is the creation of an excessive confidence in the solidity of our knowledge with all the dangers that this confidence may have in our practical decisions. This includes the encouragement of formulation of general criteria or laws when they appear supported by the theory although this support may mask the limited factual base for the proposed generalization. An example may be found in the general acceptance of a constant slope of decline of malaria parasite rates under conditions of interruption of transmission instead of the recognition that this slope of decline is an interesting variable for study as it is related to the mean duration of parasitaemia, which in turn should be a character of the species and strain of parasite modified by the immunological status of the population which is related to the length and intensity of the transmission season, among other factors.

The recognition of the significant variables and the exploration of the possibility, ease and significance of their measurements will lead to more fruitful research and meaningful knowledge even if it may imply more discomfort in the process of administrative decision-making in the absence of an easily manageable formula.

More dangerous and useless exercises are the elaboration of crude observations, generally related to different universes, together with some unmeasurable assumptions into synthetic

functions which are supposed to characterize a complicated epidemiological situation and on the comparison of which decisions are expected to be based. This can only lead to confusion and to blurring of vision of what is actually being compared. Examples of these functions are the reproduction rate, the vectorial capacity, the malariogenic potential, etc.

The climatic extremes of the Kankiya area and the simultaneous control attempts on the vector and the parasite afforded the opportunity of stressing the failure of the existing mathematical model to describe the epidemiological situation of malaria.

The need is felt for a revision of various prevalent concepts in malaria epidemiology. This implies the reformulation of the general theory to attempt a more comprehensive reordering so as to include more up-to-date knowledge in the frame of more up-to-date mathematical tools. It is most encouraging that a more sophisticated model has already been developed and is being studied in the field (Dietz, 1971; Dietz et al., 1971).

Of more immediate practical importance would be a revision of the meaning of concepts and of their measurements, estimations or indicators. This will prevent the disappointments suffered by people trying to fit into a picture as an actual measure of, let us say, the probability of survival of a mosquito for one day in the general mosquito population, a value obtained from a mere index, in this case, not even directly proportional to the variable under consideration as it is the proportion parous, calculated from a part (empty and recently fed mosquitos) of a small biased sample of the mosquito population (captures twice a month from a few accessible productive houses).

General criteria and calculated variables based in estimations of poor confidence should be abandoned as guides for administrative action in favour of simpler considerations. This will result in the lack of clear-cut administrative guidance and more dependence in many cases on educated guesses made by experienced professionals who would become more aware of the real state of our knowledge. Observations of various malaria eradication programmes has led to my opinion that one of the main causes for long-term failures of malaria eradication has been the exaggerated reliance on criteria such as pre-established values of the annual blood examination rate and the annual parasite incidence for judging the adequacy of performance and for basing decisions such as discontinuation of attack measures, etc.

Historical development of knowledge in a scientific discipline follows a pattern which shows some common characteristics with the sequence of recurrent epidemics of infectious diseases (Goffman & Harmon, 1971). The formulation of a comprehensive theory represents the culmination of an epidemic wave of scientific research, leading to an outburst of applications but to a slow-down in research interest. The slow identification and recognition of problems in applications leads to a build-up of research interest which will eventually result in a new epidemic wave of scientific research. Malariology may be currently in a pre-epidemic moment. Interest in malaria research is continuously increasing as new problems are being recognized in the efforts to control the disease (Bruce-Chwatt, 1969a; Lipes, 1969, 1972a, b).

## CONCLUSIONS

The observations of the trial and theoretical considerations suggested by them pointed out several inadequacies of the mathematical model used in representing a dynamic malaria situation and, therefore, the inadequacy of having taken the vectorial capacity or the reproduction rate, or any of the proposed single indices to characterize an epidemiological situation. This is not only due to the impossibility of obtaining widely applicable reliable estimates of the parameters involved but also to the theoretical insufficiency of those indices, as presently defined, to adequately represent either the malariogenic potential or its influence on the level of endemicity and stability of an epidemiological situation.

These rather negative conclusions should not be taken as a pessimistic view. It is obvious that scientific knowledge is reached through the accumulation of observations and the ordering of these into a comprehensive theory which may suggest further observations, that in turn would serve to confirm or suggest modifications of the theory.

It is our view, therefore, that Macdonald's theoretical model represented an outstanding contribution to our understanding of malaria epidemiology and that all efforts should be continued in following his lead of stimulating close cooperation of epidemiologists, mathematicians and other specialists in the different disciplines which may contribute to a better understanding of the reality of malaria epidemiology.

All efforts should be made to increase our knowledge of basic factors and their correlations so that more useful partial laws might be formulated. This research should go beyond the factors of the causative constellation formulated in a particular theory. For example, further exploration of climatological factors influencing malaria epidemiology (Gill, 1938) may lead to the formulation of most valuable correlations which could be used for the prediction of local outbreaks or the identification of problems.

At the same time attempts should be encouraged to realigning all our present knowledge into a more realistic mathematical model of the dynamics of malaria transmission.

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#### RESUME

De septembre 1966 à février 1969 s'est déroulé dans le nord du Nigéria un projet de recherche sur le terrain visant à déterminer s'il serait possible d'interrompre la transmission du paludisme en associant diverses mesures d'attaque dans une zone jugée représentative de la savane du nord de l'Afrique occidentale.

Le choix des mesures d'attaque, de leurs dates et cycles d'application s'est appuyé sur une simulation des résultats escomptés, au moyen de l'ordinateur, selon le modèle mathématique de l'épidémiologie du paludisme élaboré par Macdonald.

Si l'on peut avoir certains doutes au sujet de la valeur des données parasitologiques prises comme référence préopérationnelle, on sait en revanche par des données postopérationnelles très sûres que la prévalence du paludisme a fortement diminué au cours des deux saisons sèches pour atteindre à nouveau - et contrairement à ce que la simulation avait laissé prévoir - des taux élevés (plus élevés que les taux enregistrés avant les opérations) au cours des principales saisons de transmission.

On en a déduit que, si la réduction marquée des indices plasmodiques au cours des saisons sèches pouvait être attribuée à la chimiothérapie de masse, cette méthode d'attaque n'en restait pas moins insuffisante pour juguler la transmission pendant la saison des pluies et que les pulvérisations de DDT dans les habitations n'avaient pas produit l'effet escompté. Cette défaillance du DDT a été imputée à son effet d'excitation-répulsion qui a chassé Anopheles gambiae des habitations une fois pris le repas de sang, ainsi qu'à la rémanence exceptionnellement courte de l'action insecticide du DDT sur le chaume couvert de suie et sur les surfaces de boue des habitations locales.

On a relevé des différences considérables entre les prévisions du modèle et les observations faites sur le terrain. Ces différences ont été attribuées à un ensemble de causes, parmi lesquelles figure la possibilité de fautes dans l'estimation de la valeur des paramètres. Toutefois, l'analyse du projet réalisé suggère aussi que le modèle mathématique lui-même n'était pas adéquat et qu'il existe des variables plus nombreuses qu'on ne le pense généralement et dont il faut tenir compte pour qu'il soit possible d'appliquer le modèle à des situations concrètes.

Il semble que l'utilisation de la capacité vectorielle, du taux de reproduction ou de n'importe lequel des autres indices proposés pour caractériser une situation épidémiologique était inadéquate. En effet, non seulement il est impossible d'obtenir, pour les paramètres en cause, des valeurs sûres se prêtant à des applications étendues, mais encore ces paramètres, dans leur définition théorique actuelle, ne sont pas suffisants pour représenter convenablement le potentiel paludogène ou son influence sur le niveau d'endémicité et le degré de stabilité d'une situation épidémiologique.

Il ne faudrait pas cependant interpréter ces conclusions assez négatives comme un jugement pessimiste. En effet, la connaissance scientifique s'enrichit toujours par l'accumulation d'observations à partir desquelles on peut élaborer une théorie générale, elle-même génératrice de nouvelles observations qui permettent, à leur tour, de confirmer la théorie ou d'y apporter des modifications.

L'auteur estime donc que le modèle théorique de Macdonald représente une contribution remarquable à la connaissance de l'épidémiologie du paludisme, et qu'il convient de poursuivre les efforts ainsi entrepris pour susciter une étroite collaboration entre épidémiologistes, mathématiciens et autres spécialistes des différentes disciplines qui peuvent aider à mieux saisir les réalités de l'épidémiologie du paludisme.

Il faut s'employer à cerner de plus près les facteurs de base et leurs corrélations afin de pouvoir formuler des lois partielles plus utiles. Il faut aussi encourager un réalignement de toutes les données actuelles dans un modèle mathématique plus représentatif de la dynamique de la transmission du paludisme.

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