Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1968, **38**, 743-755

The Dynamics of Malaria

GEORGE MACDONALD,[1] CATON B. CUELLAR[2] & CECIL V. FOLL[3]

Previous studies on dynamic systems of transmission of malaria, and of eradication of infection following the interruption of transmission, have now been adapted for advanced techniques using the facilities offered by computers.

The computer programmes have been designed for a deterministic model suitable for a large community and also for a stochastic model relevant to small populations in which infections reach very low finite numbers. In this model, new infections and recoveries are assessed by the daily inoculation rate and are subject to laws of chance. Such a representation is closer than previous models to natural happenings in the process of malaria eradication. Further refinements of the new approach include the seasonal transmission and simulation of mass chemotherapy aimed at a cure of P. falciparum *infections.*

These programmes present models on which the actual or expected results of changes due to various factors can be studied by the analysis of specific malaria situations recorded in the field. The value of control methods can also be tested by the study of such hypothetical epidemiological models and by trying out various procedures.

Two specific malaria situations (in a pilot project in Northern Nigeria and in an outbreak in Syria) were studied by this method and provided some interesting results of operational value. The attack measures in the pilot project in Northern Nigeria were carried out according to the theoretical model derived from the basic data obtained in the field.

The present study originated in a desire to explore the belief that a powerful tool for the design of eradication and control programmes, and for the analysis of difficulties in them, could be produced by the extension of dynamic studies using computer techniques. One of us has previously developed a system of dynamics of malaria (Macdonald, 1950a, 1950b, 1952a, 1952b, 1953, 1957). This system has been satisfying in so far as it has led to the enunciation of certain principles governing the epidemiology of malaria. However, development of quantitative dynamics has been meagre; the original author (Macdonald, 1953) showed that the system could be used quantitatively to reconstitute a model of an actual epidemic and thereby to define the factors which determined it, while Macdonald & Göckel (1964) have explored some of the dynamics of diminishing parasite rates during the process of eradication. However, this development by desk techniques has been clumsy and has involved so much calculation as to be usable only for special purposes.

The practicability of quantitative dynamic studies has, however, been greatly changed by the facility of the computer whereby previously intractable aspects can now be handled with ease. It has seemed rational to pursue the previous studies with this technique, and it seems irrational not to use it to support technical knowledge and experience in the field by design techniques which can present the probable result of any suggested course of action or any number of variants on it. By doing this, the epidemiologist can refine his ideas and can have a guided method of choice between alternative lines of action, and with it a yardstick of expected results to guide evaluation month by month so that the earliest signs of deviation can be identified. For these reasons, a series of related computer programmes have been developed.

THE FORM OF COMPUTER PROGRAMMES

The previous model of the dynamic system of malaria was deterministic in that it represented hap-

[1] Lately Director of the Ross Institute of Tropical Hygiene and Professor of Tropical Hygiene in the University of London. Professor Macdonald died on 10 December 1967.

[2] Research Assistant, Ross Institute of Tropical Hygiene, London.

[3] World Health Organization Field Research Project, Kankiya, Nigeria.

penings in a large community within which neither population numbers nor case numbers ever reached very low finite numbers. Some of the main elements of this early model are set out in the Annex because it has been used as the basis of development of the computer programmes which have been run on the ATLAS computer of the London University Institute of Computer Science. The simplest of these programmes is a straight transfer of the basic deterministic model. It can fulfil those functions which were previously fulfilled but is infinitely easier to apply. For instance, instead of the very laborious simulation of an epidemic previously demonstrated by the author (Macdonald, 1953), it would be quite simple to run off a score of simulations with different parameters and then to see which most closely fitted the observed curve. Equally, the laborious calculations of the rates of fall of parasite rates with different low reproduction rates during the progress of attempted eradication (Macdonald & Göckel, 1964) can now be reproduced or elaborated with minimal trouble.

However, the opportunity has been taken to introduce a number of sophistications in order to adapt the model better to the detailed study of various preventive measures and to the process of eradication which cannot be handled by a deterministic model that deals only in numbers which never reach very low finite levels. An incubation interval has been incorporated in all programmes, to a small extent to introduce the timing influence which it exerts in nature, but principally to separate infections into two groups, overt and covert, the latter incubating in either the mosquito or man. It is only with this modification that a realistic representation can be made of drug treatment which affects overt infections and may leave others untouched.

A second sophistication has been the development of stochastic models representing happenings in finite populations and when cases grow small in number. In these stochastic models an inoculation rate, calculated daily, has been applied as a probability of infection to each separate parasite-free member of the community using a Monte Carlo technique and resulting in the conversion of an integral number of negatives into positives. A similar technique has been used in applying the recovery rate to positive cases. Both new infections and recoveries therefore occur in integral numbers determined by inoculation rates and recovery rates subject to the laws of chance. This has been the extent of the stochastic modification, no adjustment having been made elsewhere in the model or thought to be necessary. Some of the significant differences between the two types of programme are illustrated in Fig. 1, which demonstrates the application of both techniques to predicting the possible course of events in disappearing malaria with reproduction rates ranging from 0 to 1.0. The deterministic lines represent proportions positive; accordingly they never reach zero, and are quite smooth. The stochastic graphs represent numbers of positives which in the end decline to zero; they are irregular, approximately following the deterministic line so long as cases are numerous, but deviating markedly from it when they become rare, under the influence of chance. The graphs therefore represent a single possible set of happenings and need to be under the influence of chance, and several replicates have to be made before a general picture can be assumed with certainty. They all have one characteristic, however, which is that the numbers of cases round-off rather abruptly and before this would have been expected from the deterministic curve. This is the representation of the statistical actuality of " fade-out " and may be assumed to be a natural happening in the process of eradication.

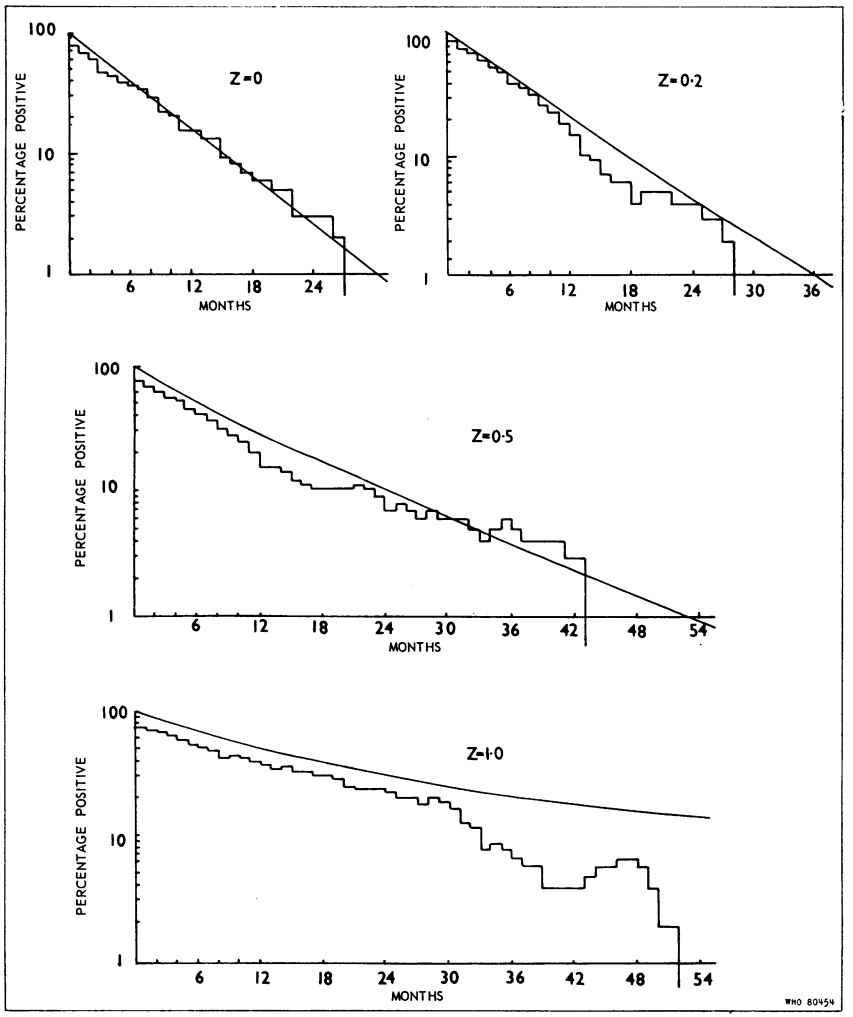
A further sophistication has been to provide for the introduction of curative or suppressive treatment of variable efficiency, and at variable intervals. Though programmes have been developed in relation to both curative and suppressive treatment, the main usage has been in the simulation of mass chemotherapy aimed at the cure of falciparum infections. Further refinements developed for the precise simulation of field conditions include the development of seasonal programmes in which 2 or 3 seasons governed by different epidemiological parameters can be simulated.

These programmes have been developed in the EXCHLF language of the ATLAS computer and are not, therefore, widely interchangeable, though the authors would be happy to provide any worker who has access to this language and system with a copy. However, there is set out in the Annex a flow diagram from which it should be possible to construct a programme in any language. It represents a model of seasonal malaria, complete with incubation interval, stochastic handling and periodic curative mass treatment. The development of a simpler deterministic model or more sophisticated model should be simple on this basis.

The model requires 4 epidemiological parameters for its working: the man-biting habit of the mosquito, the probability of mosquito survival through a day, the recovery rate from malaria in man, and the

FIG. 1

COMPARISON OF THE STOCHASTIC AND DETERMINISTIC EXPECTATION OF CHANGES IN THE PARASITE RATE FOLLOWING A REDUCTION OF A PREVIOUSLY HIGH REPRODUCTION RATE (z) [a]



[a] Reduction to 0, 0.2, 0.5 or 1.0. The size of the stochastic community is 100.

reproduction rate prevalent under the given conditions. If actual or postulated values of these 4 parameters are fed in with the data stream a complete picture of malaria can be constituted. If 3 of them are known from field observations—normally the man-biting habit, the mosquito longevity and the recovery rate—it is possible to do a large number of runs including a wide range of values of the fourth, the reproduction rate, producing corresponding curves in the prevalence of parasitaemia. Known changes in the prevalence of parasitaemia can then be matched against these specimens or " templets " and when a reasonable fit is obtained an appropriate value of the reproduction rate can be assigned to the natural happenings. This method has been extensively used on the basis of field data, including the three named parameters, and measurements of two successive parasite rates at several months' interval during the same season in the same group of people. It has been found to be readily workable and through it a complete reconstitution can be made of natural conditions for later use in testing the probable effect of preventive measures.

These 4 parameters are required because they each of them enter into the expression which represents the dynamic curve of parasitaemia. The reproduction rate is itself a composite expression including all the directly controlling factors, and also the mosquito numbers and the period of extrinsic development of the parasite. These need not be estimated separately; they can be included in the general representation of a reproduction rate which is much more accurately estimated by the indirect means described above than by any attempt at direct measurement of mosquito numbers and all the other factors involved.

A precise model requires a precise input of data which may be very difficult to achieve. In consequence, a large number of programmes have been run to determine the degree of error in the final product produced by various misrepresentations of the input data. The man-biting habit and the probability of mosquito survival always occur in the expressions jointly as the stability index.[1] Variations in this index below the value of 1.0 have a quite negligible effect on the total picture and there is little effect when it is 2.0 or less. From this it can be taken as a working rule that if the man-biting habit is known to be under 0.1 or if the probability of mosquito survival is known to be under 0.75 the index can be given an assumed value of 1.0 and analysis continued without great consequent error, provided this assumed value is maintained throughout the operation. If these requirements are not fulfilled further measurement of both is needed.

The recovery rate from falciparum malaria has previously been estimated at 0.005 and there is sound evidence (Macdonald & Göckel, 1964) that it does not vary much from place to place and this may reasonably be put as a value for this parameter. Deviations from this value have been postulated but they cannot be great: values of 0.01 or 0.0025 would produce, on the one hand, a mercurial mobility of parasite rates in non-malarious seasons and, on the other, a stiff resistance to change, such as are outside our observation. This significance of possible differences has been studied and it has been shown that in the process of analysis, insertion of a deviant recovery rate results in the deduction of a markedly deviant reproduction rate, but if these two deviant values are then inserted in a model which is to be used for checking the effect of preventive measures, their deviations are almost complementary and little difference is seen in the final product. It is therefore fully justifiable to use a standard value of 0.005 for the recovery rate.

PRACTICAL APPLICATIONS

These programmes have been designed to make models on which the actual or expected results of some change in the surrounding circumstances can be simulated and studied. They may be used in a number of ways and actual experience has been gained in the following forms of application.

(1) The testing of the potential value of the control mechanism by creating one or more hypothetical, though realistic, epidemiological models and trying out the suggested preventive measure with a number of variations in efficiency, timing, etc.

(2) The analysis of a specific malaria situation from the collection of observed field data.

(3) The design of specific control or eradication programmes, carried out by a combination of the methods listed as (2) and (1) above; and the creation of a full model from the collection of field data and the superimposition thereon of different mechanisms of control. A great variety of potentially available mechanisms can thereby be tested and when the most appropriate has been selected a yardstick of expected

[1] Stability index $= a/(-\log_e p)$, representing the mean number of bites on man taken by an average mosquito during its entire lifetime, and determining the stability of epidemiological conditions (Macdonald, 1952). For definitions of a and p, see Annex.

progress can be prepared for later comparison month by month with actual progress.

(4) The study of outbreaks of malaria. Outbreaks occur nowadays mainly on the basis of nearly successful eradication programmes starting from very low parasite rates. They differ from normal situations in that the type of data available for study is usually different and refers to incidence only.

Study of the efficacy of preventive measures: mass treatment

A study has been made of the potential value of mass treatment as an adjuvant to or substitute for insecticidal attack. It has been envisaged as being given to a high proportion of the population of an area at approximately the same time and over a very brief period, probably 1 or 2 days. A search has been made of the literature to see whether the effects of such brief courses as either curatives or suppressives can be properly evaluated. It has been concluded that a single dose of a 4-aminoquinoline may be curative to a very high proportion of cases of falciparum malaria in people previously exposed to this infection (Butts, 1950; Villarejos, 1951; Hoekenga, 1952: Covell et al., 1955; Clyde, 1958, 1961, 1967; Pringle & Avery-Jones, 1966). No similarly convincing or even generally coherent picture emerges of the effects of regimes of treatment which might be applied as mass therapy against vivax or other types of malaria. Programmes have been prepared applicable to the cure or suppression of vivax malaria but until some concept can be formed of the ratio in which these two occur there is little point in operating them. The studies have therefore been continued in relation to falciparum, in which context they are believed to be realistic. The efficiency of mass treatment has been deemed to be the product of the proportion of falciparum cases cured by the regime studied (typically 0.6 g of chloroquine base as an adult dose) and the proportion of the population to whom it is administered. A large number of programmes have been operated on widely differing epidemiological backgrounds, with treatment at intervals of 1 month upwards and with efficiencies ranging from 50% to 90%. The general form of results is illustrated in Fig. 2, which refers to the expected effect of an 80% effective mass treatment every 2 months against falciparum malaria of low stability (stability index = 1.0) and where the reproduction rate of malaria independently of this mass treatment is as shown in the graphs. The first four of these are identical epidemiological conditions to those illustrated in Fig. 1 and may be compared with them. The other three graphs extend this series to some higher reproduction rates. It will be noted that in the last of these where the reproduction rate is 4.0 the prevalence of parasitaemia declines slowly and this is about the limit of reproduction rate within which mass treatment of this periodicity could ultimately eliminate infection. It is for the operator to decide how frequently mass treatment could be applied, but it is not likely that it could be applied at this efficiency at much shorter intervals. Reproduction rates of this low value are rare in nature and it follows that mass treatment could rarely be a substitute for insecticidal attack though it could be a valuable adjuvant. Fig. 2 shows that it could be expected to accelerate the decline of parasitaemia very greatly and so reduce greatly the time from the start of attack until surveillance levels were reached, while the last four graphs dealing with reproduction rates of 1.0 and upwards show that it could convert attack by insecticides which would otherwise be a total failure into complete and moderately early success. The conclusions which have been reached from this series of studies are as follows:

(1) Mass treatment could play a very effective part in the eradication of falciparum malaria but in most conditions only as an adjuvant to insecticidal attack.

(2) The value is not limited to conditions where insecticides have failed or might fail; the speed which it introduces constitutes a valuable factor in any programme.

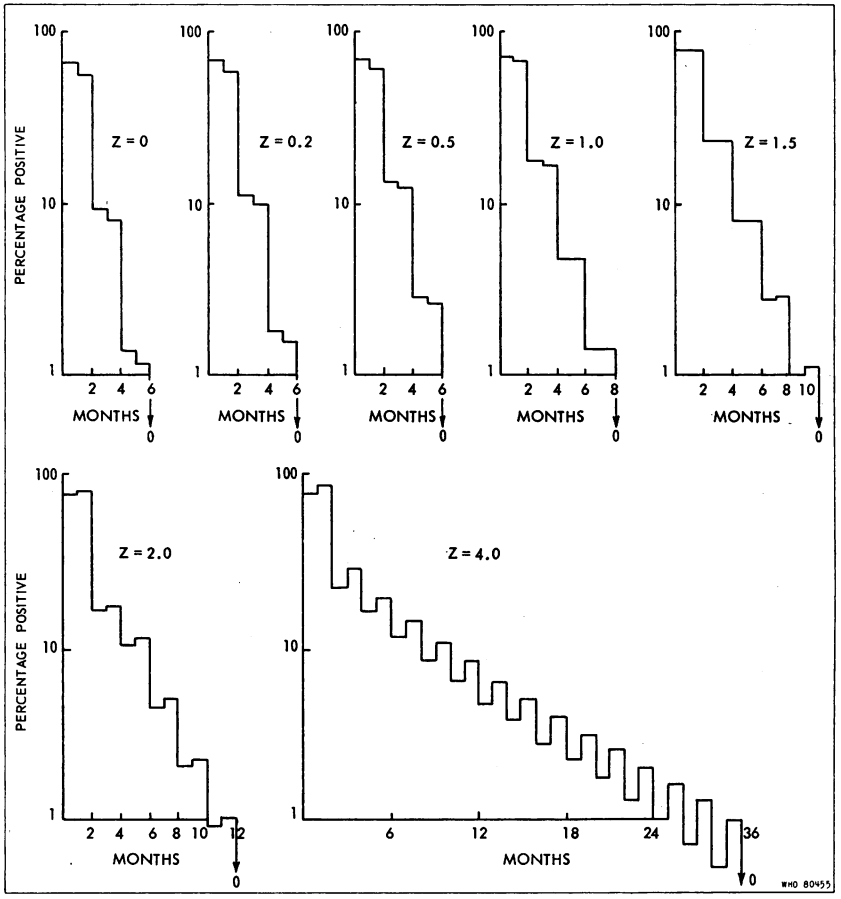
(3) The most effective time for the institution of mass treatment is during the period of minimal transmission. Where malaria is seasonal the greatest advantage is gained by the initiation of treatment early in the non-malarious or relatively non-malarious season, and this despite the absence of transmission or many clinical cases at that time.

(4) Mass chemotherapy applied at a time when the incidence of malaria is increasing, as in the early stages of an outbreak, is relatively ineffective and would have less value than is indicated by these examples.

(5) Preliminary analysis of the malaria situation along the lines which have been described is essential for the forecasting of the results of mass treatment. The data required from the field for this purpose are the man-biting habit of the vector (unless it is known to be under 0.1), the expectation of the survival of the mosquito (unless this is known to be under 0.75),

FIG. 2

EXPECTED EFFECT OF AN 80% EFFECTIVE MASS TREATMENT EVERY 2 MONTHS ON MALARIA SUBJECT TO REPRODUCTION RATES (z) SHOWN AND A STABILITY INDEX OF 1.0[a]



[a] Deterministic version.

and information on changes during each season in the prevalence of parasitaemia—this could take the form of successive parasite rates in selected communities.

Analysis of a particular malaria situation

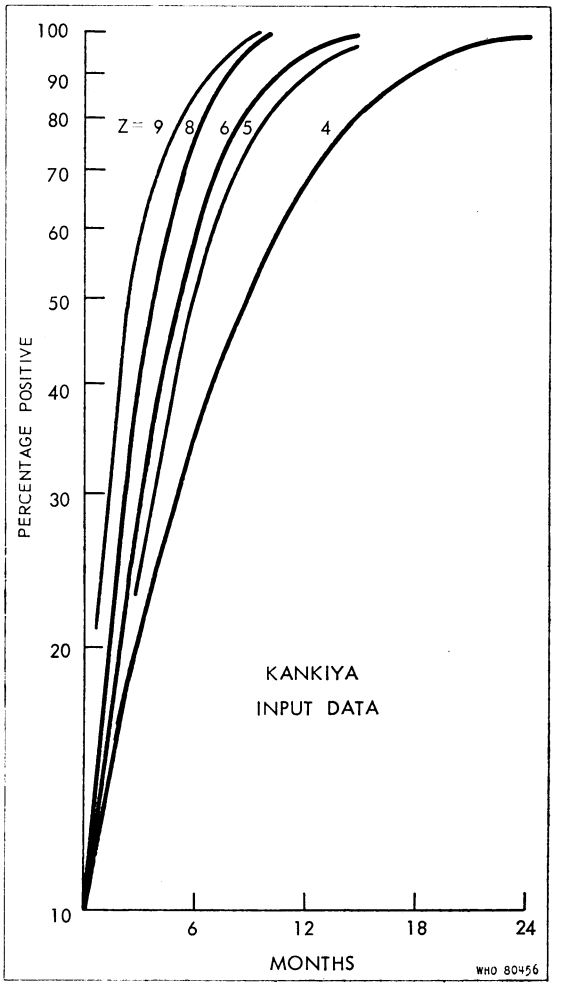
The prevalence of malaria and its epidemiological characteristics in Kankiya, Northern Nigeria, have been studied for several years and described by Foll, Pant & Lietaert (1965) and Foll & Pant (1966). Malaria is normally holoendemic; it is seasonal, the more malarious season lasts 4 or 5 months, the less malarious one lasts 7 or 8; transmission is by *Anopheles gambiae* and much of this takes place outdoors; the man-biting habit of this mosquito approaches 0.5. Falciparum malaria predominates. Several experimental control programmes have been carried out but have failed to eliminate transmission entirely and this is thought to be due to the common outdoor resting habit of the mosquito and consequent escape from insecticides, with associated transmission. Under the influence of insecticides the probability of survival of the mosquito through 1 day is about 0.8 and this probability does not vary greatly between the seasons when insecticides are applied. Two consecutive parasite rates taken in children aged 4–9 years at intervals of 3 months during the wet season were 82% and 94%, and successive examinations of

one group during the dry season at intervals of 6 months gave rates of 68% and 42%. These rates are maximal for the area concerned within which there are localities in which they are much lower, but it seemed best to devise programmes in relation to the most intense transmission that they are intended to meet.

Analysis of this situation has been carried out on the basis of the recorded man-biting habit and mosquito longevity with which a lengthy series of templets has been prepared, illustrating the expected changes in parasitaemia over a wide range of reproduction rates. A very much abbreviated series of these is shown in Fig. 3. Comparison with the observed changes showed that those in the wet season corresponded to a reproduction rate of 6.0 and those in the dry season to 1.0. These values have been re-entered on a complete model with different lengths of wet and dry season from which it has been shown that with a dry season of 7 months these parameters almost exactly reproduce the known epidemiological position with a parasite rate ranging from 48% to 89%, and this has been accepted as representing conditions at Kankiya.

FIG. 3

ABBREVIATED SERIES OF THE "TEMPLETS" RUN OFF AS A GUIDE IN THE ANALYSIS OF THE KANKIYA MALARIA SITUATION



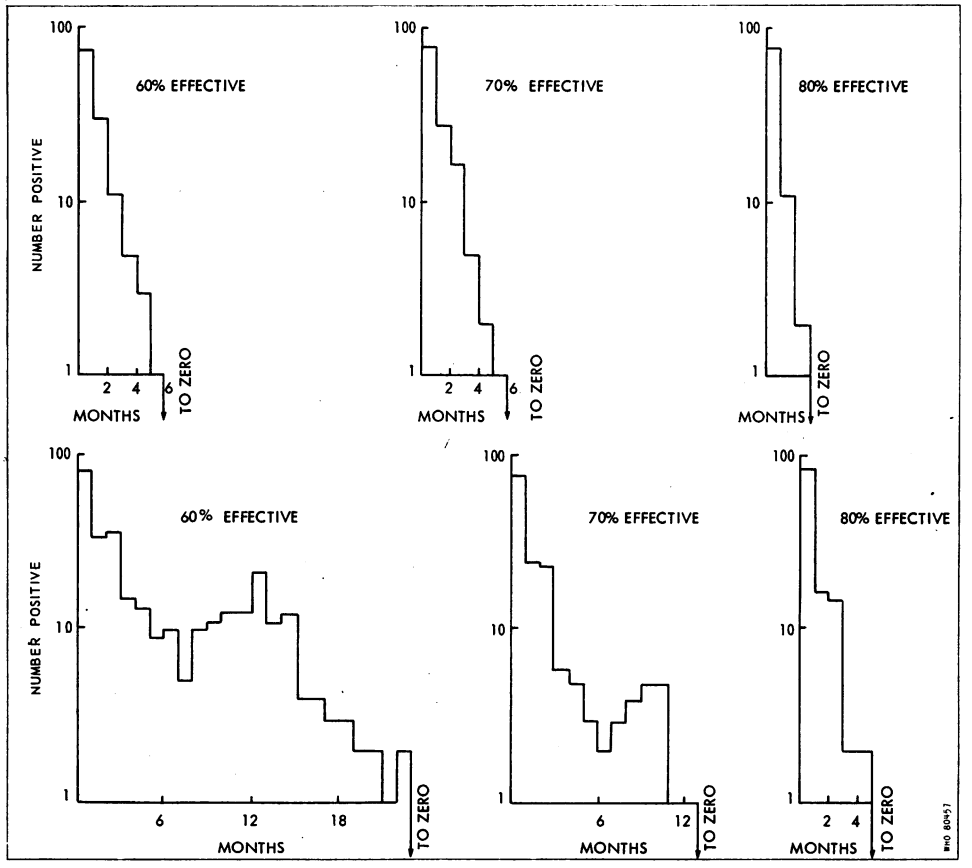
Design of specific programmes

It was suggested that periodic mass treatment as an adjuvant to insecticidal attack might make successful interruption of transmission possible. The output of a small selection of preliminary runs is illustrated in Fig. 4, showing the expected effect of mass treatment of 60%, 70% and 80% efficiency applied at intervals of 1 month and 2 months, starting at the beginning of the dry season. It seemed from these preliminary runs that either a 70% or 80% efficient treatment every month or an 80% efficient treatment every 2 months might be adequate, but reliance could not be placed on less efficient or more widely spaced treatments. Operational considerations made it desirable to concentrate on the regime carried out every 2 months for which one of us (C.V.F.) estimated that he could secure an 80% or greater efficiency. This treatment was further explored in a number of stochastic and deterministic runs; the output for one of the former, covering a population of 1000, is shown in Fig. 5. It seemed from these subsequent runs that there was a distinct probability that treatment started at the beginning of the dry season and repeated every 2 months might reduce the general parasite rate to under 1% in 6 months, at which time infection might have disappeared from several localities. If vigorous insecticidal attack was then applied this position, it was concluded, could then be maintained or improved during the rains and further very greatly improved during the early part of the ensuing dry season.

This proposed regime of combined therapeutic and imagicidal attack has been put into operation by WHO with the consent and very active support of the Ministry of Health, Northern Nigeria. A particularly pleasing aspect of the work in Nigeria has been the assistance and encouragement that the

FIG. 4

EXPECTED EFFECT OF 60%, 70% AND 80% EFFECTIVE MASS TREATMENT GIVEN ONCE A MONTH [a] AND ONCE EVERY 2 MONTHS [b] AS AN ADJUVANT TO IMAGICIDAL ATTACK TO COMMUNITIES LIVING UNDER KANKIYA HOLOENDEMIC CONDITIONS

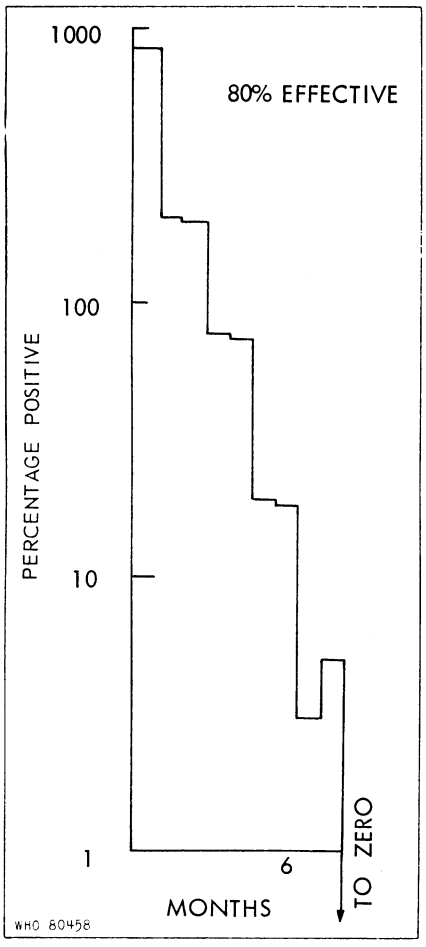


[a] Top row. [b] Bottom row.

team received from the Emir of Katsina, his Wambai, District Head, and village headmen. It was started as an experimental scheme in an area of some 300 square miles (777 km²) containing 52 000 people in which a comprehensive geographical reconnaissance was completed together with a house-to-house census of all occupants. The intention was to administer a curative dose of a combination of chloroquine and pyrimethamine to the entire population every 2 months for a total of 7 treatments and to spray DDT 3 times a year at a dosage of the technical product of 2 g/m². This programme was started in November 1966 and a coverage of 87.2%, 84.4%, 77.7% and 82.8% achieved in the first 4 rounds of mass drug administration. After the third round the parasite rate in the central indicator zone had been reduced from 24.2% to 1.0% which can be compared with a predicted decrease to 0.5%. It was at this stage that wet weather conditions ensued and DDT should have been applied; unfortunately, owing to operational failures outside the experimental area, this was not possible. Active transmission under wet weather conditions was resumed for 2 months, with the increase in the parasite rate which had been predicted in this event. The experiment is therefore incomplete but both the close coincidence of the rate of fall of

FIG. 5

EXPECTED EFFECT OF AN 80% EFFECTIVE MASS TREATMENT APPLIED AS AN ADJUVANT TO IMAGICIDAL ATTACK ON A POPULATION OF 1000 LIVING UNDER KANKIYA HOLOENDEMIC CONDITIONS



the parasite rate and of its subsequent increase with the predicted patterns justify the system of design.

Study of outbreaks of malaria

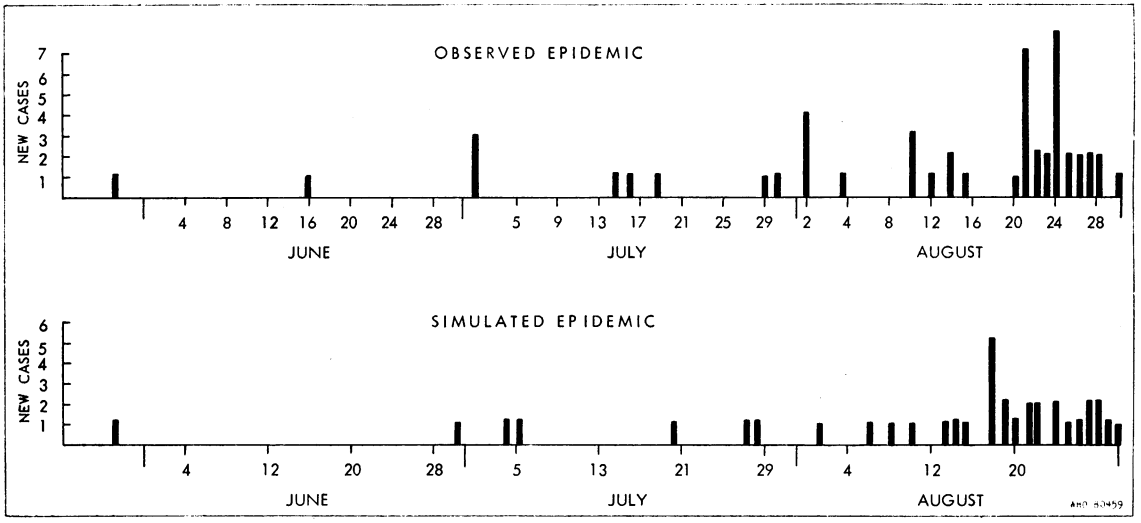
Some outbreaks of malaria have occurred in the course of consolidation and it has been desirable to study them in order to determine by what means they might have been detected at an earlier stage or remedied more quickly. In the examples studied there has been available a statement of the incidence of new cases over a period of some months without a full statement of the population at risk, so that calculation of the proportion infected has not been possible. However, if cases are known to be few in relation to the total population and the proportion infected to be small, this is not a significant barrier to analysis. A programme has been adapted to produce, for any set of epidemiological parameters fed into it, a daily print-out of the resultant number of cases. This is necessarily run on a stochastic basis subject to the laws of chance, as is the natural epidemic, so that general resemblance rather than precise conformity between the simulated and the observed happenings is to be expected.

An outbreak of this type in the neighbourhood of Damascus, Syria, has been reported to us by Dr K. El Shami. Within the area studied, Zakieh, the outbreak arose from a known relapse case, which became overt on 23 May 1965, and continued without serious check until the end of August, during which time there had been 52 known secondaries. The vector was *Anopheles sacharovi*, a highly anthropophilic and long-lived species. The epidemic was analysed in the way already described except that the daily incidence of cases in a long series of simulated models was compared with that in the observed, instead of the changes in parasite prevalence. From several runs it was concluded that a reproduction rate of 22 on the simulated model presented a very close approximation to the actual observed number of new cases, and the output from this run is shown, together with observed happenings, in Fig. 6. Statistical analysis on the basis of the number of cases during each successive incubation interval, excluding the first during which none could occur, gives a probability exceeding 0.5 that the difference is due to chance alone; a comparable analysis on the basis of cases per week gives a probability exceeding 0.35.

A number of simulations of periodic case-finding activities, representing the cure of 60%, 70% or 80% of overt cases at discrete time intervals from 14 days upward gave extremely disappointing results, and it was concluded that none of these regimes could have effectively brought the outbreak to an end without the addition of special measures. The only case-finding with treatment mechanism which could have had this result would have been continuous, operating daily over a period of at least 1 incubation interval following the discovery of an overt case. This unexpected inadequacy of periodic detection and treatment was finally identified as being due to the relative proportions of overt and covert cases. The position on 21 August at the height of the epi-

FIG. 6

DAILY INCIDENCE OF NEW CASES OF MALARIA ARISING FROM A RELAPSED CASE OCCURRING ON 23 MAY IN AN OBSERVED EPIDEMIC NEAR DAMASCUS AND IN A SIMULATED EPIDEMIC WITH PARAMETERS AS SHOWN IN THE TEXT



demic was that there were then 21 overt infections and 34 incubating in the mosquito or man but not yet manifest. The conclusion was that in such cases the function of periodic active case-detection should be to detect cases, but that once a case had been detected the significance of passive case-detection which could be continuous was greatly enhanced.

Other similar problems relating to outbreaks of malaria on Assam tea estates during the consolidation phase have been approached in a similar manner.

ACKNOWLEDGEMENT

The authors very gratefully acknowledge the facility of the use of the ATLAS computer at the University of London Institute of Computer Science.

RÉSUMÉ

Le but de la présente étude était d'explorer les possibilités offertes par les techniques de traitement électronique des données pour l'étude de la dynamique de l'infection paludéenne et l'analyse des difficultés rencontrées dans la conception et la mise en œuvre des campagnes d'éradication. Grâce à un modèle mathématique mis au point par l'un des auteurs, on a déjà pu formuler un certain nombre de principes en matière d'épidémiologie du paludisme, mais la lenteur et la lourdeur des calculs en série se prêtent mal à l'obtention de données quantitatives.

Ce modèle de base a été adapté en vue du traitement par ordinateur et un certain nombre de programmes ont été préparés par transfert direct et par adjonction de nouveaux paramètres. C'est ainsi que l'on a tenu compte de la période d'incubation, conçu des modèles stochastiques pour représenter ce qui se passe dans une population d'importance connue, et simulé les conditions rencontrées sur le terrain en incorporant au modèle les données relatives au traitement curatif ou préventif ainsi que les variations saisonnières de l'épidémiologie. Ces programmes, destinés à être traités par un ordinateur

ATLAS, sont donnés en annexe sous la forme d'un graphique de liaison à partir duquel on peut établir des programmes pour le traitement dans d'autres langages.

Les auteurs signalent certains domaines d'application pratique de ces programmes et mentionnent les résultats déjà obtenus.

On a étudié notamment la valeur potentielle du traitement de masse en tant que mesure d'appoint (ou de remplacement) à l'emploi des insecticides. Dans la lutte contre le paludisme à *Plasmodium falciparum*, le traitement de masse périodique complète utilement l'action des insecticides à effet rémanent au cours de la phase d'attaque des campagnes d'éradication, mais il ne constitue pas à lui seul un moyen de lutte suffisant. On ne doit pas y recourir uniquement lorsqu'on constate ou redoute l'échec des insecticides, car il introduit un élément de rapidité dans l'élimination du réservoir de parasites, ce qui est un grand avantage en toutes circonstances. Le moment optimal pour l'appliquer est la période de plus faible transmission. Cependant son efficacité ne peut être correctement appréciée qu'après analyse de la situation épidémiologique dans chaque cas particulier. Les modalités de cette analyse sont décrites et illustrées par la relation des observations faites à Kankiya, Nigéria, où l'on a procédé à une étude complète du contexte épidémiologique au moyen d'un modèle simulant les conditions locales.

L'emploi des programmes sur ordinateur facilite la conception des opérations de lutte spécifique. Une étude du genre portant sur les possibilités d'emploi du traitement de masse a été entreprise dans la région de Kankiya. Le travail de l'ordinateur a permis d'opérer un choix parmi un très grand nombre de schémas combinant la chimiothérapie de masse et la lutte antipaludique par les imagocides. Le projet sélectionné a été mis en œuvre par l'OMS en 1966. Bien qu'il ait dû être interrompu par suite de difficultés inopinées, les résultats obtenus sur le terrain, quoique incomplets, ont confirmé les prévisions.

Le traitement électronique permet également d'étudier les épidémies de paludisme. Un exemple de cette application est donné par les observations faites au cours d'une épidémie survenue en Syrie en 1965.

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Annex

THE MATHEMATICAL MODEL

The deterministic form has been previously described and summarized by Macdonald (1957), and part is here repeated for convenience. The symbols used are:

m = the anopheline density in relation to man;

a = the average number of men bitten by 1 mosquito in 1 day;

b = the proportion of those anophelines with sporozoites in their glands which are actually infective;

p = the probability of a mosquito surviving through 1 whole day;

n = the time taken for completion of the extrinsic cycle;

h = the proportion of the population receiving infective inocula in 1 day;

x = the proportion of people affected (that is showing parasitaemia);

L = the limiting value of the proportion of men infected when equilibrium is reached;

r = the proportion of affected people, who have received 1 infective inoculum only, who revert to the unaffected state in 1 day;

t = time in days;

z_0 = the basic reproduction rate, or the number of infections distributed in a community as a direct result of the presence of a single, primary, non-immune case.

The system is based on the definition of an over-all reproduction rate, z_0 above, and its daily element $z_0 r$ representing the number of infections distributed by a single case in 1 day. However, in a wholly independent system the reproduction rate itself becomes a function of x, the proportion of the population affected owing to the intervention of the mosquito vector in which infections may overlap when common, and thus limits the net number distributed.

The basic rate, usable only for static conditions and defined in relation to near-vanishing infections, is given by the following equation:

$$z_0 = \frac{ma^2bp^n}{r(-\log_e p)}, \tag{1}$$

and the net rate, applicable in all conditions, is given by:

$$z = \frac{z_0(-\log_e p)}{ax-(\log_e p)}. \tag{2}$$

The inoculation rate, which is largely a development of it, is:

$$h = \frac{z_0 r x(-\log_e p)}{ax-\log_e p}. \tag{3}$$

It is, however, essential to realize that, when the occurrence of new cases is to be studied, they are the product of an inoculation rate dependent on values of x of some time previously. New overt infections are the product of a reservoir of cases separated in time by both the incubation period in the mosquito and that in man, by, indeed, the entire incubation interval (i). If allowance is to be made for the incubation interval this must be taken into account, and for this purpose the effective value of the inoculation rate is:

$$h = \frac{z_0 r x_{t-i}(-\log_e p)}{ax_{t-i}-\log_e p}, \tag{4}$$

and it is this value of h which is here used in all programmes. In working examples the value of i for falciparum infections has been put at 30, to allow also for delay in infectivity. For *vivax* infections a typical value of 20 has been estimated (Macdonald, 1953). In an example recently worked, a value of 16 was postulated but fuller working suggested that 17 or 18 would have been more appropriate.

The basic differential has two forms applicable when $h < r$, and when $h > r$, the two merge when $h = r$. For programme purposes they are best represented in incompletely simplified forms which facilitate a switch from one to another at the appropriate point, and it is well to emphasize the different time scale of the parasite rate;

when $h < r$,

$$\frac{dx}{dt} = h(1-x_t)-(r-h)x_t, \tag{5}$$

and when $h > r$,

$$\frac{dx}{dt} = h(1-x_t), \tag{6}$$

the expression for h used being always that given in equation (4).

The limiting value of (5) is:

$$L_x = (-\log_e p)/a \cdot (z_0-1), \tag{7}$$

and that of equation (6) is 1.0. In practice, any observed equilibrium is represented by equation (7).

The stability index (Macdonald, 1952b) is:

$$a/(-\log_e p), \tag{8}$$

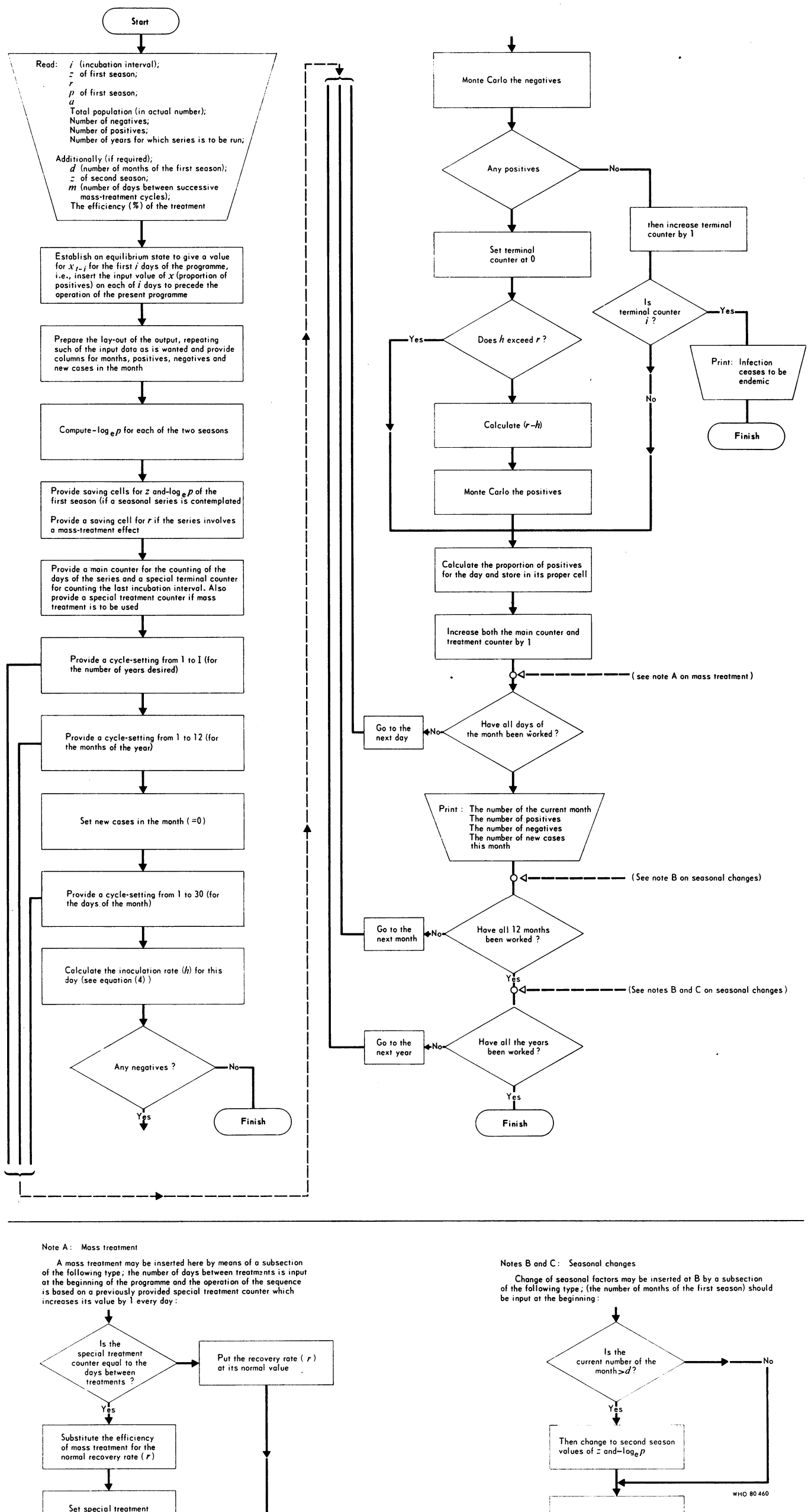
which represents the mean number of bites on man taken by a typical vector during its entire lifetime, a characteristic which determines stability because it represents the working of a density-dependent mechanism. The two elements, a and $-\log_e p$, always occur in expressions in such a way that they can be expressed as this ratio, or its reciprocal, and it is often convenient to refer to them jointly.

Computer programme: general principles

The flow diagram (Fig. 7) is an attempt to describe the layout of a programme in such a way that it could be translated reasonably easily into any com-

FIG. 7

FLOW DIAGRAM FOR THE MAIN COMPUTER PROGRAMME



Note A : Mass treatment

A mass treatment may be inserted here by means of a subsection of the following type; the number of days between treatments is input at the beginning of the programme and the operation of the sequence is based on a previously provided special treatment counter which increases its value by 1 every day :

Notes B and C : Seasonal changes

Change of seasonal factors may be inserted at B by a subsection of the following type; (the number of months of the first season) should be input at the beginning :

Also, at the end of every year, an extra instruction should be placed at point C :

puter language. It has been divided into a number of subsections in order to avoid the confusion inevitably associated with a long diagram which has many loops. The diagram describes the dynamics of a stochastic malaria model which can be modified to include provision for periodical mass treatment or for seasonal changes in epidemiology, or for both.

The stochastic element, using a " Monte Carlo " technique, is described separately and before the main programme (Fig. 8). This description is then assumed and in the main programme the whole operation is described in the words " Monte Carlo the negatives " or elsewhere as " Monte Carlo the positives ".

The programme includes a stop after cases reach zero and this is slightly complicated owing to the need to run it for a further complete incubation interval in order to check the absence of covert infections. The need for two time scales, t and $(t-1)$, has been met on ATLAS by the reservation of main variable space sufficient to cover every day for which the programme might operate, typically 1899 cells representing 5 years. This has been simple on ATLAS which is a very large machine but some modification would probably be needed for smaller machines.

The Monte Carlo system

This is used in order to apply probability rather than certainty of a proportion to the conversion of negatives into positives, or *vice versa*. This probability is first decided, the inoculation rate in one case and $(r-h)$ in the other. The machine is then instructed to select a random number between 0 and 1.0; if this random number is equal to or less than the probability already determined, the conversion is judged to have taken place. If it exceeds the probability the case remains unchanged.

It may be noted that the machine's random numbers are in truth pseudo-random and repetition of this process in a subsequent programme might result in the selection of the same " random " number. This difficulty has been overcome when multiple programmes are to be operated by the insertion of a genuine random number into the data input with an instruction to the machine to run through its pseudo-random series for this number of times before starting on its selection.

FIG. 8
FLOW DIAGRAM FOR THE MONTE CARLO SYSTEM