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EPIDEMIOLOGICAL BASIS OF MALARIA CONTROL

by

Professor G. MACDONALD
Director of the Ross Institute of Tropical Hygiene, London

INTRODUCTION

There has long been difficulty in understanding some aspects of the epidemiology of malaria in Africa, and it has not been lessened by the recognition of similarities to conditions in some other countries which at the same time showed marked dissimilarities such as severe epidemic tendencies and ready amenability of the disease to control. At about the time of the Kampala Conference in 1950 the author set out with some colleagues to explore some fundamental aspects of epidemiology, by both theoretical and practical approaches, primarily in an attempt to resolve this difficulty. The theoretical approach was necessarily a mathematical one, for all multiplication of disease is a numerical process involving many factors whose relationships can only be studied in this way. They have been published in a series of papers by Macdonald (1950a, b, 1952a, b, 1953 and 1955). Corresponding field observations have been made by Draper (1953), Draper & Davidson (1953), Davidson (1953, 1954 and 1955) and Davidson and Draper (1953), and have concerned many of the problems brought to light by mathematical studies, especially the measurement of mosquito longevity and the infectivity of man. Two of these studies (Davidson & Draper 1953,

and Davidson 1955) have consisted of complete field surveys in which an effort was made to measure all the factors involved in malaria transmission and to relate them to each other in accordance with the original theoretical work.

The object of mathematical analysis is to understand epidemiology, but it is realised that the technique is a foreign one to many who study malaria and that it will, to some extent, fail unless it is translated into ordinary words, though precision of statement is invariably lost in the process. Much of the material is therefore presented here in translation, as an effort to describe happenings in a typical part of equatorial Africa such as that covered in the special surveys. Some comparison has been made with conditions in Madras, selected because very detailed analyses are available in the works of Russell, Menon & Rao (1938) and Russell & Rao (1940, 1942a, b, c). For clarity the account has been kept clear of references except when they are especially necessary, but the points in it are substantiated by observation. Sole reliance has not been placed on the papers quoted and acknowledgement is made of the very substantial collection of factual knowledge which has been built up by many workers, which has served as a background of the studies, in which detailed acknowledgement is made.

EPIDEMIOLOGY

The extrinsic development of Plasmodium falciparum and P.vivax is brief in most of equatorial Africa, of the order of 10 to 12 days, and typically perennially so; several species of mosquito provide excellent hosts to the parasites: two of them Anopheles gambiae and A.funestus have been shown under typical conditions to enjoy the considerable longevity consequent on a daily death rate of about 5 per cent. or even less, and to bite man almost regularly every second day. These features which are commonplace to every malariologist in Africa are not universally so and are the factors which together differentiate malaria in Africa from that in most of the rest of the world, giving it its special characteristics. They immediately determine two: a common intensity which is not, however, uniquely associated with these features, and a degree of stability which is. A mosquito subject to this mortality biting an infective case has at least a 50 : 50 chance of survival till sporozoites

appear in its glands, and if it does a subsequent expectation of about 20 days life, so that its chances of conveying the infection to another may in all be as high as 5 to 1, which is over a thousand times more than the chances of A.culicifacies in Madras passing on an infection. The perpetuation of malaria is therefore secure even when anophelines are very scarce, anophelism without malaria is unknown (though it is well known in Madras) and transmission becomes intense when they are numerous.

If gametocyte carriers are few in the community the proportion of mosquitos infected will be small, and at first it will rise roughly in accordance with any increase in gametocyte carriers, and the sporozoite rate will become high when they are present in moderate numbers only. This very fact means, however, that further increase in the carrier rate must progressively produce less and less increase in the sporozoite rate, and so restrict the multiplication of cases which would otherwise occur. The occurrence of some such restriction in any circumstances must be obvious but its importance when compared with that in other epidemiological cases is not well understood. The immediate difference from the restriction occurring in some other places is moderate; in the typical African conditions used for illustration an increase in the infective gametocyte carrier rate from 1 to 100 per cent would increase the sporozoite rate to about 6 times its original level, whereas in the contrasting ones of Madras the increase would be about 25 times. However, this represents only a small part of the influence it exerts for the effect is cumulative, a rise in the gametocyte rate increasing the sporozoite rate which in turn increases the gametocyte rate and so on, though in diminishing degree. The total effect is such that if some change in environment starts off an increase in transmission the response in the parasite rate is some 200 times as great in the circumstances of Madras as in Africa. The epidemiological factors thus grant a governing mechanism to the typical African malaria which makes stability or lack of variation its most notable feature, and deny it to the zone of A.culicifacies (and many others) where instability is the rule and where recession, recurrence, epidemic and good and bad years follow each other in irregular order. It is notable that all grades

of severity of malaria occur in both sets of circumstances, the distinction between which lies in the regularity with which any degree of severity is maintained over the years rather than in the degree attained at any particular time.

The greatest degree of stability is attained when the time of extrinsic development is short, the anopheline is highly susceptible to infection by locally prevalent parasites, its mortality is low, and it bites man regularly. The stability decreases when any of these requirements are not fulfilled and especially when more than one are not met. Though the picture of stability in equatorial Africa is generally true a review of the continent will produce many exceptions, and usually also provide the reason. Epidemics and other results of instability are well known on the northern desert edge of equatorial Africa, as in Somaliland, in the mountains as in Kenya and on the southern fringe of malaria as in the Rhodesias. In the first case instability is due to increased mosquito mortality in arid conditions, the second to prolongation of the time of extrinsic development of the parasite in cool conditions, and the third probably to a combination of these two and possibly also to the zoophilism which is thought to be common in A. gambiae in those regions. Elsewhere in the world some degree of instability in comparison with Africa is very common; over great near-continental tracts truly stable malaria such as that seen in Africa is unknown and possibly the only large areas in which conditions are truly comparable with those in much of Africa is the stretch of hill and foothill land infested by A. minimus minimus in north-east India, Burma, Thailand and Indochina. In most of India, Ceylon, Malaysia, Indonesia and in most parts of the Americas the typical picture is of marked instability, often with cyclically recurring liability to severe epidemics. The epidemiological characteristics of the disease are so closely related to its stability that classification based first on this feature and only secondarily on severity seems preferable to that based on severity alone which is in common use. Admittedly it is less readily measured, but this is as much due to lack of practice as of feasibility. The first precise measurement, as of so many other aspects of malaria, was made by Christophers (1911) in the form of the "epidemic potential", but this was suitable more for differentiation of degrees of

marked instability than for examination of the entire range, and Gabaldon (1948) has for some long time insisted on the importance of a direct measure in the form of examination of the range of variation of the spleen rate over a period of years, measuring the "constitution" of malaria. Adaptation of the principles of these workers could readily provide as good and generally applicable measures as those now used for severity. The anopheline characteristics determining stability are measurable in the form of the mean number of bites on man taken by an anopheline during its expectation of life, determinable by the precipitin test, analysis of the feeding cycle, and measures of longevity such as those developed by Davidson (loc. cit.). This combined figure is a direct index of stability and is of the order of 10 in the African conditions quoted and about 0.05 in the contrasting example of Madras.

The causes of stability have been stated. Its primary features are that it can be perpetuated by very small numbers of anophelines and that the endemic level is relatively insensitive to minor changes in the environment. Secondary characteristics include a commonly intense endemicity, a regular and therefore potent stimulation of immunity in the population, a greater incidence of P.falciparum and lesser incidence of P.vivax than in most unstable conditions, and a resistance to artificial control. The mechanisms of these results are of the following order.

The average mosquito ingesting ample fully infective gametocytes might later distribute the infection to about five people. The normal prevalence of anophelines and the long duration of gametocytaemia in an untreated person, combined with this capacity as a vector, make the potential infectivity of an original case surrounded by susceptible people fantastically high, amounting in some places to the distribution of 5,000 secondary infections, the estimated number of which I have called the basic reproduction rate. This is a concept and not an actual happening in nature where reproduction is enormously reduced by immunity, but it is an important concept because in the end control must be concerned with non-immune persons and the basic rate gives a measure of the intensity of transmission which must be reduced to one or less if control is to succeed.

Whether the basic reproduction rate is of this extreme order or not, it is usually high. Moreover, transmission is regular and often continuous; infants and non-immunes are soon and repeatedly infected and a reaction of immunity stimulated in them. The anti-parasitic and antitoxic features of this immunity, which protect the individual, have received much attention at the expense of what is probably its most important manifestation, restriction of gametocyte output which protects the community. This restriction of gametocytes may come very early before any restriction of asexual parasites, and in one series was recorded in infants four months old before asexual parasitaemia had even reached its height. It is manifest first as a reduced gametocyte count and only much later as a reduced gametocyte rate; the combined effect is that the gametocyte carriers are relatively few, and that all, but a very small minority, have very few gametocytes in their blood. All relevant experimental evidence shows that very low gametocyte counts are associated both with low infectivity to anophelines feeding on the carriers, and with low grade infections in the anophelines which often fail to establish infections in persons on whom they feed. Field observation has fully supported these findings. The gametocyte rate in one group surveyed was low, 7.7 per cent. Only 0.4 per cent. had over 100 gametocytes per c.mm. of blood. Direct trial on a comparable population had suggested that only about 1.7 per cent. of anophelines feeding on such a group would become infected and very strong indirect evidence, probably more reliable than the direct, showed that only about 1.6 per cent. of feeds resulted in infection of the mosquito. There is also evidence which appears conclusive to the writer that in this area only about 1 in 100 bites on infants by sporozoite-infected mosquitos caused infections to become established in them, while in another area only 1 in 20 did so. There might be many causes for this failure and their relative importance cannot now be assessed, but amongst them some considerable weight must be given to the very small numbers of oocysts and sporozoites typically found in mosquitos in such places, which are almost negligible when compared with those commonly seen in experimental infections.

The combined effect of reduction of the gametocyte rate and especially of the gametocyte count in reducing the infectivity of man to the mosquito and again of

the mosquito to man is enormous, and sufficient to reduce the basic reproduction rate to an actual reproduction rate which is very low indeed, and in the two surveys carried out with the intention of measuring it to only 1.15 and 1 25. Apart from these two surveys data which can be used for its computation are available from several surveys carried out by different workers in equatorial Africa, and in all of which the actual rate lies between 1.05 and 1.2. Both the similarity and the nature of the figures are remarkable. The factors which together build up to form the rate are widely different in the various surveys, but in all they combine to give the same actual value to it. The resultant rate is just a fraction over the critical level of 1.0, values below which indicate a disappearing disease, whilst those above it indicate a persistent one. The implication is quite definite. The stimulus of infection of all the individuals of a community produces a reaction of immunity which limits the amount of transmission by reduction of gametocytogenesis. This reaction is in almost perfect balance with the amount of transmission, and results in the average infection rarely producing more than one secondary infection in another person. The actual complete transmission of the disease is reduced to a level which, though it may seem intense to the non-immune observer, is in fact low to the indigenous people and well within their capacity to bear without extinction. It is for this reason that infections in infants are often delayed for months when entomological study would suggest their inevitability about a fortnight after birth, and why the most extreme severity of malaria, provided the incidence is stable, does not depopulate the countryside. Variations in the basic reproduction rate, if sufficiently lasting, apparently only modify the immune response in such a way as to keep the actual reproduction rate at almost the same level, and chiefly by modifying the age at which gametocyte production is first limited.

The greater relative frequency of P.falciparum in Africa than in many other countries is also probably attributable to the stability of the disease. The essential differences between this parasite and P.vivax are its lesser stimulation of immune response and its longer cycle of multiplication due to the delayed appearance of gametocytes after first infection and to the slightly longer period

of the extrinsic cycle. These result in its slower multiplication on the start of transmission, a fact well acknowledged in all epidemic surveys, and its longer persistence when once established. Brief periods of transmission, such as are common in regions where the disease is unstable, therefore favour the multiplication of P.vivax and long ones, common where it is stable, favour P.falciparum.

Happenings in unstable conditions are quite different. They are attributable to zoophilism, high mortality in the mosquito, a long period of the extrinsic cycle, or more than one of these conditions. The probability of a mosquito passing on an infection once it has swallowed gametocytes is very small, and in consequence the disease can only be perpetuated where mosquitos are numerous. Anophelism without malaria is therefore common. If mosquitos are sufficiently numerous to perpetuate transmission, however, the sporozoite rate varies much more nearly in accord with the gametocyte rate than in the stable state, and the endemic level is infinitely more sensitive to minor changes in environment, whether of improvement or worsening. Intermissions of transmission are therefore common and at times prolonged and tend to be succeeded by epidemics, the inevitable severity of which is often aggravated by the size of the non-immune population which has grown up in the meantime. This provides a gametocyte reservoir which is not controlled by the mechanism already described until too late. In these epidemics P.vivax always precedes P.falciparum and may often continue to preponderate. The fact that communal immunity causing restriction of transmission is delayed permits intense transmission, more severe than that actually encountered in stable circumstances, and results in a correspondingly marked immune response after the epidemic, which may be sufficient to stop transmission entirely and cause the local elimination of the disease, or result in a cyclical periodicity of the disease. Both of these happenings are well known; local elimination following epidemics has occurred recently and probably many times before in the Canary Islands and many parts of Europe, while periodic conditions are well known in India, Ceylon, the Caribbean area, South America and Holland. Even here there seems to be some considerable element of local elimination of the disease, best studied in Holland where it has been shown that it becomes restricted to small foci which remain

malarious in a non-malarious terrain for some years until the disease again extends over the countryside, presumably with the dilution of communal immunity by births, immigration and the passage of time. It seems probable that any approach to elimination must have this form, and that such foci need deliberate search and intensive action.

CONTROL

The object of control is to reduce the actual reproduction rate below 1.0 and keep it there, so that successive generations of cases will diminish to zero even if immediate complete control is not achieved. In practice this means that the basic reproduction rate must be reduced below this level. As control is started the actual rate is inevitably decreased and even mild measures could bring it below 1.0; the improvement would only, however, be balanced by a decrease of communal immunity in the form of prolongation of the period of gametocyte production in infants and a restoration of the previous position. Some advantage would probably be gained, the stress of infection without immunity would be distributed over a longer age period, but would in total amount to much the same as before. As control becomes more effective the basic rate decreases towards the actual and when it sinks below 1.0 no further aid is demanded from immunity. If rapidly and effectively applied some considerable help would, of course, be given by remaining immunity in older people and the full measure of reduction of the basic rate might not be necessary.

The reproduction rate can be reduced by modification of any of the factors which go to make it up: mosquite numbers, longevity and biting habit, the recovery rate of the people and hypothetically only by change in the period of the extrinsic cycle. They have, however, very different influences on the rate. The one with least influence is mosquito numbers, the point at which the traditional attack has always been made in the form of prevention of breeding. Its influence is direct, reduction of mosquitos to, say, a tenth of their previous number reduces the basic rate to a tenth of its previous value, and if reduction

of the latter to a thousandth, or even five-thousandth, of its value is needed the hopelessness of anything except total mosquito elimination can be seen, together with a ready explanation of the many failures of larval control in Africa and its many successes elsewhere. An unaided attack on the recovery rate by treatment of cases has the same disadvantage that omission of even the occasional carrier leaves persistent transmission. Modification of the biting habit has been unintentionally practised with brilliant success in northern Europe and north America by changes in the pattern of husbandry, and has been the subject of a few preliminary experiments in the shape of deliberate zooprophylaxis. Its success in some areas, where the local anopheline readily accepts deviation to cattle, is attributable to the greater influence of man-biting habit than of mosquito numbers on the reproduction rate. Its influence is squared; reducing the anthropophilic index to one-tenth of its original value reduces the reproduction rate to one-hundredth, as this is associated with the necessity to bite twice to secure and convey infection. The change in the habit needed in Africa would be great, it would probably be necessary to reduce the anthropophilic index of A.gambiae to less than 2 per cent, and our present entomological knowledge does not suggest that this is possible. In some other species, however, it seems possible; and zooprophylaxis as a part of an agricultural pattern may well become the backbone of malaria control in the Philippines and Malaya, where A.minimus flavirostris and A.maculatus are readily deviated.

The influence of mosquito mortality on the reproduction rate is very strong; a raised mortality acts by reducing mosquito numbers, reducing the probability of survival of a mosquito through the extrinsic cycle, and reducing its subsequent expectation of life should it do so. The sum of these effects is such that an increase in the daily mortality by 10 per cent. decreases the basic reproduction rate to roughly one-tenth of its original value, by 20 per cent. to one-hundredth, by 30 per cent. to a thousandth, and so on. The worst conditions known in Africa could therefore be met by an increase in the daily mortality of the vector from about 5 to about 45 per cent.

Experiments have been made to determine the mortality achieved by different insecticides, with results which are well known. They determine, however, the

mortality amongst actual entrants to treated houses and not in the local mosquito population, populations which may be the same in the case of wholly endophilic species but different in others. Our knowledge of the endophilism or exophilism of A.gambiae and A.funestus is largely derived from this type of work and cannot therefore throw much light on it, but it appears that A.funestus is largely endophilic and A.gambiae only partly so. Transmission by the first may be stopped by insecticides producing little more than the theoretical mortality of 45 per cent., whereas control of transmission by the latter probably requires an insecticide producing a mortality of the order of 65 per cent. Certainly the prospect of anopheline eradication by imagicidal methods turns largely on the question of endophilism. Theory suggests that an actual daily mortality of about 65 to 75 per cent. should have this result, and this mortality is readily attainable in the house itself. The wide eradication of A.darlingi in South America and the local examples of eradication of A.funestus in Africa probably reflect the endophilism of the two species more than any special susceptibility to the action of insecticides.

This powerful influence of changes in the mortality rate of mosquitos on the transmission of disease by them is the explanation of the brilliant success of residual insecticides. The first trials were, by chance, made in the favourable circumstances of unstable malaria which is much more widely distributed than the truly stable form, and some in what are now known to be peculiarly favourable conditions. In many of these cases the basic reproduction rate was probably initially quite low and needed little reduction to secure elimination of the disease, such as might be attainable by a 10 or 20 per cent. increase in daily mosquito mortality. The almost universal attainment of such mortalities by even small doses of DDT or any other accepted residual insecticide explains their miraculous initial results. The first failures were in trials against A.gambiae and A.funestus in Uganda and elsewhere, but present knowledge of the order of mosquito mortality necessary and the common failure of DDT to secure it explains them adequately. It now seems that only the more potent insecticides producing a mortality higher than 65 per cent. should be used in typical African conditions, and that wherever possible the requirements of control should be checked by survey

by survey methods adapted to modern concepts and needs. There is no reason to suspect that the adequate use of potent insecticides, properly checked, should not result in the elimination of the most stable malaria in Africa, but the cost in insecticide and labour is bound to be higher than for the elimination of the unstable, and readily controlled disease. Economy is to be sought by the combination of methods such as effective mass treatment with insecticidal attack, to reduce the period of operation, and by improved survey and checking mechanisms to avoid wastage without sacrificing effect.

SURVEY

Any form of factual measurement or observation may add value to a survey and, when circumstances permit and justify, elaboration is an advantage. This is, however, no reason for the routine multiplication of techniques, rates and indices which may normally be restricted to those whose direct value in the planning and guidance of a control programme can be seen, and the writer has no doubt that the application of this criterion would relegate many standard procedures to the research department or the museum.

It is assumed that parasitological, entomological and statistical inquiries have been made sufficient to establish the presence of malaria parasites, their species, the vectors and their resting and biting habits, the season of malaria transmission and the incidence of the disease. The additional epidemiological information necessary for a major survey can then be gathered from relatively few measurements which are best made in areas where transmission is most severe. They are mosquito density, biting habit and longevity, the period of the extrinsic cycle (often legitimately estimated), the sporozoite rate and total infection rate of the vectors, and the infant parasite rate preferably classified in three monthly age groups.

Estimates of mosquito density need not usually be precise, and indeed this apparently simple measure is by far the most difficult to make precise, but should refer to greatest densities which occur for any notable time or over any notable

area. Accuracy is only necessary when the figures are to be used in some research process, and not for routine purposes. The figure required is a density in relation to the density of man, which may be estimated from the number entering trap huts harbouring people. Alternatively if an estimate can be made of the number of bites received by an average person per night an adjustment for the known frequency of biting can easily be made.

Assessment of the biting habit requires knowledge of the normal biting cycle and a study of the nature of blood meals by means of the precipitin test. African malariology suffers from the fact that this last is not carried out as often as it should be, and as often as it has been for instance in India where our knowledge of epidemiology is much more elaborate, for the biting habit is one of the most important characteristics of a mosquito. It is true that highly accurate diagnoses of large numbers of feeds without the possibility of even rare errors demand sera and techniques beyond the reach of most field workers. There are, however, centres where exact work of this nature can be done on dried specimens of blood, and it is not sufficiently known that sera and techniques sufficient for a reasonable separation of bloods into human and non-human are very simple to acquire and operate, with only the risk of confusion of simian blood which in many cases is not likely. The writer feels strongly that at least an approximate analysis should be made of blood meals in every survey with hopes of completeness.

The measurement of longevity is very new, but again the writer considers it very important. This characteristic influences transmission almost as much as the biting habit, and it is by its modification that it is hoped to secure control. To work with no knowledge of its nature therefore seems to be to work in the dark. Two separate techniques of measurement have been tested out by Davidson, and Gillies (1954) has made valuable observations and criticisms of other techniques. Davidson's methods give results which are probably nearly correct, but the object of measuring longevity is new and experimentation in technique deserves encouragement. The method depending on measurement of the ampulla is probably more generally applicable than the comparison of immediate and delayed sporozoite rates and may well prove the most appropriate technique of any.

The influence of minor variations in the length of the extrinsic cycle is small and in the perennially hot equatorial region an estimate of 12 days for P. falciparum is all that is needed for most purposes. The technique of the sporozoite rate is standard, but speciments should be dissected as soon as possible after capture, and useful information is lost if an equally careful search is not also made for oocysts, and a record made of the total infection rate as well as of the sporozoite rate, for the ratio between them is closely related to the longevity of the mosquito, which can be easily calculated from it if sufficient dissections are made to ensure reliability of the rates. The technique of the infant parasite rate is also standard, but it is desirable to record the ages of the infants, and the infection rates should be classified in three monthly age groups up to two years.

A very full epidemiological picture can be worked out from data collected in this way. The most important parts of it are the basic reproduction rate, the index of stability, the inoculation rate, and the actual reproduction rate. The numerical manipulation needed to produce the first three is simple, though unavoidable if they are to be recorded as figures and made comparable with data from other places. The expressions for the more important rates and indices mentioned above are given in an Appendix, which also includes a table giving values of $\underline{p}^n$ and $-\log_e \underline{p}$ which should greatly simplify calculation. The calculation of the inoculation rate cannot be simplified in this way, but it is less necessary to attempt it than the others. The immediate value of the infant parasite rate in all surveys is to give a general picture of the present and immediately past scale of transmission, which can be seen with sufficient accuracy for most purposes from the age classified infant parasite rates.

APPENDIX

Commonly useful mathematical expressions

Symbols

The limited number of symbols here used have the following meanings:

m the anopheline density in relation to man.

a the average number of humans bitten by one mosquito in one day.

p the probability of a mosquito surviving through one whole day.

n the time taken for the completion of the extrinsic cycle to sporozoite development.

r the recovery rate, or proportion of affected people who have received the inoculum only who revert to the unaffected state in one day. (The symbol is here only used in the basic reproduction rate, in which it is intended to refer exclusively to non-immunes, and a value of 0.0125 or one-eightieth may be appropriate when infectivity and not parasitaemia is considered.)

s the sporozoite rate, expressed as a proportion not a percentage, i.e. 0.1, not 10 per cent.

Note: Values of p^n and $-\log_e p$ are given in the table below.

Expressions

1. The basic reproduction rate (somewhat simplified) is:

$$\frac{ma^2 p^n}{r(-\log_e p)}$$

2. The index of stability is:

$$\frac{a}{-\log_e p}$$

which is the symbolic expression of the number of bites on man taken by the average mosquito in its lifetime.

Appendix

3. The actual reproduction rate can be estimated under fairly static conditions from the expression:

$$\frac{p^n}{p^n - s}$$

which is simpler to use than the full expression.

4. A mosquito's expectation of life is:

$$\frac{1}{-\log_e p}$$

5. A mosquito's probability of survival through n days is:

$$p^n$$

Values of p^n and $-\log_e p$

Value of p:	0.95	0.9	0.85	0.8	0.75	0.7	0.65	0.6	0.55	0.5
p^8	0.6633	0.4304	0.2725	0.1677	0.1002	0.0577	0.0318	0.0168	0.0084	0.0039
p^9	0.6302	0.3875	0.2316	0.1342	0.0751	0.0404	0.0207	0.0101	0.0046	0.0019
p^{10}	0.5987	0.3486	0.1967	0.1075	0.0564	0.0283	0.0135	0.0060	0.0025	0.0010
p^{11}	0.5687	0.3138	0.1673	0.0859	0.0423	0.0198	0.0087	0.0036	0.0014	0.0005
p^{12}	0.5402	0.2823	0.1422	0.0687	0.0317	0.0138	0.0057	0.0022	0.0008	0.0002
p^{13}	0.5134	0.2542	0.1209	0.0550	0.0238	0.0097	0.0037	0.0013	0.0004	0.0001
p^{14}	0.4876	0.2288	0.1028	0.0440	0.0178	0.0068	0.0024	0.0008	0.0002	
p^{15}	0.4632	0.2059	0.0874	0.0352	0.0134	0.0047	0.0016	0.0005	0.0001	
p^{16}	0.4401	0.1853	0.0743	0.0281	0.0102	0.0033	0.0010	0.0003		
p^{17}	0.4181	0.1667	0.0631	0.0225	0.0075	0.0023	0.0007	0.0002		
p^{18}	0.3972	0.1501	0.0536	0.0180	0.0053	0.0016	0.0004	0.0001		
p^{19}	0.3773	0.1351	0.0456	0.0144	0.0042	0.0011	0.0003			
p^{20}	0.3585	0.1215	0.0388	0.0115	0.0032	0.0008	0.0002			
$-\log_e p$	0.0513	0.1054	0.1625	0.2232	0.2877	0.3567	0.4308	0.5108	0.5979	0.6932

Note: The fact that $-\log_e p$ is a positive number must be borne in mind

Appendix

REFERENCES

Christophers, S. R. (1911) Malaria in the Punjab. Scientific memoirs by Officers of the Medical and Sanitary Department of the Government of India. New Series No. 46

Davidson, G. (1954) Nature (Lond.), 174, 792

Davidson, G. (1955) Ann. trop. Med. Parasit. 49, 24

Davidson, G. (1955) Trans. roy. Soc. trop. Med. Hyg. 49 339

Davidson, G. & Draper, C. C. (1953) Trans. roy. Soc. trop. Med. Hyg. 47, 522

Draper, C. C. (1953) Trans. roy. Soc. trop. Med. Hyg. 47, 160

Draper, C. C. & Davidson, G. (1953) Nature (Lond.), 172, 503

Gabaldon, A. (1949) Malariology, Chapter 31. London and Philadelphia

Gillies, M. T. (1954) Ann. trop. Med. Parasit. 48, 58

MacDonald, G. (1950a) Trop. Dis. Bull. 47, 907

MacDonald, G. (1950b) Trop. Dis. Bull. 47, 915

MacDonald, G. (1952a) Trop. Dis. Bull. 49, 569

MacDonald, G. (1952b) Trop. Dis. Bull. 49, 813

MacDonald, G. (1953) Trop. Dis. Bull. 50, 871

MacDonald, G. (1955) Proc. roy. Soc. Med. 48, 295

Russell, P. F., Menon, M. K. & Rao, T. R. (1938) J. Malar. Inst. India, 1, 285

Russell, P. F. & Rao, T. R. (1940) J. Malar. Inst. India, 3, 543

Russell, P. F. & Rao, T. R. (1942a) Amer. J. trop. Med. 22, 417

Russell, P. F. & Rao, T. R. (1942b) Amer. J. trop. Med. 22, 517

Russell, P. F. & Rao, T. R. (1942c) Amer. J. trop. Med. 22, 535

TIME OF EXTRINSIC DEVELOPMENT

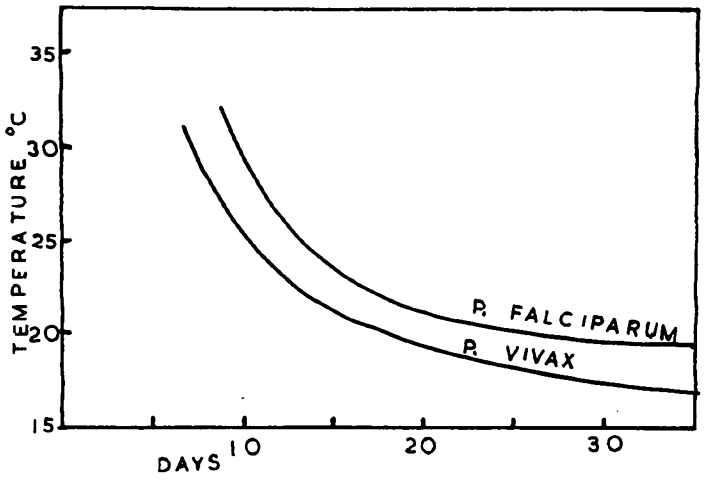

FIGURE 1. THE APPROXIMATE TIME OF THE EXTRINSIC CYCLE IN RELATION TO TEMPERATURE

MORTALITY AND SURVIVAL FOR EXTRINSIC CYCLE

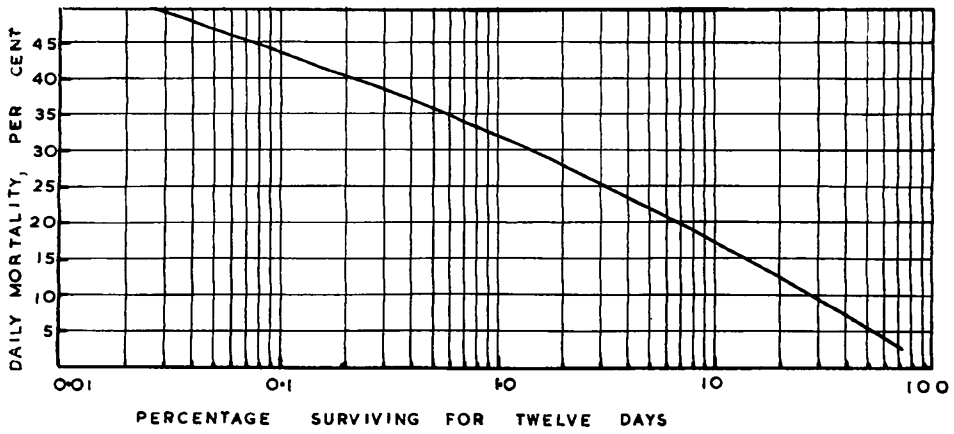

FIGURE 2. THE EFFECT OF MOSQUITO MORTALITY ON SURVIVAL THROUGH THE EXTRINSIC CYCLE

MORTALITY AND SUBSEQUENT SURVIVAL

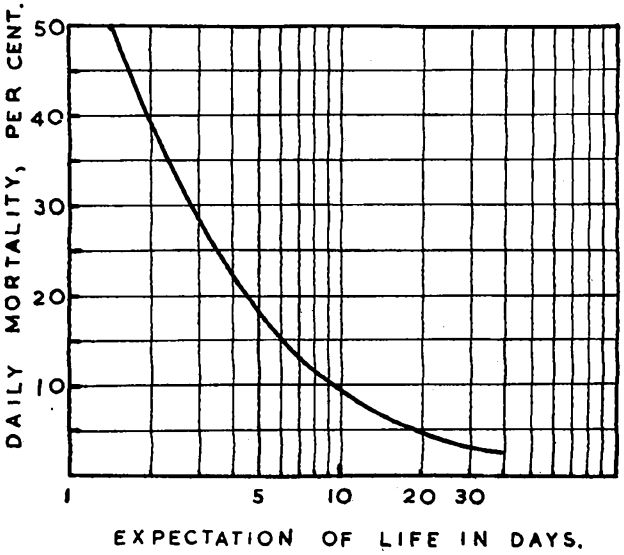

FIGURE 3. THE EFFECT OF MORTALITY ON EXPECTATION OF LIFE

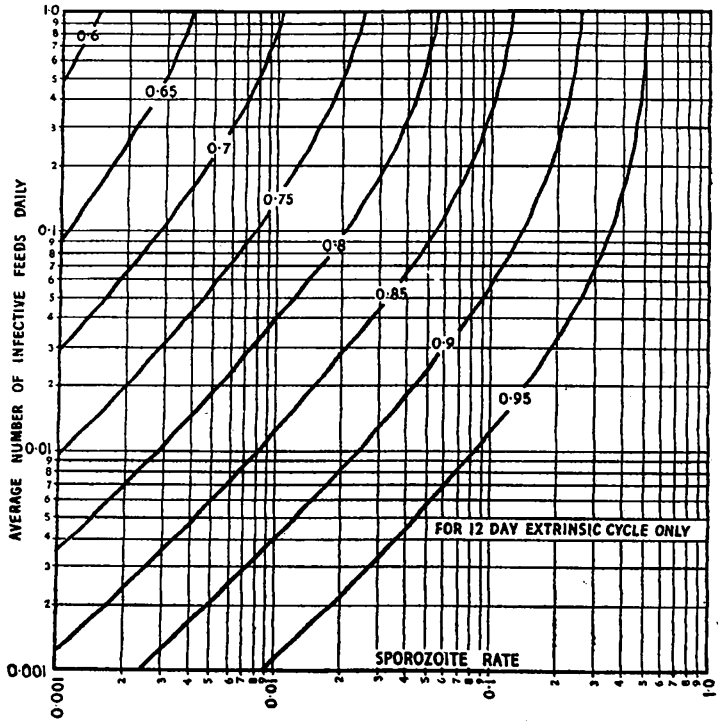

Fig. 4. —A series of graphs showing the sporozoite rate corresponding to given frequencies of infective feeds. Each graph refers to a different probability of survival which is shown on the line. The frequency of infective feeds is the product of the frequency of biting man and the infective gametocyte rate.

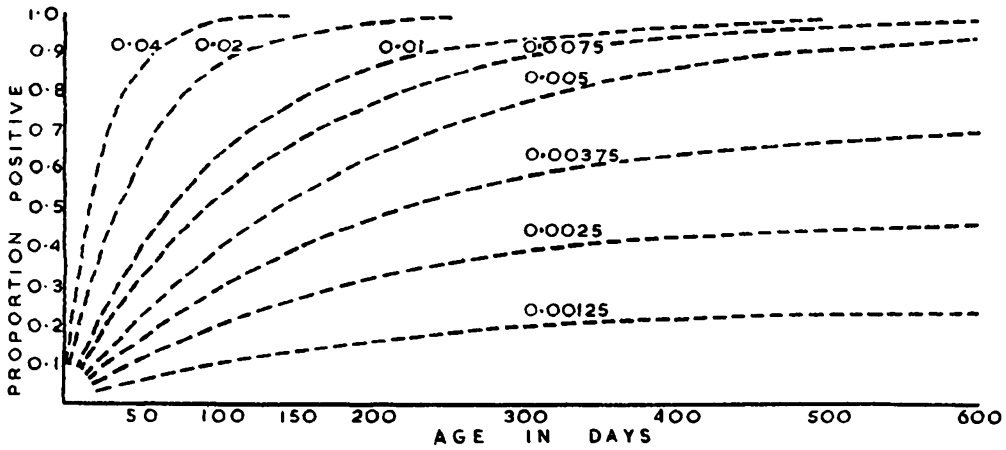

Fig 5 —Theoretical infection rates by ages corresponding to various inoculation rates (h). The limiting value for all values of h exceeding 0·005 is 1·0.

INFLUENCE OF INCUBATION INTERVAL ON EPIDEMIC TIMING