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The Malaria Parasite Rate and Interruption of Transmission

G. MACDONALD [1] & G. W. GÖCKEL [2]

Present methods for assessment of the attack phase of malaria eradication are inadequate, particularly lacking any objective parasitological criteria of success. On the basis of previous observations and development of theory, the authors first postulate that the effects of complete interruption of transmission should, ideally, include a regular progressive decrease of falciparum parasite rates in the ratios of 1 : 0.4 in 6 months, 1 : 0.16 in 12 months and 1 : 0.026 in 24 months. Analysis of a series of programmes in which complete interruption of transmission is known to have been achieved shows that this postulate is valid, and that it is not materially upset by strain differences of parasites or by differences in the ages of the subjects examined. Vivax rates appear to fall at approximately the same rate; the rarity of data for vivax malaria makes firm conclusions unsure, but the postulate can be extended to rates which are predominantly due to falciparum infection but include some admixture of other species. A second, arbitrary, postulate is made that the slowest acceptable rate of fall in 12 months should be in a ratio not less than 1 : 0.22, which would secure ultimate eradication in about one-third more time than the ideal fall; on this basis statistical standards are set up for assurance of confidence that the minimum rate is exceeded. Slower rates of fall are then related to reproduction rates causing them, the findings being illustrated graphically and by mathematical theory.

The first objective of a malaria eradication campaign is to interrupt transmission completely. Successive reports of the WHO Expert Committee on Malaria (1957, 1959, 1961 and 1962) have drawn attention to the necessity to verify interruption, and have indicated the broad general principles on which this might be done—without, however, giving precise and objective criteria of its parasitological assessment. The sixth report (1957; p. 50) said that " the main interest should lie in the attempt to discover evidence of any continuation rather than in the measurement of the exact volume of transmission. The places where blood films are sought will vary, but advantage should be taken of all possibilities, including the facilities offered by infant welfare clinics ". The seventh report (1959; p. 6) considered the place of malariometric surveys, but rather as an indication of the type of curve along which malaria was declining than as providing objective proof of interruption. It referred to the existence of two types of decline, fall by crisis and fall by lysis, " the latter indicating some impediment to success, such as unforeseen epidemiological conditions or happenings ". It also drew attention to the fact that changes in the average parasite density may be early and significant indices of the trend in the campaign without, however, giving quantitative statements which could be used for assessment in the field. The ninth report (1962) emphasized the need for a vigorous search for any possible example of transmission after the presumed full establishment of insecticide cover, and stated that, though there was difficulty in distinguishing between fresh and relapsed cases of vivax malaria, it was often possible to distinguish a fresh infection of falciparum malaria, and infections in infants born after the completion of the first round of spraying could certainly be identified as fresh. It also recommended that a sharp watch should be kept for apparent fresh cases in out-patient and infant welfare clinics, among other possibly vulnerable groups, and by occasional special inquiries in selected localities.

These methods of assessment, though no doubt correct in principle, have proved inadequate in prac-

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tice, as is shown by the fact that, in several places where transmission was thought to have been interrupted, it was later found to be continuing on a sufficiently large scale to prevent the attainment of eradication in the locality concerned. The most objective of the criteria used has been the absence of infections among infants. This has always been subject to the drawback that it is rarely possible to get enough infants to secure a statistically reliable result. Moreover, all the variants used have been subject to the difficulty that it is philosophically impossible to prove a total negative without examination of the entire population, and there has always been uncertainty on the scale of examination which was required for adequacy.

The authors have therefore undertaken a careful review of parasitological criteria for the interruption of transmission, with the intention of producing precise and objective criteria which could be readily applied in the field and from which clear-cut conclusions could be reached on the adequacy of the attack mechanism.

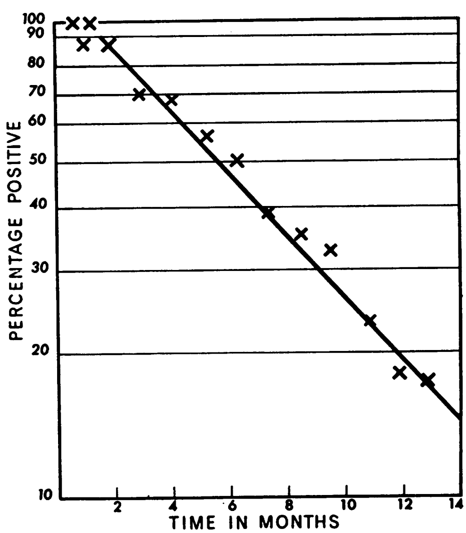
The general thread which runs through the following argument is that the total interruption of transmission should produce readily foreseeable results in terms of progressive decline of the parasite rate, total absence of fresh infections, and immediate reduction to zero of the parasite rate among infants born after the start of the campaign. However, since it is statistically impossible to prove absolute compliance with an expected trend, a decision should be made on the amount of deviation from absolute success which is tolerable for the purposes of eradication, and statistically sound criteria should be set up to enable the investigator to verify with confidence that this amount of deviation had not been exceeded.

THE DURATION OF FALCIPARUM INFECTIONS

Most of the information available has referred to falciparum infections, but for reasons stated later it is thought that the conclusions can apply wherever that parasite predominates. It is widely thought and commonly stated in authoritative works that falciparum infections rarely persist for more than a year. Search of the literature reveals the origin of this statement, though not perhaps its full justification for use in the context to which it is now applied. The relatively brief duration of disease due to this infection has been well documented by several workers, and notably by James, Nicol & Shute (1932, 1936). They amply demonstrated, within the context of their own study, that falciparum relapses continued up to but not beyond 33 weeks after the primary infection. The context was that of therapeutic malaria, and they made it clear in their text that they referred to pyrexial relapses, specifically stating that parasites may be found in the peripheral blood for long periods after the last febrile occurrence, up to 153 days in their experience. Moreover, all of their cases infected with the Sardinian strain, and most of those infected with the mild Indian strain, received " early and intensive " quinine treatment. Though undoubtedly correct in the circumstances of their thought and work, their conclusions are not necessarily applicable to present conditions, when attention is focused not on pyrexia but on the ultimate duration of parasitaemia.

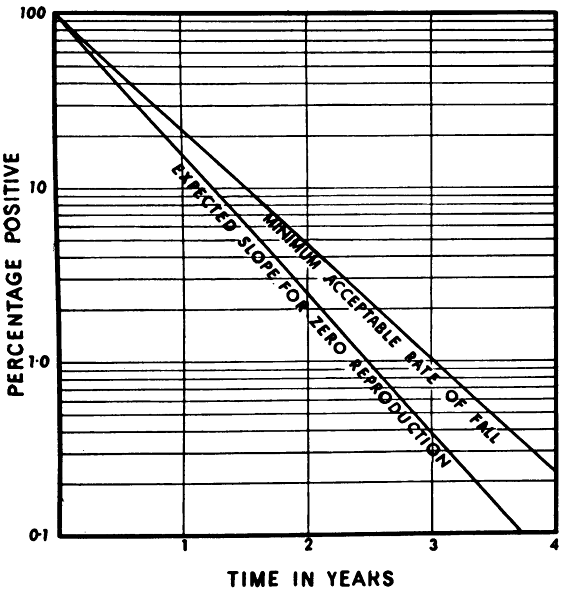
There are few detailed studies of duration of falciparum parasitaemia, but they are mutually confirmatory. Earle et al. (1939) studied the prevalence of parasitaemia at serial intervals after first infection in 76 Puerto Rican cases and their results are graphically shown, on log/metric scale or " ratio paper ", in Fig. 1. Actually 17% showed parasites at 365 days, and it was shown by Macdonald (1950) that the decrease from the origin of infection was expressed by $x = e^{-0.0048(t-31)}$, where time t is measured in days. The corresponding rate in multiple

FIG. 1
PARASITE RATE AT SUCCESSIVE INTERVALS IN 76 FALCIPARUM MALARIA CASES [a]



[a] Data from Earle et al. (1939).

FIG. 2
EXPECTED RATE OF FALL OF PARASITE RATE WITH ZERO REPRODUCTION, GIVING AN ANNUAL RATIO OF 1: 0.16, AND MINIMUM ACCEPTABLE RATE, WITH AN ANNUAL RATIO OF 1 : 0.22



cases of non-simultaneous origin is expressed with sufficient approximation as $x = e^{-0.005t}$, which represents a progressive decrease to 16% of the original value in one year. This series was used by Macdonald (1950) in the original evaluation of the "recovery rate", and has been widely tested on a great number of sets of findings without revealing any serious discrepancy. Eyles & Young (1951) found the average duration of a series of untreated or inadequately treated infections with a South Carolina strain to be 222 days, with a standard deviation of 117 days, and Jeffery & Eyles (1954) found the average duration of a Panama strain to be 279 days, with a standard deviation of 95.5 days. Ciuca et al. (1955) recorded that falciparum infections usually lasted 10-12 months and that persistence up to 27 months had been verified by transfusion.

These studies show an original period of continuous parasitaemia, subsequently becoming intermittent. The history of parasitaemia in a group of individuals, all of them at the same stage of infection, is very nearly represented by a straight line on log/metric scale, and that of a group at different stages would be more nearly represented in this way. It appears reasonable, as a preliminary hypothesis, to state that the expected history of a falciparum parasite rate following interruption of transmission would be of the same nature. Adaptation of the quantitative value adopted in a previous study (Macdonald, 1950), which seems valid in the light of later work, would suggest that following complete interruption of transmission, a falciparum parasite rate would fall off in an exponential manner, with a "half-life" of about 140 days, the ratio between any two measurements taken at 12-months' interval being 1: 0.16. The average infection has a mean duration of about 200 days.

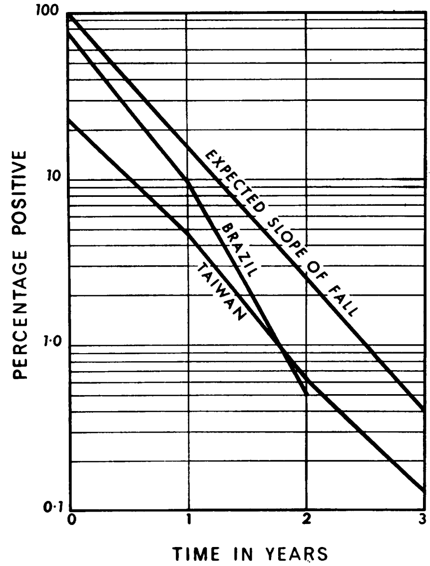
Fig. 2, on log/metric scale or "ratio paper", illustrates the expected rate of fall in accordance with this hypothesis, and also a fall of 1: 0.22, corresponding approximately to a reproduction rate of 0.2, which is put forward in a later section as the slowest acceptable rate of fall. The graph is intended to cover parasite rates between 100% and 0.1%, and it is postulated that, whatever the original value of the rate, interruption of transmission should cause it to fall in the manner here shown certainly for one year, most probably for two, and at no less a gradient thereafter.

COMPARISON OF EXPECTED WITH ACTUAL HAPPENINGS

The first method of comparison has been to select as many records of consecutive parasite rates as possible from places in which it was known by other criteria that transmission was totally interrupted, for contrast with the expectations set out above. Twelve such comparisons have been possible. In making the selection it has been necessary to verify only the interruption of transmission in the locality concerned, without insistence that this should have been through imagicidal procedures, or general throughout an entire eradication programme.

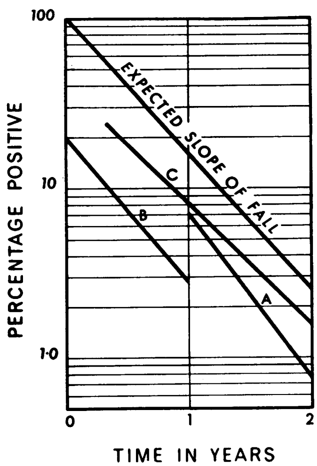
Fig. 3 and 4 show this comparison between expected happenings and actual records from some areas in which ample and complete figures are available: (1) the *Anopheles gambiae* eradication programme in Brazil (Soper & Wilson, 1943); (2) a malaria control experiment in Borneo (de Zulueta & Lachance, 1956); (3) the Sarawak antimalaria project (Colbourne et al., 1959); and (4) the malaria eradication programme in Taiwan (Taiwan Provincial Malaria Research Institute (TAMRI) & WHO Malaria Team in Taiwan, 1958). The rates for Brazil, Taiwan and Sarawak refer to falciparum

FIG. 3
FALL OF FALCIPARUM PARASITE RATES IN BRAZIL[a] AND TAIWAN[b] COMPARED WITH EXPECTED FALL



[a] Data from Soper & Wilson (1943).
[b] Data from Taiwan Provincial Malaria Research Institute & WHO Malaria Team in Taiwan (1958).

FIG. 4
FALL OF PARASITE RATES IN (A) SUNGEI KEDUP, SARAWAK,[a] (B) BATANG KAYAN, SARAWAK,[a] AND (C) BORNEO PILOT PROJECT[b, c]



[a] Sarawak data from Colbourne et al. (1959).
[b] Borneo data from de Zulueta et al. (1956).
[c] The graphs refer only to those times when two annual sprayings were carried out.

malaria only, the other being a general rate mainly due to this parasite. At one year from the start of full operations the Brazilian rate is 15% of that at the start; the Taiwan rate is 20%, and at the end of another year 13% of that; and both the Sarawak and Borneo rates fall to 14% of the original in one year. The Brazilian figures are given for seven localities, of which only two fall at a somewhat lower rate than expected. As this was an anopheline eradication programme based on antilarval measures, it is not unreasonable to think that control may not have been complete in all areas during the first year.

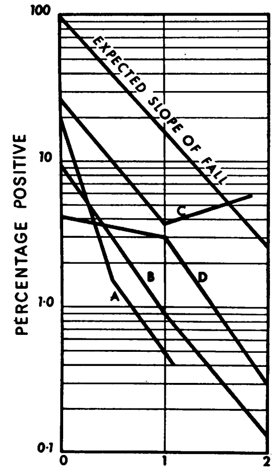
Fig. 5 makes the same comparison for (1) indicator areas in the Philippine Malaria Eradication Pilot Project in Luzon, where two cycles of 0.25 g dieldrin per m^2 were applied annually; (2) Sheikhupura District of West Pakistan; (3) the Lashio Malaria Demonstration Project in Burma, 1951-53, which was originally successful and later showed recurrence of transmission; and (4) the Yaoundé Malaria Eradication Pilot Project in Cameroon, 1954-60. All of these are from 1963 WHO records. The first two refer to falciparum rates only; the others to general rates, mainly falciparum. The figures available at the time of writing concerning these schemes are less complete than those for the previous schemes. It will be noted that the rate of fall of the parasite rate is in no case less than the expected, and is in general very comparable to it.

Fig. 6 shows the rate of fall of the parasite rate in 13 localities treated with DDT in Brazil, quoted by Pampana (1951). Further details are not available, though it is understood that a high degree of success was attained in most.

The figures for Venezuela are of special interest because Gabaldón (1956) postulated that the rate of disappearance of malaria depended on the previous constitution, or stability, of malaria being rapid in those places previously subject to unstable malaria and slow in areas of previous stability. Parasite rates in the ordinary sense are not available, records being in the form of positive slides per 100 000 house-visits, and the author records in his text that it was necessary to adjust the criteria on which slides were taken during the course of his very successful campaign. His findings are illustrated in Fig. 7, showing this rate for areas of high endemicity and low epidemicity, low endemicity and high epidemicity, and low endemicity and low epidemicity. Rises in the rates occur, apparently coincident with the changes in criteria, but during the periods of fall, with constant criteria, the rate of decrease is in close

FIG. 5

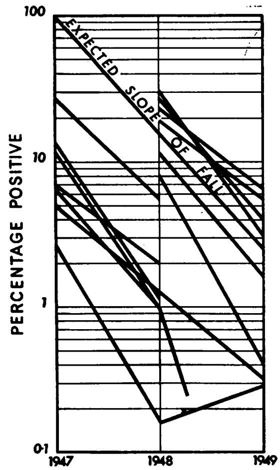
FALL OF PARASITE RATES IN (A) PHILIPPINE EXPERIMENTAL PROJECTS, (B) SHEIKHUPURA, WEST PAKISTAN, (C) LASHIO PILOT PROJECT, BURMA, AND (D) YAOUNDÉ PILOT PROJECT, CAMEROON [a]



[a] All data from WHO records.

FIG. 6

FALL OF PARASITE RATES IN SOME BRAZILIAN LOCALITIES [a]



[a] Data from Pampana (1951).

accord with expectation in all three types of locality, and shows no distinction between the different types of epidemiology.

Two well-documented series are available of schemes in which imagicidal practice has been combined with drug administration, in which the rate of decrease would be expected to exceed the normal expectation; these are illustrated in Fig. 8. They are the Kigezi Malaria Eradication Pilot Project in Uganda described by de Zulueta et al. (1961) and the Malaria Eradication Pilot Project in Selangor, Malaya.[1] Kigezi rates, mainly falciparum, fell to 2% of their original value in 12 months. The falciparum rate in Selangor fell to 5% of its original value in six months, the vivax rate falling in this time to 44% of its original value—equivalent to a fall to 19% in a year. This difference presumably reflects the different reaction of the species to drugs, though other figures available suggest that the rates of disappearance of the two species following interruption of transmission, without chemotherapy, are very similar.

Area B of the Liberian Malaria Eradication Pilot Project (Guttuso [2]), in which the falciparum rate fell in one year to 39% of its original value, has been omitted from this comparison. *Anopheles gambiae*, the vector, disappeared from the area and transmission was brought to an end. However, Guttuso comments in his text on the complication introduced into the interpretation of parasite rates by the free movement of infected people into the small area involved. For this reason the omission was thought justifiable. Happenings in the Sardinian anopheline eradication programme (Logan, 1953) are not here quoted, though they support the general thesis. Rates fell and rose alternately according to variations in the campaign and all decreases were in accord with the expected picture.

DECREASE OF VIVAX PARASITE RATES

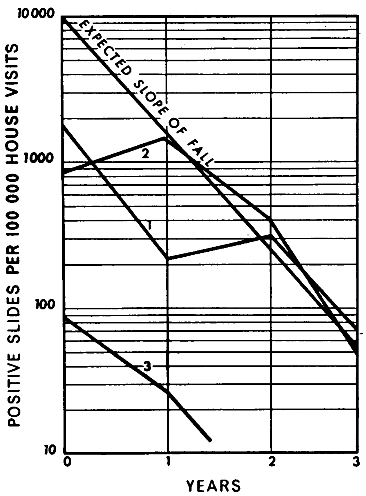
Fig. 9 illustrates the rate of fall of vivax parasite rates in the well-documented cases of Brazil and Taiwan (Soper & Wilson, 1943; TAMRI & WHO Malaria Team in Taiwan, 1958), which may be compared not only with the expected lines, but with the equivalent fall in falciparum rates shown in Fig. 3. In Brazil the fall in the first year was to 9.8% of the original level. In Taiwan the rate fell more slowly between 1953 and 1954, to 37% of the original value, and to 13% of this in the second year. It may tentatively be concluded that vivax rates show greater variability, sometimes falling more slowly than

[1] D. E. Moorhouse—unpublished records, 1962.

[2] Guttuso, C. (1962) Unpublished document AFRO/Mal/9/43 of the WHO Regional Office for Africa.

FIG. 7

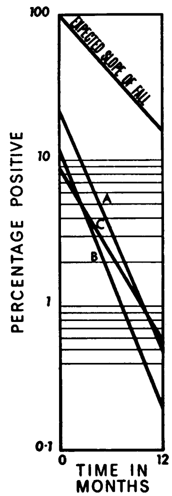
POSITIVE SLIDES PER 100 000 HOUSE VISITS IN VENEZUELA IN AREAS OF (1) HIGH ENDEMICITY AND LOW EPIDEMICITY, (2) LOW ENDEMICITY AND HIGH EPIDEMICITY, AND (3) LOW ENDEMICITY AND LOW EPIDEMICITY [a]



[a] Data from Gabaldón (1956).

FIG. 8

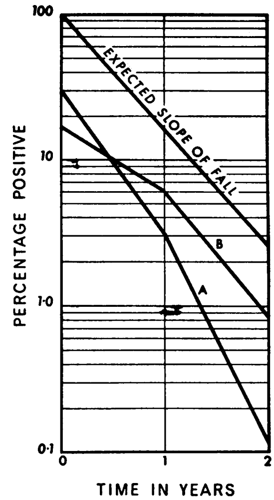
FALL OF PARASITE RATES IN AREAS WHERE DRUG TREATMENT WAS ASSOCIATED WITH HOUSE-SPRAYING: AREAS OF (A) HYPERENDEMICITY AND (B) MESOENDEMICITY IN KIGEZI, UGANDA; [a] (C) SELANGOR, MALAYA [b]



[a] Data from de Zulueta et al. (1961).
[b] From unpublished records (1962) of D. E. Moorhouse.

FIG. 9

FALL OF VIVAX PARASITE RATES IN (A) BRAZIL [a] AND (B) TAIWAN [b] COMPARED WITH EXPECTED FALL



[a] Data from Soper & Wilson (1943).
[b] Data from Taiwan Provincial Malaria Research Institute & WHO Malaria Team in Taiwan (1958).

falciparum rates during the first year but thereafter following a similar course.

HAPPENINGS IN UNSUCCESSFUL SCHEMES

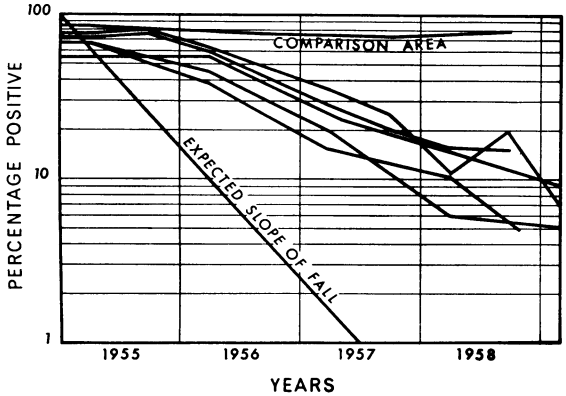
A search has been made for records of well organized, managed and documented schemes which at first seemed to give promise of success but later proved to have been unsuccessful in completely interrupting transmission, to see whether utilization of the technique now under discussion might have provided a clearer guide to the prospects of the schemes than the methods then open to the workers operating them. Two admirably fulfilling these criteria are selected for illustration—the Taveta-Pare scheme in East Africa (Wilson, 1960) and a pilot project in New Guinea described by Metselaar (1957, 1961)—in both of which the predominant parasite was *P. falciparum*. Both of these schemes were thought for some long time, and apparently justifiably, to have considerable promise. Taveta-Pare results are given for five areas, by age-groups, and are illustrated in Fig. 10 by the rates for the 5-9-year age-group in each area. It is clear that happenings in none of these areas could be confused with the expected result of interruption of transmission, though it may have been briefly approached in three of them late in 1957-58. The changes in Metselaar's projects, shown in Fig. 11, can be distinguished from the expected happenings with equal ease. Results of several other projects have been examined and all show an equal or greater distinction from expected happenings. Comparison of successive parasite rates could clearly have identified the deviation of happenings in these projects from those expected following interruption of transmission, and found in every successful project examined.

VARIATION IN STRAINS OF PARASITE

Supporting evidence for the thesis put forward has been quoted from Borneo, Brazil, Burma, Cameroon, West Pakistan, Panama, the Philippines, Puerto Rico, Sarawak, Sardinia, Taiwan, the USA (South Carolina), and Venezuela, apart from Malaya and Uganda where drugs also were used.

FIG. 10

CHANGES IN PARASITE RATES IN A CASE OF INCOMPLETE INTERRUPTION OF MALARIA TRANSMISSION, TAVETA-PARE, EAST AFRICA [a]



[a] Data from Wilson (1960). Five subsections of the project are shown. Spraying started in mid-1955. The slope corresponds to that of a reproduction rate of about 0.7.

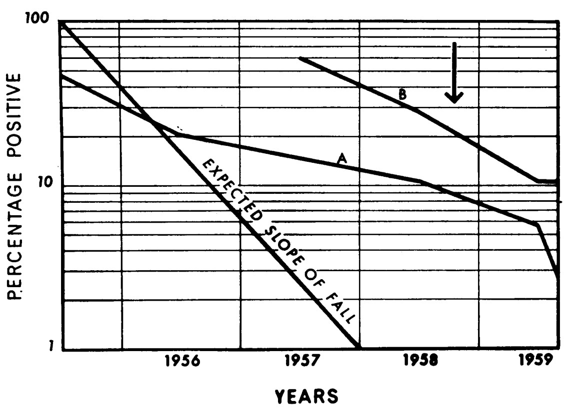
No difference appears between them which could be attributed to variations in the character of strains of parasite. The hypothesis therefore seems widely applicable despite this potential objection.

HAPPENINGS IN DIFFERENT AGE-GROUPS

The fact that age *per se* has no effect on the rate of fall of parasitaemia is clearly shown from the age

FIG. 11

CHANGES IN PARASITE RATES IN AREAS OF INCOMPLETE INTERRUPTION OF MALARIA TRANSMISSION: (A) SENTANI AND (B) NIMBORA, NEW GUINEA [a]



[a] Data from Metselaar (1961). Mass medication was started at the point indicated by the arrow.

analysis in Soper & Wilson (1943), the difference between age-groups being no more than would be attributable to random error between the necessarily smaller groups. A difference attributable to the influence of immunity developed with age might perhaps be expected. Data suitable for analysis are given in the papers by Wilson (1960) and Metselaar (1957). In both there is relatively faster initial decrease in the youngest age-group than in others, though it seems that this would not have appeared if the more appropriate method of cohort analysis had been applied. Happenings in all other groups, from 2-4 years to over 40 years, are very similar to one another in the slope of fall despite the variation in origin between 20% and 80%. It seems to be immaterial which age-group is examined in this connexion.

CONCLUSIONS FROM COMPARISONS

It is concluded that the working hypothesis put forward above is substantiated; that the quantitative values given may be applied to falciparum rates, to rates which are predominantly due to this parasite, and they may be used as a good working guide for vivax infections; that variations due to strain differences in parasites are of little importance; that happenings are not materially affected by the age-groups studied; and that the comparison of successive parasite rates constitutes a highly sensitive method for the evaluation of interruption of transmission which could be practically applied during the eradication process.

It can therefore be stated with confidence that, if transmission is totally interrupted, successive parasite rates predominantly due to falciparum infections, and taken from a representative sample of the population of suitable ages, should fall progressively to about 16% of the original value in 12 months and to 2.6% of the original value in 24 months.

As a minor matter of working technique it is apparent that the graphic representation of successive parasite rates on log/metric or "ratio" scale, as used here, has the great advantages of clarity, of facilitating comparison of rates taken at intervals other than 12 months, and of drawing attention to variations in rate of fall of parasite rates. It is suggested that this method should be routinely used, in addition to numerical statement of rates and the ratio between them, and Fig. 2 has been prepared as a workable routine guide for this purpose.

TOLERABLE LIMITS OF DEVIATION

While the expected rate of decrease of the parasite rate can be stated with some certainty, the production of statistical proof that this rate has been achieved may still present formidable difficulties owing to the large numbers of examinations which would have to be made to give confidence in the result. The only practical way of overcoming this difficulty is to make a decision on the slowest rate of fall which could be considered compatible with the attainment of eradication in acceptable time, and to set up standards to show that this minimum tolerable rate is exceeded. This choice is necessarily empirical. It has already been shown (Macdonald, 1952) that ultimate eradication will be achieved if the reproduction rate is kept continuously below 1.0, but it is also shown in a later section of this paper that eradication would be delayed for an unacceptably long time unless the reproduction rate fell far below this level. An annual decline of the parasite rate to 22% of its original value has therefore been arbitrarily chosen as the slowest acceptable rate, and decline at this rate would mean that the result hoped for in three years was in fact attained in about four. It will be shown later that this decline could not be achieved unless the reproduction rate were well below 1.0, actually 0.2, and it is therefore fully consistent with the attainment of eradication, although after some delay. On this basis it is possible to prescribe criteria of a satisfactory progress of the attack phase towards eradication. Successive parasite rates in any age-group of the population over 3 years old should decline progressively, ideally to 16% of their original value in 12 months, and certainly to 22% or less in that time, and it should be possible to demonstrate with statistical confidence that at least this latter rate of fall has been achieved.

Tables 1 and 2 show the numbers of people which it would be necessary to examine to attain confidence in a fall to 16% of the original value in 12 months, or to 40% of the original value in 6 months. It is clearly desirable to design the size of the first sample in such a way as to ensure that a valid comparison is possible on the second sample. It will be found on a study of the tables that there is in fact an optimum size of the first sample for each

TABLE 1

RECOMMENDED MINIMAL SIZES OF SAMPLES WHEN MAKING COMPARISONS OF SUCCESSIVE PARASITE RATES AT A 12-MONTH INTERVAL

Original rate (%)	Minimal number to be examined when the size of the original sample was:									
	25	50	100	200	300	400	500	1 000	2 500	5 000
90	140	130	120	120	120	120	120	120	120	120
80	210	170	150	140	140	140	140	140	140	140
70	410	230	190	170	170	160	160	160	160	160
60	—	360	240	210	200	200	200	190	190	190
50	—	—	350	280	260	250	240	230	230	230
40	—	—	620	390	350	330	320	300	290	290
30	—	—	—	670	540	490	460	420	400	390
20	—	—	—	—	1 200	920	830	690	620	600
10	—	—	—	—	—	—	3 500	1 800	1 400	1 300
5	—	—	—	—	—	—	—	7 800	3 300	2 800
4	—	—	—	—	—	—	—	—	4 600	3 700
3	—	—	—	—	—	—	—	—	7 600	5 300

Notes: 1. If the parasite rate found in the second sample does not exceed 16 % of the original rate, it is concluded with statistical confidence (95 % probability) that the true successive rate is in a ratio of not more than 1 : 0.22.

2. If the required sample size indicated in this table turns out to be large relative to the size of the population group under study, e.g., if it exceeds 2/3 of the population size, it is recommended that all members of the population group be examined rather than its sample.

TABLE 2

RECOMMENDED MINIMAL SIZES OF SAMPLES WHEN MAKING COMPARISONS OF SUCCESSIVE PARASITE RATES AT A 6-MONTH INTERVAL

Original rate (%)	Minimal number to be examined when the size of the original sample was:										
	50	100	200	300	400	500	1 000	2 500	5 000	7 500	10 000
90	220	190	170	170	170	170	160	160	160	160	160
80	490	270	230	210	210	200	200	190	190	190	190
70	—	480	310	280	270	260	240	240	230	230	230
60	—	1 500	480	390	360	340	310	290	290	290	290
50	—	—	910	600	510	470	410	380	370	360	360
40	—	—	—	1 200	860	740	570	500	490	480	480
30	—	—	—	—	2 300	1 500	910	740	690	680	670
20	—	—	—	—	—	—	2 000	1 300	1 200	1 100	1 100
10	—	—	—	—	—	—	—	3 800	2 800	2 500	2 400
5	—	—	—	—	—	—	—	—	8 100	6 300	5 700
4	—	—	—	—	—	—	—	—	13 200	9 000	7 700
3	—	—	—	—	—	—	—	—	—	15 400	12 100

Notes: 1. If the parasite rate found in the second sample does not exceed 40 % of the original rate, it is concluded with statistical confidence (95 % probability) that the true successive rate is in a ratio of not more than 1 : 0.47.

2. If the required sample size indicated in this table turns out to be large relative to the size of the population group under study, e.g., if it exceeds 2/3 of the population size, it is recommended that all members of the population group be examined rather than its sample.

original parasite rate which will lead to the greatest ultimate economy in the total number of slides to be examined. The basis of the construction of these tables, which were prepared by Mr. K. Uemura and Dr B. Grab, World Health Organization, is reproduced in Annex 1.

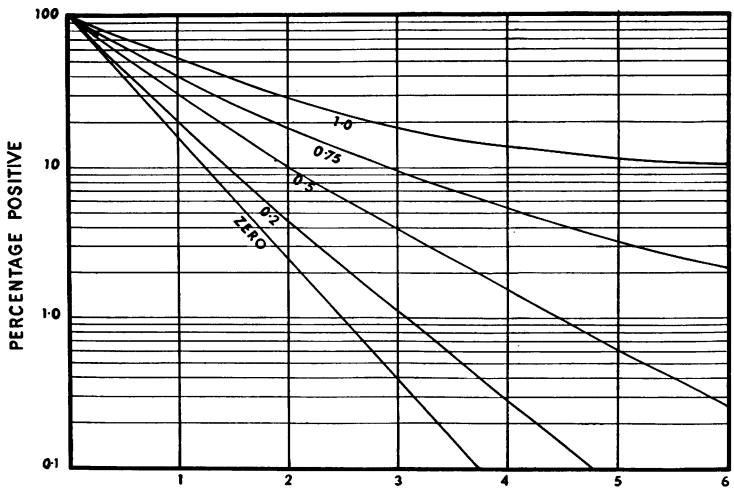
An effort should be made to attain these numbers whenever possible. Where they are not attainable, a comparison of rates may still be highly instructive though the results can be taken with lesser confidence.

THE REPRODUCTION RATE AND PARTIAL INTERRUPTION OF TRANSMISSION

The argument already presented is not based on an estimate of the reproduction rate otherwise than in the very minor form stated therein. Having decided on this minimum tolerable rate of fall, it would be, however, most helpful to relate it to the reproduction rate for the purpose of making further analyses of the number of fresh infections which might be expected in association with it. The method described by Macdonald (1953) was first used to calculate the rates of fall of the parasite rate expected in association with given values of the reproduction rate for purposes of comparison. This technique, which is cumbersome, was later replaced by a simpler method devised by H. O. Irwin (personal communication, 1963), which permits ready calculation of the slope of fall for any number of values of the reproduction rate and for variations in associated factors. As might be expected from the nature of the identities originally produced (Macdonald, 1953), the rate of fall depends to some extent on the stability of the malaria, as affected by the mean number of bites taken by the vector anopheline on man during its lifetime, and Fig. 12 refers to conditions where that number is low, as might usually be the case during an eradication campaign. It can be seen that the initial rate of fall is dramatic for any value of the reproduction rate of 1.0 or less, but for this value (and those approaching it) the rate of fall becomes progressively less marked, and nearly levels off when the parasite rate is low. The postulated slowest tolerable rate of fall of the parasite rate, to 22% of its value in 12 months, coincides almost exactly with the fall which could be expected for a reproduction rate of 0.2 for the conditions given. It is therefore concluded as a working basis, corresponding to the

FIG. 12

RATES OF FALL OF PARASITE RATES ACCORDING TO INDICATED REPRODUCTION RATES [a]



[a] The curves relate to moderately unstable conditions, with $a/\text{-}\log_e p = 1.0$, such as might commonly occur during partially effective imagicidal measures.

fall in parasite rates, that the highest tolerable value of the reproduction rate is 0.2.

It is not suggested that the field worker should concern himself with the mathematical theory concerning the fall of the parasite rate with varying reproduction rates, but the development of this theory is of considerable importance for the relation of other features of disappearing malaria, such as the frequency of fresh infections, to the minimum acceptable rate of fall of the parasite rate, and also for the evaluation of unsatisfactory rates of disappearance. The theory of the relationships between low levels of the reproduction rates is set out in Annex 2, and is based on a general theory of the epidemiology of malaria developed by Macdonald (1958). The relationships are illustrated in Fig. 12

TABLE 3

FALL OF THE PARASITE RATE IN ASSOCIATION WITH REPRODUCTION RATES OF 1.0 AND LESSER VALUES

Time	For unstable [a] conditions, $-\log_e p/a = 1.0$					For stable conditions, $-\log_e p/a = 0.1$				
	Reproduction rate:					Reproduction rate:				
	0.0	0.2	0.5	0.75	1.0	0.0	0.2	0.5	0.75	1.0
Zero	100	100	100	100	100	100	100	100	100	100
1 year	16	22	30	40	53	16	18	20	22	26
2 years	2.4	4.7	9.8	18	29	2.4	3.6	5	7	8.6
3 years	0.4	1.1	3.9	9.6	18	0.4	0.7	1.7	2.5	4.2
4 years	0.06	0.28	1.7	5.2	14	0.06	0.2	0.7	1.3	2.4
5 years	—	0.07	0.6	3.3	11.5	—	—	0.4	0.7	1.5
6 years	—	—	0.3	2.2	10	—	—	—	0.5	1.0

[a] Either natural or as caused by partially effective imagicidal control.

for a standard set of circumstances such as is probably very common during the course of malaria eradication and is representative of most examples of partial success in imagicidal attack. Table 3 (in Annex 2) sets out happenings for this set of conditions, and also for conditions of stable malaria where the longevity of the mosquito has not been altered by insecticidal attack, as might be the case in a larvicidal programme, and almost all examples should fall between these two limits.

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RÉSUMÉ

Les méthodes actuelles d'évaluation des résultats de la phase d'attaque, au cours des campagnes d'éradication du paludisme, sont inadéquates, faute d'un critère parasitologique objectif. Jusqu'ici l'absence d'infection chez les nourrissons était le critère le plus objectif. Or, il est le plus souvent impossible d'examiner un nombre de nourrissons assez élevé pour obtenir des résultats statistiquement valables, et l'on n'a pas pu préciser non plus quelle fraction de la population de ce groupe d'âge il fallait soumettre à l'examen pour obtenir des résultats sûrs.

Les auteurs ont donc entrepris de proposer des critères parasitologiques d'interruption de la transmission, permettant de tirer des conclusions nettes sur l'efficacité des méthodes d'attaque.

Théoriquement, l'interruption totale de la transmission doit donner des résultats faciles à prévoir: baisse progressive de l'indice plasmodique, absence d'infections nouvelles, et chute à zéro de l'indice plasmodique des jeunes enfants nés depuis le début de la campagne. Mais, comme il n'est pas possible de satisfaire à ces exigences idéales, il faut déterminer une marge d'approximation acceptable, et s'y tenir dans l'interprétation des faits observés.

Les auteurs estiment que la baisse régulière de l'indice plasmodique à falciparum doit être de 1: 0,4 en 6 mois; 1: 0,16 en 12 mois; et 1: 0,026 en 24 mois. Les observations faites sur le terrain, au cours de campagnes où la transmission a été interrompue, ont montré que ces chiffres sont conformes à la réalité et qu'ils sont indépendants de la souche de parasites ou de l'âge des sujets examinés. Les taux d'infection à vivax semblent s'abaisser dans les mêmes proportions. La rareté de ce type d'infection ne permet cependant pas de l'affirmer avec certitude; mais on peut considérer les chiffres précédents comme valables pour une infection prédominante à falciparum, dans laquelle peuvent intervenir secondairement d'autres espèces.

Un second postulat, arbitraire mais pratiquement utile concerne la rapidité de l'abaissement du taux d'infection plasmodique. Le rapport en 12 mois doit être au moins 1: 0,22. Ce chiffre correspond à une augmentation d'un tiers, par rapport au chiffre idéal, du temps nécessaire pour obtenir l'éradication. Sur ces bases, on peut calculer des normes statistiques permettant de s'assurer que le niveau minimum requis est dépassé. Des taux de baisse de l'indice plasmodique plus lents sont liés aux taux de reproduction qui les conditionnent. Les auteurs donnent les expressions mathématiques de ces diverses relations.

REFERENCES

Ciuca, M. et al. (1955) *Bul. sti. Sect. Şti med. (Bucureşti)*, **7**, 61

Colbourne, M. J. et al. (1959) *Sarawak Mus. J.*, **9**, No. 13-14

Earle, W. C. et al. (1939) *Puerto Rico J. publ. Hlth*, **14**, 391

Eyles, D. E. & Young, M. D. (1951) *J. nat. Malar. Soc.*, **10**, 427

Gabaldón, A. (1956) *Amer. J. trop. Med. Hyg.*, **5**, 966-976

James, S. P., Nicol, W. D. & Shute, P. G. (1932) *Proc. roy. Soc. Med.*, **25**, 1153

James, S. P., Nicol, W. D. & Shute, P. G. (1936) *Proc. roy. Soc. Med.*, **29**, 879

Jeffery, G. M. & Eyles, D. E. (1954) *Amer. J. trop. Med. Hyg.*, **3**, 219

Logan, J. A. (1953) *The Sardinian project : an experiment in the eradication of an indigenous malarious vector*, Baltimore, Md., Johns Hopkins Press (*American Journal of Hygiene Monographic Series*, No. 20)

Macdonald, G. (1950) *Trop. Dis. Bull.*, **47**, 915-938

Macdonald, G. (1952) *Trop. Dis. Bull.*, **49**, 813-829

Macdonald, G. (1953) *Trop. Dis. Bull.*, **50**, 871-889

Macdonald, G. (1958) *The epidemiology and control of malaria*, London, Oxford University Press

Metselaar, D. (1957) *A pilot project of residual insecticide spraying in Netherlands New Guinea ; contribution to the knowledge of holo-endemic malaria*, Leiden

Metselaar, D. (1961) *Amer. J. trop. Med. Hyg.*, **10**, 327

Pampana, E. J. (1951) *Lutte antipaludique par les insecticides à action rémanente*, Geneva (*World Health Organization : Monograph Series* No. 3)

Soper, F. L. & Wilson, D. B. (1943) *Anopheles gambiae in Brazil : 1930 to 1940*, New York

Taiwan Provincial Malaria Research Institute & WHO Malaria Team in Taiwan (1958) *Bull. Wld Hlth Org.*, **19**, 595-620

Wilson, D. B. (1960) *Report on the Pare-Taveta Malaria Scheme, 1954-59*, Dar es Salaam

World Health Organization, Expert Committee on Malaria (1957) *Wld Hlth Org. techn. Rep. Ser.*, **123**

World Health Organization, Expert Committee on Malaria (1959) *Wld Hlth Org. techn. Rep. Ser.*, **162**

World Health Organization, Expert Committee on Malaria (1961) *Wld Hlth Org. techn. Rep. Ser.*, **205**

World Health Organization, Expert Committee on Malaria (1962) *Wld Hlth Org. techn. Rep. Ser.*, **243**

Zulueta, J. de & Lachance, F. (1956) *Bull. Wld Hlth Org.*, **15**, 673-693

Zulueta, J. de et al. (1961) *E. Afr. med. J.*, **38**, 1

Annex 1

MATHEMATICAL FORMULAE USED IN THE CONSTRUCTION OF TABLES 1 AND 2

Comparison of successive parasite rates at a 6-month interval

If the original rate, $p\%$, was established in a sample of size n_1, and the second rate, $0.4p\%$, was established in a sample of size n_2, the difference between $0.47p\%$, where p was measured in the first sample, and $0.4p\%$, which was measured in the second sample, would be statistically significant at the 5% one-sided probability level, if

$$\frac{0.07p}{\sqrt{\dfrac{0.47^2 p\,(100-p)}{n_1} + \dfrac{0.4p\,(100-0.4p)}{n_2}}} \geqq 1.645$$

Solving this equation for the minimum value of n_2 in terms of n_1 and p, we get

$$n_2 = \frac{4000 - 16p}{0.18108p - \dfrac{22.09\,(100-p)}{n_1}}$$

Comparison of successive parasite rates at a 12-month interval

When the original rate is $p\%$, the second rate, in this case, should be $0.16p\%$ under complete interruption of transmission and the difference between $0.22p\%$ and $0.16p\%$ would be statistically significant at the 5% one-sided probability level, if

$$\frac{0.06p}{\sqrt{\dfrac{0.22^2 p\,(100-p)}{n_1} + \dfrac{0.16p\,(100-0.16p)}{n_2}}} \geqq 1.645$$

Solving this equation for the minimum value of n_2 in terms of n_1 and p, we get

$$n_2 = \frac{1600 - 2.56p}{0.13304p - \dfrac{4.84\,(100-p)}{n_1}}$$

Annex 2

MATHEMATICAL ASPECTS OF THE DECLINING PARASITE RATE

The following symbols are used:

a = the average number of bites on man by one mosquito in one day.

h = the proportion of the population receiving infective inocula in one day (the inoculation rate).

r = the proportion of affected people who have received one inoculum who revert to the unaffected state in one day (the recovery rate).

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

x = the proportion of the population affected (the parasite rate).

t = time in days.

z = the number of infections distributed by a single primary non-immune case (the basic reproduction rate).

L_x = the limiting value of x.

e = the base of natural logarithms.

It has previously been shown (Macdonald, 1958) that the basic differential of malaria prevalence is

$$\frac{dx}{dt} = h - rx \qquad (1)$$

when $h \leq r$, as may always be assumed during an eradication programme. The inoculation rate, h, is, however, a dependent function of x, with the value

$$h = zx\left(1 - \frac{ax}{ax - \log_e p}\right) \qquad (2)$$

$$\text{whence } \frac{dx}{dt} = \left(\frac{-\log_e p}{ax - \log_e p}\right) zx - rx \qquad (3)$$

When transmission is totally interrupted, z reduces to zero, and in this case

$$\frac{dx}{dt} = -rx$$

$$\text{whence,} \quad x_t = x_0\, e^{-rt} \qquad (4)$$

which is the basis of the graphs showing the expected slope of fall of the parasite rate following total interruption of transmission.

It is necessary also to consider happenings when interruption of transmission is incomplete, and the reproduction rate, z, has a remaining finite value, though less than its original value. The derivative in (3) then remains valid, just as in epidemic conditions previously considered (Macdonald, 1958). Accordingly, serial calculations similar to those used in connexion with epidemics were made for the decline of a parasite rate from 100%, through a period of five years, for reproduction rates of 1.5 and 1.0, attributing values of 1.0 and 0.1 to the factor $\frac{-\log_e p.}{a}$. This calculation proved extremely laborious and time-consuming, and the curves for values of z between 1.0 and zero were filled in by interpolation. The authors are therefore greatly indebted to Dr H. O. Irwin (personal communication, 1963), who later produced a general solution for differential equations of the type of (3), showing that when

$$\frac{dx}{dt} = \frac{k\,a\,x}{ax+b} - rx$$

with the limiting value

$$L_x = \frac{k}{r} - \frac{b}{a}$$

and when this limiting value is negative, t_0 is the time when $x = 1.0$ and t is a later time; then

$$e^{t - t_0} = x^{\frac{b}{a\,r\,L_x}} \left(1 - \frac{1-x}{1-L_x}\right)^{-\frac{1}{r} - \frac{b}{a\,r\,L_x}} \qquad (5)$$

In the adaptation of these expressions to the present context,

$$b = -\log_e p$$

$$\text{and} \qquad L_x = \frac{-\log_e p\,(z-1)}{a}$$

Expression (5) therefore modifies to

$$t - t_0 = \frac{1}{r(z-1)} \left[\log_e x - z\log_e\left(\frac{x - L_x}{1 - L_x}\right)\right]$$

Operation of this expression is relatively easy, curves for any given values of z and other constants being readily prepared. The expression makes no allowance for the influence of an incubation interval, which it was thought might be insignificant in the present context. As a check on this, curves were calculated for the same values as had been used in the serial calculations, which necessarily included provision for the incubation interval, and the two were found to tally very closely, thus confirming the validity of the simplified technique despite this omission.

Fig. 12 has been prepared by this method, and the numerical values of annual parasite rates declining under the influence of some selected low reproduction rates are set out in Table 3.