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The Secretary of the Expert Committee on Malaria
has the honour to communicate hereunder
a report on

MALARIA TRANSMISSION RATES AND INFANT PARASITE RATES
(Section 5.4 of the Agenda)

by

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INTRODUCTION

A subject of urgent controversy in African malariology is that of immunity and particularly how it is acquired; whether the known tolerance which is developed by adults in some areas is always related to the amount of infection they have received, or whether there is a racial element which encourages its development in some people. This matter cannot be settled until both the tolerance and the degree of transmission producing it can be measured with reasonable accuracy. The first is possible by examination of parasite densities, the second has only been attempted by the laborious and very uncertain means of analysis of mosquito numbers and infectivity. There is, therefore, a need to develop a more usable and accurate means of measuring transmission.

Such a means would also be of great value in the measurement of the results of malaria control by different methods. Residual spray campaigns have, for instance, been carried out in Uganda, and while the entomological results are beyond serious question the effect on the transmission of disease is a matter of considerable doubt, as the meaning of the parasite rates observed is not understood.

There have been several studies of the transmission rate based on anopheline analysis, such as those of GORDON and DAVEY (1932), WALTON (1947) and GARNHAM (1950). They are all, however, based on a series of assumptions which are of two types; concerning anopheline habits and anopheline infectivity. Those of the first type concern the relation between the numbers of anophelines in the house in the day and of those biting at night; the frequency of biting; the numbers of people bitten on any night by one hungry mosquito; and the proportion of the species which bite man and animals. Few of these assumptions are based on reliable evidence. Even if they were secure, data would have to be collected from a very large number of houses at short intervals for at least a year to give any reliable general figure.

The assumption which does not seem to be even questioned in the literature is the infectivity of mosquitoes with sporozoites in the salivary glands. All the studies known to the writer take it for granted that 100 per cent of such mosquitoes are infective and calculate transmission rates on this basis, but it is a quite untenable assumption. Most of the direct evidence concerns Plasmodium vivax, but it is all in direct opposition to the idea. BOYD (1940), inoculating susceptible people, showed that two bites from anophelines with less than 50 oocysts in the stomach only infected half the subjects, and even six to ten such bites only infected 87 per cent. Most natural mosquito infections are of this order. JAMES (1931) made an elaborate study of this matter. Dealing with susceptible people and with anophelines infected in the laboratory on heavy gametocyte carriers, he was only successful in infecting 935 out of 1,356 subjects, or 72 per cent. In considering his failures he came to the following conclusion:

"The test of finding sporozoites in the salivary glands of a mosquito after biting is not good evidence that sporozoites were injected by that mosquito when it bit the patient Taking this into account, it

is obvious that great caution is necessary in coming to a decision that failure is due to the patient being "insusceptible" or "immune." It is preferable in our opinion to meet the difficulty of explaining failures such as are recorded in the above examples by assuming that a requirement for successful infection is that sporozoites, in addition to being present in the cells of the salivary gland, must be lying free in the common salivary duct of the mosquito at the time of biting..." (Italics in the original.)

This is a necessary standard when dealing with anophelines infected from carefully selected carriers having numerous gametocytes in their blood, and with the deliberate object of assuring heavy infection of the mosquito. There is no example of this standard having been applied to estimate infectivity in nature, and its omission alone invalidates all conclusions based on the sporozoite rate as a measure of the transmission rate. There are, however, other additional sources of error in the field. BARBER (1936) showed that in very large proportions of infected anophelines the sporozoites were degenerate. Working in the Mediterranean lands he found that degeneration was commoner in winter than in summer in A. sacharovi, but in A. superpictus only 9.5 per cent of those examined in the summer had healthy sporozoites, and laboratory experiments showed that this degeneration might occur in quite young infections.

There are statements in the literature which give concrete figures for the inoculation rate. They all appear to be based on anopheline analysis, and cannot be accepted unless they are considerably elaborated in the ways suggested by the above findings, or confirmed by some other means.

THE INFANT PARASITE RATE

Several observers have examined infants of different age groups and observed the rising incidence of infection in monthly or three monthly periods. Studies of this nature from places where malaria is transmitted more or less perennially have been made by BLACKLOCK and GORDON (1925), DAVEY and GORDON (1933), BARBER and

OLINGER (1931), WALTON (1947) and GARNHAM (1949). These all show graduated curves, and it is clear that the curve must in some way be determined by the frequency of inoculation, the speed of recovery from infection, and the extent to which superinfection is possible.

The actual part which these play has not been satisfactorily elucidated. ROSS (1916) made a general mathematical analysis of the probabilities, but was dealing not with malaria but with infections of all types. His formula cannot be applied to happenings in malaria, at least not without considerable modification, as the recovery rates which must be stipulated to make theoretical and observed curves agree are far lower than any malariologist would accept as credible. It is now realized that the reason why they cannot be applied is that he assumed that superinfection did not take place, whereas it is common. BARLOVATZ (1940) has tackled the problem of malaria and produced simple theoretical curves which explain happenings in highly malarious parts of the Belgian Congo. However, his theoretical basis does not permit any chance of recovery, or of superinfection, and cannot be taken as a general case. It does not appear, in fact, that the author so intended it. WALTON (1947) has produced a theoretical analysis. Whilst dealing with superinfection it omits correct reference to recovery and, in fact, if his constants are agreed, shows the level of the parasite rate after one year of exposure only.

The present writer has prepared* elsewhere (MACDONALD, 1950) a mathematical analysis of the expected happenings on the following assumptions:

- (a) The superimposition of infections with P.falciparum is a common happening in nature at least during the early years of life.
- (b) The common form of recovery from initial parasitaemia (due to a single infection) is its interruption by progressively lengthening periods of freedom.

* Prepared with the intention of submission to this Conference, but production made impossible by an industrial dispute in the printing trade. The material is not susceptible to rapid reproduction by other means than printing, and this brief statement is submitted in its place. A single copy of the original can be made available for any wishing to study it.

The insertion of a proper allowance for the superimposition of infections makes the resulting formula differ radically and in principle from previous ones, though it is related to that of ROSS, whose methods of working were followed. Its effect is to reduce the probability of the occurrence of periods of freedom from infection in proportion to the probability of superinfection having occurred, that is in proportion to the inoculation rate.

The inoculation rate, referred to in following mathematical equations as h , is defined as the proportion of the population receiving infective inocula in unit of time. (The unit of time used in this work is one day). The recovery rate, referred to as r , is the proportion of affected people (who have received one infective inoculum only) who revert to the unaffected group in unit of time. The standard of positive or negative used is the presence or absence of parasites in a blood film, 150 fields of a thick film being suggested for examination.

It is found on mathematical analysis that two different basic formulae must be used; one for those cases where the inoculation rate does not exceed the recovery rate; one for the cases where it does exceed the recovery rate. These will be referred to hereafter as the cases "where recovery is probable" and "where recovery is improbable."

In both cases the theoretical curves produced are regular, concave to the time axis, and asymptote to a final level, to which they constantly approach nearer and nearer without ever finally reaching it. This final value is known as the Limit, referred to in the formulae as L . Curves of this nature are shown in Figure 1.

Case when recovery is probable

In the case where recovery is probable, L is equal to $\frac{h}{r}$, and because in this case h is always less than r (see above) this value is always less than 1.0.

This limit represents the parasite rate when stability is reached or approached, at about two years of age. It expresses the rate as a proportion, and to turn it into a percentage it should be multiplied by 100. For ease of mathematical statement rates will henceforth be expressed as proportions, and they can be converted into percentages, if that is desired, by this multiplication.

The parasite rate at 2 to 3 years can be measured; it is clear that if the recovery rate were also known it would be possible to calculate the inoculation rate from the two known figures. The recovery rate can be measured directly in one series of observations by EARLE et al (1939) on P. falciparum malaria in Puerto Rico. The figure deduced from this series is 0.005. A subsequent study of several African series shows that this figure could have been derived indirectly from them and that it is impossible to explain African happenings except on the basis that it is at least approximately correct. This value of r , 0.005, has therefore been adopted as a standard one.

Where the proportion positive at 2 to 3 years is well below 1.0 (that is well below 100 per cent), the inoculation rate causing it can easily be determined from the identity

$$h = rL$$

or the inoculation rate is equal to the proportion positive multiplied by 0.005.

The curve which precedes the attainment of stability can be expressed by a more complicated formula, given in the papers referred to. In the case now considered, where recovery is probable, and which is characterized by the fact that the ultimate level of the parasite rate remains permanently below 1.0 (or 100 per cent), the information needed can be derived direct from the parasite rate of children aged 2 onwards to about 5 years. The more complicated formula need not, therefore, be used for routine purposes in analyzing this case.

Case when recovery is improbable

This covers all examples when the parasite rate at any age (usually 2 years or before) reaches 1.0 or 100 per cent. As error and chance happenings might produce occasional negatives even in this group, it is best to consider its use in every case where the parasite rate at any age exceeds 0.9 or 90 per cent. When there is doubt as to which type an example falls into, the parasite rate at age six months should be noted. The dividing line is 0.61 or 61 per cent. Figures above this indicate that the example is one of the present case, below it that the example belongs to the previous case. An alternative means of differentiation is given in a later part of this paper.

In these cases the limit is always 1.0. No further information can be derived from the final value of the parasite rate other than that the example falls into the present group. It is, therefore, necessary to study the age incidence amongst infants from birth to two years to measure the inoculation rate. The basic formula is:

$$\underline{x} = 1 - \underline{e}^{-\underline{h}t}$$

in which:

- x is the proportion affected,
- e is the mathematical constant 2.71828,
- h is the inoculation rate, and
- t is the age in days after subtraction of 10 days to allow for the incubation period.

This formula may be converted into a logarithmic form which is very much easier to work:

$$\underline{h} = \frac{\text{Log } (1 - \underline{x})}{-0.4343 \underline{t}}$$

In using this, the expression $\text{Log } (1 - \underline{x})$ is derived from the parasite rate (x) in any particular age group, which after conversion into a mean age in days is the t in the denominator. Tables I and II give values of $\text{Log } (1 - \underline{x})$ and of $-0.4343 \underline{t}$ for representative parasite rates and age periods. If a series of examinations of different age groups is available, the value of h can be readily worked out for each of them from these tables, and the average value so found taken as the ruling one.

Figure 1 shows the formulae for the two cases graphically. Each curve represents the changes with age in the parasite rate which would be expected with different inoculation rates, which are given on the curves themselves.

Comparison with observed happenings

A detailed comparison of observed results in the field with expected values shown by the formulae has been made in the original paper. The method was to derive a value of h from the actuals, and then to draw a curve using this value of h and putting r at 0.005 in each case.

The original illustrations are reproduced in Figures 2 to 7. Two curves were drawn to compare with BARBER and OLINGER'S data (Figure 7.) because those authors suggested that there were changes in the transmission rate during their observations, which would have resulted in young and old infants having been exposed to different degrees of infection. The lower curve is therefore intended to represent conditions before six months of age, the upper one conditions after that age.

It will be noted that in each case a reasonable degree of correspondence has been attained between the actual and theoretical happenings. This is taken first to establish that the general form of the formulae used is correct, and that it represents the type of happenings which are influencing the parasite rate. It should particularly be noted that no correspondence could be achieved with any value of the recovery rate differing greatly from 0.005, and it is therefore taken that this figure is quite sufficiently correct for general use in Africa.

The inoculation rate was calculated in each of the examples. In some cases there was information in the original authors' paper on the transmission rate as derived from anopheline analysis. The compliance between the two figures, derived from the parasite rate and from anopheline examinations, is very poor. The relevant figures are:

<u>Series</u>	<u>Daily inoculation rate</u>	
	<u>Derived from infant parasite rate</u>	<u>Derived from anopheline analysis</u>
BLACKLOCK & GORDON, Freetown:	0.00205	None given
DAVEY & GORDON, Freetown:	0.00441	? 0.0033
WALTON, Freetown:	0.00036	0.00002 *
DAVEY & GORDON, Kissy:	0.0133	0.1
GARNHAM, Kenya:	0.006525	0.02
BARBER & OLINGER, Lagos:	0.00435 **	? 0.079

* WALTON comments that this is clearly inadequate to account for the malaria found.

** Mean of the two values used.

The calculated values are by their origin closely related to the infant parasite rates. The observed values show no constant relation. WALTON's figure is totally insufficient to account for any material amount of malaria in the population. Only 0.7 per cent of children would get infective bites in a year, but the parasite rate at 18 months was 6.5 per cent. He showed from observation on children that 16 to 20 per cent of children received such bites annually. WALTON explained this by saying that the children must get malaria elsewhere, not in the places where he made his anopheline observations. Whatever the explanation, and his is a possible one, his inoculation rate does not represent the amount of infective bites to which the children were exposed, in Freetown or elsewhere.

The figures given by DAVEY and GORDON, and by BARBER and OLINGER, differ in the opposite way. Their inoculation rates are grossly higher than those now calculated. The writer has attempted to relate the observed parasite rates to the given inoculation rates by every means he can imagine, not only by the use of the present theory, and has failed to produce any consistent explanation. A rate such as that given by DAVEY and GORDON would inevitably result in the infection of 90 per cent of children by the age 33 days, but this proportion is not reached until after six months. The recovery rate does not enter into the formula used, the fact that it should not do so is shown by the actual curve touching 1.0 (100 per cent) at one year, which is incompatible with the consistent occurrence of recoveries. The formula used merely represents the summation of cases, for which no alternative explanation can be found to the one that they increased by about 0.0135 or 1.35 per cent per day whilst recoveries were few or virtually non-existent. the Lagos figures do not reach a level of 1.0 at any age, so the existence of recovery must be allowed. The substitution of different recovery rates produces quite different shaped curves which cannot be made to approach the shape of observed ones.

Other series of observations of the age incidence of infections have been made in Africa, but most concern the group simply described as "under 1," which is inadequate for any analysis. It is, however, clear that in most cases the inoculation rate derived by the present method would be much lower on the whole than those derived from anopheline studies. The present method, however, contains many fewer sources of

material error than do the anopheline studies, and any errors are likely to be more or less constant from one series to another so that they should not invalidate comparisons.

Practical use

The first object of the malariologist in many of his studies is, in fact, to determine the inoculation rate, of which he has previously only had an indirect knowledge, or knowledge gained through a cumbersome and inaccurate method of anopheline analysis. The inoculation rate is the final measure of the intensity of malaria, and information on it is needed in studies of control measures, and in estimations of different degrees of endemicity.

To make an estimate, examination should at first be made of children under 2 years of age, their age in months being recorded. If the parasite rate does not reach or approach 1.0 at any age, examinations may be extended to older children up to a maximum of about 5 years. The results should be prepared in graph form and only analyzed if they fall into some consistent curve.

If the parasite rate does not exceed 0.9 at any age the highest level, or the average of several high ones, should be taken as representing the limit, and the daily inoculation rate simply calculated by multiplying it by 0.005 (remembering that the parasite rate should be expressed as a proportion, such as 0.85 and not 85 per cent).

If the value reaches 0.1 at any age, the value of the inoculation rate should be calculated for all values before it does so, using the expression:

$$\underline{h} = \frac{\text{Log } (1 - x)}{-0.4343 \underline{t}}$$

and the values for the numerator and denominator of this fraction given in Tables I and II.

There may be a few cases when there is doubt as to which method should be used. In such cases a value of L can be calculated from the observations on the young groups of infants. Take each group separately, and note for it the proportion

positive, or \underline{x} . A value of L can then be calculated from the equations:

$$L = \frac{\underline{x}}{1 - e^{-0.005 \underline{t}}}$$

Table II gives values of the denominator in this identity, so that the calculation is a simple division.

If the value of L so found is below 1.0, the example falls into the first case of probable recovery. If it is above 1.0 the example is one of the second case, of improbable recovery. The working for both of these is described above.

TABLE I.

Values of $\log (1 - x)$ for various values of x

<u>x</u>	<u>$\log (1 - x)$</u>	<u>x</u>	<u>$\log (1 - x)$</u>
0.05	- 0.02228	0.55	- 0.34679
0.10	- 0.04576	0.60	- 0.39794
0.15	- 0.07058	0.65	- 0.45593
0.20	- 0.09691	0.70	- 0.52288
0.25	- 0.12494	0.75	- 0.60206
0.30	- 0.15490	0.80	- 0.69897
0.35	- 0.18709	0.85	- 0.82391
0.40	- 0.22185	0.90	- 1.00000
0.45	- 0.25964	0.95	- 1.30103
0.50	- 0.30103		

TABLE II.

Values of $1 - e^{-0.005t}$ and $0.4343t$ for different values of t

<u>Age group</u>	<u>$1 - e^{-0.005t}$</u>	<u>$0.4343t$</u>
Under 1 month	0.02456	-2.1715
1 month	0.16171	-15.2065
2 months	0.28109	-28.664
3 "	0.38432	-42.127
4 "	0.48213	-55.156
5 "	0.54615	-68.619
6 "	0.61028	-81.648
7 "	0.66388	-94.677
8 "	0.71213	-108.14
9 "	0.75397	-121.60
10 "	0.78777	-134.63
11 "	0.81732	-147.66
1 year	0.93280	-234.52
2 years	0.99889	-390.87

Note: Where age groups such as 3 - 4 - 5 months are handled, the corrected median age is that for the median month, in this case 4 months.

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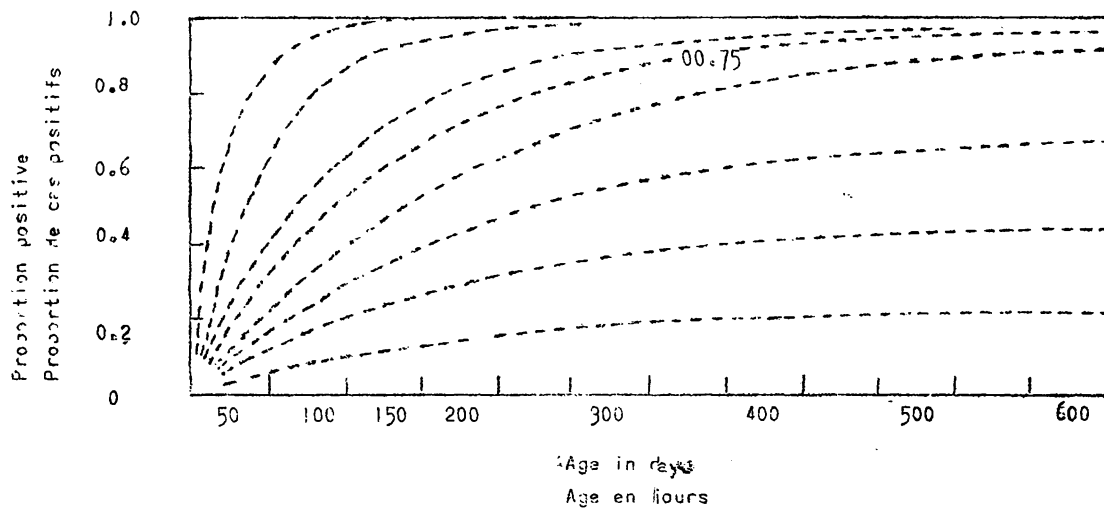


Fig. 1. Theoretical infection rates corresponding to various inoculation rates.
 Fig. 1. Taux théoriques d'infection correspondant à différents taux d'inoculation.

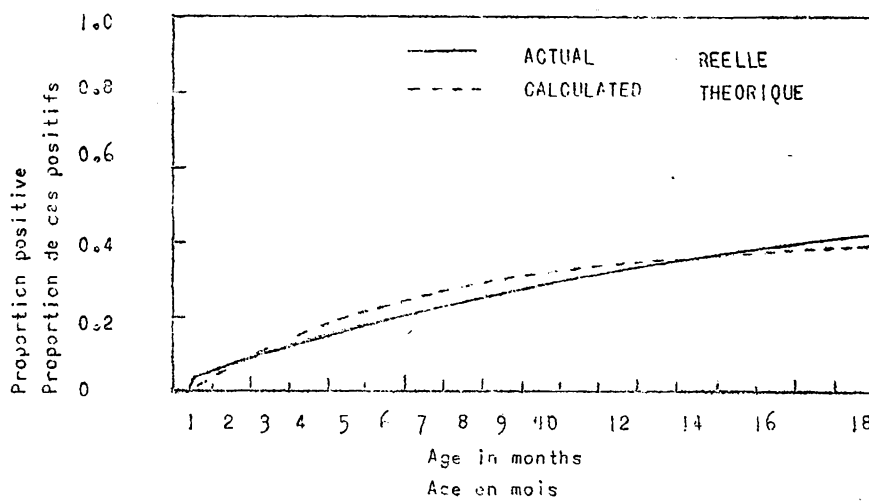


Fig. 2. Actual and theoretical curves from Freetown, BLACKLOCK and GORDON (1925).
 Fig. 2. Courbes réelles et théoriques pour Freetown, BLACKLOCK et GORDON (1925).

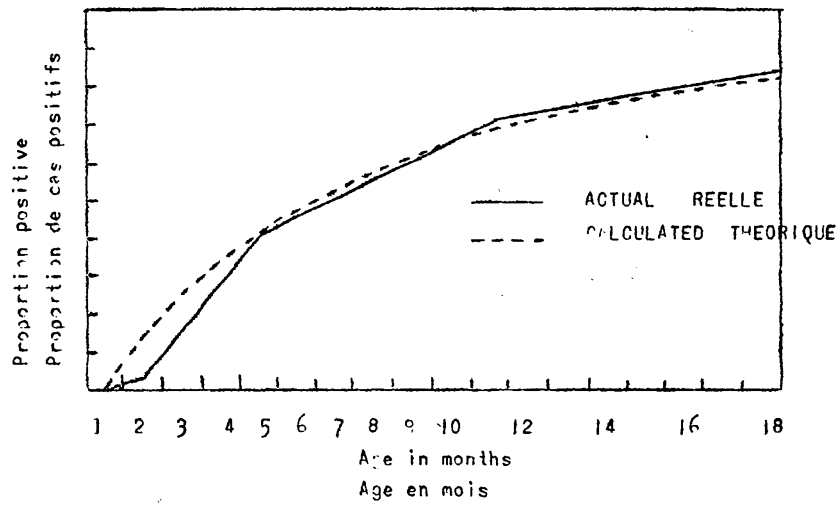


Fig. 3. Actual and theoretical curves from Freetown, DAVEY & GORDON (1933).

Fig. 3. Courbes réelles et théoriques pour Freetown, DAVEY & GORDON (1933)

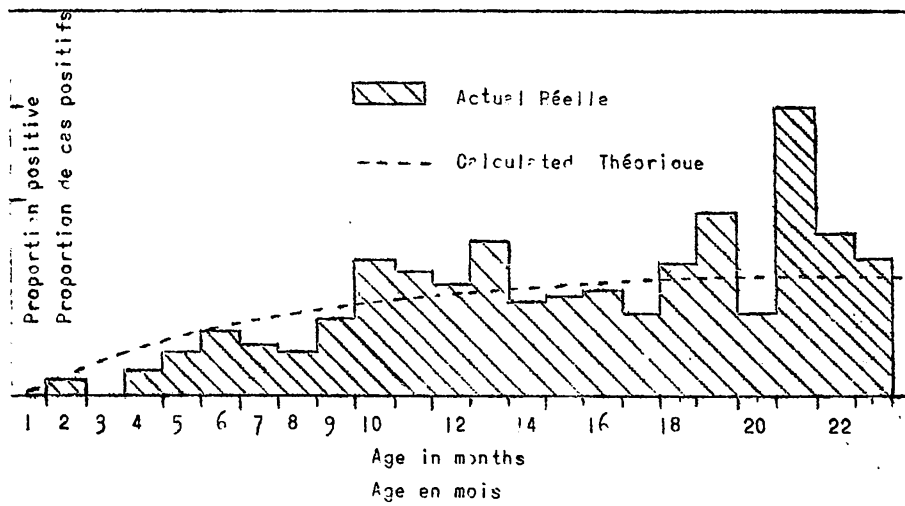


Fig. 4. Actual and theoretical curves from Freetown, WALTON (1947).

Fig. 4. Courbes réelles et théoriques pour Freetown, WALTON (1947).

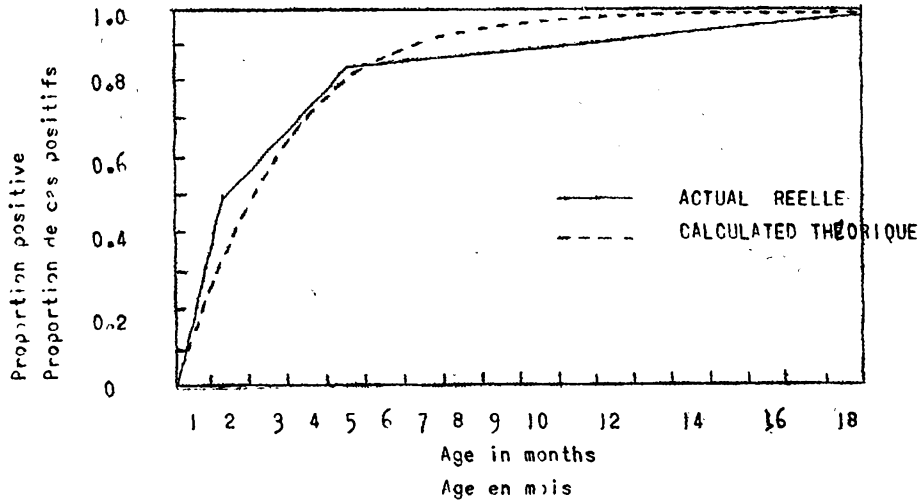


Fig. 5. Actual and theoretical curves from Kissy, DAVEY AND GORDON (1933)
 Fig. 5 Courbes réelles et théoriques pour Kissy, DAVEY AND GORDON (1933)

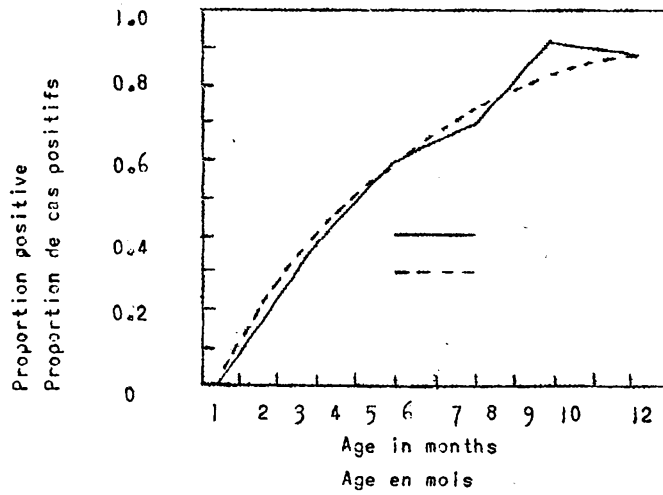


Fig. 6. Actual and theoretical curves from Kisumu, Kenya, GARNHAM (1949)
 Fig. 6. Courbes réelles et théoriques pour Kisumu, Kenya, GARNHAM (1949).

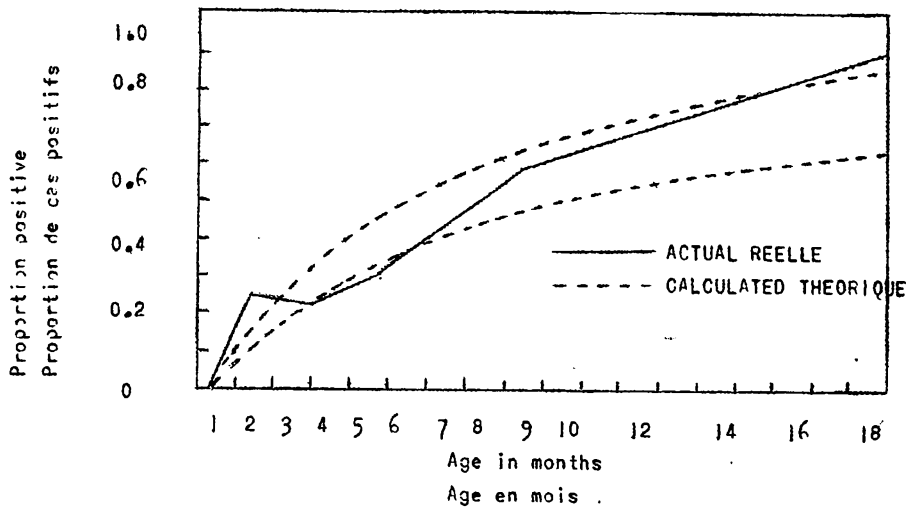


Fig. 7. Actual and theoretical curves from Lagos, BARBER & OLLINGER (1931)
 Fig. 7. Courbes réelles et théoriques pour Lagos, BARBER & OLLINGER (1931)