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Problems of Epidemiology in Malaria Eradication

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With an increasing number of malaria eradication programmes approaching or entering the consolidation phase, the epidemiological features of disappearing malaria are getting better known and defined. At the same time, the old classical methods of measuring malaria prevalence have become inadequate and new methods for the epidemiological assessment of the progress of eradication are being developed.

In this article the new methods of assessment and epidemiological and statistical criteria for discontinuing residual spraying and for the stability of consolidation are discussed on the basis of field experience in several countries during the past two or three years. Some prominent epidemiological features of malaria at reduced levels of transmission are described, special attention being given to the role of the asymptomatic carrier in malaria eradication.

INTRODUCTION

Several of the many programmes of malaria eradication initiated in the last five years are now faced with the epidemiological problems of " disappearing malaria ". This applies not only to those programmes which have reached the phase of consolidation[2] but also to many in the later stages of the attack phase. It is thus understandable that while during the past few years a maximum of attention in eradication programmes has been given to the perfection of general organization and thoroughness of spraying operations, attention and efforts are now increasingly focussed on epidemiological evaluation.

The problems encountered are of two kinds: on the one hand, new epidemiological phenomena peculiar to low-level transmission brought about by eradication measures are being defined and indicate the need for appropriate measures for overcoming the last small, but often obstinate, obstacles to eradication; on the other hand, the old methods of "malariometry " are being found inadequate even for the simple but essential task of assessing year by year the general volume of malaria in the population. This inadequacy of the old methods often becomes apparent as early as the second year of an eradication campaign.

Both these epidemiological aspects of malaria eradication were fully recognized by the WHO Expert Committee on Malaria at its 1956 meeting and discussed in its sixth report, published in 1957. The general nature of the problems to be expected was well described and the principles of new methods of assessment needed were laid down. The practical application, however, of these concepts and principles has met with considerable difficulties in the field of operations.

During the last two or three years considerable experience has accumulated in this field. The knowledge gained is still patchy and the methods of work used are still in the stage of experimentation. Hence from a strictly scientific point of view the writing of an article on this subject would seem premature at the present juncture and the presentation of even tentative conclusions and practical suggestions somewhat rash. The only justification for doing so is the universally felt need for every scrap of available information on epidemiological facts and on experience with methods of evaluation and surveillance in malaria eradication.

It is hoped that this attempt at consolidating some of the valuable information forthcoming from various programmes the world over may help to satisfy this need and that some of the suggestions made may prove useful at least in so far as they stimulate discussion.

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[2] No attempt is made in this article to review, however briefly, the basic concepts and principles of malaria eradication. Those readers who are not familiar with the subject are referred to the sixth report of the WHO Expert Committee on Malaria (1957).

METHODS OF ASSESSMENT OF MALARIA PREVALENCE AND INCIDENCE IN ADVANCED STAGES OF ERADICATION

In its seventh report the WHO Expert Committee on Malaria (1959) discussed in some more detail evaluation of techniques following the basic principles laid down in the sixth report. The following relevant passages from the seventh report may by quoted here:

> " An eradication programme requires continuous evaluation, starting either before or in the very earliest part of the preparatory phase and continuing until the end of the programme. The techniques to be used vary greatly at different stages of the programme... Once the phase of attack starts... evaluation must concern itself with malaria as a dynamic condition which is rapidly diminishing and later disappearing, and techniques adapted to this dynamic stage, many of them relatively new, must be adopted."

In the framework of this article we are chiefly concerned with these " relatively new " techniques, but a few sentences must be devoted to the discussion of the old classical methods of assessment in malaria in order to indicate the limitations of their use in malaria eradication programmes. The principal classical method is that of the malariometric survey, which establishes spleen and parasite rates. It must be clearly understood that these are prevalence rates, i.e., they constitute a purely static measure of the amount of malaria at one given moment of time. The amount of malaria is measured in terms of percentages of persons found with enlarged spleens and of persons found with malaria parasites in their blood at that time. Furthermore, these rates are not, strictly speaking, " rates " because not the whole population is examined for this purpose, but are *indices* obtained through the examination of a sample of the population, the classical malariometric survey being a sample survey.

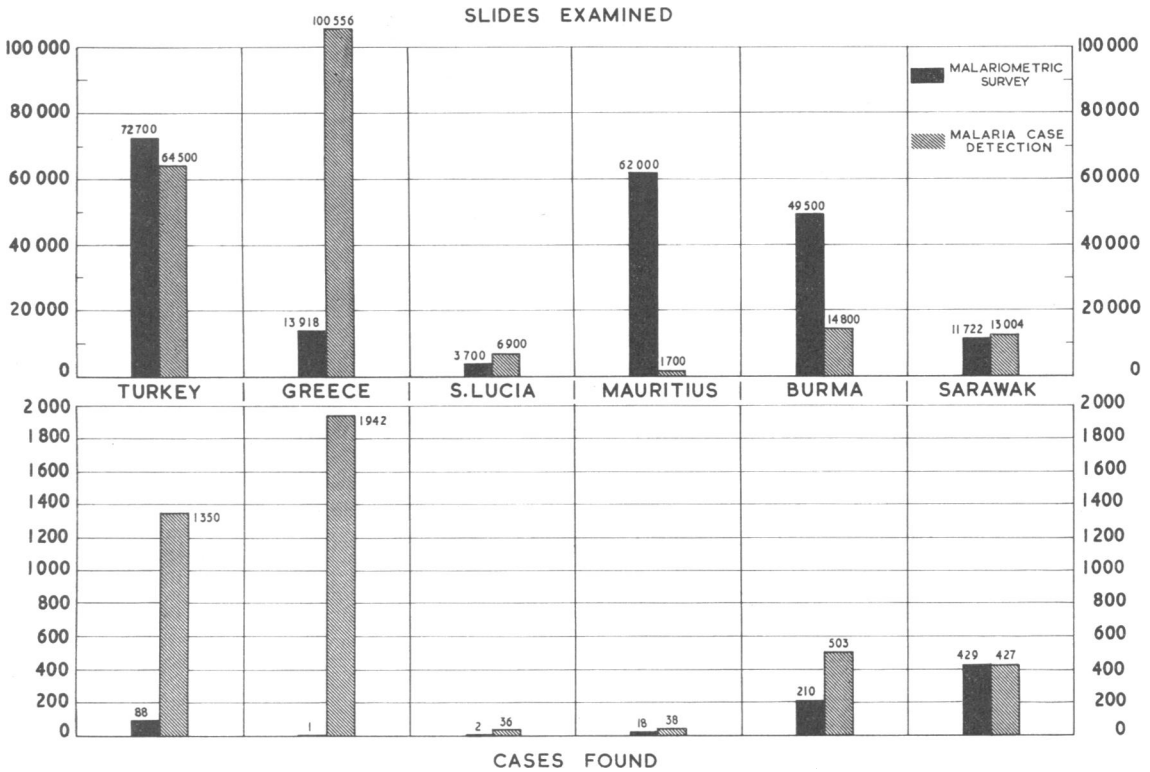
In a malaria eradication programme the data obtained through malariometric sample surveys are useful in the preparatory phase in that they describe and define the degree of endemicity of the malarious areas. They are also useful in the first two years of the attack phase in that a proportionate decrease of the rates will give an indication of the general impact of the spraying programme. As soon, however, as the general volume of malaria has been reduced to any considerable extent, the indices furnished by malariometric surveys are no longer sensitive enough to measure further progress. In addition, it then becomes imperative to have not only an indication of the relative reduction of malaria but also more accurate knowledge about the total amount of infections still appearing throughout the course of the year and throughout the whole population covered by the programme.

Analysis of evaluation data from eradication programmes as well as closer observations in the field have shown that the point at which malariometric surveys cease to be sufficiently sensitive is reached when parasite rates have dropped to a level of between 1% and 3%. This is usually the case as early as the second year of the attack phase. At this time it is necessary to change to a method of evaluation which measures malaria in a continuous way in the whole population. The methods used for this purpose have been termed " malaria case detection " (WHO Expert Committee on Malaria, 1959). They are often loosely referred to as " surveillance "; this, however, is not correct since they constitute only part of the activities covered by the term " surveillance operations ".[1] Basically the process of malaria case detection is one of continuous search for cases in the population by the taking of blood slides from all fever cases encountered. This can be done either through a system of " active detection ", in which personnel of the malaria eradication programme visit all houses at regular intervals, or by a system of " passive detection "—whereby patients with fever visit medical dispensaries or fever posts operated by voluntary collaborators and in which blood slides are taken—or by a combination of both systems. Once the total population is well covered by either or both systems of malaria case detection, the total number of cases detected during one calendar year can be expressed as a proportion (% or ‰) of the total population; this figure, which then constitutes an *incidence rate*, is used in health statistics for the measurement of many diseases. The figures of incidence rates, as opposed to the prevalence rates of malariometric surveys, constitute the only reliable basis of assessment in malaria eradication programmes when the critical point of withdrawal of spraying operations is approached and during the consolidation phase.

The loss of usefulness of malariometric surveys during the later stages of an eradication programme is shown by a comparison of the results of malario-

[1] There is at present a considerable degree of confusion in the use of various terms describing surveillance operations and their component parts, and different meanings are attached to some of these terms in different parts of the world. A standardized terminology will be considered by the WHO Expert Committee on Malaria.

COMPARISON OF RESULTS OF MALARIOMETRIC SURVEYS AND MALARIA CASE DETECTION PROCEDURES IN SIX COUNTRIES IN 1958



metric surveys and malaria detection procedures in 1958,[1] as illustrated for some countries in the accompanying figure.

To take the example of Turkey, the data shown in the figure are taken from an area where spraying had been discontinued but where consolidation had not yet truly been reached. It is seen that the examination of 72 700 blood slides from malariometric sample surveys resulted in the finding of 88 cases (0.12%) while the examination of 64 500 slides from malaria detection resulted in the finding of 1350 cases (2.1%). The practical importance of these figures lies not only in the much higher productivity per slide in malaria detection procedures (as expressed in the percentages of positives above) but also in the absolute number of cases found—1350 as against 88. The example of Sarawak is given in the figure to illustrate a situation where malariometric surveys are still of some use. The data refer to an area which is still under spraying, where a fair amount of transmission is still going on and where malaria detection procedures were introduced as an operational exercise for later surveillance operations. It is seen that in this case the parasite rate found in the malariometric surveys was 3.7% (429 cases found through the examination of 11 700 blood slides) and a similar number of blood slides (13 000) taken in the course of malaria detection did not reveal a higher number of cases (427=3.3%).

It is interesting to review the use of malariometric surveys and malaria detection methods made during the past few years in malaria eradication programmes of various regions, at a time when the relative merits of these methods in malaria eradication were not yet well defined. Generally speaking the tradition of classical malariology has had a strong influence on eradication programmes in South

[1] Yekutiel, P. & Göckel, C. W. (1959) *Analysis of data on evaluation and surveillance* (unpublished working document WHO/Mal/229).

East Asia, the Eastern Mediterranean and (to some extent) the European Region. Under the influence of this tradition, malariometric surveys were used as the only or principal method of assessment in several programmes for what must now be considered far too long a period. As a result the decision to cease spraying was based in a number of these programmes on malariometric indices, and the true situation (of continuing transmission) was revealed only when " surveillance " was instituted *after* the cessation of spraying. The opposite situation was found in the majority of the programmes in Central and South America. Here the method of malariometric surveys was discarded as obsolete for the purpose of malaria eradication from the very beginning and malaria detection methods were used as the only means of assessment from the first year of the attack phase. It is clear that for operational and financial reasons alone, it is impossible to have a comprehensive system of malaria detection in the total population from the very beginning of the programme. The result was that with the gradually expanding scope of malaria detection activities (called " evaluation operations " in the Americas) the number of cases found often *increased* during the first three years. This was almost always due to the increasing proportion of the population covered and not to a true increase in malaria morbidity, but it was thus impossible to assess the effect of the first two years of spraying operations. While this would never lead to a premature cessation of spraying, we consider the impossibility of assessing the effect of residual spraying in the first two years a serious drawback.

One possible solution to the problem is the use of malariometric surveys during the first two or three years for an over-all assessment, while malaria detection procedures are gradually built up so as to reach a total coverage by the third year, by which time malariometric surveys would probably have reached the limit of usefulness.

Alternatively a general assessment through the use of indicator districts, in which either malariometric surveys or full malaria detection procedures are used, may offer a second solution to this problem in the first two years.

An interesting study has recently been made in Mexico. The attack phase of the malaria eradication programme there started in 1957 and a system of malaria detection was gradually built up from the beginning and is now fairly comprehensive and functioning well. In 1959, i.e., the third year of the attack phase, a malariometric sample survey in schoolchildren was carried out in many localities where data from similar surveys were available for the time before the malaria eradication campaign. In a certain number of localities the blood slides of 61 344 schoolchildren were examined in 1959, revealing 44 positives for malaria—a percentage of 0.07. In the same localities, during malaria case detection activities in 1959 (search for fever cases) 9047 slides were examined, revealing 197 positives for malaria—a percentage of 2.17.

CRITERIA FOR CESSATION OF SPRAYING AND STABILITY OF CONSOLIDATION

In the advanced stages of a malaria eradication programme there are three critical periods in which the soundness and success of operational decisions depend entirely on the epidemiological assessment of the malaria situation. The first is the moment when it has to be decided whether spraying can be discontinued. The second period lasts throughout the consolidation phase, when it depends on the epidemiological assessment whether spraying may have to be reinstituted in circumscribed areas or surveillance procedures modified. The third period is when the achievement of final eradication has to be assessed. We shall limit our discussion to the first two periods.

Criteria for cessation of spraying

In regard to the criteria for determining the point at which spraying should or can be interrupted, the seventh report of the WHO Expert Committee on Malaria (1959) states the following:

> " There are two criteria for determining the point at which spraying should be discontinued: (*a*) interruption of transmission, and (*b*) reduction of the number of cases to zero or at least to a level so low that endemicity cannot readily be re-established . . . The reservoir of infection may be said to be practically depleted when no cases can be found in a reasonably intensive search."

The difficulty with these criteria is that the terms " a level so low that endemicity cannot readily be re-established " and " reasonably intensive search " are statements of principles but do not give quantitative measurements for guidance, and there is therefore little wonder that the practical application of these definitions has met with difficulty. In default of any laid-down maximum or minimum quantitative terms arbitrary values have been used in several eradication programmes to determine the " sufficiently low level of cases ". In a small number of programmes the statement, " reduction of the num-

ber of cases to zero ", was taken literally and spraying operations were unnecessarily prolonged. The principle is, however, an epidemiological one, and its basic meaning is that cases should be so low in number that either they could not *per se* re-establish transmission under the prevailing entomological conditions, or, more important, they can be detected and treated in time in the course of surveillance operations with the same result. " The concept of eradication and of surveillance as an integral part of its terminal phase is thus epidemiological and does not necessarily include within it the biological challenge of total elimination of human plasmodia ".[1] On the other hand, in a considerable number of programmes the decision to discontinue spraying has been made on the basis of arbitrary values of parasite rates, as determined by malariometric sample surveys (such as parasite rates of 1% or 2%); and experience has shown that the levels thus allowed were usually too high, so that serious break-downs occurred in situations which were presumed to represent the consolidation phase. Frequently infant parasite rates have been used as the main indication for achieved interruption of transmission. If a positive infant parasite rate is a definite indication of continuing transmission, the reverse is, however, not true, and a negative infant parasite rate is by no means a safe indication of complete interruption of transmission. The reason for this will become apparent when age distribution of malaria cases in the later phases of eradication is discussed below. We have already pointed out that after the second year of the attack phase malariometric surveys are no longer sensitive enough to assess the situation and that malaria detection procedures have to be used. The question then remains how to judge the adequacy of these detection procedures—or, in other words, what constitutes " a reasonably intensive search "—and what is a reasonably low figure of annual incidence, determined by the malaria detection activities, which would permit the decision to discontinue spraying. We consider that quantitative guidance on these points is most necessary, and we believe that some conclusions on these subjects can already be drawn from the experience in the field during the past two or three years.

In regard to the permissible level of incidence, scrutiny of data from surveillance operations towards the end of the attack phase or in the consolidation phase (true or assumed) in various countries has shown that in areas in which consolidation was successfully maintained after withdrawal of spraying annual incidence rates per thousand per population per year are invariably below the figure of 0.5.

In Table 1 incidence rates for 1959 are shown for attack-phase and consolidation-phase areas in a number of countries, some having both types of area and others only one. It will be seen that the only country in which the incidence figure for the consolidation phase is higher than 0.5 per thousand is the Philippines, where it is 3.1. As a matter of fact, it was recognized there that, although spraying had been discontinued, consolidation in this area was not stable enough and there was a resumption of transmission on a considerable scale; this will be gone into more detail below.

Admittedly one has to be careful in drawing epidemiological conclusions from general rates applied to relatively large and non-homogeneous populations. The correctness of the critical figure of incidence as postulated by us can, however, also be demonstrated from close detailed observations in the field, of which two examples are given.

In the Philippines, it was decided in 1958 to cease spraying in large areas containing altogether approximately 5 million people. Intensive malaria detection and surveillance operations were instituted at

TABLE 1

ANNUAL MALARIA INCIDENCE (PER 1000 POPULATION) IN CERTAIN COUNTRIES IN 1959, BASED ON EXTENSIVE CASE DETECTION ACTIVITIES

WHO Region	Country	Incidence in attack-phase areas	Incidence in consolidation-phase areas
Americas	Argentina	3.7	0.07
	Costa Rica	5.2	
	Venezuela	2.0	0.07
Eastern Mediterranean	Iran	1.3	0.02
	Iraq	0.5	0.01
Europe	Spain		0.06
	Turkey	0.9	0.4
South-East Asia	Afghanistan	2.5	
	Ceylon	0.4	0.02
Western Pacific	Laos	13.1	
	Philippines	16.1	3.1
	Sarawak	3.1	

[1] Viswanathan, D. K. (1958) Working paper No. 10, submitted to the WHO Expert Committee on Malaria, Lisbon.

the same time. During the subsequent year it was revealed—through the data obtained by surveillance operations—that in large parts of this " consolidation-phase area " (termed " discontinuation area " in the Philippines) considerable renewed transmission was occurring, which eventually made it necessary to put these districts back under the protection of residual spraying. The Philippines are, for the administration of the malaria eradication programme, divided into 30 zones, for each of which a malaria field unit is responsible. Analysis of the evaluation data, zone by zone, showed a number of zones in which the extrapolated annual malaria incidence for discontinuation areas ranged from 0.02 to 0.4 per thousand per year. In many other zones the incidence ranged from 2.0 to 15 per thousand. In the latter areas it could be assumed, and has been proved, that local transmission was resumed on a considerable scale and with a fairly widely scattered distribution. This was borne out by the fact that of all the cases investigated in these zones by the zone malariologist, one-third to two-thirds were considered to be recently contracted indigenous infections. In the areas with incidence rates below 0.4 per thousand, investigation of the cases had shown that none or very few of them originated from recent indigenous infection (mainly imported and some sporadic cases). There were only a few zones showing incidence figures between 0.4 and 2 per thousand, and closer scrutiny of the data in these areas showed that these intermediate rates resulted from the lack of epidemiological homogeneity of these zones: they usually comprised one large area where transmission had not been resumed and a smaller well-defined area where it had.[1]

In Taiwan [2] the malaria eradication programme, which had started in 1953, progressed so satisfactorily that in 1957-58 spraying was discontinued in the majority of the formerly malarious areas of the island. Malaria detection activities, which had already been instituted in 1955, were considerably intensified at that time. In order to organize these malaria detection and surveillance operations in the most efficient way the whole island was divided into five types of area, according to epidemiological criteria. Area I was classified as active malaria foci and Area II as potential malaria foci. In both these comparatively small areas spraying was continued and at the same time malaria detection and surveillance activities were greatly increased. Areas III and IV were considered to be in the consolidation phase. Spraying was discontinued and surveillance procedures were continued and strengthened. Area V contained both formerly non-malarious districts and those in which malaria—formerly hypoendemic—was considered eradicated. A certain amount of surveillance was, however, also carried out in this last area. The classification was not made on the basis of over-all incidence rates but on more detailed epidemiological grounds, based chiefly on a thorough analysis of all malaria cases detected and registered in 1955, 1956 and 1957 according to geographical distribution and classification (indigenous, sporadic, imported). The entomological conditions in the various districts were also taken into consideration. The most important definitions were those of Areas I and II, in which it was considered necessary to continue spraying. The classification of Area I (active malaria foci) was based on the proof of recent local transmission. A district was classified as Area II (potential malaria foci) when a considerable number of sporadic cases (relapses) or imported cases could be expected because of the vicinity of active foci or because of relapses of a fair number of indigenous cases that had occurred during the two previous years (although actual transmission had been interrupted by 1957). A dangerously high level of parasite reservoir was thus assumed in this area on epidemiological rather than on statistical grounds.

The annual incidence for these various types of area in 1958-59, based on the results of extensive and intensive malaria detection and surveillance, was as follows:

Area I:	13.6	per thousand
Area II:	1.01	,,
Area III:	0.06	,,
Area IV:	0.017	,,
Area V:	0.003	,,

It is seen that the areas in which spraying was continued had incidence figures well above and the other areas incidence figures well below 0.5 per thousand population.

It is not by chance that in the examples of the Philippines and Taiwan we have used the results of detailed epidemiological case investigation for substantiating the significance of the statistical criterion. While we believe that an over-all indication and guidance can be obtained from the incidence rate we deem the thorough investigation of every case

[1] Unpublished report to WHO by P. Yekutiel (1959).

[2] Ch'en, C. T. (1959) *The malaria eradication programme in Taiwan. Annual report for financial year 1959* (mimeographed report of the Taiwan Provincial Malaria Research Institute).

detected to be essential both during the period immediately preceding the cessation of spraying and during the whole time of the consolidation phase. In the former case these investigations should prove the absence of recently contracted indigenous infections, thus substantiating the claim of interrupted transmission.

There are a number of other epidemiological factors that should be considered before discontinuing spraying. Of these we would here mention only two: the entomological situation and a social factor. It is clear that the situation has to be judged differently in areas in which the vector species has been practically eliminated through two or three years of spraying and in areas where this has not occurred. The social factor deserving special attention is that of migration and potential large-scale import of parasites. It has happened in several instances that when spraying was discontinued in an area where malaria incidence had reached a satisfactorily low level and where there was sufficient proof of locally interrupted transmission, transmission was renewed after a short while because of large-scale migration of people between this area and neighbouring districts (in the same country or across the border) where transmission had not yet been interrupted, resulting in a large volume of import of parasites. This social factor has therefore to be studied well before the withdrawal of spraying, and it might often be wiser to continue spraying, in a " satisfactory " district, until large enough areas in the neighbourhood have reached the same status.

Criteria for the stability of the consolidation phase

It will be clear from the foregoing that the situation in a consolidation-phase area cannot be considered satisfactory unless the annual malaria incidence is below at most 0.5 per thousand. Not only is an incidence higher than this often an indication of residual transmission already occurring, but also, from an operational point of view, such numbers of cases cannot be handled efficiently and rapidly enough to prevent the renewal of transmission in the absence of the protection of residual spraying. In the last stages of the attack phase the epidemiological investigation of cases is necessary, as explained above, but the omission of a few cases may be tolerated and the treatment of cases at this stage, though desirable, is not essential. In the consolidation phase both investigation and radical treatment of every case are an integral part of the surveillance operations, as important as, if not more important than, the basic procedure of case detection. If the number of cases to be investigated and treated is too large, the surveillance system will break down.

Unfortunately, some of the factors upsetting a presumed equilibrium may become apparent only after the cessation of spraying. It is therefore not enough to carry out surveillance operations and to calculate incidence rates at the end of the year; data have to be scrutinized continually month by month so that special investigations and measures can be quickly instituted. Obviously an annual incidence of 0.5 per thousand is a permissible level only at the beginning of the consolidation phase, and the result of surveillance should show a steady decrease of the figure towards total eradication within the prescribed time of two or three years.

Adequacy of case detection

We wish to make it quite clear that no reliance can be placed on conclusions derived from incidence rates unless those rates are based on a method of malaria detection that can be considered satisfactory both in quantity and quality; in other words, the claim of a " reasonably intensive search " has to be substantiated. It is remarkable that malariologists working in eradication programmes in all continents have, during the past two years, independently reached a very definite conclusion on the question of *quantity*, and it can be taken as generally agreed that the minimum of slides to be examined in the course of a year should represent a figure in the neighbourhood of 10% of the population concerned. We do not think it necessary to justify this figure on theoretical, epidemiological and statistical grounds, as practical experience all over the world has shown that information derived from smaller numbers of slides per population is deficient and unreliable. It is interesting to see from the annual questionnaires on malaria eradication programmes transmitted by governments to WHO headquarters that from 1958 to 1959 there has been a considerable increase in the number of countries reaching this scale of evaluation operations.

The number of slides taken per population depends, of course, to a large extent on the fever rate of the population concerned, since the majority of blood slides in malaria detection procedures are taken from fever cases. In the past there has been some doubt whether in fact the general fever rate is everywhere high enough to supply the postulated 10% of slides per population per year. The experience accumulated in malaria detection and sur-

veillance operations during the past two years makes it possible now to make a definite statement on this point. In routine reports from such operations, general fever rates range from 3% to 60% per year. In the majority of projects, however, the rate is between 10% and 20%. In more scientifically directed special field studies, such as pilot projects for the evaluation of mass chemotherapy or experimental studies on surveillance, general fever rates are invariably above 20% per year. We wish to point out that these general fever rates are very little influenced by malaria, since in the later stages of the attack phase and in the consolidation phase the percentage of fever-case slides positive for malaria rarely exceeds 1%.

In regard to the *quality* of malaria detection procedures, the first principle to be observed—as in spraying operations—is that of *total coverage*, that is to say, malaria detection activities must reach every locality in the operational area and blood slides as well as general information must be received several times during a year from all localities, at least during the transmission season. With active detection procedures this total coverage can be easily regulated. It is a much more difficult task in areas covered only by passive methods, but it is an essential part of the supervision of passive detection. Once the principle of basic total coverage is assured, it is not necessary—or in fact desirable—that the intensity of blood examination be uniform—i.e., uniformly 10% per year per population over the whole area of the campaign. In some areas it may be quite safe to be content with a smaller number of blood slides per year, while in other areas far more than this average figure is necessary in order to control the situation. It has often been found useful to increase the number of blood slides to be taken—sometimes by occasional mass blood surveys—in "problem" areas or areas with residual transmission, even though these might still be under the cover of insecticide spraying. The examples of Venezuela and Taiwan may be quoted, where in such well-defined areas the blood slide examination rate per year per population ranged between 50% and 900%, i.e., up to 9 blood slides per inhabitant per year.

EPIDEMIOLOGICAL FEATURES OF DISAPPEARING MALARIA

The asymptomatic parasite carrier

What is the proportion of asymptomatic parasitaemias out of all malaria infections in various phases of malaria eradication ? In the later stages of an eradication programme this is a vital question, since symptomless infections may be the main cause of persistent residual malaria foci, being at the same time difficult to detect and to deal with. It is an important question in all stages of malaria eradication since the sampling in all malaria detection and surveillance procedures is based chiefly on the symptom of fever.

A good deal is known about this subject in regard to undisturbed endemic or hyperendemic malaria. This knowledge is derived from a number of intensive longitudinal studies carried out on small groups of people in which repeated blood examinations were frequently (daily to weekly) combined with clinical observation. Such studies were, for instance, undertaken in Puerto Rico (Earle et al., 1939), Portugal (Hill et al., 1943), Sardinia (Pampana & Casini, 1940), Liberia (Miller, 1958) and Nigeria.[1] In these studies the proportion of person/days of parasitaemias with symptoms to parasitaemias without symptoms ranged from 1:5 to 1:16; in other words, 83% to 94% of infections were symptomless at the time of the blood examinations.[2] Under the conditions of high endemicity in these studies this relationship was found for *P. falciparum* infections as well as for *P. vivax* and *P. malariae* infections. It it obvious that the results of these studies cannot and should not be directly applied to the conditions of gradually disappearing malaria in eradication programmes. The facts have, however, a bearing on the situation found in the various phases in malaria eradication.

Information on the quantity and significance of symptomless infections in hypo-endemic malaria, or malaria greatly influenced by control or eradication measures, is as yet very incomplete. Only during the last two or three years have some interesting observations on this subject been made in various parts of the world. In the following, an attempt is made to summarize these, alas, still fragmentary data and to discuss their significance.

In Taiwan[3] mass blood surveys were instituted in 1958 in residual malarious foci and areas in their

[1] Bruce-Chwatt, L. J. (1959) *A longitudinal survey of natural malaria infection in a group of West African adults.* Working paper submitted to the WHO Scientific Group on Malaria Research, Geneva.

[2] With the exception of those in Bruce-Chwatt's paper, these ratios were not calculated in the publications listed. They were calculated by the present author on the basis of the detailed data.

[3] Ch'en (1959) *op. cit.*, and unpublished report to WHO by P. Yekutiel and M. E. Farinaud (1960).

vicinity (Areas I and II, as described on page 674), in addition to or replacing malaria case detection by monthly house-to-house fever surveys. These areas had, up to 1952, been hyperendemic. Total-coverage spraying began in Taiwan in 1953 and by 1957 stable consolidation was reached everywhere (including the formerly hyperendemic areas) except in the relatively small areas here referred to, where— through the combined influence of sociological and entomological factors— a low grade residual transmission continued. In 1958-59 the annual malaria incidence in Area I was 13.6 per thousand and in Area II 1.01 per thousand. The mass blood surveys were introduced with the dual purpose of finding hidden small foci and of detecting and treating all cases of infection in the known foci, thereby helping to bring about interruption of transmission. Both purposes were served admirably. In addition, some insight was gained into the question of the ratio of asymptomatic to symptomatic infections, as is shown by the comparison of the results of a fever survey with those of a subsequent mass blood survey in the same population in Area II (Table 2). Since transmission in this region does not vary between September and October and since the large majority of the cases found were not due to recent transmission, it is permissible to compare the two findings, which would indicate that in this specific situation the proportion of infections with symptoms to all infections was 1 : 11, or, in other words, that about 91% of the infections were symptomless. The practical importance of this finding for the Taiwan programme was proved through the success of eradication measures based on it.

TABLE 2

COMPARISON OF MASS BLOOD SURVEY AND HOUSE-TO-HOUSE FEVER SURVEY IN TAIWAN, AREA II, EASTERN PART

Population	Measure	Slides taken	Positive (cases found)
115 000	One monthly fever survey, September 1958	3 497	5
115 000	One mass blood survey, October 1958	93 201	49

Mastbaum [1] summarizes two years of experience of surveillance in Swaziland after withdrawal of spraying. He states that while one would have expected a waning of acquired immunity or clinical tolerance during the years of control it was a common experience to detect parasitaemias without signs of ill health two to three years after complete interruption of transmission. Accordingly the system of surveillance instituted consisted of monthly house-to-house visits during which blood slides were taken by random sampling in addition to those taken from sick persons.

The WHO Regional Office for South-East Asia is at present conducting experimental field studies on surveillance in India and Ceylon. Amongst other subjects the question of asymptomatic infections is also being investigated in these studies. This is done by checking the results of fever surveillance through mass blood surveys in a sample of villages. It would be premature to present any data, which will be published at the completion of these studies. The following general observations can, however, be recorded now. In one of the districts of these field studies a small epidemic episode of renewed transmission occurred. Almost all the cases were detected through the mass blood surveys and not through fever surveillance and the majority of persons infected did not present any clinical symptoms. In other areas where, on the whole, very few infections had so far been found fever surveillance and mass blood surveys detected approximately the same number of cases.[2]

In the USSR a comprehensive programme for the country-wide elimination of malaria was embarked upon in 1951. By 1958 eradication had been achieved in the majority and in the most populated of its Republics. In the remaining Republics malaria had been reduced to a fraction of its former incidence and complete eradication will probably be achieved within the next two years (Bruce-Chwatt, 1959).

The problem of asymptomatic carriers and their importance in the last phase of malaria eradication has received increasing attention in the USSR during the last three years (Buslaev, 1959; Sergiev, Rashina & Lysenko, 1959; Zdhanov, 1959). In 1958, out of the total of 4839 malaria infections recorded in the USSR, 2388—49.5%—were asymptomatic carriers

[1] Mastbaum, O. (1958) *Some observations with regard to surveillance and malaria eradication in Swaziland.* Working paper No. 17, submitted to the WHO Expert Committee on Malaria, Lisbon.

[2] Unpublished information (1959) from D. K. Viswanathan, G. D. Chetty and G. L. Adan.

TABLE 3
MALARIA CASES IN THE RYUKYU ISLANDS, AUGUST 1957 TO AUGUST 1959

Period	Total population	Malaria cases				Annual malaria incidence per 1000 population
		Total number	Symptomatic	Asymptomatic	Proportion of asymptomatic to total	
Aug.-Dec. 1957	47 411	1 118	944	174	16%	56
1958	51 109	370	321	49	13%	7
Jan.-Aug. 1959	51 109	54	50	4	7%	1.6

detected through mass blood surveys. It would, however, be wrong to draw conclusions from this over-all figure. Scrutiny of the component figures given for the various Republics (Bruce-Chwatt, 1959) reveals that 2070 of these asymptomatic carriers were found in Azerbaidzhan, where they constitute 74% of all cases (2829) detected in 1958. Azerbaidzhan is the only Republic in the USSR where some outbreaks still occurred in 1958 and fairly extensive insecticidal measures were carried out. The over-all annual incidence in Azerbaidzhan was 0.9 per thousand in 1958. In other Republics of the USSR in a more or less advanced phase of consolidation, the figures for asymptomatic carriers amongst cases detected in 1958 ranged from 5.5% to 8.5%. Annual incidence figures for these Republics ranged from 0.05 to 0.01 per thousand. Apart from Azerbaidzhan, a high percentage (59%) of asymptomatic carriers was found in only one of the other Republics—Kazakhstan. Many of these were recent immigrants from China.

On the subject of symptomless carriers among immigrants there is some interesting information from the Netherlands (Kraan, 1957). It is believed that the autochthonous strain of *P. vivax* was eradicated in the Netherlands by 1952. The health authorities have, however, to deal with a certain number of malaria cases every year, the majority of which are imported but some of which are indigenous cases infected with foreign strains of parasites transmitted from these immigrants by the local mosquito, *A. maculipennis atroparvus*. The majority of these *importateurs de germes* come from Indonesia (repatriated Netherlands subjects) and Netherlands New Guinea. During the last few years not only have certain categories of migrants from Indonesia been questioned as to their history of malaria, but also blood samples have been taken from all of them. In 1955, in 91 immigrants from Indonesia thus examined, 7 asymptomatic carriers of malaria parasites were found, and in 1956, 4 out of 180. The majority of these infections were with *P. malariae*. The Netherlands health authorities stress the importance of these asymptomatic carriers as sources for renewed local transmission, and a number of measures are carried out to prevent this occurrence, amongst them the spraying of houses of asymptomatic carriers revealed through the screening blood examination.

In the Ryukyu Islands extensive malaria control measures have been in operation for many years, and in 1957 these were converted into a full eradication programme with total-coverage spraying beginning in August 1957. Some interesting data have been made available (1960) to WHO by Colonel I. H. Marshall [1] in regard to the general incidence of malaria and the number of asymptomatic infections revealed in extensive malaria detection operations since. Blood slides were taken during malaria detection procedures from between 20% and 80% of the population per year. The number of cases, proportion of asymptomatic infections and annual incidence are summarized in Table 3 for the years 1957-59.

It will be noted that as the annual malaria incidence decreases as a result of the spraying operations, the proportion of asymptomatic cases also decreases.

Observations made during a small outbreak of malaria in the maintenance phase of eradication in Sicily (Cefalù & Gulotta, 1959) are of outstanding interest. This outbreak occurred in Palma di

[1] Director, Public Health and Welfare Department, United States Civil Administration, Ryukyu Islands.

Montechiaro in the summer of 1956, producing 77 cases of *P. vivax* malaria. In this formerly highly endemic area, large-scale DDT spraying began at the end of the 1940's and eradication had been reached by 1953. No cases had been found between 1953 and 1956. All 77 cases in this outbreak presented frank clinical symptoms. In the course of the epidemiological investigation of this localized epidemic 3000 blood slides were taken from persons residing in the affected area. The microscopic examination did not reveal a single positive slide. This complete absence of asymptomatic infection may be contrasted with the finding of 87% asymptomatic infections by Pampana & Casini (1940) in Sardinia in 1938-39. The endemicity and epidemiology of malaria in Palma di Montechiaro before DDT spraying must have been very similar to that in Sardinia.

Reviewing the data from the examples given above for various countries and various stages of eradication programmes, the divergence of observed proportions stands out, the percentage of asymptomatic infection ranging from 91 in the data from Taiwan to 0 in the example of Palma di Montechiaro in Sicily. This, in our opinion, does not indicate unreliability of these data or a chance variation which would make it impossible to predict the proportion of asymptomatic infections to be expected in a given programme. On the contrary, the range of proportions shown in these various examples seems to indicate a close relation between this factor and the epidemiological conditions in the region concerned. In areas where malaria was recently hyperendemic and where some residual transmission is still going on, the proportion of asymptomatic infections is comparatively high (as, for instance, in the examples of Taiwan and Azerbaidzhan). In areas where malaria was not highly endemic or where transmission had been interrupted a long time ago (say, more than six or seven years), the percentage of asymptomatic infections is low. This would point to some degree of persistence of the clinical tolerance originally acquired under hyperendemic conditions (a persistence that is helped by the presence of residual transmission even on a low scale) as the chief factor in the occurrence of asymptomatic infections.

The example of the Ryukyu Islands, where the percentage of asymptomatic infection falls *pari passu* with the fall in the annual malaria incidence, and the example of various Republics in the USSR, showing the close positive relation between percentage of asymptomatic infections and annual incidence, support this view. The views of Sergiev [1] are also in complete accordance with this hypothesis:

> " It seems that during malaria eradication, parasite carriers in foci of low endemicity disappear very quickly, almost as fast as the cases of acute malaria. No special investigations of this have been made, however. It is possible that the longer persistence of parasite carriage in foci of high endemicity is connected with residual cases of reinfection."

In countries with a substantial number of immigrants from malarious countries abroad, the proportion of asymptomatic infections might be much higher in these immigrants than that in the local population, as it is determined not by the local epidemiological situation but by the situation in the countries of origin of the immigrants. This point is illustrated by the immigrants from China into the USSR and the immigrants from Indonesia into the Netherlands mentioned above.

While most of the information so far available would thus indicate acquired clinical tolerance (concomitant to but not synonymous with acquired immunity) as the most important factor, other factors cannot be entirely excluded. Among these we may mention inherited clinical tolerance in Africans and the possibility—at least theoretical—of a natural selection of asymptomatic strains of parasites in the process of eradication. Information on these factors is, however, so far very scanty. From a practical point of view the considerable proportion of asymptomatic infections in certain situations and phases of malaria eradication would indicate the need for modifications in detection methods, viz., that in such situations fever surveillance is not enough and mass blood surveys—as, for instance, carried out in Taiwan—are necessary. We would, however, warn that extreme conclusions should not be drawn from this statement. While in certain situations asymptomatic infections may outnumber those accompanied by fever, the percentage of malaria infections found in fever cases will still be larger than that found in the general population. We may illustrate this point with a small example.

Gramiccia [2] carried out a mass blood examination in a group of villages in Iraq. At that time the area concerned was in the attack phase with a considerable

[1] Sergiev, P. G. (1960) *The importance of asymptomatic parasite carriers in malaria eradication* (unpublished working document WHO/Mal/253).

[2] Unpublished report to WHO (1957).

amount of transmission still going on. The population of these villages was 600, and the results of his investigation, in which every person was examined and questioned about fever symptoms, are presented in Table 4.

TABLE 4
RESULTS OF MASS BLOOD EXAMINATION IN A GROUP OF VILLAGES IN IRAQ

Clinical status	Number of persons	Number positive	Percentage positive
No fever	569	51	9
Fever	31	10	32
Total	600	61	10

It is seen that, out of the total of 61 infections revealed, 51 were in persons with no symptoms of fever. In other words, 83.5% of the infections were asymptomatic and would have been missed in a fever survey. On the other hand, the percentage of positive slides from persons with fever was 32 (10 out of 31), while the percentage of positive slides from persons without symptoms was only 9 (51 out of 569). This shows that the examination of blood slides from persons with fever is a good screening method. The final value of fever surveillance depends, however, on the rapidity and thoroughness of epidemiological investigation following the discovery of positive cases. In such investigations blood slides will be taken from all persons in the neighbourhood of the case, and this should, in the majority of situations, reveal most of the asymptomatic infections. Only when the results of routine fever surveillance and the epidemiological investigations connected with it reveal a very large number of asymptomatic infections, and in special situations where there is a suspicion that these asymptomatic infections are the cause of continued residual transmission, would it be advisable to carry out mass blood surveys in selected localities or areas.

Our discussion so far is based on the assumption that it is important to detect, if not all, at least almost all malaria infections in the later stages of an eradication programme. However, the question may well be asked whether asymptomatic infections, many of which have very low parasite and gametocyte densities, constitute a real danger from the point of view of infectivity to mosquitos. Information on this point is so far not conclusive enough to give a definite answer to this question. A large number of studies on infectivity thresholds of gametocyte densities for mosquitos have been carried out in many countries in the past twenty years. The results of these studies are summarized on page 605 of this issue by Sir Gordon Covell. The threshold found in different parts of the world with different species of parasite and different species of anopheline varies between 10 and several hundred gametocytes per mm^3 of blood. There are, however, at least five studies in which the successful infection of mosquitos with very low densities of gametocytes were reported (Young et al., 1948; Muirhead-Thomson, 1954, 1957; Shute & Maryon, 1957, 1959 [1]). In these studies threshold densities as low as 1 gametocyte per mm^3 were reported as well as infectivity to mosquitos of persons in whose blood no malaria parasites could be found by ordinary microscopic examination. The question whether the low percentage of mosquitos infected by such low densities would be sufficient to re-establish transmission under natural (as opposed to laboratory) conditions is, however, still open, and it is hoped that further studies on this subject will elucidate the matter. From a practical point of view we do not believe that this point is of outstanding importance in malaria eradication procedures, since a person found with very few parasites in his blood today might show very much higher densities of parasites and gametocytes in his blood a few days hence, and it would therefore seem advisable to make every effort to detect as many asymptomatic infections as possible.

Other host factors

The factor of asymptomatic parasitaemia is clearly dependent on physiological and biological phenomena in the human host himself (immunity, clinical tolerance, etc.). Other epidemiological phenomena in the phase of disappearing malaria in eradication programmes concerning the human host depend mainly on social habits. One outstanding problem is that of reintroduction of malaria into more or less

[1] Shute, P. G. & Maryon, M. (1959) *A study of the infectivity of patients to mosquitos in the asymptomatic phase of parasitic relapses of induced infections with* P. vivax *(Madagascar strain)* (unpublished working document WHO/Mal/233).

" cleared " areas through interchanges of population. In undisturbed malaria or in partially-controlled malaria, these factors certainly also exist but their influence on the local malaria situation is usually very small in comparison with the influence of local transmission. It is for this reason that these factors were formerly not studied very thoroughly, but they have now become of primary importance in the later stages of malaria eradication. There are many instances of areas in which local transmission was successfully interrupted through several years of spraying, the parasite reservoir dwindled to a very low level and spraying was discontinued, and yet in which considerable local transmission of malaria was resumed, sometimes after only a few months, owing to massive importation of symptomatic and asymptomatic parasite carriers. The sources of these parasites were areas with still active malaria transmission, sometimes bordering on the cleared area but in other instances situated at considerable distances. There are two ways in which parasites are thus imported, one being the temporary or permanent migration of persons from the malarious areas into the cleared area, and the other, not less important, being visits to malarious areas by permanent residents of the cleared area to which they return with an infection acquired in the former area. The most frequent reason for the second phenomenon is seasonal farming or harvesting in sparsely inhabited jungle areas by people having their permanent residence and basic agricultural livelihood in a more densely populated and permanently cultivated area in which malaria has practically been eradicated. The two outstanding examples of such occurrences are Ceylon in 1955-56 and the Philippines in 1958.

The changing age distribution of malaria cases in the later phases of eradication is another factor deserving attention. In undisturbed or only partially controlled malaria the great majority of cases is usually found in children owing to the developing immunity and clinical tolerance in growing persons. This factor operates not only in hyper- or holoendemic areas, where the immunity of the adults is almost complete. In areas where an eradication programme has greatly reduced transmission it is invariably seen that 50%-90% of malaria cases still occurring are in persons over the age of 15. This is true not only in the consolidation phase but, generally speaking, as early as the third or fourth year of the attack phase. The main cause of residual transmission is very often a certain amount of extradomiciliary transmission which may be due to a secondary exophilic vector or to such transmission effected by the main vector outside the sprayed houses. In the consolidation phase, as mentioned above, persons may become infected by visiting distant malarious areas. In all these circumstances adult persons are far more exposed to these risks than children, who, on the whole, will spend more time during the night in their huts and houses than adults and who travel less. Infants in particular constitute the class of person best protected by residual spraying, and they may therefore escape infection while malaria incidence amongst adults is still well marked. An interesting example of this is given by A. Gilroy (personal communication, 1959) for West Bengal, where in a tea estate, for several years under DDT spraying infant parasite rates as revealed by fortnightly blood examination of all infants were consistently zero while a fair number of frank malaria cases were occurring in the adult labour population.

From all the facts listed above it will be clear why infant parasite rates are such an unreliable indicator of the interruption of transmission and why in general the search for residual cases of malaria at the end of the attack phase and during the consolidation phase must be made with the same intensity in the adult population as in the child population.

Entomological factors

One of the chief problems of the epidemiologist in the later phases of malaria eradication is the elucidation of causes of residual transmission. There is no getting away from the fact that there is only one cause of residual transmission: a fair number of mosquitos of a vector species are able to survive long enough for the completion of the extrinsic cycle of the malaria parasite in spite of the insecticide used in the area. The possible causes of this are manifold and the most publicized one—namely, the developing physiological resistance to an insecticide by certain vectors—is by no means the most frequent nor the most important one on a global scale. Among these causes the following entomological ones may be mentioned:

(*a*) the existence of an exophilic secondary vector, not previously recognized;

(*b*) irritability to insecticides and development of behaviouristic avoidance of them by the main vector;

(*c*) a change of biting and resting habits of the anopheline vector, increasing its degree of exophily.

While the occurrence of extradomiciliary transmission depends in the first place on a vector which will bite outside houses and on a sufficient proportion of such anophelines also resting outside houses and thereby avoiding contact with insecticides, it also depends on the human social factor of sleeping outdoors mentioned before.

Another important entomological factor is that of the influence of several years' insecticide spraying on the over-all prevalence of the main vector. In a number of areas and eradication programmes, several years of insecticide spraying have resulted in the complete disappearance of the vectors. In other instances their population was very greatly reduced and not built up again for several years after the cessation of spraying so that the complete elimination of the parasite reservoir in the consolidation phase —i.e., complete eradication of malaria—was achieved in the absence or virtual absence of anopheline vectors. In other eradication programmes with other anopheline vectors and different ecological conditions interruption of transmission was achieved without a great reduction of the population of the malaria vector. It should be clear that accurate observations on this entomological situation are important from a practical point of view during the consolidation phase. In the complete absence of anopheline vectors, or when their numbers remain consistently at a very low level, it may be permissible to space surveillance visits at considerably longer intervals than when this is not the case.

ENTOMOLOGICAL METHODS FOR EPIDEMIOLOGICAL EVALUATION

It is obvious that the entomological problems just mentioned can only be studied and tackled by entomological methods. It is, however, considered that the use of entomological methods in malaria eradication should *not* be restricted to these specific problems. On the contrary, we believe that entomological methods can greatly contribute to the over-all epidemiological assessment in all stages of an eradication programme. In our presentation of methods of assessment and criteria for cessation of spraying and stability of consolidation, we have limited our discussion to parasitological methods of assessment. It is by no means always easy to reach a reliable judgement of the situation in a programme by these methods alone, and entomological methods should be integrated into the total process of epidemiological evaluation. For instance, the initial expected fall in malaria prevalence and incidence in the first two years of spraying is not easily assessed by parasitological methods owing to the impossibility of building up a complete system of malaria detection at so early a stage. Comprehensive entomological data, showing not only the absence or greatly reduced number of anopheline vectors in sprayed houses but also the effect of the spraying on the age distribution (survival rate) of the vector populations and on their indoor and outdoor man-biting rates, might give an earlier and even more reliable indication of interrupted transmission than parasitological assessment alone. If it is generally agreed that the old-established methods of parasitological assessment have to be greatly modified so as to suit them to the purposes of malaria eradication, the same is true for entomological methods and for very similar reasons. In the days of malaria control comparatively simple and crude entomological methods were sufficient. With large numbers of mosquitos present, the dissection of mosquitos for salivary gland and gut infections was a useful method to define situations or changes in situations. So were the crude methods of measuring mosquito densities by morning catches in houses or stables. Under the conditions of malaria eradication these methods no longer produce such useful results and it is necessary to improve and develop techniques, such as the determination of survival rates of mosquitos in houses by the use of outlet traps, the determination of age of the mosquitos by modern techniques of dissection of ovaries, the determination of 24-hour man-biting rates, and others.[1] A full account of these entomological methods and a discussion thereof is beyond the scope of the present article and we have mentioned this subject mainly in order to stress that entomological methods must be used in conjunction with others for the over-all epidemiological assessment in malaria eradication programmes.

[1] A detailed list of these techniques and their use in malaria eradication is given in: Garrett-Jones, C. (1959) *The place of entomology in malaria eradication* (unpublished working document WHO/Mal/231).

RÉSUMÉ

L'épidémiologie du paludisme aux stades avancés de l'éradication présente des caractères qui n'ont été que récemment mis en lumière. Par stades avancés, on entend la fin de la période d'attaque, à partir de sa troisième année, et toute la durée de la phase de consolidation. Pour évaluer les résultats des campagnes parvenues à ce stade, il a été nécessaire de modifier les méthodes paludimétriques classiques et d'introduire de nouvelles techniques.

La méthode d'enquête paludimétrique qui n'utilise que l'indice splénométrique et l'indice plasmodique ne donne plus une image exacte de la situation, passées les premières années de pulvérisations. Il faut dès lors rechercher les cas de paludisme parmi la population en effectuant des examens microscopiques du sang de toute personne présentant de la fièvre. L'intensité du paludisme dans une région s'exprimera par le nombre de cas trouvés au cours d'une année parmi la population exposée, ce qui représente la fréquence annuelle des nouveaux cas.

Il est nécessaire de disposer de critères épidémiologiques quantitatifs, pour déterminer le moment où les pulvérisations peuvent être interrompues et pour évaluer la stabilité de la phase de consolidation. On propose qu'une fréquence annuelle des cas nouveaux de 0,5 pour 1000 habitants soit considérée comme le taux limite supérieur, en deçà duquel il est justifié de supprimer les pulvérisations. Pour être valable, ce critère doit avoir été établi selon des règles précises. C'est ainsi que le repérage des cas doit atteindre *toutes* les localités de la région considérée. Il sera procédé à un nombre minimum annuel de prélèvements de sang et d'examens microscopiques, évalué à 10% du chiffre de la population.

Pour justifier l'arrêt des pulvérisations, il faut faire la preuve de l'absence de cas d'infection autochtone — ou celle d'un nombre très restreint de tels cas dans un périmètre limité.

Le rôle des porteurs asymptomatiques de parasites est discuté par l'auteur. Dans les régions où le paludisme évolue sans obstacle — ou dans lesquelles la lutte n'est que partielle — les porteurs asymptomatiques constituent jusqu'à 50% des cas. Leur nombre décroît à mesure qu'est plus lointaine dans le temps la brusque réduction initiale de la transmission provoquée par les pulvérisations.

Le changement de la répartition des cas selon l'âge dans les phases ultimes de l'éradication, et la réinfection sous l'effet de faibles mouvements de population — plus importants que durant la phase initiale — sont également discutés.

Il y a lieu d'appliquer les méthodes entomologiques parallèlement aux méthodes parasitologiques, afin d'évaluer la situation épidémiologique avec le plus de précision possible.

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