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Lessons learned from applied field research activities in Africa during the malaria eradication era

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The Malaria Conference in Equatorial Africa, convened by the World Health Organization in 1950 in Kampala, Uganda, was a milestone in the history of modern malaria control activities on the continent of Africa. It presented and assessed the available international information on epidemiological aspects of this disease and attempted to coordinate the various methods of research and control of malaria. Its two main recommendations were that malaria should be controlled by all available methods, irrespective of the degree of endemicity of the disease, and that the benefits that malaria control might bring to the indigenous population should be evaluated.

The first period of field research and pilot control projects in Africa was between 1950 and 1964. A large number of studies in several African countries showed that the use of residual insecticides such as DDT and HCH might decrease, at times considerably, the amount of malaria transmission, but interruption of transmission could not be achieved, except in two relatively small projects in the forest areas of Cameroon and Liberia. During the second period, from 1965 to 1974, the difficulties of malaria eradication and control in Africa became more evident because of the development of resistance of Anopheles gambiae *to DDT, HCH, and dieldrin; moreover administrative, logistic, and financial problems had emerged. It became clear that the prospects for malaria control (let alone those for eradication) were related to the availability of a network of basic health services. A number of "pre-eradication" programmes were set up in order to develop better methods of malaria control and to improve the rural health infrastructures. Much field research on the chemotherapy of malaria was carried out and the value of collective or selective administration of antimalarial drugs was fully recognized, although it became obvious that this could not play an important part in the decrease of transmission of malaria in Africa.*

The role of research as one of the ways of solving the technical problems of malaria control in tropical Africa was stressed from the early days of the global malaria eradication programme; the past ten years have seen an immense expansion of this activity.

ENVIRONMENTAL BACKGROUND

The definition of what constitutes the "eradication era" is controversial. Some believe that it dates from 1940, when the last evidence of *Anopheles gambiae* was found in Brazil, after the successful eradication of this vector, brought in 1930 into north-east Brazil from West Africa. Others consider it began in 1948, when the concept of eradication was mooted at the Fourth International Congresses of Tropical Medicine and Malaria (*1*), while still others prefer to choose the date of 1955 when the objective of malaria eradication was adopted by the Eighth World Health Assembly.

When it comes to the continent of Africa, where the aim of malaria eradication has never been formally recommended (*2*), it may be convenient to choose as the first milestone the year 1950. This was the date of the first Malaria Conference in Equatorial Africa held in Kampala (Uganda), when a major effort was made to coordinate the information available from various national sources on the distribution, epidemiological, and economic aspects of malaria and when the results of research and control of malaria were thoroughly discussed by an international group of experts. This was also the first attempt at planning the future continental activity under the overall guidance of the World Health Organization (*3*).

The introductory section of the report of the Kampala Conference outlines many aspects of malaria in

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tropical Africa and it may be appropriate to summarize some parts of it, as a preamble, if only to stress the environmental background to a situation that has not changed much during the past 30 years.

The distribution and frequency of malaria in tropical Africa depend more or less directly on the climate and, among the various climatic factors involved, two surpass the others in importance: rainfall and temperature. Thus, the duration of the transmission period of malaria, as well as its intensity, are closely related to the amount of rainfall and its distribution throughout the year. The mean temperature, varying from region to region and decreasing as the altitude increases, also affects the limits of the transmission period, or at least modifies the intensity of transmission. Nevertheless, since in the greater part of tropical Africa the temperature is sufficiently high to enable the vectors and parasites to develop throughout the year, or at least during a long season, the rainfall is by far the most important factor.

In a general way, transmission of malaria diminishes progressively from the equator as latitude increases, passing from the savanna zones to the desert areas. Many factors may intervene to make transmission possible during the long periods of the dry season. Among these factors are the existence of marshes and watercourses that provide breeding-places throughout the year, and the existence of depressions in the ground or man-made excavations containing water during the dry period. Thus, despite unfavourable climatic conditions during the dry season, transmission may be sufficiently long and intense to maintain malaria in a perennial hyperendemic state.

In a general way also, the transmission of malaria takes place throughout the year along the African coasts, whether in the west or in the east, up to a more or less considerable distance inland, as well as in a large part of the continent situated between the latitudes of 15° north and south, wherever the altitude is below about 1400 m. These are areas where hyperendemicity is the rule. However, as regards the west coast the transmission period is shortened, even in regions very near the sea, southwards from latitude 8° south, because of the cold Benguela current, which has the effect of markedly reducing the length of the rainy season.

As the altitude increases, the transmission period becomes shorter. At 1400 m the incidence of malaria is still high, but, around 1800 m, the epidemic type becomes the rule. The temperature at altitudes between 1400 m and 1800 m may already be sufficiently low to arrest completely or diminish transmission during a more or less long period of the year.

However, the limiting altitude at which malaria ceases cannot be fixed. For example, in Kenya, malaria of the epidemic type is still prevalent towards 2000 m and does not disappear until 2700 m. Transmission throughout the year is seen in the following regions: the West African coastal areas, from about latitude 8° south; the southern part of equatorial Africa and the Congo basin, the central basin, and the southwestern part of Angola; in Uganda, Kenya, and the United Republic of Tanzania, in those areas where the altitude is below about 1400 m; in Zambia and the northern part of Mozambique, at altitudes below about 1000 m and in the valleys of the large rivers in the latter territory; along the whole of the east coast of the continent up to Natal; in the low veld of the Transvaal and in the bush veld areas of Swaziland; in certain parts of the coastal zone of Mauritius; and also in certain parts of the east coast of Madagascar.

The endemicity is intense in the greater part of the western zone of the continent, particularly in Benin, Ghana, Guinea, the eastern part of Guinea-Bissau, the Ivory Coast, and northern Nigeria; in the greater part of East Africa in the central and eastern parts of Angola; in some parts of the west coast of Madagascar and in Mauritius at altitudes below 300 m; from the Transvaal to Swaziland, wherever the altitude is between 300 and 800 m, and in Natal; in the northern part of south-west Africa and in the Okavango swamps in Botswana; and in the coastal zones of south-west Mauritius.

The endemicity is less intense wherever the altitude is greater than 1400 m; in the southern part of Angola and in the highlands of Angola and Mozambique, above 1500 m; in the higher parts of the middle veld, in Swaziland and in the Transvaal above 1000 m; in the higher parts of Madagascar and in Mauritius, above 300 m but below 700 m.

The endemicity is slight, or moderate, in the central part of Kenya at altitudes above 2000 m, in the high region of south-east Uganda, in the high veld in Swaziland, in those parts of Angola situated at about 1800 m altitude, and in the Transvaal between about 1000 and 1500 m.

Other parts of the comprehensive report of the Kampala Conference described the main aspects of parasitology of malaria, its main vectors and their bionomics, the immune response of the population, the economic importance of the disease, and the types of malaria control applicable in various areas.

In the course of a heated discussion on the relation between high endemicity of malaria and subsequent collective immunity, two opposing views were expressed.

According to one view, "hyperendemicity" (later classified as holoendemicity) is a state demanding for its production a high intensity of transmission and resulting in a high degree of tolerance to the effects of reinfection. This tolerance is accompanied by a capacity to contend rapidly and effectively with the

parasites. In the presence of this intensity of infection, infants may suffer severe attacks of malaria and a proportion of them may die in the absence of treatment. Late in the second year of life, they are usually out of danger and from then on there is no increase in the parasite rate or parasite density.

The other school of thought maintained that malaria occurs in all degrees of endemicity from sporadic infection to perennial and frequent superinfection. High endemicity results in the development of immunity; the degree of such immunity varies with the amount of previous infection.

Before the attainment of "resistance", individuals suffer from the disease and some of them die. The acquisition of resistance by adults reflects the frequency of infection suffered by younger groups and does not represent the attainment of wellbeing by the population as a whole. There is considerable evidence of definite damage inflicted on the community.

It was agreed that the amount of information on the immune response and on the economic importance of malaria in Africa was small. This was the main reason for the lack of a consensus with regard to the appraisal of the effect of this most prevalent African disease on the distribution of population, on population movements, on demographic trends, on agriculture, industry, transportation, education, and social welfare.

Nevertheless, there was a growing amount of evidence that throughout most of the African continent malaria plays a very important part in the reproductive wastage of the indigenous population.

THE FIRST PERIOD (1950–64)

The Kampala Conference stimulated a stream of relevant studies in Africa and in many countries of other continents. The epidemiological concept of the interruption of malaria transmission by insecticide spraying seemed to be simple. After taking her blood meal, the female anopheline mosquito generally rests on a nearby indoor surface for several hours while the blood is digested and the batch of eggs matures. The female mosquito feeds every 2–3 days and the malaria parasite (*Plasmodium falciparum*), after being ingested with the blood, requires at least 10–12 days for its full development to an infective stage. Spraying all inside wall surfaces of human dwellings and other domestic shelters with a long-lasting insecticide like DDT would therefore create conditions in which a substantial proportion of anopheles would be killed before they could transmit the infection. The quantitative analysis of malaria showed that, while density changes in a vector population have an *arithmetic* effect, changes in the longevity of such a population have a *geometric* effect on the transmission potential. A number of field trials aimed at the eradication of malaria in a defined area took place and many were reported at the Second African Malaria Conference held in Lagos in 1955. Their early results were often controversial.

Field trials conducted in Uganda, in Sierra Leone and in Zaire (then Belgian Congo) have confirmed the very high degree of initial toxicity of HCH to adult mosquitos (*A. gambiae*, *A. funestus*, and *A. moucheti*) and its value when used as a wettable powder. In one four-year field experiment in a rural area of Zaire, the results indicated that HCH wettable powder applied at six-monthly intervals reduced malaria (mostly *P. falciparum*) parasite rates in children by about 66%, whereas in areas treated with DDT, both solution and wettable powder, there was little, if any, significant change in parasite rates. In Sierra Leone and in Zaire, however, although it reduced the vectors *A. gambiae* and *A. moucheti* very strikingly, the spraying had little influence on malaria parasite rates. Smaller field experiments conducted in Nigeria and the United Republic of Tanzania produced results that seemed to indicate that, in African mud huts, HCH wettable powder was not only more toxic against *A. gambiae* than DDT at equivalent dosages, but that DDT, in the doses used, irritated and repelled this mosquito before it had acquired a lethal dose, to such an extent that DDT treatment has been considered of little value against this type of mosquito (*4*).

Excellent results were obtained in 1949–53 in Ilaro, a small, forested area in south-western Nigeria, where HCH residual spraying seems to have reduced malaria transmission to a very low level. However, a much larger project in north-western Nigeria (1953–60) was less encouraging, since a substantial decrease in malaria was recorded only in the central portion of the vast area, inhabited by 125 000 people (*5*).

As early as 1955, *A. gambiae* in northern Nigeria was reported to be resistant to dieldrin and partly so to HCH, but it remained susceptible to DDT in most parts of Africa until 1968 when a high level of resistance was reported from Upper Volta. In 1972, a trial was carried out in Togo and no mortality of mosquitos was observed with standard exposure to DDT, nor was there any reduction of man-biting or house-resting. Similar results were obtained in Senegal with DDT spraying.

All this must have influenced the WHO Expert Committee on Malaria, which in its sixth report (*6*) made the following statement:

> "In tropical Africa . . . it seems premature to plan in terms of continent-wide eradication. The problem of finding an effective and economical method of eradicating malaria in tropical Africa

has not yet been solved. Pilot projects are being carried out and these require increased emphasis and assistance in order that a solution may be obtained as quickly as possible."

What were these field research projects, often described as malaria control pilot projects, carried out by the various African countries but often with advice and assistance from WHO? They included the field trials carried out in Benin, Cameroon, Kenya, Liberia, Nigeria, Senegal, Togo, United Republic of Tanzania, and Upper Volta. Most of these projects were based on the use of residual insecticides at different dosage schedules. While all of them brought about a decrease in the amount of malaria, in no case was there an early interruption of transmission, a failure due partly to the development of dieldrin or HCH resistance in *A. gambiae* and partly to other factors. Some projects were carried out in small areas and did not produce clear-cut results. Thus, in Benin and Togo, with the relatively small size of the areas and extensive population movement, interruption of transmission could not have been achieved. In the savanna areas of northern Cameroon, northern Nigeria, Senegal, and Upper Volta, there was no evidence of interruption of transmission, although malaria prevalence was greatly reduced in the central part of the area. Two pilot projects, in Liberia and southern Cameroon, both in forest areas, reported that the total spray coverage resulted in the interruption of malaria transmission. In the western highlands of Uganda, in an area of hyperendemicity, where residual spraying at three 4-monthly cycles was associated with single-dose mass distribution of combined chloroquine and pyrimethamine, interruption of malaria transmission was also reported.

The Western Sokoto Malaria Control Pilot Project (*5*) in northern Nigeria, and the Taveta-Pare Malaria Scheme (*7*) carried out in the adjoining zones of the United Republic of Tanzania and Kenya, were probably the most important residual insecticide spraying field projects in holoendemic areas of Africa. The latter study covering the years 1954–59 succeeded in greatly decreasing the amount of transmission of malaria. There was a marked decline in infant mortality and a fall in the crude death rate of the population protected.

While most of the difficulties were due to the behaviour pattern of the mosquitos or to the early development of physiological resistance, it was felt at that time that these failures were due to the small scale of operations and that, if the borders were extended sufficiently, the reintroduction of vectors or parasites from outside the protected zone would be prevented. Some believed that the time-scale was too short, and that the situation would be remedied if the spraying was extended over a longer period: usually there were operational difficulties, so that many houses remained unsprayed or inadequately sprayed.

Insecticide resistance was not felt to be a major threat to malaria eradication. However, the appearance of dieldrin resistance in *A. gambiae* in northern Nigeria, reported at the Second Conference on Malaria in Africa, was a major event that shook confidence in the programme. Some consolation was provided by the success in eradicating *A. funestus*. This vector of tropical Africa is highly anthropophilic. It seeks out man, even in the presence of alternative hosts, but it also spends a large part of each gonotrophic cycle resting in houses. It is not easy to locate the breeding sites of *A. funestus* and, on occasions, one fails to find the larvae completely. The extreme endophily is matched by its susceptibility to house-spraying. In the malaria eradication campaign in Mauritius, where *A. funestus* was the main vector, adults and larvae disappeared almost immediately and the species has never been found there since. Elsewhere in West and East Africa, wherever comprehensive house-spraying projects were initiated, the first result was always the disappearance of *A. funestus*. In the Taveta-Pare Scheme in Kenya this vector species was not detected again until three years after the last round of spraying, that is, after an absence of seven years. In the surroundings of Lake Bunyoni in Uganda, at an altitude of 1900 m, two spraying rounds with DDT led to the prompt elimination of the vector. Eight years later it was apparently still absent from the district (*8*).

The Technical Meeting on Malaria Eradication in Africa held in Brazzaville in November 1959 recognized "the formidable financial, administrative and technical difficulties which exist and which may be expected to continue". It considered, however, that "if the administrative and financial difficulties could be overcome, malaria eradication should be technically feasible in the African region".

In the early 1960s the general consensus among experts on the epidemiological features of malaria in Africa south of the Sahara was as follows (*9*):

> "The most striking feature of malaria in tropical Africa is its high endemicity with hardly any seasonal or annual changes. The climatic conditions favour an intensive transmission of *Plasmodium falciparum* — the prevailing malaria parasite — through mosquito vectors of which the notorious and ubiquitous *Anopheles gambiae* is the most important because of its wide distribution, breeding habits, large numbers and preference for human blood. The ensuing degree of almost perennial transmission is so high that in an unprotected African community few if any members escape the infection. The individual is infected at an early stage and throughout his life

will be subjected to repeated infections. Many children die, some directly from malaria, others from a combination of malaria and other diseases. It is well known that malaria interferes with the normal development of many African children; lower birthweights are commoner in those newborn whose mothers' placentas were infected, and the disease causes anaemia, enlargement of the spleen and liver, and contributes to nutritional deficiencies.

"There is ample proof that malaria causes high mortality and that in other continents the institution of control schemes or malaria eradication programmes has caused dramatic improvements in public health and decreases in mortality. The indirect effects of this disease on the morbidity and mortality rate, and thus on the economic efficiency of the community, are most difficult to assess, but must be enormous. Besides taking heavy toll of life and causing intense human suffering, the disease is responsible for lowering the physical standards of millions and decreasing their productivity. In many countries malaria is one of the most important factors retarding economic development."

THE SECOND PERIOD (1965–74)

By 1965, it had been estimated that out of some 362 million population in endemic malarious areas where eradication programmes had *not* been put into action, about 190 million were in WHO's African Region. While in South Africa, Southern Rhodesia (now Zimbabwe), and Swaziland much progress in malaria control had been reported, the islands of Mauritius, Reunion, and Zanzibar had WHO-assisted malaria eradication programmes, but only the first two had obvious chances of success.

It became clear that the prospects of malaria eradication in Africa were related to the availability of basic health services. The concept of pre-eradication programmes aimed at the parallel development of such services, together with preparation for an early malaria eradication programme, was enunciated as early as 1961 and soon "pre-eradication programmes" were organized in 17 countries on the African continent; these have consisted of action to develop simultaneously both the malaria service and the rural health infrastructure.

However, correlated development of the anti-malaria and general health services proved to be difficult because it takes far longer for the general administrative and health services to reach a level that would enable the country to undertake a malaria eradication programme than it does for the country to initiate a degree of malaria control.

By 1967, pre-eradication programmes covered a population of some 100 million in the African Region of WHO. It was not possible to give practical effect to the concomitant development of general health services and the malaria service and subsequently propositions were submitted to the governments of the Region for conversion of the pre-eradication programmes into the development of basic health services. Most of the countries accepted these proposals and only a few retained a malaria service as part of the general health services. As a result, effective antimalaria activities gradually became limited in quantity and quality.

The problem of malaria eradication in developing countries — and particularly the African continent — has been given much attention in reports of the WHO Expert Committee on Malaria. The eighth and ninth reports endorsed the concept of pre-eradication programmes, outlined the needs for their implementation and approved their planning.

Events took a similar course in African countries situated in the Eastern Mediterranean Region of WHO. In the Sudan, from 1948 the spraying of houses with residual DDT was introduced and continued, but malaria remained an ever-present threat to people in rural areas. Mosquito control activity was carried out by the general health services of the country. From 1956 until 1970 antimalaria activities were restricted to a pilot project to demonstrate the feasibility of interrupting malaria transmission, followed by a pre-eradication malaria survey and, later, by a pre-eradication programme. However, a countrywide malaria eradication programme could not be undertaken with prospects of success. The reasons were clear: the feasibility of interrupting transmission had not been demonstrated in all areas of the Sudan; basic health services were not sufficiently developed to support a malaria eradication programme; and the Sudan is surrounded by a number of countries in which malaria was endemic and in most of which no malaria eradication programme was in progress. Thus the importation of the infection would continue.

In Ethiopia, the malaria service maintained its autonomy within the Ministry of Health and implemented a long-term antimalaria programme. The meagre existing health structure would take many years to become effective, and the internal political and administrative problems have greatly affected the malaria control activities (*10*).

The Third African Malaria Conference, held in Yaoundé in 1962, recommended that the peripheral health units might carry out antimalaria work in addition to their basic tasks. However, it was soon realized that the main contribution of the peripheral network of health units in Africa was in the field of

clinical or microscopic diagnosis of malaria, in the treatment of individual cases, and (on a limited scale) in the chemoprophylaxis of vulnerable population groups.

Nevertheless, the Expert Committee on Malaria stated in its thirteenth report (*9*) that:

> "Antimalaria activities should be developed as part of the general health services and conducted in such a manner as to lead ultimately to the development of malaria eradication programmes. The activities of the antimalaria and general health services are mutually beneficial: antimalaria work provides an incentive and a stimulus for the development of the general health services and for eventual malaria eradication, besides being a preparation for both and for the later development of other disease-specific campaigns. At the same time the health services provide support for all types of antimalaria activity."

The main conclusions of this report were:

"1. There is no doubt that malaria is a most important communicable disease in Africa and that its ultimate eradication from the continent is desirable for the benefit and well-being of its peoples, and also to lessen the hazard of this disease to other countries by the elimination of the vast reservoirs of malaria infection.

"2. The approach to malaria eradication in Africa will have to vary from country to country depending on the resources of the country, the status of health services and the local epidemiological factors of malaria.

"3. Operational research projects should be established with the assistance of international agencies to study and try out ways and means of interrupting the transmission of malaria, particularly in African savanna areas. Appropriate laboratory research should also be pursued.

"4. The pre-eradication programme is a first step to malaria eradication. The concept is sound, even though its implementation has been slow and may have to be modified according to circumstances.

"5. Antimalaria activities should be intensified and expanded and made an integral part of the national health services at all levels. This may require a re-organization of national health services with the purpose of making the existing facilities available for supporting antimalaria activities."

In 1969, the report on the re-examination of the global strategy of malaria eradication, presented by the Director-General to the Twenty-second World Health Assembly (*2*), assessed realistically all the setbacks to the global programme and considered its future strategy in terms of workable methods and all the available resources. It pointed out that in the African Region of WHO little progress had been made, although pilot projects and field research activities had been of value (*10*). Among technical difficulties, resistance of mosquitos to insecticides, excito-repellency, exophily and exophagy of vectors, and resistance of plasmodia to drugs, were the most important. The increased tolerance of *P. falciparum* to chloroquine, first observed in 1960 in South America, was soon reported from south-eastern Asia.

The report concluded that no single or combined practicable technical method of interruption of transmission in tropical Africa was available. It also added that, even where the technical feasibility of eradication had been proved, lack of resources had prevented the implementation of eradication programmes in tropical Africa. Moreover, it stressed that administrative and financial factors, together with those related to human behaviour (such as migration, housing conditions, etc.) had an adverse effect. The report emphasized that where the feasibility of interruption of malaria transmission had not been demonstrated (as in the savanna areas of tropical Africa) research should be pursued, with the objective of evolving new methods of control (*11*). Simpler methods of breaking the malaria transmission cycle needed to be found, through intensive research in vector and parasite biology, insecticides, chemotherapy, and immunology. However, it was considered unrealistic to expect quick results or any early major breakthrough from such studies to meet the immediate needs of the global programme.

A reduction in the incidence of the disease may be obtained by various methods—for example, by a malaria control programme concentrating on areas of high endemicity or through routine health services. The simplest approach is by the provision of antimalarial drugs to the population affected. In such situations every effort must be made to develop the basic health service which will ultimately provide the necessary means for an eradication programme and later ensure the maintenance of the results obtained.

In 1972, a WHO Interregional Conference on malaria control in countries where time-limited eradication had proved to be impracticable took place in Brazzaville (*12*). By that time, out of the total population of at least 250 million in the African Region of WHO, some 230 million were living in originally malarious areas. Only 4.4 million people were in parts of the continent where eradication was claimed, while nearly 20 million were probably protected by some local measures, chiefly in urban zones. In Ethiopia and the Sudan,[a] with a total population of 42 million, over 10 million were in areas without protection from malaria.

[a] These were both in the Eastern Mediterranean Region of WHO at that time, but Ethiopia was transferred to the African Region in 1975.

The comprehensive report of the Conference must be read in its entirety to appreciate its scope. It provided much new information on the epidemiology of malaria in tropical Africa, thus adding to the existing knowledge of its parasitology, as outlined in 1969 in the report of a WHO Scientific Group (*13*). It reported on the results of previous antimalaria projects, confirming that generally none of the major ones had succeeded in interrupting transmission of malaria although the amount of control was substantial. The report stated that resistance of *A. gambiae* to residual insecticides was the main technical problem, together with the growing evidence of DDT behaviouristic (excito-repellent) resistance. Any large-scale use of alternative, more expensive new insecticides, such as organophosphorus compounds or carbamates, was not possible because of financial implications.

The opinion was expressed that some methods of source-reduction might have been neglected or forgotten. Such methods required greater participation of the community. While it was admitted that a good degree of malaria control could be achieved by chemoprophylaxis or chemotherapy in small, highly organized groups under supervision, it was noted that such a degree of malaria control had never been attained in ordinary communities in tropical areas because of practical difficulties. On the other hand, association of residual spraying with chemotherapy may be the only way of gradually eliminating malaria from some tropical areas (*12*).

The role of research as the main way of solving technical problems of malaria control in tropical Africa has been recognized from the early years of the global programme. An outline of the principal subjects for both basic and applied studies was given in the report of the WHO Interregional Conference in Brazzaville (*12*), but a more detailed summary of the results obtained during the first ten years of the eradication era had been presented earlier (*14*).

A number of points touched upon in the present review of field research activities during the period 1950–70 have been mentioned in the introduction to the recent WHO study on epidemiology and control of malaria in the Sudan savanna of West Africa (*15*). This outstanding field project carried out during the period 1969–76 provided us with a wealth of scientific evidence concerning the characteristics of African holoendemic malaria. It stressed the extraordinary intensity of transmission of infection in that part of the world; it quantified the malaria inoculation rate as being some 100 times greater than the threshold value needed to maintain endemicity; it elucidated the role of outdoor biting activity of the *A. gambiae* complex of the vector species; it demonstrated the demographic effect of malaria on the community; it explained the impact of infection on the immune response. It also tested the new mathematical model suitable for simulation of various control measures. However, when it comes to results of present methods of malaria control, the Garki project merely confirmed the conclusions of most of the previous malaria eradication pilot projects. The residual indoor spraying of an apparently effective insecticide might have reduced the vectorial capacity of transmission by some 90%, but the prevalence of *P. falciparum* had decreased only by a quarter of the original value, although the operations were well conducted. The combination of periodic mass drug administration with residual spraying might have achieved a much higher degree of control if carried out in ideal conditions; however, in conditions of ordinary life in a rural area of tropical Africa with an undisturbed mobility of the population the random coverage of the community by mass drug administration cannot produce more than a partial effect. An alternative, namely selective chemotherapy of some groups of the population, however beneficial to the community, would have only a small effect on the amount of transmission, and presents less risk in selecting drug resistant strains of *P. falciparum*.

OVERVIEW OF FIELD RESEARCH ON CHEMOTHERAPY OF MALARIA IN AFRICA, 1950–75

Most antimalarial drugs in general use by 1950–60 were the fruits of the intensive investigations carried out half a century ago. Of some 20 000 synthetic compounds submitted for final selection, only a few gained lasting importance; these are amodiaquine, chloroquine, primaquine, proguanil, and pyrimethamine. Of these, no single drug is equally effective against all species, strains, and developmental stages of malaria parasites. Moreover, the dosage of some drugs was based on experimental data from a limited number of subjects, and the relationship between the therapeutic response and the amount of the active compound in biological fluids was not fully known. Studies on the comparative therapeutic values of single doses of mepacrine, proguanil, pyrimethamine, chloroquine, and amodiaquine were carried out during the 1950s, mainly in West Africa, on groups of indigenous inhabitants suffering from naturally transmitted malaria, the efficacy of the treatment in eliminating infections was assessed and single-dose administration was recommended for outpatient clinics. All these drugs eliminated the parasites from peripheral blood in most subjects in two to three days, with an average clearance time of about two days, but the results achieved with 4-aminoquinolines appeared to be the best and the most consistent.

Trials aimed at the protection of whole village

populations were carried out with success in East Africa and West Africa; a malaria epidemic was prevented by chemoprophylaxis in a highland agricultural estate in Kenya. A malaria control programme designed to protect the entire child population in a large central area by chemoprophylaxis started in Madagascar in 1949 and, by 1955, the distribution centres were treating a total of 760 000 children. While various antimalarials were used at the beginning, chloroquine was the mainstay of this campaign for most of the 16 years of its duration. Similar projects based on a network of medical assistants or voluntary collaborators were launched in the 1970s in Cameroon, Senegal, and Zambia. Countrywide schemes aimed at regular chemoprophylaxis of young children and expectant mothers and at treatment of febrile patients by community primary health workers have recently been initiated in the United Republic of Tanzania and in Mozambique.

During the development of the concept of malaria eradication, the role of drugs was not fully appreciated; its importance was recognized in the 1960s, even though some shortcomings of all available plasmodicidal compounds became increasingly obvious. There is a difference between the approach of the clinician dealing with an individual case of malaria and the malariologist facing a sick community. Working in highly malarious countries, usually with undeveloped public health services, the latter is unable to achieve his objective unless he is supplied with a drug having longer activity than any now available. The often expressed wish for an "ideal antimalarial" combining the virtues of causal prophylaxis, suppression, rapid and complete curative action, sporontocidal effect, and inability to create resistance, together with low toxicity, prolonged action, palatability, and (last but not least) low cost, is not likely to be rapidly fulfilled.

A WHO Scientific Group (*16*), discussing in 1967 the shortcomings in the chemotherapy of malaria, concluded that there is an urgent need for at least two new compounds with the following characteristics: (1) a potent and safe schizontocidal drug that would maintain its effect for 3–6 months after a single dose; (2) a good and safe antirelapse drug capable of effecting a radical cure of *P. vivax* and *P. malariae* infections when given as a single dose or at most in a 3-day treatment. It has often been stated that a drug with a long-acting effect would be of great value in African antimalaria programmes, especially if given in one single dose, as this would permit a less frequent administration. Two approaches to a long-acting antimalarial were attempted: (i) to prolong the effect of already existing compounds, and (ii) to search for new compounds that, after having been fixed by the tissues, would then be slowly released.

The antimalarial action of a long-acting injectable cycloguanil, dihydrotriazine pamoate, developed in the USA in 1963, was assessed in field trials in several countries, including Gambia and the United Republic of Tanzania. In a single injection at the dosage of 5–10 mg per kg body weight, this compound gave protection against *P. vivax* infections for 5–24 months; between 4 and 12 months' protection was obtained against mosquito-induced infections with strains of *P. falciparum* susceptible to proguanil and pyrimethamine, but strains resistant to antifolic drugs did not respond to the cycloguanil compound.

Various drug combinations have been investigated in the past in Africa and the mixtures of 4-aminoquinolines and pyrimethamine or chlorproguanil have been used. Mixtures of 4-aminoquinolines and 8-aminoquinolines were assessed in a field trial carried out in an endemic area in the United Republic of Tanzania; the combination of the two compounds decreased the malariometric indices to a very low level, but at the same time showed the shortcomings of mass drug administration with any available drugs unless they were given at least twice a month.

In the attempt to solve the difficult problems of mass drug administration in Africa, the distribution of medicated salt, also known as Pinotti's method, was considered. Field trials in different parts of the world have shown the potential value of this method, as well as its limitations. Early results of the trial in the United Republic of Tanzania have been promising, but this method proved to be disappointing in Ghana. The main drawback of this method is that the age groups most heavily infected (infants and small children) usually receive little or no salt with their daily diet. A study of the use of medicated salt for treating workers and their families on industrial estates in Kenya indicated the beneficial effect of this method, as evidenced by a decrease in sickness and absenteeism attributed to malaria.

The preparation of a stable drug and salt mixture has presented certain difficulties. The only suitable drugs for medicated salt are the 4-aminoquinolines —chloroquine or amodiaquine—though the latter was somehow neglected for this purpose. However, chloroquine diphosphate and sulfate, owing to their high solubility in water, are easily "leached out" of the drug and salt mixture under tropical conditions of high humidity. This has been partly remedied through the development of a chloroquine concentrate in which the drug is protected by a special coating. Another possibility of preventing "leaching" is the use of 4-aminoquinoline compounds of very low solubility in water, such as chloroquine dihydroxynaphthoate, tannate, or silicate, or amodiaquine base, which have the advantages of being tasteless. Studies in the United Republic of Tanzania have shown that some of these compounds are fully effective when given in small daily doses and could be

used for medicated salt.

Although sporadic observations of lessened sensitivity of some strains of malaria parasites to quinine, pamaquine, and mepacrine have been reported in the past, the problem of drug resistance of human malaria parasites has become significant only since 1948–50 with the discovery of proguanil resistance in *P. falciparum* and *P. vivax* in Malaya. Considering the wide use of proguanil and the relative ease with which experimental resistance to this drug can be produced, the number of confirmed cases of resistance to it have been relatively small and usually limited to conditions in which the dosage of the drug was low and its administration irregular.

Evidence of resistance of strains of *P. falciparum* to pyrimethamine was produced first in East Africa in 1954 but later also in West Africa. Although it has been assumed on the basis of mainly experimental data that cross-resistance between pyrimethamine and proguanil is invariable, no convincing studies to confirm this assumption have ever been carried out in the field in Africa. The problem of resistance of *P. falciparum* to chloroquine and other 4-aminoquinolines has been of far greater potential importance and drew much attention. By the end of 1960, a *P. falciparum* strain originating in Colombia was found highly tolerant to chloroquine, and within the next 3 years chloroquine resistance was reported from Brazil, British Guyana, Cambodia, Malaya, Thailand, and Vietnam.

In 1970, a review of all published and unpublished reports on the alleged chloroquine resistance in Africa came to the conclusion that there was no convincing evidence of this phenomenon in Africa. Although some early reports on chloroquine resistance in West Africa appeared in the 1970s, they were unreliable and rightly discounted. However, since 1979, a number of cases of malaria in non-immune visitors to East Africa failed to respond to the usual dosage of chloroquine. By 1979 the presence of resistant strains of *P. falciparum* was confirmed in several parts of East Africa and recently, incipient resistance to chloroquine in the semi-immune population was fully documented in the United Republic of Tanzania (*17*). There is no need to emphasize the great impact of this phenomenon on the practice of malaria control by chemotherapy in Africa.

CONCLUSIONS

Since most of the field research projects carried out during the period 1950–75 were aimed at elucidating the role of chemotherapy in malaria control in Africa, the following conclusions are presented based on the results achieved:

(1) General protection of groups of people residing in malarious areas and of populations living there permanently can be achieved temporarily by collective chemotherapeutic measures. This method has been used with success in army units, organized labour forces, and similar communities. The rapid excretion of nearly all commonly available drugs means that they must be administered frequently and regularly. This demands good organization, efficient distribution and, above all, considerable persuasion. In such malaria control programmes, drugs may be used to give protection to particular categories of people; in some countries a more general distribution is made in an attempt to protect the whole population. This may be necessary as the immediate first step in the event of an epidemic of malaria, to be followed up by more lasting control measures.

(2) In countries where a comprehensive malaria control programme cannot be undertaken, the national health system may carry out antimalarial drug distribution as one of the services provided in the rural areas. The aim of such a measure is mainly to prevent or reduce the effects of malaria. Although transmission of the infection cannot be interrupted by this measure, it has some beneficial effects, since it not only protects each individual but also reduces the infective seed-bed and thus decreases transmission in the mosquito.

(3) In carrying out such a programme special attention should be paid to the following: (*a*) extent of coverage, i.e., whether the aim should be to cover the whole population or only specific categories of people; (*b*) long-term effects on the community; (*c*) selection of the appropriate drug and dosage; (*d*) method of drug distribution, timing, regularity, frequency, and means of supervision of its management and evaluation.

(4) There is little doubt that collective drug distribution is of immediate benefit to the indigenous population living in a malarious area. It has been shown in Africa that regular drug distribution decreases the total amount of sickness due to all causes, that it somewhat reduces absenteeism in schools, and that in other groups it may be followed by a modest but definite gain of weight and increase in blood haemoglobin.

(5) It is not less obvious that wherever any collective drug distribution is proposed, it must be adapted to the epidemiological conditions of the area. In areas with moderate endemicity and seasonal transmission, all the groups of the population would benefit from drug distribution (adjusted to the start of the transmission period), while in highly endemic areas the long-term protection of young, more vulnerable age groups is preferable. It is impossible to administer any drug to the entire population or even to a particular category of people with absolute regularity.

However, even a less-than-total level of coverage may have an appreciable effect on the amount of malaria, depending upon the level of transmission.

(6) The possible undesirable long-term effects of a distribution of an antimalarial drug should be considered from two angles: the toxic action of the drug and possible interference in highly endemic areas with the acquired tolerance to the infection. As far as the first point is concerned, it seems that, with the exception of mepacrine and some 8-aminoquinolines, harmful effects of most of the well-known drugs are very few, particularly when assessed in the light of the benefits that the drugs confer. The possible interference of regular drug distribution with the degree of acquired immunity to malaria is uncertain; definite information on this point is lacking, probably because in all field trials the absolute regularity of drug distribution has never been achieved and any reinfection, even of short duration, has been sufficient to maintain a degree of immunity.

(7) In areas where chloroquine-resistant *P. falciparum* strains occur, the amount of protection to be expected from the distribution of 4-aminoquinolines will be less than elsewhere. In such situations, the periodic monitoring of drug response is mandatory. The use of alternative drug combinations in restricted areas might be considered, but the wide use of combinations containing sulfonamides or sulfones entails the risk of inducing sulfonamide resistance in some of the important pathogenic bacteria in the area, such as meningococci. In areas where chloroquine resistance is already present it may be preferable to restrict the distribution of chloroquine to acute cases of malaria, evidenced by the presence of fever. However, such restriction will leave the symptomless infections of some individuals without any drug protection to lessen the burden of parasitaemia and without any attempt to lessen the amount of transmission.

(8) The frequency of administration is related not only to the dosage of the drug but also to the convenience of its distribution. Generally, once weekly administrations are most appropriate to assure regularity, though fortnightly distribution may sometimes be desirable, depending on many local conditions, especially on the level of transmission; a reasonably strict observance of weekly or fortnightly routines is not too difficult. In areas of high endemicity, the risk of reinfection is greater when the treatments are more widely spread.

(9) Two groups of the population must be given the highest priority: (*a*) pregnant and nursing women and (*b*) infants and toddlers. The distribution of drugs to these two groups is normally through the established health service or through other systems, such as primary health care, but there will always be a proportion of women and children missed, since the total drug coverage is almost impossible to achieve in rural areas. In highly malarious areas, regular once-weekly or once-fortnightly administration of drugs to febrile children attending the "under 5-years clinics" is of special value, since in children of this age-group malaria can be a severe and often fatal disease.

(10) Drug protection from malaria should be the responsibility of the national health service and the cost must be met mainly by the government, though substantial organizational and financial assistance may be forthcoming from other sources.

RÉSUMÉ

L'ENSEIGNEMENT TIRÉ DES ACTIVITÉS DE RECHERCHE SUR LE TERRAIN EN AFRIQUE, PENDANT LA PÉRIODE D'ÉRADICATION DU PALUDISME

La Conférence sur le paludisme en Afrique équatoriale, convoquée par l'Organisation mondiale de la Santé en 1950 à Kampala (Ouganda), a constitué un jalon dans l'histoire des activités modernes de lutte antipaludique sur le continent africain. Elle a permis d'exposer et d'évaluer les données disponibles au niveau international sur les aspects épidémiologiques de cette maladie et tenté de coordonner les diverses méthodes de recherche et de lutte antipaludique. Ses deux principales recommandations ont été de souligner la nécessité 1) de combattre le paludisme par tous les moyens, quel que soit le degré d'endémicité de la maladie, et 2) d'évaluer l'avantage, pour les populations indigènes, d'un endiguement de cette parasitose.

La première période de recherche sur le terrain et de projets de lutte pilotes en Afrique se place entre 1950 et 1964. Un grand nombre d'études menées dans plusieurs Etats africains montrent que l'utilisation d'insecticides à effet rémanent tels que le DDT et l'HCH peut faire diminuer, parfois considérablement, la transmission du paludisme, mais qu'on n'a pu stopper cette transmission, sauf dans le cadre de deux projets relativement mineurs réalisés dans des zones forestières du Cameroun et du Libéria. Au cours de la seconde période, de 1965 à 1974, les difficultés d'une maîtrise et *a fortiori* d'une éradication du paludisme sont devenues plus patentes en raison du développement de la résistance d'*Anopheles gambiae* au DDT, à l'HCH et la dieldrine; en outre des problèmes administratifs, logistiques et financiers ont surgi. Il est apparu clairement que la perspective d'un endiguement de la maladie (sans parler de l'éradication) est liée à l'existence d'une infrastructure médicale suffisante. On a mis sur pied un certain nombre de programmes de "prééradication" afin de développer de

meilleures méthodes de lutte antipaludique et d'améliorer l'infrastructure sanitaire rurale. Bon nombre de recherches portant sur la chimiothérapie antipaludique ont été menées sur le terrain et la valeur de l'administration collective ou sélective d'antipaludéens a été reconnue sans conteste, encore qu'il soit désormais évident que cette mesure ne peut jouer un rôle décisif dans la diminution de la transmission du paludisme en Afrique.

Dès les premiers jours du programme mondial d'éradication du paludisme, on avait souligné le rôle de la recherche, qui peut contribuer à la solution des problèmes techniques de la lutte antipaludique en Afrique tropicale. On assiste d'ailleurs depuis une décennie à un développement immense de cette activité.

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