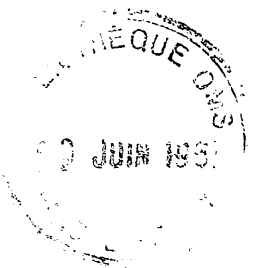


WORLD HEALTH
ORGANIZATION

261949



ORGANISATION MONDIALE
DE LA SANTE

1 June 1961

ORIGINAL: ENGLISH

Supplement to WHO/Mal/294

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1. PRINCIPLES OF PLANNING AND ORGANIZATION OF FIELD TRIALS OF ANTIMALARIAL DRUGS

At the Technical Meeting on Chemotherapy of Malaria held in Geneva in November 1960, the planning and organization of field trials of antimalarial drugs were discussed as part of the agenda.

The evaluation of the chemotherapeutic efficiency of an antimalarial drug follows today a standard pattern which begins in the laboratory with the preparation of the chemical compound and progresses through intensive and varied screening procedures to the stage where toxicity and therapeutic efficiency in humans are observed in a series of, usually small, clinical trials. Only at the end of this sequence of events comes the large-scale trial of the drug in the field. The experimental administration of a drug to a sizeable population does not constitute a rapid method of drug evaluation, nor does it in any way reduce the need for thorough prior laboratory and clinical investigation. Before a large-scale field trial is contemplated sufficient general information should be available to indicate clearly the mode of action and the value of the new drug. Data such as effective dosage, rate of absorption, duration and mode of antiparasitic action, full information on toxicity and on milder side-effects should be available.

In short, it is not the purpose of field trials to find out basic data on dosage and drug action, but to confirm these data under field conditions, and to provide general information on the usefulness of the drug in malaria eradication campaigns.

Since the principal objective of the drug trial will be to assess the value of the drug in question as a weapon in malaria eradication programmes, the new drug should be known to fulfil certain essential requirements. It must produce no side-effects whether mild or severe which would prejudice the community against it. It must be capable of achieving satisfactory action when given not too frequently, and preferably at a single dose.

The sequence of events in the appraisal of a new antimalarial drug, once its use in human subjects has been approved, should run according to the following pattern:

- (1) Clinical trials in hospitals.
- (2) Field trials (1st stage), among small samples of population.
- (3) Field trials (2nd stage), among samples of at least 1000 people.

(1) Clinical trials in hospitals (mental hospitals, volunteers), under carefully supervised conditions aim at establishing:

- (a) immediate clinical and parasitological response;
- (b) pharmacological data on absorption, elimination, plasma concentration, duration of effective blood levels;
- (c) toxicological observations and appraisal of contra-indications;
- (d) effective dose and route of administration;
- (e) effects of recrudescence and relapse.

(2) Field trials (1st stage) are those in which maximal control operates under optimal conditions. The activity of the drug under trial must be assessed in comparison with a standard drug the effect of which is known. The dosage of the two drugs tested must be such as to protect the least immune group of the population concerned. Field trials should be designed to answer specific questions, for example the value of a proven regimen amongst a relatively small sample, and may supply the following information:

- (a) optimal dosage and regimen;
- (b) further evidence of side-effects;
- (c) evidence of possible resistance or cross-resistance;
- (d) acceptability of the drug by the population.

At this stage, certain definite data are required such as parasite clearance times, parasite rates and densities, evidence of sporontocidal effect, etc. The latter effect may be determined on colonized or wild caught mosquitos fed on gametocyte carriers.

(3) Field trials (2nd stage) are carried out in larger groups under less controlled conditions. These trials should cover several areas to provide data concerning local differences in response. It should be borne in mind that the drug dosage must be sufficiently high to protect the least immune group of the population in each area, this having been ascertained in the 1st stage field trial.

The malarimetrical data should be supplemented by the assessment of changes in the sporozoite rates of local vectors. In some areas, observation of relapse rates will be of value.

A large-scale field trial represents an attempt to observe the consequences of mass drug administration in a given population and as such a trial may reasonably be expected to:

- (a) confirm (or otherwise) the intrinsic value of the drug and its action at a given dosage level;
- (b) indicate the acceptability of the drug to the population and in consequence provide an assessment of its value in malaria eradication campaigns;
- (c) demonstrate, when combined with the requisite entomological investigations, the effect of drug administration on the malaria transmission indices of the area;
- (d) detect, perhaps at an early stage, the existence of strains of plasmodia resistant to drug action.

In the trials on a smaller scale, control groups can be found within the area of the particular trial and can be examined concurrently with the treated group of population. In field trials, of the second stage, it will generally be necessary to achieve complete coverage of the area with whatever drug is being tested; the control will consist either of pre-treatment data from the same area, when seasonal and transmission factors remain unchanged, or of data obtained from another area epidemiologically similar. The latter is frequently very difficult to find.

In the planning of large-scale trials of antimalarial drugs three factors must be taken into consideration: (a) the people and their malaria infection to be treated, (b) the drug and its dosage, and (c) the administrative and logistic aspects of the endeavour to ensure regular distribution of the drug to every individual.

For all field trials the population should be as stable as possible, fully co-operative and should be prepared to submit to pre-treatment examination, accept the drug willingly and permit examination as long as necessary. A good campaign of public health education adjusted to the population concerned plays an important part in obtaining such co-operation and should precede and accompany the field trial. Best

public relations are usually obtained by enlisting some important local people as active members of the team but in some conditions the assistance of a sociologist with a sound knowledge of local beliefs and customs is of great value.

Nevertheless, the best public relations are shortlived if the drug trial does not fulfil the following basic requirements. It should involve minimal dislocation of normal community life, it must not be attended by an appreciable incidence of undesirable side-effects and its benefits should be patently obvious to the population.

All pertinent data regarding the population (size, density, geographical distribution, census data, accessibility, stability, local customs, socio-economic conditions) should be known before the trial is started. The decision on the size of the population studied is most important and should be made in consultation with a statistician so that the community is large enough to satisfy statistical requirements, without being too large for adequate medical supervision.

The selection of the population with regard to the prevalence of malaria, the degree and the duration of transmission depends to some extent on the specific drug that is being tried. Drugs which are assessed as to their suppressant or sporontocidal value should preferably be used under conditions of prolonged and heavy transmission. On the other hand, the anti-relapse properties of a drug can be established only in areas where transmission has been interrupted or is at a very low level.

Most of the field trials of antimalarial drugs can be carried out at the present time on large numbers of infected individuals only in hyper- or holoendemic areas where the inhabitants have some degree of immunity to the disease.

The following indices should be used for the assessment of results of drug trials in relation to the baseline established: (1) crude parasite rate; (2) parasite density index and parasite clearance time; (3) species prevalence; (4) gametocyte rate and density; (5) spleen rate and average enlarged spleen; (6) sporozoite rates in each vector species.

The need for an accurate record system is obvious and much thought should be given to this in the early stages. The system adopted must not only record all the essential information but also do so in a manner which facilitates statistical

analysis of results. A most important point to ensure is the accurate identification of individual members of the population.

In under-developed countries the most important factors contributing to success are the prestige and personality of the individuals conducting the trial. The greatest care, therefore, should be taken in ensuring that not only the team-leader but each team-member who comes into direct contact with the population has a personality fitted to the task on hand.

In addition some well-known and highly respected member of the local community should be appointed to act as public relations officer. The medically qualified members of the team must be prepared to examine and treat sick individuals encountered during the investigation in addition to coping with their normal duties.

Adequate staff, transport and equipment must be made available to ensure regular drug administration and subsequent examination of the population.

The greatest problem in a large-scale drug trial is that of ensuring drug consumption. The only satisfactory mode of administration is where team-members distribute the drug by nominal roll and observe and record ingestion. All side-effects should be recorded immediately but the greatest care must be exercised in the questioning of individuals concerning possible toxic effects. Direct questioning should always be avoided for inherent in it is the risk of creating suspicion and apprehension of the drug taken.

It is prudent to anticipate failure of the drug and in such case an analysis of the cause of failure should be made taking into account the following possibilities: (1) lack of absorption of the drug; (2) under-dosage; (3) drug toxicity or vomiting; (4) drug resistance by the parasite.

Throughout the post-treatment observational period a close watch must be kept for the occurrence of any positive blood film. When one is detected the dosage record of the donor should be checked without delay. Should this indicate satisfactory drug ingestion, and provided vomiting did not occur shortly after ingestion - a point that will always be checked at this stage by direct questioning - a possibility of drug resistance must be considered. The indubitable diagnosis of drug resistance is beset

with difficulties for it is always conceivable that persistence of parasitaemia after apparently successful drug administration may be due to drug failure rather than to an intrinsic characteristic of the parasite. Drug failure may be due to some defect in the patient such as inability to absorb an effective quantity of the drug or abnormal metabolism of it after absorption. The final conclusion can only be arrived at by demonstrating the persistence of parasitaemia despite adequate treatment when the parasite is transferred to a new and susceptible individual either by subinoculation of the blood or by the bite of a mosquito infected from the original subject. Such an investigation is not a practical possibility in the field and there exists a need for the establishment in some non-malarious region of an international centre in which "resistant" parasites detected in field campaigns could be studied with precision.

Finally, at all stages it must be remembered that a large-scale field investigation represents an essay in public relations. Any field trial which requires the goodwill and active participation of a community busily engaged in the many tasks of everyday life should be planned with understanding and undertaken with tact and tolerance.

2. IMPROVEMENTS IN SPRAYERS AND NOZZLE TIPS

A meeting in November 1960 at the UNICEF Headquarters in New York, attended by representatives of the United Nations Children's Fund, the World Health Organization (American Regional Office), the United States Public Health Service and the Hudson Company, was convened to consider sundry changes and modifications in insecticide sprayers which had been made or proposed over the past eighteen months and also to take note of the position relating to research work which is currently in progress.

Nozzle Tips

The problem of nozzle tips is one that has been exercising the minds of everyone for several years past. Current provision is based on the standard T8002 S.S. tip made by Spraying Systems Company; but this tip has been proved to be far from satisfactory; in fact the standard tip needs to be changed at least once a month, which is costly. A T8002 S.S. tip made from hardened stainless steel, also marketed by Spraying Systems Company has been used by ICA, - it costs a little more -

but the result hardly justifies the extra cost; UNICEF has not used the hardened tip. Spraying Systems Company, working in conjunction with CDC and the Hudson Company has now developed a tip made from a new alloy and trials to date indicate that this tip should last at least 2-3 months. It is made from a hardened stainless steel alloy incorporating nickel, and is now available at a cost of 69 cents each, compared with the present price of the standard T8002 S.S. tip of 58 cents.

The tolerance of the new tip, to be known as T8002-HSS, is reported by the manufacturer to be plus or minus 5% on discharge and plus or minus 3% on angle; it was agreed that the tolerances were reasonable.

It was decided that UNICEF would immediately change over from the present T8002 S.S. tip to the new hardened steel alloy tip, known as T8002 HSS.

T8004 Stainless Steel Tip and Pressure Regulator

Reports were received on the result of a new design which had proved satisfactory in field tests in Guatemala. The design incorporates a T8004 S.S. tip, plus a small pressure regulator plus a polyethylene gasket, the gasket and regulator being inserted immediately behind the nozzle tip; the standard nozzle body can accommodate this new feature. The advantage appears to be that the corrosion rate at the tip orifice is about 1/35th of that experienced with the standard T8002 S.S. presently in use, that is, if the foregoing statement can be substantiated by full-scale field trials, it should be possible to use a single tip without change for at least three months, if not for a whole spraying season.

The estimated cost of the pressure regulator and washer is approximately \$ 1.00; however the regulators are not yet in mass production and before reaching a final decision it was deemed advisable to make more extensive field trials.

It was decided that field trials would be instituted in Guatemala, Honduras and Nicaragua using the T8004 S.S. tip and pressure regulator combination, subject only to confirmation that recalibration of nozzle tips which had been returned from Guatemala after use in an earlier trial proved satisfactory. It would not be expected necessary to provide the higher priced T8004 HSS tip.

Pressure Gauges

The general trouble which has been experienced in the field in maintaining the efficiency of the present pressure gauges is due to a tendency for the insecticide to permeate into the operating mechanism of the gauge. Many experiments have been made to resolve this difficulty, but to date the best solution appears to be for the gauge to be manufactured with a brass casing in lieu of steel, heavy quality plastic for the window, a wider port and a thread on the internal port. The tolerance of accuracy of the gauge was reported to be plus or minus 10% and it was agreed that while this was acceptable for the present, the matter should be further investigated.

Experiments will continue into the provision of an oil filled plastic sleeve (or wire mesh) which would be inserted below the gauge in the threaded internal port.

It was agreed that the gauge with a brass case and other modifications was undoubtedly an improvement over the old model and should be introduced immediately. UNICEF has already ordered this style for several recent programmes.

Sprayer Specifications

The representative of the United States Public Health Service was at present revising the ICA specifications for sprayers and hoped that the revised specifications would be acceptable to UNICEF as well as ICA so that a more complete standardization could be achieved. He proposed to include the following changes:

- (1) Copper to be added as an acceptable material for metal parts coming in contact with insecticides.
- (2) Special stainless steel alloys for use in springs may be used, under certain conditions which would be defined.
- (3) The overall height of the tank may be increased by 1", (i.e. from a maximum of 21" to 22").
- (4) The maximum diameter of the tank to be defined.
- (5) The clips on the strap hangers to be drilled to take a cotter key, thus preventing accidental removal of the carrying strap.
- (6) The use of soft (sweat) solder on the extension lance to be permitted.

Miscellaneous

Reference was made to the inclusion of an 8" "Gosseneck" extension rod as a standard accessory with all sprayers provided by UNICEF. It was felt that this was not necessary as it was seldom used; it was agreed, however, to inquire from other areas regarding the need for continuing to supply this feature as standard.

3. DIFFICULTIES ENCOUNTERED IN SOUTHERN IRAN

In the northern parts, including the Caspian littoral and central plateau of Iran where A. maculipennis and A. superpictus are the main vectors, considerable progress has been made since malaria control was intensified in 1950 and a malaria eradication programme has operated since 1957. But in the south and south-east of the country in the Ostans of Chechom, Haftom and Hashtom much greater difficulties have been encountered.

Dr Mofidi, Director of the Institute of Parasitology and Malariology, Teheran, discusses these problems in a recent paper (Publication No. 824 of the Institute, November 1960). In these southern areas there are a number of vectors - A. stephensi, A. fluviatilis, A. superpictus, A. sacharovi and even A. culicifacies in the eastern part, each vector creating problems. There is a long transmission season in some areas and two seasons in others. The habits of the people - nomadism with seasonal migration, outdoor sleeping and the absence of permanent habitations - do not assist, and the physical geography of the country and lack of communications make investigations and the provision of supplies a time-consuming and laborious business. There is in addition an absence of a rural health network. A further complication has been the development of resistance by A. stephensi first to DDT and later to dieldrin.

In the Ostan Chechom or Khouzistan, covering the head of the Persian Gulf and the hinterland to the north and east of Abadan, A. stephensi was first found resistant to DDT in 1957 with subsequent malaria outbreaks in the area, and dieldrin was substituted as an insecticide; but susceptibility tests made at the end of 1959 and early in 1960 revealed the development of resistance of A. stephensi to dieldrin as well, though the resistance to DDT was now found to be only half that recorded in 1957.

It was during the period of dieldrin spraying (1957 onwards), which at first eliminated most of the A. stephensi, that the importance of A. fluviatilis as a vector was recognized. Though anthropophilic, it was not noticeably affected by normal insecticide spraying, because of its exophilic and exophagic habits, and maintained malaria infection at a low endemicity.

Similar results were obtained by investigating teams in the Ostan Haftom (Fars) and Ostan Hashtom (Kerman) on the southern coast of Iran. In Kerman the teams made a preliminary report from which it was concluded that:

- outbreaks of malaria are occurring in the area;
- the inability to detect infection in mosquitos (A. stephensi and A. fluviatilis) was probably caused by the mass distribution of pyrimethamine to the population of the area;
- A. stephensi was resistant to dieldrin and to a lesser degree to DDT;
- A. fluviatilis was still susceptible to the chlorinated hydrocarbons;
- it would be necessary to consider using organic phosphorus insecticides supplemented by mass chemotherapy; this would be more costly and difficult to organize.

Summarizing the studies in Fars, Dr Mofidi mentions the following points:

- (1) From 1958 to August 1960, when A. stephensi had apparently disappeared from the area, other anophelines, more particularly A. fluviatilis, have continued to maintain and transmit malaria.
- (2) Because of the resistance developed by A. stephensi to dieldrin and the increase in the numbers of A. fluviatilis and A. superpictus caused by unusually favourable breeding conditions, local outbreaks of malaria have occurred.
- (3) All three vectors, A. stephensi, A. fluviatilis and A. superpictus, were found to be infected when examined for sporozoites or oocysts in a number of villages.

(4) It was shown that A. fluviatilis, with its natural exophilic tendency and its exophagy, had an important part in transmitting and maintaining malaria because of the outdoor sleeping habits of the people.

(5) While A. fluviatilis was found susceptible to both groups of insecticides used, ordinary indoor total coverage would not be likely to interrupt transmission of malaria by this vector.

Experimental trials have been carried out with malathion using the 50% emulsion concentrate at 1 g/m^2 in two villages in southern Iran. The huts sprayed were made of mud or thatch. The indications are that the residual effect of the insecticide is of very short duration; it was found that on mud when tested by bioassay methods the residual potency rarely exceeded 15 days and on non-sorbent surfaces (thatch, etc.) it was 35-40 days.

This review of problems now encountered in southern Iran emphasizes two points in malaria eradication, first the importance of detailed pre-eradication surveys and secondly the urgent need for alternative long-acting insecticides.

4. PRACTICAL APPLICATION OF ANTIMALARIAL DRUGS IN MALARIA ERADICATION PROGRAMMES

Recommendations concerning the use of antimalarial drugs during the various phases of malaria eradication programmes, made at the Technical Meeting on Chemotherapy held in November 1960 at Geneva, are of considerable interest.

Although residual insecticide spraying on total coverage basis is the fundamental measure of eradication, chemotherapy plays an important part in all phases of malaria eradication programmes. It is recognized that the time required for achieving complete interruption of transmission may be greatly reduced by the judicious use of antimalarial drugs. It is also agreed that the elimination of all residual infections and hence the prevention of the appearance of new foci of transmission can most rapidly be obtained by the use of drugs.

Where insecticides alone are fully effective in interrupting transmission, chemotherapy is not essential during the first year of the attack phase, although the

supplementary use of drugs may accelerate the success of the spraying campaign. During the second or third year of the attack phase, as soon as surveillance is in operation, the use of drugs becomes increasingly important. The aim of chemotherapy at that stage is primarily to provide immediate relief of clinical symptoms, presumably due to malaria, and to make the patient non-infective to mosquitos at least for some time, until the result of the blood examination becomes available. In some parts of the world the administration of antimalarials to fever cases encountered by the surveillance agents may increase the co-operation of the population. It seems however that the use of drugs for such a purpose can be fully justified only in the late attack phase and consolidation phase.

During the consolidation phase, after the total coverage spraying has come to an end, the use of antimalarial drugs is of primary importance. Single dose treatment of all persons suspected of malaria and subsequent radical treatment of all confirmed cases are the principal measures for the elimination of all remaining infections and for prevention of the establishment of new foci of transmission.

Radical treatment of relapsing infections should preferably be already in operation during the last one or two years of the attack phase, in order to eliminate the largest possible number of infections before the cessation of spraying.

Finally, during the maintenance phase antimalarial drugs are essential for the rapid radical cure of every imported case of malaria in order to prevent any new spread of the disease.

Whilst these general principles are agreed upon by most malariologists, there are naturally differences with regard to the degree and timing of their practical application. Thus in highly endemic areas there is an increasing trend to associate mass drug administration with residual spraying from the beginning of the attack phase. In several countries of the Western Pacific Region (Sarawak, North Borneo and Netherlands New Guinea) and in some pilot projects in Africa (Uganda) mass drug administration of a single dose of combined chloroquine and pyrimethamine is carried out at the time of spraying. Although it is expected that this method will lead to

the shortening of the attack phase there is, up to the present, no definite evidence on which to decide whether drug administration has in fact speeded up the success of spraying operations.

It was agreed that in ideal conditions of a stable, fully co-operative population, given the guarantee of a complete drug coverage of an epidemiologically delimited area, a well organized mass administration of schizontocidal and sporontocidal drugs may eradicate malaria within a year, barring its reintroduction from the outside. It was emphasized however that the conditions described above are exceptional and not generally found in large populated areas especially at the present time when the mobility of human communities in under-developed countries has greatly increased. Nevertheless the interest of such a project is considerable and an attempt at confirming this possibility should be made.

Mass drug administration of antimalarial drugs may be carried out either as a sole measure or, preferably, in conjunction with residual spraying. In eradication programmes this measure must be applied to the entire population of an area or to the whole group when dealing with nomadic or other mobile communities.

The interval between mass distribution of drugs depends on whether chemotherapy is employed together with residual spraying or as a sole measure. In the first case the frequency of drug distributions depends on the epidemiological conditions of the area, on the efficacy of anti-mosquito measures and also on operational conditions of the programme; the drugs can be given less frequently than once a month.

In the second case when the drugs are used as the only measure the frequency of their distribution must be greater. The drugs at present available are eliminated relatively quickly and the necessary frequency of mass drug administration is once a week. It is realized that operational problems of mass drug administration in under-developed areas might be such that drugs could not be given with adequate supervision more often than once a month. Naturally in the case of migratory groups only a single drug administration is possible.

For mass drug administration at intervals of one week the preferred drug is a 4-aminoquinoline at an adult dose of at least 300 mg of the base. It may be

associated with 30-45 mg of primaquine base or with 25-50 mg pyrimethamine or with 20 mg of chlorproguanil depending on local conditions.

For mass drug administration carried out at intervals of one month or longer the adult dose of 4-aminoquinoline should be 450-600 mg of base. The dose of primaquine should be 30-45 mg of the base. The use of other drugs and especially those that might easily produce resistance of the parasite is not advisable in such conditions, especially if they are used alone. Mass drug administration is advisable in the presence of small foci of persistent transmission within a large area where transmission has been interrupted. In such conditions once weekly administration of a combination of 4- and 8-aminoquinolines is of particular interest on account of the combined sporontocidal and radical curative effect.

5. SIMIAN MALARIA

Dr R. S. Bray, of the Liberian Institute of the American Foundation for Tropical Medicine, Incorporated, Harbel, Liberia, has drawn our attention to an omission of some importance from section 8 of the Eighth Report of the Expert Committee on Malaria, 1961, (WHO TRS No. 205), dealing with simian malaria in relation to malaria eradication.

There is no mention in this section of Plasmodium schwetzi, the benign tertian parasite of African apes. This parasite, found in a chimpanzee from the Belgian Congo, was transferred by blood inoculation to man by Rodhain and Dellaert in 1955.¹ The Belgian investigators have succeeded in infecting experimentally A. maculipennis atroparvus up to the oocyst stage. In man the parasite produced a tertian form of malaria of some intensity causing several rigors but was considered to be benign. In 1958 Bray also tried to transmit this parasite through mosquitos but without much success.² Thus P. schwetzi should be included in the list of malaria parasites of primates when the malaria status as a zoonosis is being considered.

¹ Ann. Soc. belge Méd. trop., XXXV, No. 1, 73-76

² J. Parasit., 44, 46-51

6. TRANSFER OF BLOOD PARASITES BETWEEN THICK BLOOD FILMS
DURING MASS STAINING:

We have received from Mr G. T. Shute, Laboratory Technician, WHO Malaria Team, Zanzibar, a note on his further investigation on the effects of detergents on the staining of blood films with Giemsa stain. The detergents were used in order to prevent the transfer of malaria parasites between thick blood films. A previous account of Mr Shute's work which was quoted in document WHO/Mal/280 demonstrated the transference of red blood cells and parasites between blood films during mass staining, Mr G. T. Shute has now come to the conclusion that a product known by the name of Lissapol N, which is a non-ionic detergent of the alkyl-aryl-polyether alcohol group, has little effect on the staining of malaria parasites when added to distilled or buffered water at concentrations of up to 0.1%, and could be used to obviate this tendency of transfer. On the other hand, another detergent known by the name of Teepol, which is a sulfated fatty alcohol, is quite unsuitable for use with Giemsa or any other Romanovsky stains even at a concentration of 0.01% or less.