

LEAGUE OF NATIONS.

~~C.H.1103.~~

Annex 3.

(C.H./Malaria/227).

HEALTH ORGANISATION.

MALARIA COMMISSION.

M A L A R I A

TREATMENT AND PREVENTION OF MALARIA IN THE FIELD,
USING SYNTHETIC DRUGS IN COMPARISON WITH QUININE.

Programme of co-ordinated experiments to be carried out
in Algeria, Italy, Roumania and U.S.S.R.

Note by the Secretary of the Commission.

The following programme is a summary of the conclusions adopted by Professor Ed. Sergent, Professor M. Ciuca, and Professor G. Lega (representing the Italian Committee presided over by Professor G. Bastianelli) at the Gorki and Moscow (February 22nd - 26th) meetings, which were also attended by Professors P.C. Serguief and C. Moshkowski, Drs. L. Anigstein and L.W. Hackett, and, for the Secretariat, Dr. E.J. Pampana.

GENERAL METHODS FOR ALL THE SELECTED EXPERIMENTS (EXPERIMENTS
IN CLINICAL PROPHYLAXIS, TREATMENT AND ERADICATION).

The experiments will be continued for at least twelve months. The whole population subject to the experiments (prophylaxis, treatment or eradication) including control groups, will be examined once in April, before the campaign, and once at the end of the campaign, in November, in order to establish the splenic index, splenometric index and parasitic index.

Method of estimating endemic indices.

In Algeria, these indices are ordinarily calculated up to 15 years of age; in other countries up to various ages. Moreover, the methods of estimating spleen enlargement differ in the four countries. The experimenters thought that it would be preferable for the doctors of each country to adhere to the methods they have hitherto followed. In view, however, of the desirability of submitting endemic indices for the same age groups in the various populations, the experimenters have

agreed to register the results of splenic and parasitological examinations, for each separate year of age up to 15 years, and in a single group for subsequent ages, so that at the end of the experiments it may be possible to present the indices in a single table according to the age groups proposed by Professor Sergent, namely:

(0-2, 3-5, 6-10, 11-15) = (endemic indices); over 15;

at the same time allowing the data to be grouped into other categories according to the methods applied in each country.

The examination of the spleen should be made with the subject in the standing position. Splens that are merely palpable behind the false ribs should not be considered in calculating the index, though a record should be made of them. Only splens which definitely extend beyond the costal margin are to be counted.

The splenometric index is recommended by Professor Sergent; nevertheless in view of the various methods utilised to record and classify the size of the spleen; it is doubtful whether this index will be able to provide comparable data.

The parasite rate will be registered for each year of age up to 15 and thereafter in one single group (as for the splenic index).

As it is necessary to standardise as far as possible the method of testing the blood, the blood examination of each individual of the population subject to the experiment, both for the determination of the parasitic index and the periodical blood test, should comprise on each occasion three thick drops and one smear. The total duration of the three thick drop examinations shall be 10 minutes. If parasites are observed the species of which is not certain, the smears shall be examined.

The population subject to the experiment should have its blood examined twice monthly up to December 31st, 1935, and thereafter once a month until the beginning of the new malarial season. For the rational apportionment of the work it is proposed that a sample of blood should be taken every day except Sundays of one-twelfth (or one-twenty-fourth) of the population so that the whole population will be examined in 15 (or 30) days.

The sporozoitic index will be calculated once monthly from the beginning of the campaign up to December 31st, 1935. It is proposed that anopheles be captured every day or whenever possible in order that an adequate number of examinations may be made during the month.

Administration of drugs and medical supervision.

The drugs shall be administered direct by the staff responsible for the experiments, if possible after meals, a glass of water to be drunk immediately afterwards.

The aristoquine shall be administered in chocolates containing 0.10 grm. or in mucilaginous julep in the proportion of 2 grm. of aristoquine per 100 c.c. so that a dessert

spoon shall contain 0.10 grm. aristoquine. Failing aristoquine, tannate chocolates may be used, the dose indicated for aristoquine being in this case the tannate content estimated in terms of quinine bisulphate (method adopted for tannate chocolates by the Turin State Quinine factory). Chocolates shall be broken up into small pieces before being administered to young infants. The neutral quinine hydrochloride shall be administered in the form of sugar-coated tablets containing 0.20 of quinine-salt and 0.30 sugar.

As regards the method of administering the synthetic drugs to very young infants, Professor Schulemann has been consulted, on the request of the experimenters, and states that it is advisable that liquorice preparations, to hide the bitter taste, should be added, either in water or in milk, to the atebirin solutions or suspensions. If desired, a suspension with the ground tablets directly in a liquorice syrup might be prepared.

The population will be subjected to daily medical supervision at any rate until the beginning of the following malarial season in 1936, in order to detect all clinical attacks particularly in children under 2; whenever an attack is noted an additional blood sample should be taken. Any clinical symptoms, general state of health, and toxic trouble should be looked for and noted daily.

METHODS OF CONDUCTING THE VARIOUS EXPERIMENTS.

a) Experiments in clinical prophylaxis.

Experiments with atebirin will be made in Algeria, Italy and Roumania; in the U.S.S.R. experiments will also be carried out with German atebirin if it is available for the Russian experimenters, otherwise with acriquine, an identical drug.

The drugs will be administered daily in doses 0.05 for adults. In Italy this method will be adopted for one group of the population while another group will only be given 0.20 (adult dose) twice weekly.

Experiments with quinine will be conducted in the same countries except in Italy. The drug will be administered daily at the rate of 0.40 neutral hydrochloride per diem for adults.

A control group which will not receive any prophylactic treatment will be studied in each country.

The prophylactic campaign will be begun on April 1st and will end on October 31st in Algeria. In Italy and in Roumania it will commence on May 1st and will also be continued until October 31st. In the U.S.S.R. it will begin two weeks after the appearance of the first generation of anopheles, its duration varying according to different localities.

The case record cards of this experiment will be prepared according to the experimenters' usual methods and will be kept by them. The experimenters will merely transmit to Geneva the detailed results of their experiments.

The dosage for the experiment in prophylaxis is as follows for the various age groups:

<u>Age</u>	<u>Atebrin</u>	<u>quinine</u> daily
0 - 2	0.025 every 2 days	0.10 aristoquine
3 - 4	0.025 ditto	0.20 ditto
5 - 8	0.025 daily	0.20 neutral hydro- chloride (sugar-coated tablets)
9 - 12	0.05 daily	0.20 ditto
÷ 12	0.05 ditto	0.40 ditto

For the group which is to be studied in Italy and will receive atebrin intermittently, twice weekly, the doses communicated by Professor Schulemann, on March 25th, 1935, on the request of the experimenters, are the following:

<u>Age</u>	<u>Atebrin</u> , twice a week
0 - 2	0.05
3 - 4	0.10
5 - 8	0.15
÷ 8	0.20

If any clinical attacks of malaria are observed in the population-groups subjected to the clinical prophylaxis experiment, they should be treated for seven days with the same drug as that employed for prophylactic purposes (i.e. atebrin or quinine, without subsequent administration of plasmoquine) in the doses specified for the treatment experiments. These cases will remain in the prophylaxis group and will all (except the controls) resume the prophylactic routine at the end of the seven days treatment. If purely parasitical attacks are discovered at the time of the blood test, no curative measures are to be taken.

From the beginning of the prophylaxis campaign and until December 31st, the blood of the whole population shall be tested twice monthly.

After December 31st, 1935, medical supervision shall continue in the same manner, but the blood of the whole population will only be tested once monthly.

b) Treatment experiments.

Experiments in treatment with atebrin, and atebrin followed by plasmoquine, will take place in Algeria, Italy and Roumania. They will also be conducted in the U.S.S.R. if these drugs are available for the experimenters. If not, they will be made with acriquine and plasmocide.

Experiments with quinine and quinine followed by plasmoquine will be made in the same countries, except Italy. The reservation noted above concerning the

*To avoid any ambiguity, the following notation has been used: 0-2; 3-4, 5-8 etc.....instead of 0-2; 2-4; 4-8.

In the group 0-2 are included all children from 0-24 months of age; in the following, children from 24 months to 4 years, i.e., in the 3rd and 4th year; in the group 5-8, the children of the 5th, 6th and 7th year, etc...

U.S.S.R. also applies in the case of these experiments.

It is proposed that patients be assigned to the several forms of treatment, namely: quinine, atebryn, quinine + plasmoquine, and atebryn + plasmoquine, in the order in which they come to the dispensary. This system will be adopted in Algeria, but in Roumania it will be preferable for each village to have its type or types of treatment, it being understood that the epidemiological situation of the population of all villages subject to the experiments must be the same. The experiments in Italy and the U.S.S.R. may be conducted on either plan. Only in Algeria would it be possible to keep a control group of malaria patients who have not been treated or at any rate not subjected to any specific treatment.

The experimenters are prepared to adopt the same dosage for all forms of malaria, i.e.: 1 gramme of neutral quinine hydrochloride or 0.30 atebryn for adults per diem for seven days. In the series in which plasmoquine will be associated either with atebryn or quinine, the experimenters agree that an interval of three days should be allowed between the end of the administration of the schizontocide drug and the administration of the plasmoquine, which should be given at the rate of 2 centigrammes per diem (in the case of adults) for five days. The administration of plasmoquine should be discontinued as soon as any epigastric pains, vomiting or cardiac troubles, etc. are observed.* In the matter of cyonosis the doctor must use his own judgment in each case.

The experimenters agree that each patient shall always be given during any clinical or parasitical relapses the same treatment as that given at the first attack during the experiment. The dosage for the various age groups is indicated on the treatment cards: C.H./Malaria/222. These cards should be filled in for each clinical or parasitical attack as each attack will necessitate a period of treatment. They will be distributed by the Health Organisation to which they will be returned on completion. It is understood that the treatment shall be applied under strict medical supervision. Details concerning the administration of the drugs are given on the card.

Blood tests will be entered on the card the day previous to treatment, every day of the first week of the treatment, and the eighth, eleventh and fifteenth days. The condition of the spleen shall be entered on the day before treatment and on the fifteenth day.

During the treatment campaign and until December 31st, blood will be tested twice monthly; in Algeria the whole population subjected to the experiment will be examined whether under treatment or not; in the other countries only the blood of the subjects treated during the experiment will be tested. In November the indices will be compiled as in April in the manner specified in the section "General Methods".

* It may be that instead of administering plasmoquine 5 days running, it will be necessary (in view of toxic symptoms) to give it for only three days. (Italian and Roumanian observations).

From January 1st, 1936, until the following fever season the blood of the whole population, or of the malaria patients under treatment, as the case may be, shall be tested only once a month.

c) Eradication Experiments.

These experiments can only be conducted this year in Roumania and possibly in the U.S.S.R. Consequently it would be preferable for Professor Ciuca and Serguief in charge of these experiments to consult each other by correspondence in order to establish their plans on the following basis:

1. Preliminary treatment of the population for five days with atebirin 0.30 per diem.
2. Continuous treatment throughout the whole malaria season, either:
 - (a) two days a week, with 0.02 plasmoquine, or
 - (b) two days a week with 0.02 plasmoquine and one day in the same week with 0.20 atebirin.

Any relapse or re-infection occurring during the "continuous treatment" should be treated with the therapeutic doses adopted for the experiments in treatment with atebirin and plasmoquine, i.e.: seven days atebirin 0.30 per diem; three days rest; five days plasmoquine 0.02 per diem. (Proposals communicated by Professor Schulemann and Dr. Peter). If Professors Ciuca and Serguief decide to work in accordance with a common plan, it is recommended that this plan be communicated to the Health Section.

The experimenters have accepted the recommendation to communicate to the Health Section, for subsequent transmission to the other experimenters participating in the co-ordinated research work, any alteration which they may find themselves obliged to make in carrying out this programme.

NOTATION OF OBSERVATIONS DURING THE EXPERIMENTS.

(For the technique of the observations and administration of the drugs, see text).

Before the campaign.	Once in April 1935.	Indices (registration of observations for each year of age up to 15; see details in the text).
During the campaign. Algeria: April 1st- Oct. 31st.	Twice a month.	1) Blood testing of the whole population. (In the <u>treatment</u> experiment, in countries other than Algeria, it is intended to test only the treated cases). i.e.
Italy) May) 1st Roumania) Oct.) 31st. U.S.S.R. to begin 2 wks after the apparition of the 1st anopheles generation—the duration of the campaign varying in the different places.	Every day	(except on Sunday) blood samples to be taken of 1/12th of the population to be examined. 2) <u>Medical supervision</u> : Detect clinical attacks (particularly in children under 2). If <u>clinical attacks</u> an additional blood sample should be taken (see <u>infra</u>) 3) Note clinical facts (general state, toxic troubles). 4) Catch anopheles, make smears of their salivary glands to establish the <u>monthly sporozoitic index</u> .
	In case of a fever or parasitical attack.	See detailed instructions in the text of the programme and in the treatment card C.H./Malaria/222.
Intermediary period, until Dec. 31st 1935.	Every day.	Note same observations as above 1) 2) 3) and 4).
	Once in November.	Indices (as in April).
After the campaign, from Jan. 1st 1936, until the next fever season.	Once a month. Every day.	Testing of the blood of the whole population, as under 1), but taking except on Sunday, blood samples on 1/24th of the population. (Medical supervision as under 2).