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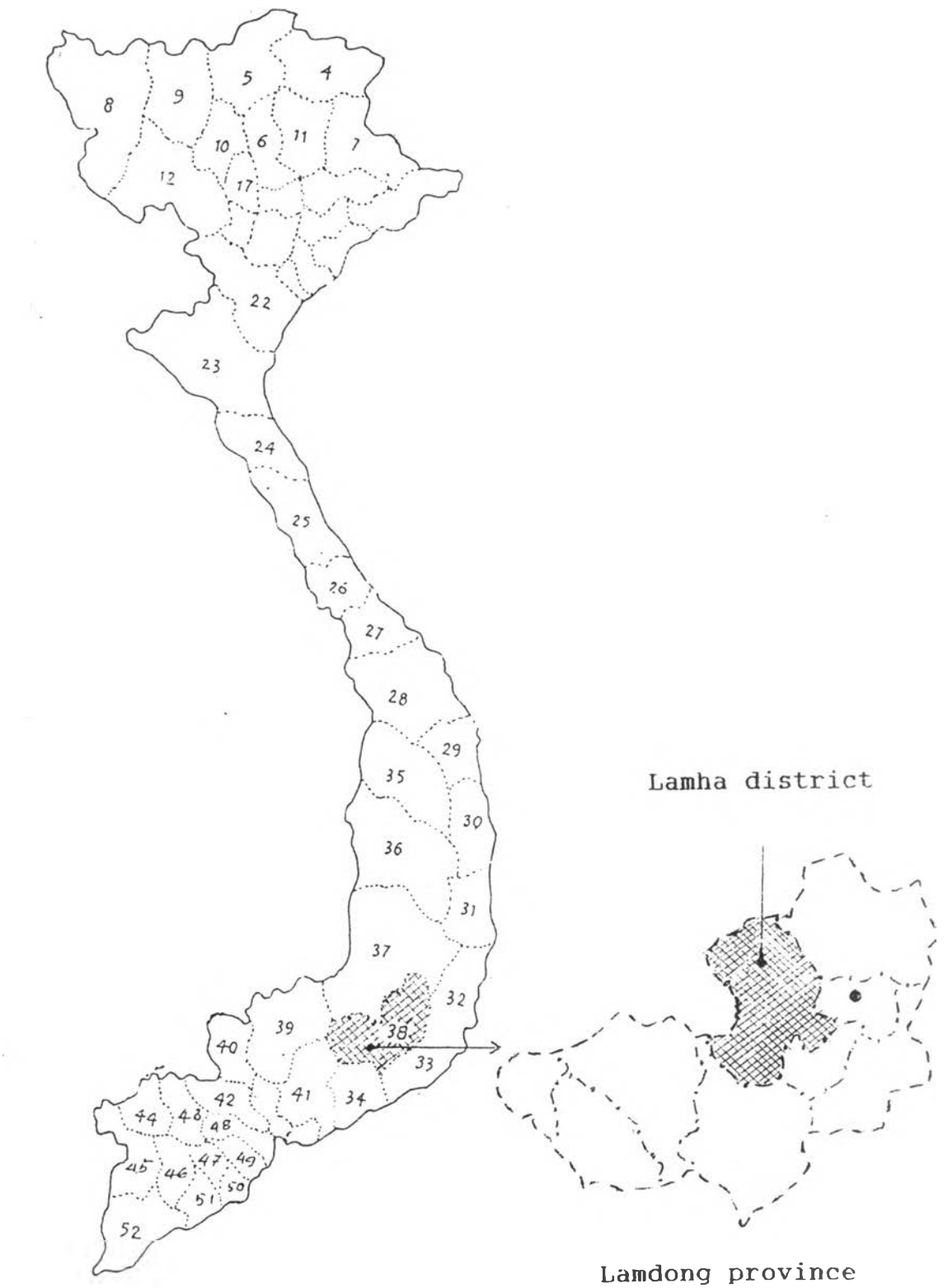
APPENDICES

1. Appendix 1 THE STUDY SITE



Appendix 2

IN VIVO TEST

(WHO Extended Test 28 Days Observation)

ANNEX 5

PROCEDURES FOR ASSESSING THE RESPONSE OF MALARIA PARASITES TO DRUGS *IN VIVO*[1]

The first step in assessing drug response is to collect baseline data on the sensitivity of *P. falciparum* to chloroquine not only in localities from which reports of suspected resistance have been received but also from areas of distribution of this parasite where the drug response appears to be normal. Several tests are available. Selection of the appropriate one should take into account the level of immunity of the subjects to be tested, their clinical condition, and the period of time within which they can reasonably be followed up. A further factor to be considered is the local epidemiological situation that will determine the likelihood of the subjects' becoming reinfected during the course of the observation period. The options available are the following:

(1) The WHO Standard Field Test consisting of the administration of 25 mg of chloroquine base per kilogram of body weight over 3 days, with a 7-day observation period (sometimes referred to as the "7-day test").

(2) The same test with the observation period extended to a total of 28 days, referred to as the "extended test".

(3) The single-dose test, or "alternative test", consisting of the administration of 10 mg of chloroquine base per kilogram of body weight. This test is applicable:

(*a*) where for any reason treatment cannot be pursued for 3 days;

(*b*) in areas of high endemicity where, owing to the elevated level of immunity in the population, a single dose of chloroquine has been accepted as the standard form of treatment; or

(*c*) as a preliminary screening procedure prior to applying the standard 3-day treatment.

All these procedures are designed for use under field conditions, although the extended test often presents difficulties in the field. They all give an indication of the response of the local *P. falciparum* strains to the dosage of chloroquine used. In principle, they should exclude various causes of drug

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[1] From: WHO Technical Report Series, No. 529, 1973 (*Chemotherapy of malaria and resistance to antimalarials*), pp. 32-37.

failure that might otherwise lead to the erroneous belief that chloroquine resistance is present in the area.

Although there is some possibility of vomiting after the first dose when chloroquine is administered by mouth, oral administration is preferred to injection because of its safety, ease, and uniformity.

The test must be evaluated by the examination of thick blood films.

Since transmission cannot always be excluded under field conditions, recrudescences cannot always be distinguished from reinfections. A determination of resistance at the RII or RIII level is therefore based on the response of asexual parasitaemia during the first week of treatment. Only if new infections can be excluded will further observations over an additional 3 weeks yield more conclusive evidence as to the recrudescence of parasitaemia, thus permitting the observer to distinguish between sensitivity (S) and the RI level of resistance.

Experience has confirmed that all steps of the test must be carried out, or at least supervised, by responsible and qualified technical staff.

Field test for response to a standard regimen of chloroquine

This field test may determine the response of a strain of malaria parasite to a standard test dosage of chloroquine (25 mg/kg over 3 days, starting on day 0). The test may be performed on subjects irrespective of age, parasite count, and previous suppressive therapy. However, it should not be carried out on a person who is seriously ill.

(1) *Procedure for standard and extended field tests*

One dose of chloroquine is given on each of 3 successive days (a total of 1.5 g of base for a 60 kg adult) according to the following schedule:

day 0 : first dose—10 mg/kg (600 mg of base for a 60 kg adult)
day 1 : second dose—10 mg/kg (600 mg of base for a 60 kg adult)
day 2 : third dose—5 mg/kg (300 mg of base for a 60 kg adult)

The chloroquine tablets must not be coated and must comply with the standards laid down by the International Pharmacopoeia or the national pharmacopoeia of the country. At the time of each drug administration precautions must be taken to ensure that the drug is swallowed and retained. To avoid nausea or vomiting, the drug should not be taken on an empty stomach. Subjects who vomit should not be used for the test.

For obvious reasons, severely ill patients should be excluded from the test. Those with mixed infections should also be excluded so as to avoid confusion over species identification. It is desirable, where possible, to include persons with high parasite counts; in practice, this will mean young children in highly endemic regions.

At all times the clinical condition of the patient must take precedence over the conduct of the test. If the parasite count is excessively high or the patient is ill at any time, it is advisable, in areas of suspected chloroquine resistance, to administer drugs of other types, such as quinine.

The subjects of the test should be observed daily for 7 days after the first day (day 0) of drug administration. Even a 7-day observation period may be impracticable under field conditions but should be insisted upon if possible. The standard 7-day field test does not permit the distinction between sensitivity (S) and resistance at the RI level. Extended observation for an additional 21 days will usually distinguish between sensitivity and RI resistance; this is the extended field test.

The results of the test may be recorded on a form such as that shown on page 209.

Duplicate thick and thin blood films should be made immediately before the first test dose and repeated daily for at least 7 days, one of each set being kept for reference. Parasite counts should be made and the species of parasite identified, because *P. malariae* trophozoites may persist for 7 days after the start of the test procedure. A thick film is considered negative when the examination of 100 fields fails to reveal any asexual parasites. Whenever possible the urinary excretion of chloroquine should be determined by a suitable method.

Urine should be collected prior to drug administration on day 0 or the previous day, and at least once during days 1–3 after the beginning of treatment (preferably on day 1 or 2).

The number of persons with symptomatic or asymptomatic asexual parasitaemia subjected to the test will depend upon the circumstances. The test can, of course, be used individually, but if information on the baseline sensitivity of the local parasites is being sought, proper sampling methods are required to give confidence in the interpretation of the results. As a working guide, tests should be made on at least 30 persons in a given locality whenever possible. If a detailed search is being made for the presence or absence of resistant strains, larger numbers should be tested. It is advisable that the results of blood examinations be available within 12 hours at the latest, or sooner if patients with clinical malaria are included in the test. Tests carried out on partially immune asymptomatic carriers with fewer than 1000 trophozoites per mm^3 of blood probably do not provide a sound basis for the thorough assessment of the action of the drug on nonimmune subjects.

(2) *Interpretation of the WHO Standard Field Test (7-day test)*

This test is interpreted as indicated in Fig. 27 (see page 105).

(*a*) If no *asexual* parasites are found by day 6 and none are present on day 7, the infection may be either sensitive (S) or resistant at the RI level.

(*b*) If asexual parasites disappear for at least 2 consecutive days but return and are present on day 7, they are resistant at the RI level.

(*c*) If asexual parasitaemia does not clear but is reduced to 25 % or less of the original pre-test level during the first 48 hours of treatment, the parasites are resistant at the RII level.

(*d*) If asexual parasitaemia is reduced by less than 75 % during the first 48 hours or if it continues to rise, the parasites are resistant to the standard dose of the drug at the RIII level. *Note:* Resistance at the RIII level may exist when the count on day 2 markedly exceeds the count on day 0. In this case the test should be suspended and the patient given effective treatment if his clinical condition so demands

(3) *Interpretation of an extended test*

This test will distinguish between sensitivity (S) and the kind of resistance that is demonstrable only by recrudescence following a normal initial response. It is interpreted as follows:

(*a*) If no *asexual* parasites are found by day 6 and parasites do not reappear by day 28, the parasites are sensitive (S).

(*b*) If asexual parasites disappear as in (*a*) but return within 28 days, reinfection having been excluded, the parasites are resistant at the RI level.

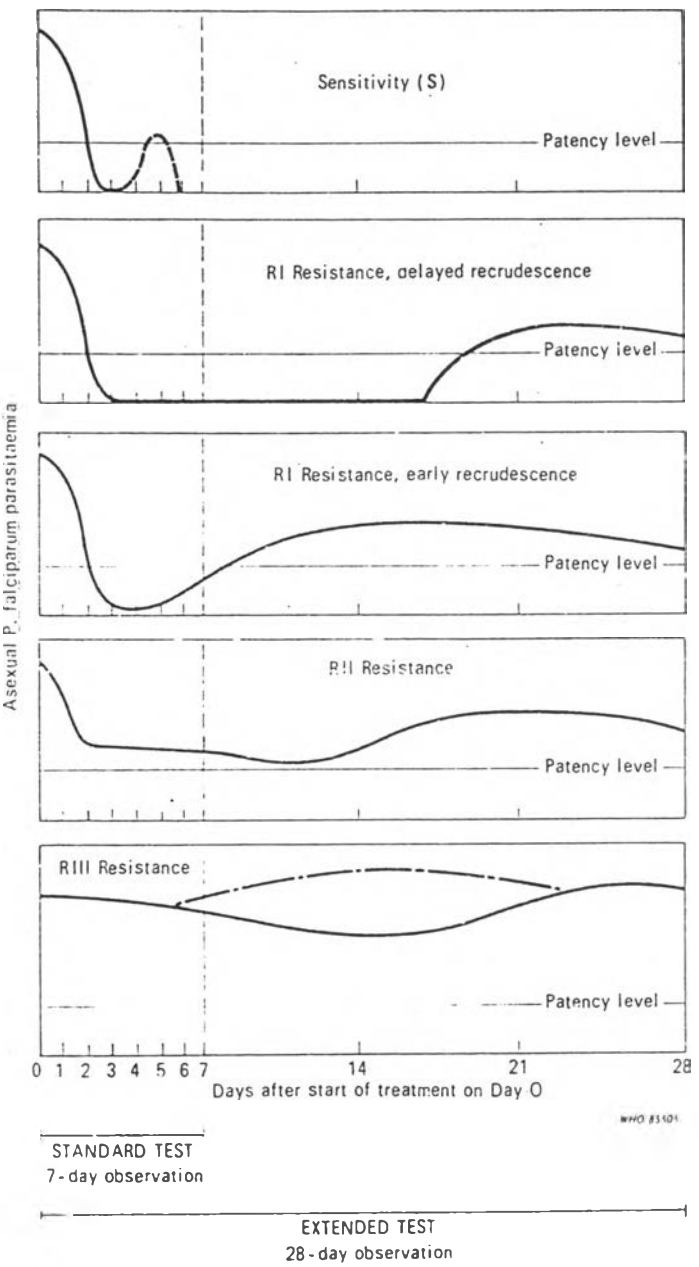
(*c*) If the asexual parasitaemia does not clear but is reduced to 25 % or less of the original pre-test level during the first 48 hours of treatment, the parasites are resistant at the RII level.

(*d*) If asexual parasitaemia is reduced by less than 75 % during the first 48 hours or if it continues to rise, the parasites are resistant at the RIII level (see cautionary note under (*d*) above).

Alternative test with single-dose treatment

An alternative test using a single dose of 10 mg of chloroquine base per kilogram of body weight can be utilized instead of the 3-day regimen. The observation period is limited to 7 days and the test is interpreted as in the WHO Standard Field Test. However, should the parasitaemia fail to respond within 7 days or recrudesce during this time, the 3-day regimen should be applied. *Here, too, it should be stressed that the clinical condition of the patient must at all times take precedence over the conduct of the test.*

Fig. 27. Response to field test for sensitivity of falciparum malaria to chloroquine[1]



[1] From: WHO Technical Report Series, No. 529, 1973 (amended)

SAMPLE FORM FOR REPORTING INDIVIDUAL RESULTS OF FIELD TESTS

RESULTS OF FIELD TEST FOR STRAIN SENSITIVITY TO A STANDARD DOSE OF CHLOROQUINE IN FALCIPARUM MALARIA*

Investigator: Date:
Name of patient: Case No:
Age: Sex: Weight (kg): Locality:
Date of first administration of drug (Day 0):
Particulars of chloroquine tablets:
Brand and origin: Dose of base per tablets:

Day	Parasites			Drug dose (mg base)	Urine test	Remarks***
	Species	Trophozoites				
		Count**	per mm³			
– 1						
0						
1						
2						
3						
4						
5						
6						
7						
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