

Malaria Prophylaxis in Indonesia*

Wita Pribadi

Abstrak

Kuinin merupakan obat malaria pertama yang digunakan di Indonesia untuk kemoprofilaksis sejak tahun 1919, kemudian disusul oleh obat lain, yaitu plasmokuin, mepakrin, proguanil dan klorokuin dengan hasil yang cukup memuaskan, akan tetapi *Plasmodium falciparum* (dan *P. malariae*) menjadi resisten terhadap beberapa obat. Penelitian mengenai penanggulangan malaria dengan klorokuin sebagai kemoprofilaksis mingguan melalui peran serta masyarakat di daerah pedesaan yang hiperendemik di Sumatra dan yang hipoendemik di Jawa Tengah menunjukkan hasil yang baik. Kemoprofilaksis perorangan dengan klorokuin yang dilakukan di Kalimantan Timur dan Irian Jaya mengalami kegagalan karena *P. falciparum* resisten terhadap klorokuin. Akhir-akhir ini dilaporkan beberapa kasus infeksi dengan *P. vivax* yang juga resisten terhadap klorokuin di Irian Jaya dan Pulau Nias (Sumatra Barat). Obat kombinasi sulfadoksin dan pirimetamin sebagai profilaksis perorangan di daerah malaria resisten klorokuin menunjukkan resistensi di Irian Jaya, Kalimantan Timur dan Timor Timur. Pada saat ini doksisisiklin merupakan obat alternatif lain, yang dapat digunakan sebagai profilaksis perorangan di Irian Jaya dengan *P. falciparum* yang multiresisten. Untuk mencegah infeksi *P. vivax* sebaiknya dikombinasi dengan klorokuin. Meflokuin mungkin merupakan obat kemoprofilaksis lain untuk Irian Jaya, akan tetapi obat ini belum beredar di Indonesia. Klorokuin masih tetap merupakan obat terpilih sebagai kemoprofilaksis dan pengobatan di daerah malaria yang sensitif terhadap klorokuin di Indonesia. Proteksi perorangan terhadap gigitan nyamuk sangat dianjurkan untuk orang yang berkunjung ke daerah malaria.

Abstract

Quinine, the first known antimalarial drug has been used as chemoprophylaxis in Indonesia since 1919, followed by plasmokuine, mepacrine, proguanil and chloroquine with good results, but *Plasmodium falciparum* (and *P. malariae*) became resistant to these drugs. Recent studies on control of malaria with weekly chloroquine chemoprophylaxis through community participation in a rural hyperendemic and hypoendemic area in Sumatra and Central Java respectively, showed good results. Individual chemoprophylaxis with chloroquine carried out in East Kalimantan and Irian Jaya failed because of *P. falciparum* becoming resistant to chloroquine. Recently *P. vivax* in Irian Jaya and Nias (West Sumatra) was reported resistant to chloroquine. A combination of sulfadoxine and pyrimethamine as individual chemoprophylaxis in areas resistant to chloroquine showed resistance in Irian Jaya, East Kalimantan and East Timor. At present, doxycycline seems to be the other alternative drug for individual chemoprophylaxis in Irian Jaya with multidrug resistant *P. falciparum*. However, for protection of *P. vivax* infection it is preferable to combine with chloroquine. Mefloquine may be considered as another chemoprophylactic drug in Irian Jaya, but this antimalarial is not yet available in Indonesia. On the other hand, chloroquine is still the drug of choice for chemoprophylaxis and treatment in chloroquine sensitive malaria areas in Indonesia. Individual protection against mosquito bites should be highly recommended to persons visiting a malaria area.

Keywords : Malaria prophylaxis, Drug resistance, Antimalarials

INTRODUCTION

The control of malaria may be an individual matter, for the protection of one man or one house, or a community. Prevention of malaria in individuals and for a large group of individuals include 1) elimination of malaria parasites in the human host and suppressing the infection with chemoprophylaxis and 2) prevention of mosquitoes from feeding on man.

Chemoprophylaxis (or drug prophylaxis) implies that drugs are used before infection takes place or prior to its manifestation, with the aim of preventing either of the occurrences.

Chemoprophylaxis may refer to absolute prevention of infection (causal prophylaxis) or to suppression of parasitemia and its symptoms (clinical prophylaxis). Causal prophylaxis aims at destruction of the pre-

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* Presented at the Third Western Pacific Congress of Chemotherapy and Infectious Diseases, Bali, 7-9 December, 1992

erythrocytic forms of the parasite. The drugs employed as causal prophylaxis are primary tissue schizontocides (proguanil, pyrimethamine) which eliminate the infections before the merozoites are liberated into the blood stream. Clinical prophylaxis or suppression aims at early action on erythrocytic forms when they are released by the primary tissue forms.

All blood schizontocides namely 4-aminoquinolines (chloroquine), dihydropteroate-synthetase inhibitors (sulfones and sulfonamides), tetrahydrofolate-dehydrogenase inhibitors (pyrimethamine and proguanil), mefloquine and doxycycline, are suppressive drugs when taken in regular small doses. This paper is intended to review malaria prophylaxis in Indonesia.

MALARIA CHEMOPROPHYLAXIS IN INDONESIA

Quinine

In Indonesia malaria chemoprophylaxis has been known since 1899. Quinine, the first known antimalarial was used by Visser¹ to prevent malaria in soldiers stationed in Meulaboh on the West Coast of the Aceh Province with a dosage of 500 mg twice weekly. Visser and his wife took it for more than one year without side effects.

In 1919 Terburgh² performed malaria control in Kendal, Jepara, Semarang, Central Java, with quinine treatment and followed by prophylaxis. He gave two tablets of 200 mg daily for one month and two days a week thereafter, to adults and children over 12 years old. Also in 1919, Walch and Walch-Sorgdrager³ gave 1.5 g quinine bisulfate for five consecutive days and thereafter two days a week under good supervision to suppress an epidemic in a coconut estate in Sungai Tuan, Sumatra. In 1925 Nicolai in Kuala Simpang, on the East Coast of the Aceh Province⁴ did not favor the administration of quinine once every fourth day as prophylaxis, a method which Ziemann and others had found satisfactorily. Mooij in 1940 gave the colonial army stationed in a malarious area also 0.4 g quinine daily as prophylaxis together with other measures, such as mosquitoproof living rooms and the use of veils and gloves. Malaria took a less severe course in this population.⁵

Plasmoquine

Doorenbos used plasmoquine 40 mg and 0.5 g quinine daily for all parasitic carriers and those with an enlarged spleen. With extensive antimosquito measures,

plasmoquine treatment and the use of paris green, he succeeded in keeping malaria under control.⁶

Mepacrine

Soesilo et al did a controlled clinical trial of Atebrin (mepacrine) using human volunteers infected with *P. falciparum* and *P. vivax* through the bites of infected laboratory mosquitoes.^{7,8} As a causal prophylaxis it protected 70% of the volunteers from parasitemia, while the other 30% had parasitemia 15-24 days after the infective bite. In the control group without Atebrin, parasitemia appeared after 8-13 days. Small quantities of Atebrin in children under 2 years of age 3 times weekly in the course of 13 weeks as prophylaxis could also reduce the parasite rate to 0.

As early as 1936, Tillema reported drug resistance of *P. falciparum* cases to quinine, mepacrine, or both, in Samarinda, East Kalimantan. The patients did not respond to the normal dose of quinine or mepacrine for 17 to 20 days and only by switching drugs were the patients cured.⁹

Proguanil

De Rook¹⁰ did prophylaxis studies with proguanil in Remu, Irian Jaya, in a closed community of prisoners with a dosage of 100 mg twice a week for three months. The spleen and parasite rates dropped and also the number of clinical attacks.

In 1950-1951 Van Goor and Lodens¹¹ did a similar test with proguanil (Paludrin) and chloroquine (Nivaquine) in 3 villages in West Java. Proguanil was given 100-200 mg weekly for two years and chloroquine 100-200 mg weekly for one year. With chloroquine prophylaxis the parasitemia dropped almost to zero and the spleen rate to 10%. No side effects were encountered. At the beginning proguanil prophylaxis also gave good results, but after 6 months the parasite rate gradually increased again as *P. falciparum* and *P. malariae* became resistant to proguanil.

Pyrimethamine

Meuwissen (1961) reported *P. falciparum* resistant to pyrimethamine and proguanil in Irian Jaya.¹²

Chloroquine

In 1958 Van Dijk¹³ did mass drug prophylaxis in the Demta area, Irian Jaya, to prevent outbreaks of malaria, in addition to DDT spraying, where spraying had been going on in this area twice a year since 1954, at a rate

of 2 g/m². He gave chloroquine once a week for eight successive weeks and he achieved 93% coverage of the population. Before 1954 the area was holoendemic, with a spleen rate of 88%. The parasite rate was 41% and was reduced to 2.3% after mass drug prophylaxis.

In 1964 Meuwissen¹⁴ reported a trial with the Pinotti's method in the hyperendemic areas of Arso, Waris, Upper Tor, and on the east coast of Sarmi, Irian Jaya, to interrupt transmission. Pyrimethamine salt was used initially, but later this was changed to chloroquine salt because *P. falciparum* became resistant to pyrimethamine. This method could be useful in combination with spraying, if the salt intake is not less than 5 g per adult daily and a certain level of socioeconomic development has been reached by the community.

In 1983-1985 a study of malaria control with weekly mass chemoprophylaxis using chloroquine through community participation during a period of two years was carried out in a rural hyperendemic malaria area in Sumatra (outside Java and Bali).^{15, 16, 17} After one year of intervention the spleen and parasite rate dropped dramatically from 69.2% to 30.3% and from 24.5% to 6.2% respectively and remained about the same after two years of intervention.

In 1985-1987 a similar study was also conducted in a rural hypoendemic malaria area in Central Java, but only children under 10 years of age were given weekly chloroquine prophylaxis for nineteen months. The spleen, parasite and infant parasite rates dropped to zero.¹⁸ Weekly chloroquine and sulfadoxine-pyrimethamine (S-P) mass prophylaxis were given at random to a battalion of military personnel on 8 months' duty in a chloroquine resistant malaria area for 6 months.¹⁹ The prevalence of malaria in the group with S-P prophylaxis were 0.6%, 1%, 0.7% and 8.4% respectively after 2, 4, 6, and 8 months, the latter being without chemoprophylaxis for the last 2 months. In the group with chloroquine prophylaxis, the prevalence was respectively 1.6%, 9.9%, 16.5% and 21.8%. No side effects with either drug were observed. Malaria infection in the military group with S-P prophylaxis was less than in the group with chloroquine prophylaxis. Discontinuation of chemoprophylaxis caused a significant increase in the number of malaria cases in the S-P group but not in the chloroquine group.

INDIVIDUAL CHEMOPROPHYLAXIS

In Indonesia, individual chemoprophylaxis was also used and reported by scientists doing malaria studies in several malarious areas. Reports of individual chemoprophylaxis have been connected with the find-

ings of chloroquine and other antimalarial resistant cases.

Chloroquine

In 1975 Ebiwasa and Fukuyama²⁰ reported 2 cases with chloroquine prophylaxis 300 mg weekly in West Irian and 4 cases in West Kalimantan also with the same standard chloroquine prophylaxis, resistant to chloroquine. All resistant cases were treated with Fansidar (sulfadoxine and pyrimethamine).

In 1979 Rumans et al²¹ reported a case of Fansidar resistant *P. falciparum* in Irian Jaya, who used chloroquine prophylaxis 300 mg base twice weekly for four weeks. Three tablets of Fansidar single dose was administered, but after 4 weeks the blood was again positive for *P. falciparum*. The patient was cured with quinine sulphate 650 mg three times daily for 10 days, pyrimethamine 50 mg daily for 3 days, and sulfadiazine 500 mg four times daily for 10 days.

In 1991 Baird et al²² reported the first chloroquine resistant *P. vivax* cases in 16 of 24 residents in Arso PIR II, Irian Jaya, taking supervised weekly chloroquine prophylaxis (5 mg base/kg bw) during eight weeks of surveillance. An American working in the same village developed symptomatic *P. vivax* parasitemia despite chloroquine prophylaxis. In a trial conducted by Murphy et al²³ to document chloroquine resistant *P. vivax* in an endemic area in Irian Jaya, nine of the 20 volunteers (45%) taking standard chloroquine prophylaxis developed *P. vivax* parasitemia within 8 weeks despite high chloroquine levels in the blood.

Doxycycline

Recent personal experience of chemoprophylaxis in 8 persons with a combination of doxycycline 100 mg daily and chloroquine 300 mg weekly starting on the day of exposure and continued 2 weeks after leaving a hyper- and holo-endemic area in Timika, Irian Jaya, which was suspected to be a highly chloroquine and multidrug resistant *P. falciparum* area, showed good results. All 8 persons were fully protected. Another person who took only doxycycline prophylaxis contracted *P. vivax* infection 3 days after leaving the area. Apparently, chloroquine prophylaxis is still needed in this area to prevent *P. vivax* infection.

Mefloquine

Mefloquine prophylaxis was also carried out in 6 persons in Timika. All were fully protected with weekly doses of 250 mg mefloquine.

PROBLEMS ASSOCIATED WITH CHEMOPROPHYLAXIS

In recent years chemoprophylaxis as a malaria control strategy has become more difficult, owing in part to the expansion of drug resistance and the increasing recognition of the adverse side-effects of several prophylactic drugs. WHO²⁴ recommends chemoprophylaxis for special groups who are at high risk from severe and complicated malaria, notably non-immune travelers to areas of malaria transmission, pregnant women, and non-immune persons living in closed communities in endemic areas, e.g., labor forces, police, and army units. In Indonesia, newly arrived non-immune transmigrants settling in a malarious area, are given chemoprophylaxis for the first three months.

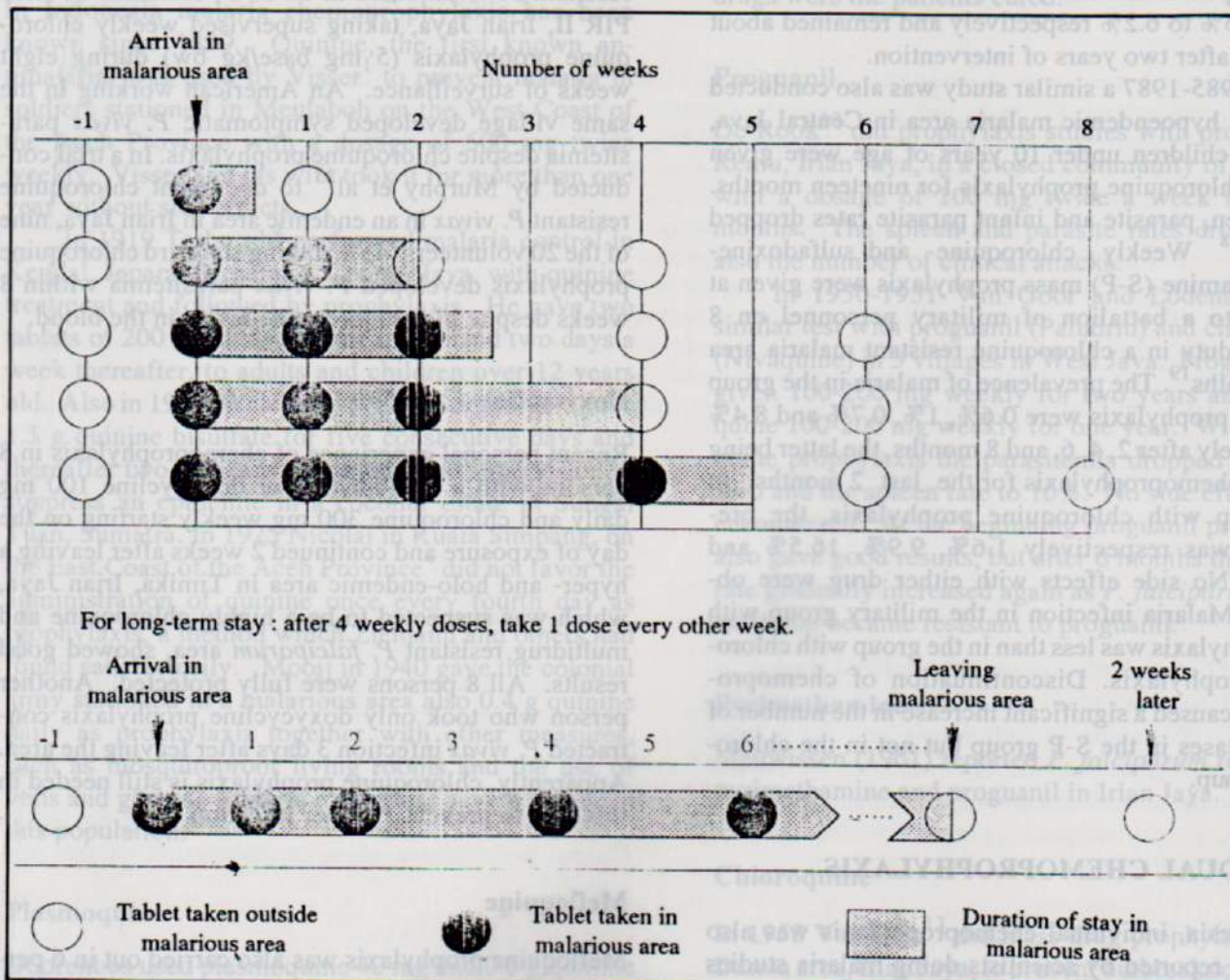
In the past, it was often assumed that malaria chemoprophylaxis in non-immune people was of benefit and without serious complications and that, consequently it was preferable to recommend prophylaxis to travelers whose risk of acquiring malaria was uncertain. But now it is no longer true that

chemoprophylaxis is always better than no prophylaxis, nor is it true that a more effective but less safe drug is always preferable to a less effective but safe one.²⁵

Since certain drugs are contraindicated in certain groups of individuals, pregnant women, very young children and the very old should carefully consider the urgency and need to travel to areas where there is transmission of *P. falciparum* and particularly of its drug resistant strains.

Chemoprophylaxis

If travel to malarious areas is unavoidable, chemoprophylaxis should be considered. Malaria chemoprophylaxis should preferably start with the intake of the drug 1-2 weeks before travel to a malarious area (except for doxycycline, 1-2 days before) and continue during travel in the malarious area and for 4 weeks after leaving the malarious area (except for mefloquine, 2 tablets after the end of exposure²⁶) (see Figure 1).



From MMWR 1990; 39 / No RR 3

Figure 1. Recommended doses of mefloquine at various lengths of stay in malarious areas

DRUGS FOR CHEMOPROPHYLAXIS

The range of drugs available for prophylaxis is limited and at present there is NO drug that guarantees 100% protection in any endemic area. Most of these drugs are schizontocides that must be maintained at suitable blood concentrations to be effective against the parasites in the blood. The available drugs differ in their efficacy, speed of action, side-effects and suitability, for use in combination with other antimalarials. These factors are influenced by the pharmacokinetics and metabolism of the drug in humans.

Therefore, the design of prophylactic dosage should be based on sound pharmacokinetic knowledge to maintain optimal efficacy and to reduce or prevent toxicity.²⁵

Chloroquine

This drug has been the most widely used antimalarial for prophylaxis in the last 40 years. Its efficacy is very high, but *P. falciparum* has become more resistant to this drug and spreading throughout the world. In Indonesia, there have been reports from all 27 provinces and recently *P. vivax* was reported to be resistant to chloroquine in Irian Jaya and Nias. The drug is well tolerated and safe for pregnant women and children.

The side effects are (1) pruritus especially in persons with dark pigmented skin, (2) irreversible retinopathy caused by accumulation of chloroquine in the retina, (3) and gastrointestinal disturbances. The dosage is 300 mg base weekly (5 mg base/kg bw). Peak plasma levels of chloroquine are reached within 1-6 hours. Chloroquine is always eliminated from the body; after a single dose of 300 mg base, the drug and its metabolite can be detected in plasma for up to 56 days. The half life is initially 5 days, but in the terminal phase it is up to 12-14 days.

Proguanil, Chlorproguanil

These compounds are dihydrofolate reductase inhibitors. Its efficacy as causal prophylactic is good but as suppression it has a slow action and is less effective than chloroquine. *P. falciparum* and *P. vivax* have become resistant to both compounds. It is not contra-indicated for pregnant women and has a very low toxicity. The dosage of proguanil is 100 mg or 200 mg daily and can be given in combination with chloroquine weekly. Chlorproguanil can be given 20 mg weekly. Combination of proguanil and amodiaquine may cause agranulocytosis and hepatitis.

The pharmacokinetic studies are limited, the absorption is very rapid. Peak plasma concentration of proguanil is achieved within 4 hours and the plasma half life is 12 hours, while that of chlorproguanil is longer (24 hours). These compounds are not available worldwide, also not in Indonesia. There is a presence of resistant *P. falciparum* and *P. vivax* to both compounds.

Pyrimethamine and its combination with other drugs

Pyrimethamine and sulfadoxine (Fansidar, Suldox)

Efficacy of this drug combination in Southeast Asia is quite low, particularly in Thailand and Burma, and reduced in Bangladesh, Papua New Guinea, Solomon Islands, Vanuatu, and in the eastern part of Indonesia (Irian Jaya, East Timor) because of resistance of *P. falciparum*. It is not recommended in pregnant women. Fatal cutaneous reactions (Stevens - Johnson syndrome) occur occasionally.

The dosage is one tablet weekly containing 500 mg sulfadoxine and 25 mg pyrimethamine.

Pyrimethamine and sulfalene (Metakelfin)

This combination is widely used in India, but it is not available in Indonesia.

Pyrimethamine and dapsone (Maloprim)

This drug combination is used in UK., Malaysia, South Africa, but it is not available in Indonesia.

Mefloquine (Lariam)

The efficacy of this drug is very high against multi-resistant *P. falciparum* and against *P. vivax*. Its safety is not well known. Side effects are gastro-intestinal disturbances and dizziness. It is not recommended in children less than 15 kg bw, pregnant women, airline pilots who require fine coordination and spatial discrimination, and travelers using beta blockers (because of its interaction with cardio-active drugs).

The dosage is 250 mg base weekly for 4 weeks, followed by one dose every other week²⁶ (Figure 1). The drug is expensive and it is not widely available, and not available in Indonesia. Pharmacokinetics of this drug varies in rate of absorption and plasma half-lives. Peak blood levels are reached within 2-12 hours and the half life varies between 6 to 36 days. A carboxylic metabolite that is inactive as an antimalarial, has been identified as the major metabolite,

but others (as yet uncharacterized) exist. The role of these metabolites in the production of side-effects is unknown.

Doxycycline

This drug is effective against multidrug resistant *P. falciparum* according to limited and small scale trials in Thailand. In Indonesia it appears to be not effective against *P. vivax* when used as prophylaxis. It is reasonably safe, but not recommended in pregnant women and in children under 8 years old. The side effects are nausea and vomiting, oesophageal ulcers, pseudomembranous enterocolitis, monilial vaginitis, photosensitivity under extreme sunlight. The dosage is 100 mg daily. The plasma half life is 14-22 hours.

Primaquine

Its efficacy is against tissue stages, and has a gametocytocidal effect; in combination with chloroquine it is used against *P. vivax* and *P. ovale*. The drug is not recommended in persons with lupus erythematosus and rheumatoid arthritis. Its side effects are severe hemolysis in G6PD deficient subjects, and causes leukocytosis, anemia, and methemoglobinemia.

The dosage is 15 mg base daily during the last 2 weeks of the 4-week period of prophylaxis after exposure in an endemic area has ended.²⁷

Quinine

Quinine is not used for prophylaxis since its kinetics are inappropriate, and the incidence of side effects is unacceptably high.

CHEMOPROPHYLAXIS FOR CHILDREN

Pediatric doses should be calculated carefully according to body weight. Overdose of anti-malarial drugs can be fatal. Mefloquine is not indicated in children less than 15 kg bw and doxycycline is contraindicated in children less than 8 years of age.²⁶ Infants who require chemoprophylaxis should receive the recommended dosage of antimalarials, because the quantity of antimalarials transferred in breast milk is not sufficient to protect against malaria.

PROPHYLAXIS DURING PREGNANCY

Women who are pregnant or likely to become so, should avoid travel to areas with chloroquine-resistant

P. falciparum because mefloquine and doxycycline should not be used during pregnancy. Chloroquine and proguanil are not contraindicated in pregnancy.²⁶

PROTECTION AGAINST MOSQUITO BITES

Traveler's exposure to infection may vary according to: a. the area visited, whether it is urban or rural; b. the time and duration of stay (transmission season and relative intensity of transmission); c. purpose of visit (business, hunting or camping); d. type of accommodation (air-conditioned, screened, camping); e. use of protective measures (drugs), compliance with them and their efficacy.²⁶ Because of the current epidemiological situation of malaria and the lack of completely safe and effective drugs for prophylaxis, individual protection against mosquito bites might play an important role in malaria prevention. However, personal measures of protection are not always properly or fully utilized.

To reduce contact with mosquitoes, the following measures should be taken²⁶:

1. If possible, choose air-conditioned or screened accommodation.
2. When not available, use a mosquito net, impregnated with permethrin-emulsifiable concentrate (0.08 - 0.2 g active ingredient per m²).
3. Wear long-sleeved clothing and long trousers when outdoors between dusk and dawn, and keep the ankles protected.
4. Apply a mosquito repellent sparingly, only on exposed skin (Dimethyl phthalate, DEET = NN - diethyl-toluamide).
5. Use an insecticide aerosol, preferably a synthetic pyrethroid to clear the screened room of any resting mosquitoes. Permethrin may be sprayed on clothing for protection against mosquitoes.

In Indonesia, generally chloroquine is the drug for individual chemoprophylaxis except when visiting multidrug resistant areas. Foreign travelers visiting Indonesia should use the drug given or prescribed by their own physicians before leaving their countries.

CONCLUSION

1. Malaria chemoprophylaxis in Indonesia has been known since 1899.
2. Drug resistance was reported since 1936, predominantly present in the eastern part of Indonesia.
3. Drugs for chemoprophylaxis should be used with caution.

4. Individual protection against mosquito bites should be highly recommended to persons visiting malarious areas.

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