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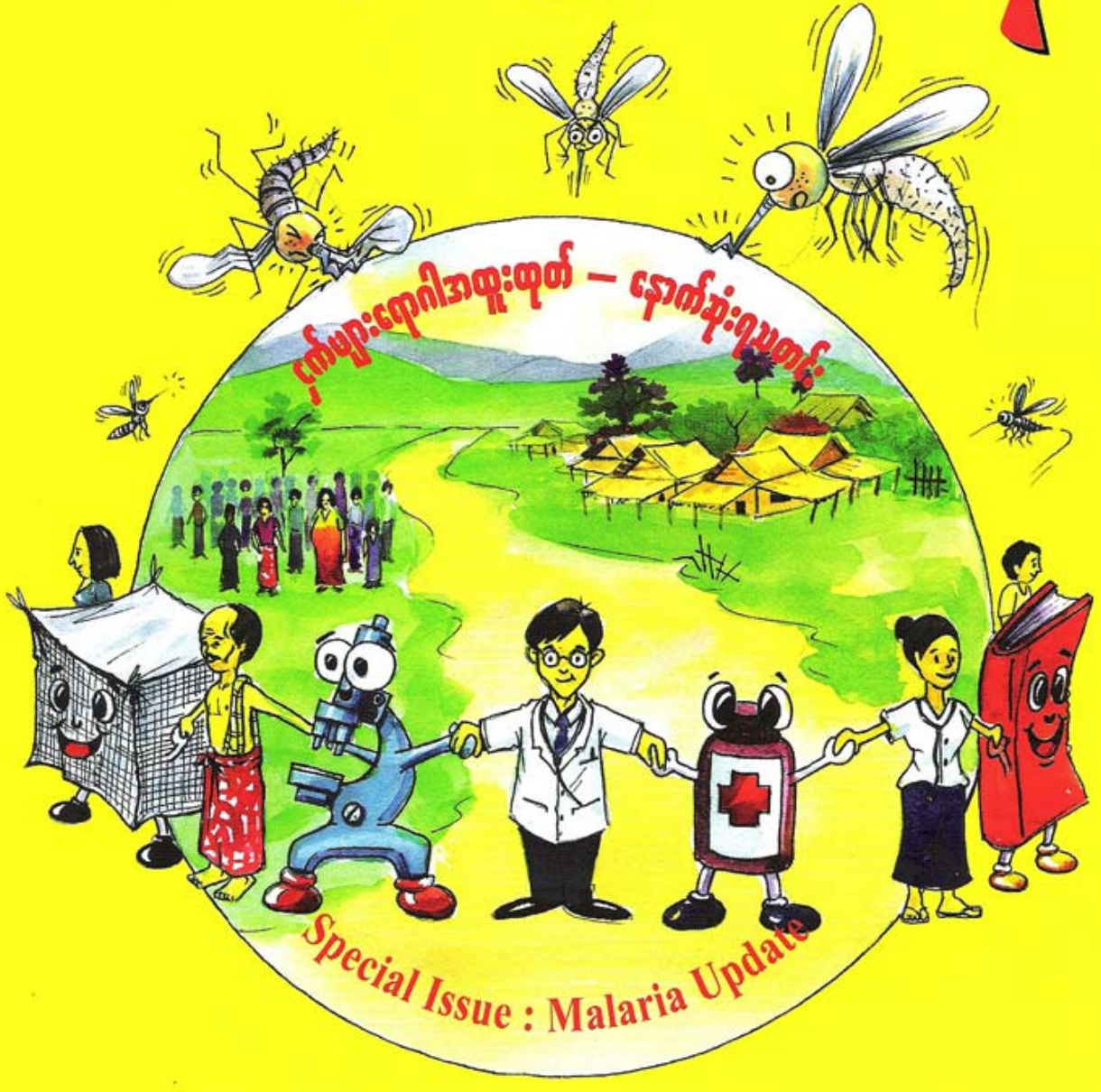

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Thanks to Mr. Myo Aye (IRC), other translators for translation, Mr. Stephen Look for English proof-reading and Mr. Suchit Mingmalee for drawings.

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Editorial

Dear Readers,

At the beginning of the rainy season this issue will bring you some current information on malaria, which will focus on its diagnosis, treatment, malaria in pregnant women. Also discussed here is non-falciparum malaria, and some important issues on completing antimalarial treatment.

A special edition of Saytaman (May-June, 1997), discussed Malaria in detail. After the XIIIth Malaria Meeting in Mae Sot (27-28 November, 2001), we have continued our efforts to add more information to enhance the knowledge of our readers. We are grateful to the Shoklo Malaria Research Unit (SMRU) for their contribution and sharing of research findings with our readers.

We hope this issue will bring up-to-date knowledge on malaria to our readers.

Enjoy your reading.

Best regards.
Dr. Seerat Nasir
Editor

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Students drafting questions to ask community members about malaria.

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Participatory Learning and Action for Community-Based Malaria Control

James Hopkins, Kenan Institute Asia

This article describes a process for community empowerment using participatory learning to develop and apply life skills for community action against malaria.

Rationale

The global movement for Roll Back Malaria now recognizes malaria as a local and focal disease that varies considerably even from village to village, depending on interactions of many types of factors, e.g. economical, social, cultural, ecological, and biological. Therefore, effective malaria control requires understanding of the local situation — the causes and incidence of infection and disease of that particular area — and emphasizes participation of affected populations. The population can be involved in community-based assessment, analysis, planning, action, monitoring and evaluation of malaria prevention and control programmes.

Traditionally, the responsibility for malaria control goes to public health authorities in national malaria control programmes and to international humanitarian agencies in camps for refugees and displaced persons. This has resulted in the deep-rooted perception that ownership of the malaria problem lies with external intervening agencies, rather than with the affected populations themselves.

Malaria epidemiological information systems typically compile, aggregate, and communicate data to serve the needs of those external agencies in managing control operations. People in communities and camps affected by malaria usually lack

Roll Back Malaria

On assuming office in 1998, the new Director-General of WHO, Dr. Gro Harlem Brundtland, identified malaria as one of the organization's top priorities, and launched the Roll Back Malaria initiative. RBM is a global partnership of malaria-affected countries, UN organizations, bilateral development agencies, development banks, NGOs, and the private sector. Its common purpose is to significantly reduce the global malaria burden through interventions adapted to local needs and by reinforcement of the health sector. RBM strategies are based on regional, epidemiological, and health system needs and focus on community and district-level action. The principal mechanism for achieving this is through intensified national action by country-level partnerships working together towards common goals.

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access to and understanding of malaria epidemiological information on their local situation, thus severely limiting their ability to actively participate in malaria prevention and control programmes.

School-Based Community Participatory Learning and Action Process

Kenan Institute Asia's Border Action Against Malaria Project is collaborating with The Life Skills Development Foundation on pilot implementation to build a model process for empowering communities using a 'participatory learning and action' approach. This approach aims to develop life skills and mobilize local resources to address multi-drug resistant malaria, initially in 25 villages along the Thai-Burma border in Tak and Mae Hong Son Provinces.

Life skills: "Abilities for adaptive and positive behaviour, that enable individuals to deal effectively with the demands and challenges of everyday life" (WHO, 1993). Psycho-social competencies (creative and critical thinking, problem-solving and decision-making, planning and management, setting goals, teamwork, etc.).

The school-based community **participatory learning and action (PLA)** process promotes teaching reform by using participatory learning methods and strengthens linkages between the school and community. Trained teachers help primary and middle school students to develop life skills using a community case study approach, infusing the malaria theme across the curriculum in subjects including health education, social studies, mathematics, science, art, Thai and English languages. The emphasis is on school-community participation in data collection, situation analysis, and communication of epidemiological information among members of the affected population for use in decision-making and problem-solving.

Through this process, communities become empowered to take ownership of the malaria problem, generate locally feasible solutions, and initiate community-based actions against malaria with support from local government, health services, and other enabling sources.

Throughout the school-community PLA process, communication in local languages is a critical success factor. Students are encouraged to use their own languages when conducting community surveys, presenting results to the community, and for discussions

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Students presenting results of community malaria situation analysis to community leaders.

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Key steps in the process include:

1. Orientation to the process for all stakeholders.
2. Training using active participatory learning methods in community malaria situation assessment for teachers, health/malaria workers, community health volunteers, and local government council members.
3. Collection of data by students on the general context of the community, knowledge, attitudes, and practices of the community regarding malaria.
4. In-depth study of the community malaria situation by students using data from malaria/health officials and from direct surveys of the community which include:
   - risk analysis of malaria infection including risk groups (sex, age, occupation, residents/migrants), key sites of infection (village, other villages, farm huts, forests, foreign countries), monthly occurrence of infection and transmission peaks.
   - characteristics and behaviour of local *anopheline* vectors.
   - community behavior for personal/family protection against mosquito bites and reasons for lack of use of various methods.
   - vector control measures and reasons for lack of cooperation.
   - diagnosis/treatment seeking behaviour, drug use practices, and barriers to early diagnosis and rapid effective treatment.
   - personal, family, and community impact of malaria (monetary and non-monetary).
5. Presentation of results to the community by students, discussions, validation of findings.
6. Study and assessment of feasible alternatives for action by the community to reduce the malaria problem.
7. School-community workshops to present and review results of the situation analysis, create a common vision, and build consensus to decide on the best alternative actions to be taken by the community to reduce the malaria problem.
8. Formulation of school-community action plans and projects to reduce the malaria problem and conduct further studies.
9. Meeting of civil society shareholders and local councils to mobilize technical and financial support for community-designed action plans and projects.
10. Implementation of school-community action plans and projects.
11. Participatory monitoring and evaluation of school-community action plans and projects.

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Student-made posters on methods for reducing density of Anopheles mosquito population and impact of malaria on individual, family, and community.

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Student-made poster on community behaviour in seeking treatment for malaria.

on comparing alternatives and formulating plans and projects. Students create many different types of colourful and interesting materials to show their learning and illustrate the local malaria situation, including graphs, mind maps, big books, small books, drawings, maps, etc. Communities find these materials much more interesting than mass-produced materials.

Community-Based Malaria Control

In addition to raising awareness, the PLA process **empowers** communities by developing and applying correct knowledge, positive attitudes, and life skills necessary to analyze problems, make informed decisions, plan and organize for action. Once community/local ownership, empowerment, and participation have been activated, external agencies can shift their role to promote an **enabling** environment through capacity building, technical and financial support. Building on a successful PLA, the next step is to develop simple and sustainable models for community-level malaria epidemiology, epidemic early warning, and monitoring information systems. To be useful, these models need a network for two-way communication of key site-specific information in a timely manner, linking communities, decentralized health systems, and local governments to enhance self-reliance in prevention and control of malaria.

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Community members discussing results of community malaria situation assessment presented by students

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Community members listening to student presentation in the community malaria situation assessment.

The process described in this article is now in pilot implementation in Tak Province (Mae Ramat and Tha Song Yang) and in Mae Hong Son Province (Muang and Sop Moei).

Readers who would like more detailed information on the process and results emerging from its implementation may contact:

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Non-Falciparum Malaria

Dr. Francois Nosten, SMRU

This article will describe briefly three kinds of malaria other than P.falciparum.

There are 3 non-falciparum malarial parasites: *Plasmodium vivax, P. ovale and P. malariae*. The most common of the 3 species is *P.vivax*.

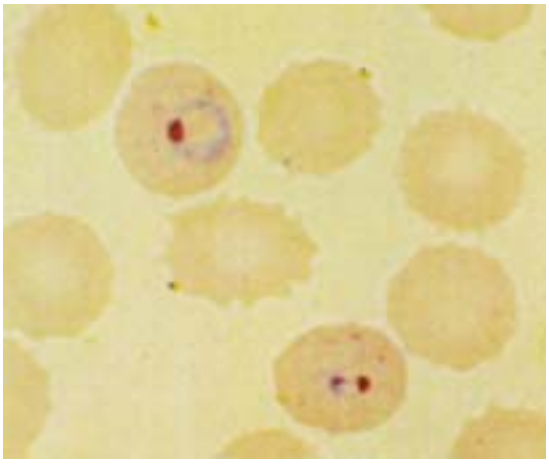
Along the Thai-Burmese border, *P.falciparum* was the most common species in the camps (70%) and *P.vivax* was less common (30%). However, since 1994 all cases of falciparum malaria have been receiving a combination treatment of mefloquine and 3 d artesunate, which interrupts the transmission of falciparum by destroying the gametocytes. This treatment is not given to *P.vivax, P.malariae* or *P.ovale* cases. As a result, the non-falciparum infections have now become the dominant species.

Characteristics of non-faliparum malarial parasites

Each malarial parasite species has its own characteristics. *P.vivax* and *P. ovale* are the only ones that produce hypnozoites. The hypnozoites can remain in the liver for weeks, months or years without symptoms. One day, for unknown reasons, the hypnozoites (sleeping forms) wake up and multiply and start a new malaria attack.

Clinically, there are not much differences among the 3 non-falciparum malaria species. In uncomplicated cases it is also impossible to find the clinical difference between a *P.falciparum* case and the others, except may be for the rigors that seem more frequent in vivax than in falciparum infection.

The various species of plasmodium can infect the same patient at the same time.



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Blood film in P. malariae infection showing ring form trophozoites in red cells

P.falciparum and *P.vivax* (not rare on the border) or *P.falciparum* and *P.ovale* or *P.malariae*. In exceptional cases all 4 species are seen in one slide. We know little about the influence of one species on the others, but we have evidence that during pregnancy, the women who are first infected by *P.vivax* have a lower risk of getting a *P.falciparum* infection later. In children, those with a mixed infection *(P.falciparum* and *P.vivax*) have a lower risk of getting a severe infection, have less gametocytes, less anaemia and have a lower risk of treatment failure than those who have a *P. falciparum* only infection. It looks like *P.vivax* may be protective against *P.falciparum*, but the mechanisms of this protection, if it exists, are unknown.

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Selected Characteristics of the Four Species of Human Malaria

	P. falciparum	P. vivax	P. ovale	P. malariae
Incubation days (range)	12 (9-14)	13 (12-17) or up to 6-12 months	17 (16-18) or longer	28 (18-40) or longer
Exoerythrocytic cycle (days)	5.5-7	6-8	9	12-16
No. of merozoites per liver cell	40,000	10,000	15,000	2,000
Erythrocytic cycle (hours)	48	42-48	49-50	72
Red blood cell preference	younger cells, but can invade cells of all ages	Reticulo-cytes	Reticulo-cytes	Older cells
Relapses	No	Yes	Yes	No
Fever periodicity (hours)	none	48	48	72
Febrile paroxysm length (hours)	16-36 or longer	8-12	8-12	8-10
Severity of primary attack	severe in non-immune	mild to severe	mild	mild
Drug Resistance	++	+	-	-

Non-falciparum infection in children and pregnant women

P.vivax (and also *P.ovale* and *P.malariae*) are considered benign because they rarely cause severe disease. **However, *P. vivax* can be fatal in very young infants, mainly because of the severe anaemia it may cause**. Small babies with vivax malaria should be watched carefully in the first 48 hours following treatment. *P.vivax* (and probably the other non-falciparum species) are also indirect causes of death because of their impact on pregnancy. During pregnancy, *P.vivax* causes anaemia in the mother and a reduction of the birthweight. Fever can cause premature labour and abortion. Low birthweight and prematurity

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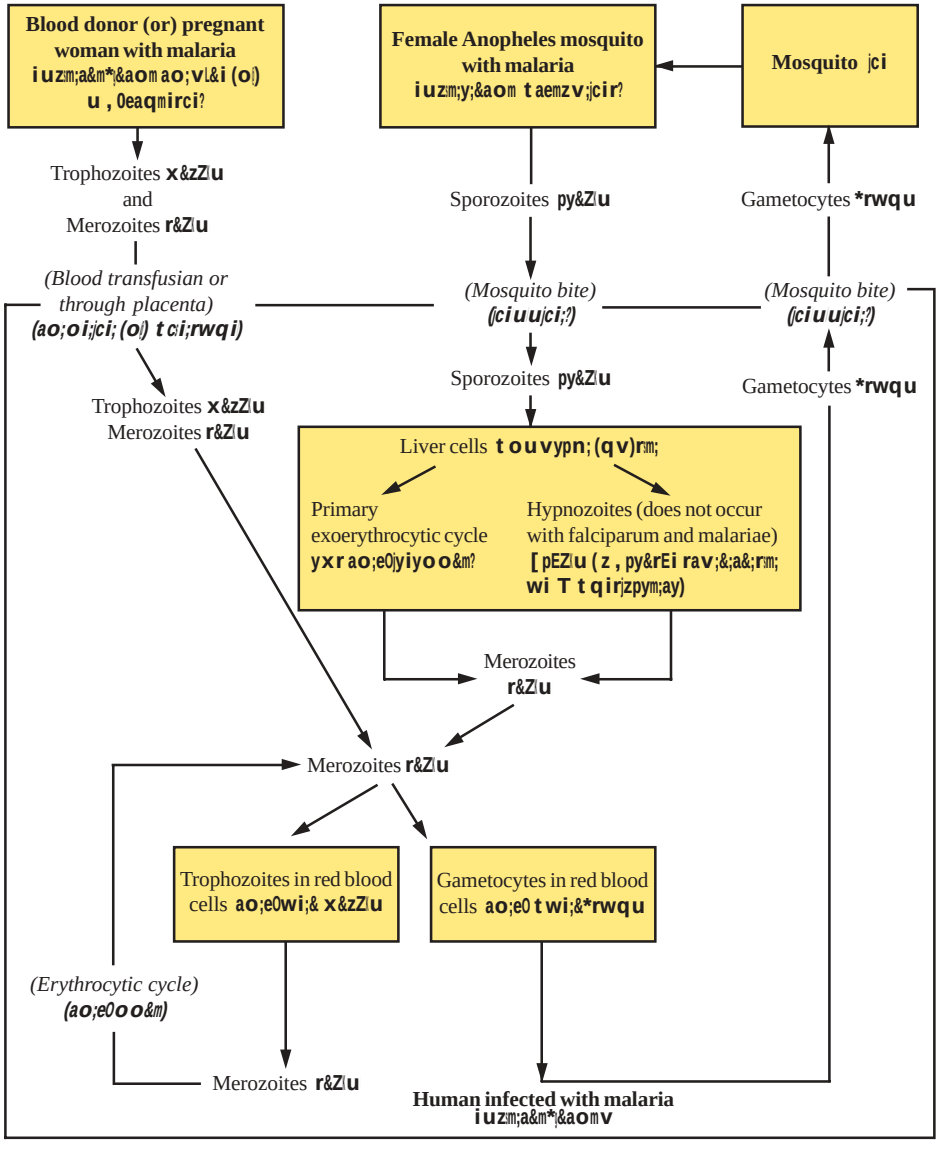
The graphic below represents the malaria parasite cycle in the host (human) and the vector (anopheles mosquito)



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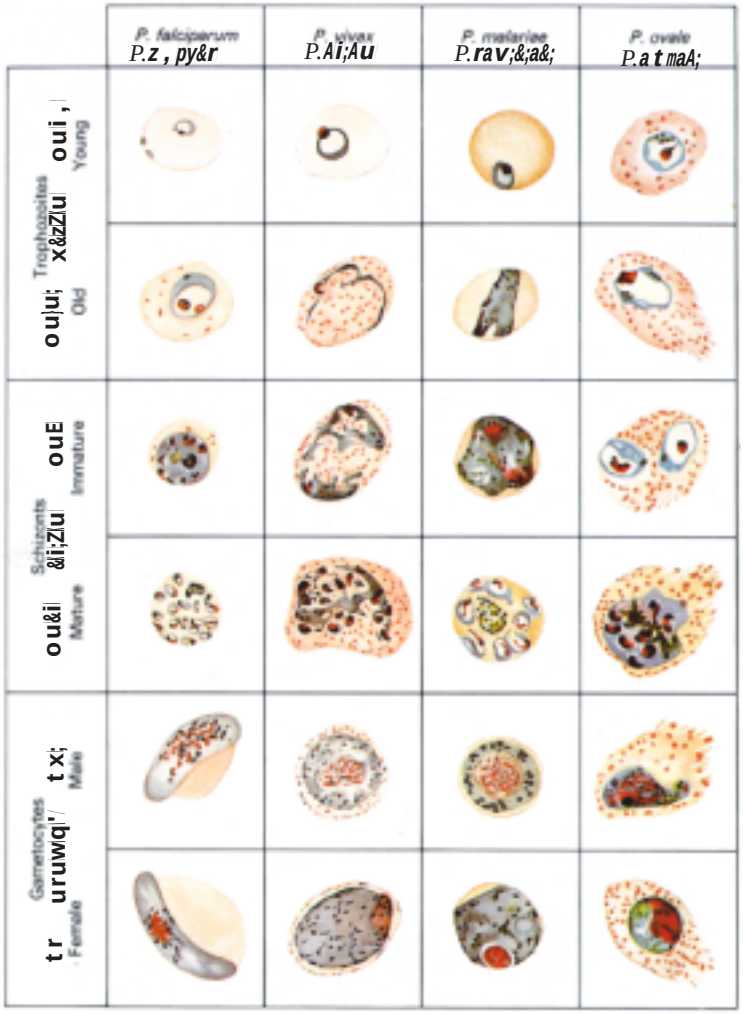

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Appearance of parasite stages in Giemsa-stained film

are two major factors of neonatal death. It means that treating *P.vivax* early and effectively during pregnancy can improve the survival of the infants (See page 22 or more details).

Treatment of non-falciparum malaria

The non-falciparum parasites remain sensitive to chloroquine in most areas, but resistance to *P.vivax* has emerged in Indonesia and may be in the north of Burma.

On the Thai Burmese border *P.vivax* remains sensitive to chloroquine and the treatment regimen consists of 25 mg base/kg over 3 days. This treatment will clear the fever and the parasites from the blood within 48 hours in most patients. The problem is that 63% of the patients have a relapse of vivax within 9 weeks after treatment with chloroquine. These relapses do not mean that the parasite is resistant to chloroquine. They are caused by the hypnozoites in the liver. These are not eliminated by chloroquine. Eighty-five per cent of the cases of relapse are symptomatic (fever and other signs of malaria) and children have more frequent relapses than adults. The only drug that can kill the hypnozoites is primaquine. If relapse cases

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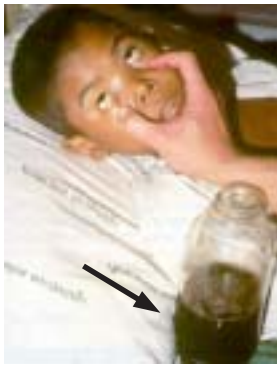

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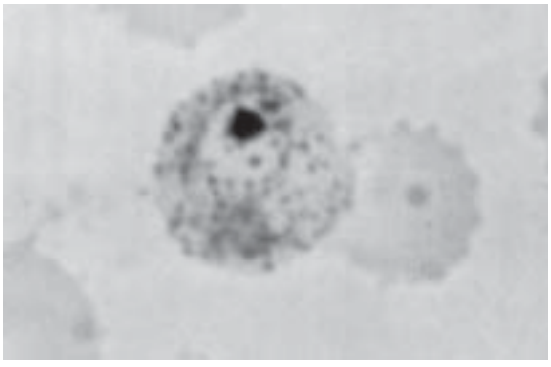
Haemoglobinuria in a Thai patient with G6PD deificiency who took primaquine. (Photo: D.A. Warrell)



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Fully developed schizont of P.vivax. (Wellcome Museum of Medical Science).

are treated with chloroquine again, 80% will have another relapse in the following 9 weeks. If the relapse cases are treated with chloroquine and primaquine (0.25 mg/kg/day for 14 days), 90% will be cured without relapse in the following 9 weeks.

The problems of using primaquine are many. For example:

It must be taken for 14 days and adherence is very poor if the treatment is not supervised.

It must not be given to pregnant women.

It is toxic and can cause haemolysis in patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency (10% of the population on the border is G6PD deficient).

It also causes gastro-intestinal side effects.

In practice we do not recommend the systematic use of primaquine in patients living in the area. Certainly, the single dose of primaquine given occassionally to patients with falciparum malaria is not justified. For vivax infection, a 14-day course of primaquine should be considered in patients with frequent relapses. **The G6PD test should be done before starting primaquine**. If the patient is G6PD deficient, care should be taken for the use of primaquine and the Hb or Hct of the patient monitored every 2 days. ***Primaquine should be interrupted immediately if the Hct (Hb) on day 7 falls by more than 3% of the baseline value or if it falls below 30%. For example, if the baseline Hct on day 0 is 35% and the Hct on day 7 is 33%, the reduction is (35-33/35)x100=5.7 and the drug should be stopped.***

In conclusion, it can be said that the main non-falciparum malaria species along the border is *P.vivax*. It causes more morbidity (anaemia especially in pregancy) and mortality than most people think. It must be treated with chloroquine. Primaquine should be used if relapses are frequent.

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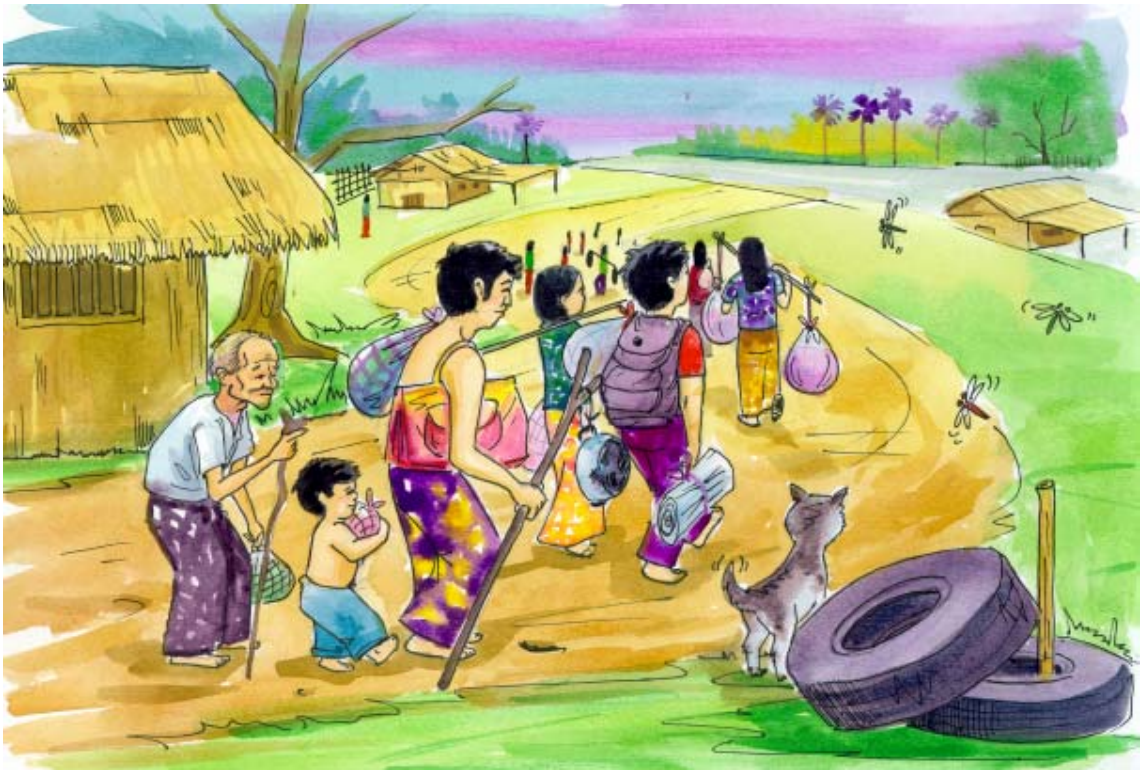

Population Movement and Malaria

Dr. Naw Nhai. M, SMRU

Identifying and understanding the effects of population movements on the spread and control of malaria can improve prevention measures and effectiveness of the existing malaria programmes!

Malaria is one of the major tropical diseases, causing many deaths and morbidity as well. Malaria is transmitted through the bite of an infected female Anopheline mosquito. Many factors can affect the transmission of malaria. For example, unusually warm and humid weather, heavy rain, and favorable environmental conditions such as colonization of tropical jungle areas by successive agricultural settlers, displacement of large numbers of people, e.g., migrant workers and refugees, especially those living in the border areas. The northwestern border of Thailand that harbours the drug resistant *Plasmodium falciparum*, can be taken as a typical example of one of the many obstacles to successful malaria control. Several different ethnic groups reside along the border and they are usually a mobile population. Population movement can precipitate or increase malaria transmission. It constitutes a major challenge to the control of malaria and is now probably the major factor contributing to the spread of resistant strains of malaria.

One of the factors contributing to the re-emergence of malaria is human migration. People move for a number of reasons, including economic reasons, conflicts and natural disasters. These factors are most likely to affect the poor, many of whom live in or near malaria prone areas. A large number of people move along the Thai-Myanmar border. There are approximately 480,000 living along the northwestern

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A refugee family (Photo from Mekong Malaria Forum, issue no. 2, May 1999)

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border of Thailand. Among them 400,000 are Thai, who are permanent residents and the other 80,000 are hill-tribe and ethnic minority groups. The "border population" can be seen as a mosaic of various communities linked by cultural and/or geographical similarities, including Thai nationals (the majority are Karen), migrant workers from Myanmar and refugees.

The mobile population looks for jobs, and works in the forests and farms. Not only do they lack knowledge concerning the features and dangers of malaria, but they are also poor and have no money to buy mosquito nets, repellents or seek antimalarial treatment. This complicates the task of Malaria Control Programmes because of language, cultural differences and inaccessibility. As a result, many individuals remain out of reach of the malaria control efforts. Identifying and understanding the influence of these population movements can improve prevention measures and existing malaria programmes.

If control of malaria can be achieved in this mobile population, this will offer considerable and sustainable health benefits to all.

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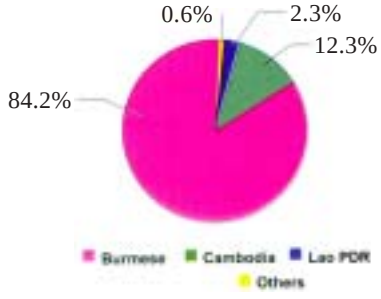
Figure 1 Malaria Cases among Foreign Nationals in Thailand, 1998.



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Source: Mekong Malaria Forum (Issue no. 2, May 1999)

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Figure 2 Thai and Foreign Malaria Cases Detected in Thailand, 1993-1998.

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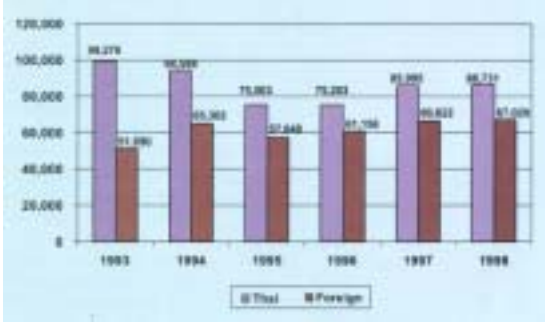

Source: Mekong Malaria Forum (Issue no. 2, May 1999)

There are many strategies to combat malaria in mobile populations, such as

- Early diagnosis and providing effective artemisinin containing combination treatment.
- Vector control measures.
- Personal protection and use of mosquito repellents.
- Strengthening accessible sites for health care services.
- Technical collaboration with all organizations involved in people's health.
- Health education concerning prevention and treatment of malaria.
- Adoption of effective national policy for control of resistant malaria.

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Malaria in Pregnancy : Important Issues

Dr. Rose McGready, SMRU

This article will focus on the complications of malaria in pregnancy and care of the pregnant women infected with malaria and their babies.

Studies conducted by Karen midwives in different refugee camps along the Thai–Burmese border over the past 15 years have helped us understand a lot more about malaria in pregnancy and how to improve our care of pregnant women. After reading this article, you should know more about:

- The main complications for the mother and baby.
- The care of the mother and child when the woman is infected with malaria during pregnancy.

From the limited available information on malaria in pregnancy, we can deduce that a pregnancy makes a woman more likely to be severely affected by malaria.

Effects of malaria in pregnancy can be shared in 2 groups:

1. Effects caused by the systemic infection, comparable to the effects of any severe febrile illness (such as pyelonephritis or dengue) in pregnancy: **maternal/fetal mortality, abortion, stillbirth and premature delivery.**
2. Effects caused by the parasitization itself: **birthweight reduction, maternal/foetal anaemia, interaction with HIV, susceptibility of the infant to malaria.**

These effects are discussed separately below:

Maternal/foetal mortality

In the late 1980's on the western border of Thailand with Burma prior to the introduction of weekly antenatal screening, death from maternal malaria occurred in more than one in every one hundred pregnant women[1]. This figure for maternal mortality is very high. For example, today if

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Pregnant woman having smear in Maela Camp. (Photo: SMRU).

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we did not do weekly antenatal screening in Maela Camp (about 1,200 women of around 40,000 inhabitants, get pregnant every year), malaria would be responsible for more than 12 maternal deaths in a year. Overall, maternal death in the last 10 years in Maela Camp from ALL causes is less than 12. **Weekly antenatal screening has eliminated maternal death from malaria in women who attend clinic every week.**

Pregnant women along the Thai-Burmese border are 3 times more likely to develop severe malaria than non-pregnant women of the same age. Maternal mortality can come from the severe complications of *Plasmodium falciparum* infection, such as cerebral malaria, pulmonary oedema, profound anaemia and disseminated intravascular coagulation (DIC) or renal failure. In Shoklo Refugee Camp 80% of pregnant women with cerebral malaria died. Pregnant women and patients with severe life threatening disease due to *P. falciparum* infections are at particular risk of hypoglycaemia, which may be profound and recurrent. Studies of cerebral malaria conducted in Thailand found that 50% of pregnant women developed hypoglycaemia, with a fatality rate of 50%. The factors relating to hypoglycaemia in malaria are quinine therapy, late pregnancy, a high parasite count and poor renal function and due to increased activity of pancreatic β cells (that produces insulin) function and peripheral insulin resistance.

Foetal loss - abortion / stillbirth / premature labour / perinatal death

A long time ago in 1899, a man called EDMONDS said fever was responsible for a large number of stillbirths in women with malaria. Another study from Thailand showed that the height of the fever was related to the intensity and frequency of contractions of the uterus. In the study area fever from any illness such as urinary tract infection, pneumonia, or malaria is associated with premature labour and mid-trimester abortion. The mechanism of foetal death is unknown. Autopsies performed on foetuses of women who died from severe malaria found some foetuses to be infected with *P. falciparum*.

A symptomatic *P. falciparum* infection can cause premature labour. The highest mortality in babies in the camps is in those born prematurely. Fever from *P. vivax* infection in pregnancy can also cause premature labour. This is why it is important to **treat fever in pregnant women with paracetamol and fluids, to bring the temperature down and maintain hydration.** Weekly malaria screening cannot prevent malaria, but it can pick up the parasitaemia at low levels often before the woman starts to complain of fever. **So, weekly malaria screening reduces the injurious effects of malaria because it allows early detection and treatment of malaria.**

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On the left a low birth weight baby (1.8 kg), on the right the baby is average for Karen infants (2.7kg).

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Birth weight reduction

Even if *P. falciparum* does not cause abortion, premature labour or stillbirth because it is detected and treated early, a woman can still expect her infant to be born with low birth weight. *P.falciparum* in this area causes a mean of 151 g in primigravida and 185 g in women in their 2nd and 3rd pregnancies. *P. vivax* causes a mean reduction in birth weight of 108 grams. So what? The greatest single factor related to neonatal and early infant mortality is low birth weight. The results of the follow-up of 1,500 babies born to women from Maela, Shoklo, Mae Salit, Bono and Tee Law Thee Camps shows that babies born with low birth weight (less than 2500 grams) had higher morbidity, anaemia and impaired growth. **Weekly malaria screening can help reduce but cannot eliminate the harmful side effect of low birth weight caused by malaria.**

Maternal and foetal anaemia

Plasmodium falciparum (and also *P.vivax*) parasitization in pregnancy commonly produces maternal anaemia. Severe maternal anaemia is associated with low birthweight and perinatal mortality, maternal morbidity and increased danger of fatal post-partum haemorrhage.

Maternal malaria contributes to foetal anaemia, but in developing countries the long term effects of anaemia during pregnancy on anaemia in infancy are unknown. In a recent report from this area where women followed weekly ANC and were systematically treated for anaemia if their haematocrit fell below

Interaction with HIV

Although the prevalence of HIV in pregnant women in the camps is low, the situation for women in Burma is likely to be much higher. In Africa, worse outcomes such as higher malaria prevalence and parasite density, poor response to routine prophylaxis such as chloroquine or Fansidar, increased severity and prevalence of anaemia in pregnancy and increased infant mortality have been confirmed in pregnant women infected with *P. falciparum* and HIV.

Susceptibility of infants to malaria

Many factors interplay on infant morbidity and mortality in the tropics and assessing the associations of the effects of maternal malaria on infant mortality is difficult. Infants with intrauterine growth retardation (term babies with low birth weight) frequently have impaired (defective) cell-mediated immunity (the T-cell side of the immune system), which can lower their chances of survival by increasing their susceptibility to infection, including malaria. In this area, infants born to mothers who had *P. falciparum* during the first trimester were 2.8 (1.5-5.1) times more likely to develop malaria in infancy, than infants born to mothers who had malaria during later pregnancy or no malaria.

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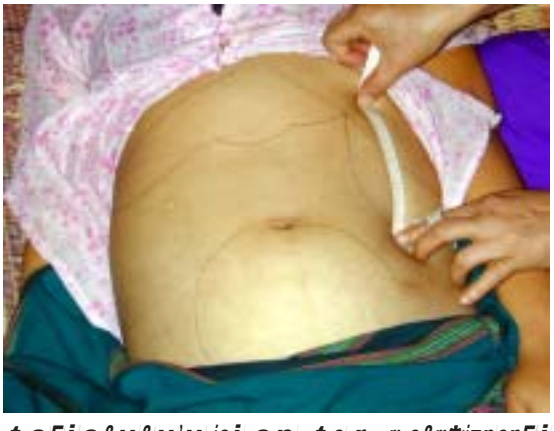

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Big spleen and liver (hepatosplenomegaly) can cause sever anaemia and the women must be screened for malaria. (Photo : SMRU)

30%, severe anaemia was uncommon. Only 17% of women developed severe anaemia and 91% of these women had a haematocrit between 20-25%. In this group maternal anaemia had no independent effect on birthweight or neonatal and post-natal death. **Weekly malaria screening reduces severe anaemia and provision of ferrous sulphate (200 mg TID) and folic acid (5mg OD) to all pregnant women may prevent poor long-term effects of maternal anaemia on infant morbidity and mortality.**

Care of the pregnant woman infected with malaria

As some of the other articles in this issue point out, the major concern is the increasing resistance of *P. falciparum* to the drugs used against it. *P. falciparum* is becoming increasingly resistant to all drugs used against it. The number of effective compounds is limited and even more so for use in pregnancy because of the concerns over teratogenicity and embryotoxicity.

Quinine is the only antimalarial considered to be safe in pregnancy, but it is not well-tolerated and in some areas of Southeast Asia, its efficacy is declining. We now have one in 3 pregnant women fail a supervised 7 day course of quinine. All the other drugs are either contraindicated, ineffective or of unknown toxicity to the foetus. For severe malaria and for women with a failure of quinine, the artemisinin derivatives (artesunate, artemether) are probably the best therapeutic options, but the experience with these compounds in pregnancy is limited. **It is very important to check whether any woman of child-bearing age that you are treating for malaria is pregnant or not.** This can be done by asking about menstrual history but if there is any doubt, a pregnancy test should be offered to the woman.

The difficulties in treatment underline the importance of other methods of prevention such as mosquito repellents and impregnated bed nets. However, these options are difficult to employ in the tropics because of the

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Important management points specific to pregnant women

1) Uncomplicated malaria

- If quinine is used, then it should be supervised.
- If quinine is used, then the pregnant woman needs an explanation that this treatment is safe in pregnancy (i.e. it does not cause abortions), but it can fail and *P. falciparum* may not be completely killed. If a woman gets fever or headache after treatment, she should get a repeat malaria smear. Better still, she should follow weekly antenatal screening.
- If a woman with malaria is not anaemic at the time she starts treatment, she has a very high risk of becoming anaemic. In over 1,000 treated cases of malaria in pregnancy, only 15% of women did not become anaemic. When a woman is smear negative, ferrous sulphate 250 mg TID and folic acid 5 mg OD can be given to the woman daily until she delivers. This reduces the levels of severe anaemia which are associated with increased maternal mortality rates.
- Artesunate for 7 days (2 mg/kg/day) is the usual treatment for women who have failed a course of quinine and still have uncomplicated malaria. **Remember, doxycycline and mefloquine cannot be given to pregnant women.**
- When a woman has her 3rd or 4th *P. falciparum* episode in the same pregnancy, treatment options are limited. Artesunate alone can be repeated and a full 7day treatment should be given. If it can be purchased, clindamycin (5 mg/kg/per dose TID) can be used in combination with artesunate (at the usual dose).
- Mefloquine treatment should not be given in pregnancy, as its use in treatment doses has been associated with an increased risk of stillbirth. **Please be diligent when treating women of child-bearing age so that they are not mistakenly given mefloquine (because it causes stillbirth) and artesunate (because we don't know if it is safe in the first trimester). Giving these drugs to a woman without even asking her whether she could be pregnant is a medical mistake.**

logistics involved and their high cost and low effectiveness.

Care of the neonate

Care of the neonate begins during pregnancy. A woman who has had malaria needs good antenatal care. Adequate supplements of ferrous sulphate and folic acid and possibly other vitamins, including B_1 (thiamine) may be needed. If you can get a pregnant woman who had malaria to term without her being anaemic, then your antenatal care has done a good job. Malaria around the time of delivery can be particularly dangerous for the mother and newborn. Antimalarials should be given and small amounts may cross into the milk. We have not found breast-feeding while taking antimalarial treatment to be a problem for the newborn. Quinine and chloroquine definitely can be found in the milk but in low

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2) Severe malaria

Severe malaria is difficult to treat and the problems are compounded in pregnant women. **There are a few disorders that are more apparent in pregnant women with severe malaria and they include hypoglycaemia, pulmonary oedema, septicaemia and anaemia.**

The treatment of choice for severe malaria is intravenous artesunate, but intravenous quinine is still effective. There are less complications when using artesunate, which makes it easier to use. Again artesunate should be given with a loading dose (2.4 mg/kg IV) followed 12 hours later with a routine dose (1.2 mg/kg IV), which is then given every 24 hours and changed to oral when the patient can tolerate fluids by mouth (total dose of artesunate=18 mg/kg).

Complications

- Hypoglycaemia

This can be profound in pregnant women with *P. falciparum* infection especially when treated with quinine. Untreated or inadequately treated it can lead to death. The medic has to be aware of it and actively detect it as it may just look like the woman has coma or is sleeping. It should be managed aggressively and promptly with 50% dextrose 1 mg/kg IV and 10% dextrose should be infused continuously. Repeated blood glucose measurements are required.

- Pulmonary oedema

Fluid management can be complicated by the changes in blood volume and distribution that occur in pregnancy. All women with severe malaria will need a urinary catheter and fluid balance charts to assess their fluid status. Pulmonary oedema in pregnant women with severe malaria is a medical emergency as the mortality rate can be as high as 80%. Sometimes the patient develops an acute respiratory distress syndrome (ARDS) that is not caused by fluid overload and does not respond to diuretics. The management includes artificial ventilation (often impossible) and the mortality is very high.

- Septicaemia

There is a higher incidence of secondary bacterial infection in pregnant women, so slow fever clearance times should alert the medic to search for other causes of fever such as urinary tract infection or lower respiratory tract infection and to treat these promptly with antibiotics.

- Anaemia

Anaemia may also be profound in pregnant women with severe malaria. It will need prompt management and a unit of blood should be given with lasix 40 mg IV or IM (after appropriate screening and cross-matching).

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3) Uncomplicated hyperparasitaemia (>4% RBC infected with P. falciparum)

• Oral artesunate is the preferred treatment (starting with a loading dose of 4 mg/kg and followed by 2 mg/kg per day for a total of 7 days treatment) because there is much less risk of hypoglycaemia than when quinine is used, parasite clearance is rapid and the woman feels better quickly and can walk to the clinic daily rather than being kept as an inpatient (as with quinine).
• The risk of anaemia is greater than for uncomplicated malaria and blood transfusion may be required. Folate treatment can commence on the same day artesunate is started and ferrous sulphate can commence when the patient becomes malaria smear negative. As with all patients with hyperparasitaemia, 6-12 hourly smears should be done to make sure the patient is responding to the treatment and that they become smear negative.
• If a woman is symptomatic with her hyperparasitaemia be prepared for premature labour. If a woman is genuinely in premature labour, (2-3 contractions in 10 minutes lasting > 20 seconds), then the medic should consider the use of dexamethosone (8 mg every 8 hours for 3 doses) and ventolin (start with 8 mg oral TID, reducing the dose by half if the contractions are decreasing, if there is no hypertension or cardiac abnormalities) to try and prevent the labour.

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P. vivax, P. malariae* and *P. ovale

Many people do not worry about *P. vivax*. *P. malariae* and *P. ovale* infections because they do not kill them. In pregnant women, besides causing low birth weight and anaemia (less than *P. falciparum*), symptomatic infections can cause premature labour. **Again, fever should be treated quickly and adequately: paracetamol and fluids.** Chloroquine can be supervised in pregnancy to increase compliance and reduce the risk of recurrent *P. vivax* infection. **Be wary of premature labour in pregnant women with symptomatic *P. vivax* infection.**

concentrations. Early and frequent breast-feeding keeps the baby well-hydrated and lowers the risk of hypoglycaemia. Congenital malaria is a rare event and will be discussed in a later issue.

Pregnancy increases the susceptibility to, and the effects of malaria infections; this being true for ***P. falciparum*** and ***P. vivax*** parasites. Weekly malaria screening is the only proven tool we have on the western border of Thailand to prevent maternal death from malaria. Weekly screening and early detection and treatment reduces but cannot eliminate the adverse effects of low birth weight and anaemia. Treatment with quinine fails for one third of supervised treatments, so women need to be explained this risk and to return for a smear if they have fever or headache. Artesunate is the 2nd line treatment for uncomplicated malaria in pregnancy. It needs to be given for 7 days. Anaemia should be suspected in all pregnant women with malaria in pregnancy and needs adequate treatment.

This article is a combination of information from more than 10 published articles. If you want to know more about this subject, the references can be provided by Shoklo Malaria Research Unit (SMRU).

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Questions and Answers

Case 1. A 17 year old, 7-month pregnant woman came to the clinic. She was not unconscious. As she could not stand or walk, so her relatives carried her to the clinic. She could not drink by herself and did not respond to questions clearly. The relatives told you that the patient had been suffering from fever for 7 days. She had already received one quinine drip at home but they could not bring her earlier as they lived too far from the clinic. Moreover, the patient was too weak to walk to the clinic all by herself. A malaria smear was done. The result showed PFT 78/1000 RBC with PFS1/1000 RBC and PFG 50/500 WBC.

Q1.1 What would be the diagnosis? What malaria treatment would you give this pregnant woman?
A1.1. Severe malaria.
Treatment: Artesunate 2.4 mg/kg (followed by 1.2 mg/kg at 12 hrs and every 24 hrs after that) OR, artemether IM 3.2 mg/kg, then 1.6 mg/kg once daily (OD) at 12 hrs and every 24 hrs after that) OR, IV quinine 20 mg/kg over 4 hours followed by 10 mg/kg every 8 hrs, until she can take oral treatment.

Q1.2. What IV fluid should be given to this woman and why?
A1.2. 10% Dextrose IV. Due to the risk of hypoglycaemia in pregnant women. Pregnancy & falciparum infection induces hypoglycaemia and IV quinine causes hypoglycaemia in 50% of pregnant women.

Q1.3. Is there any risk for the foetus with artesunate treatment?
A1.3. More than 500 treatments in pregnant women with artesunate to date have not shown any adverse effects on the foetus. The primary focus of treatment in severe malaria is to save the mother's life. Artesunate and artemether do not induce hypoglycaemia like IV quinine. The patient with severe malaria is already difficult to manage. So artesunate or artemether is a much less complicated regimen than IV quinine.

Q1.4. On the 2nd day of treatment the woman had a RR of 40. BP 90/50 and PR of 120 and temp of 36.7°C. What would be your two main differential diagnoses?
A1.4. Severe anaemia or pulmonary oedema.

Q1.5. When you checked her Hb (hct) you found HB=4.5 (hct 15.5%). Her lungs are clear and she has no peripheral oedema. What would you need to do?
A1.5. Transfusion of 350 cc blood with compatible donor screened for HIV, HEP B, MS, Hct and cross-match.

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Q1.6. On the 4th day of treatment the woman's malaria smear is negative for trophozoites but there are still a large number of PFG 250/500WBC. On the morning of the 4th day the woman was able to take oral artesunate and had a small meal and said she felt better. At 3 pm in the afternoon the woman spikes a fever of 39.5°C. Her lungs were found to be clear. Urine stick test yielded positive for blood and protein. The had woman had no burning urination or loin pain. She said she was only feeling the fever. A laboratory test of the urine sediment found 3+ bacteria and WBC 20 / HPF. **What would be the diagnosis?**

A1.6. Urinary tract infection – possibly pyelonephritis.

Discussion: Pregnant women with severe malaria are at increased risk of bacterial infection particularly gram negative infection. Untreated infection can be a source of ongoing fever in pregnant women with severe malaria and can cause death from septicaemia. Fever clearance with artemether after severe malaria is usually around 2-3 days (compared to 82 hours (3 1/2 days) with IV quinine).

Q1.7. What would be the treatment?

A1.7. IV ampicillin and gentamicin.

Case 2. A 36 year old pregnant woman came to the antenatal clinic on a routine ANC visit. It was her her 3rd consultation. She complained of fever for one day and joint pain but could eat and drink well and her malaria smear was PFT 43/ 1000RBC and PVT 36/500WBC.

Q2.1. What would be the diagnosis?

A2.1. Uncomplicated hyperparasitaemia with mixed infection.

Q2.2. After taking her consent you checked for the fundal height. The uterus was not palpable . A pregnancy test was done. It was positive. What would be the treatment?

A2.2. Supervised artesunate 4mg/kg on day 0 with 2mg/kg for the remaining 6 days of treatment (total dose 16mg/kg).

Q2.3. Why would you use artesunate and not quinine in the first trimester?

A2.3. The advantages of artesunate outweigh the disadvantages of quinine IV. There is a 3% mortality of patients (non-pregnant) who initially present with uncomplicated hyperparasitaemia. The risk in pregnant women has not been studied but is probably greater than 3%. Artesunate has better fever clearance, parasite clearance and cure rates,and is cheaper than IV quinine, and does not have the added risk of hypoglycaemia. The treatment should be supervised. If you give an artemisinin in pregnancy it is important to examine the baby at birth.

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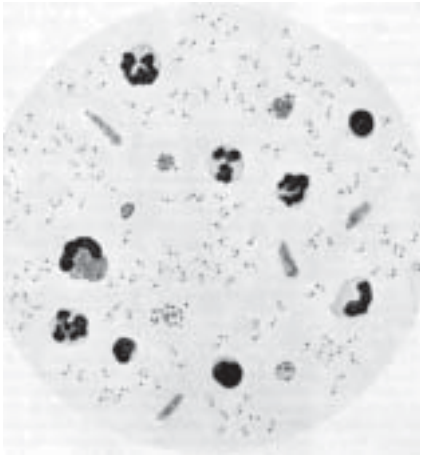

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Heavy infection with P. falciparum in a thick blood film stained by Giemsa-Romanowsky. (Wellcome Museum of Medical Science).

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Diagnosis of Malaria

Sarika Pattanasin. Lab technician, S.M.R.U.

This article reviews the main methods used for diagnosing malaria in the field.

Clinical Diagnosis

Malaria symptoms are non-specific and overlap with those of other febrile illnesses. A diagnosis of malaria based on clinical symptoms alone is unreliable. Therefore, a biological diagnosis is needed to diagnose malaria. The most commonly used methods in the field are microscopy and/or rapid diagnostic tests (RDTs).

A) Microscopic Diagnosis

It is considered as "gold standard" and offers many advantages when done by skilled persons:

- It is sensitive when used by skilled technicians: parasitaemia of 50-parasites/ µl (3/ 500 WBC or 3 to 6 / 100 fields of a standard thick smear) are detected.
- It is informative. Parasites can be characterized in terms of species (*P.falciparum, P.vivax, P.ovale, and/or P.malariae*) and of the stage of development (e.g. trophozoites, schizonts, gametocytes). In addition, the parasite density can be quantified. Such quantification is needed to assess hyperparasitaemia (> 4 % of RBCs parasitised), which requires a different treatment.
- Microscopy can be used to diagnose other diseases such as tuberculosis, intestinal parasites, S.T.D, filariasis, urinary tract infections…etc.
- It is relatively inexpensive. Cost estimates for endemic countries range from about US$ 0.12 to US$ 0.40 per slide examined.

Microscopy has the following disadvantages:

- It requires well-trained and experienced technicians: proper training

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S M R U laboratory at Maela Camp. (Photo:SMRU)

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(about 5 weeks), followed by 1 year of close supervision, is needed to get a reliable laboratory technician.

- It is logistically demanding: a regular supply of reagents and good maintenance of materials and microscope is needed.
- Proper and regular quality control (QC) must be organized.
- It is labour-intensive and time-consuming.

Therefore, reliable microscopy is very difficult to implement in remote areas with difficulty of access. Quick turnover of the staff also has a negative impact on the quality of microscopy.

B) Rapid Diagnostic Tests (RDTs)

These tests are based on the detection of "Antigen" substance derived from malaria parasites in lysed blood. These tests can be performed in about 15 minutes and the development of a coloured test line indicates a positive result. Several commercial test kits are available.

There are two antigens detected by currently available RDTs.

- Histidine-rich protein 2 (HRP-2) e.g. Paracheck Pf (Orchid Biomedical Systems, India).
  Comments: Since only P .falciparum releases HRP-2, these tests will give negative results with patients infected with P. vivax, P. ovale, or P. malariae.
- Parasite Lactate Dehydrogenase (pLDH) e.g. OptiMAL (Diamed, Switzerland). This RDT can detect *P.falciparum* and non-falciparum *(P.vivax, P.malariae and P.ovale*) but cannot detect mixed infections or distinguish between *P. vivax, P. ovale* and *P. malariae*.
  Comments: Unlicensed products with the name OptiMAL (one produced in India and one in Australia) have been found in the market. These products have very poor sensitivity.

Test performance of RDTs

1. Sensitivity

Test performance of RDTs has been conducted in many areas. The sensitivity of the RDTs has been thouroughly studied for *P. falciparum* because HRP-2 detected commercial kits have been available for a longer time.

These rapid tests normally give a **global sensitivity of over 90% in the detection of *P. falciparum* compared to microscopy**; this means that the test will give about 10 negative results (false negative) for 100 *P.falciparum* microscopically confirmed.

The sensitivity of OptiMAL for the detection of non-*P.falciparum* species is between 80% and 95 %.

False negative results are associated with low parasitaemia under 100 parasites/µl; often these patients are asymptomatic.

Important note: False negative results have been reported in patients with severe condition and very high parasitaemia (> 20 % of RBC parasitized). This phenomenon is rare, but severe malaria should not be excluded on the sole basis of a negative test.

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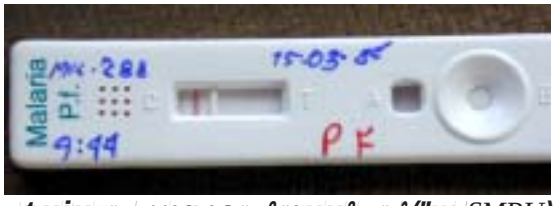

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Paracheck for P.F. (Photo: SMRU)

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2. Specificity

The specificity of RDTs targeting HRP-2 is high (> 90%): this means that the test will give about 10 positive results (false positive) for 100 negative patients microscopically confirmed.

False positive results are partly explained by the fact that the body slowly eliminates HRP-2 after parasite clearance: **HRP-2 tests can remain positive for up to one month** after parasite clearance.

As a result, patient history is important when diagnosis is based on HRP-2; if possible, all patients with a positive test **and** a history of *P.falciparum* infection ADEQUATELY TREATED in the previous month should have a malaria smear for confirmation.

Note: Pregnant women may remain HRP-2 positive after parasite clearance for a much longer time than non-pregnant patients.

False positive HRP-2 results are also reported in patients with autoimmune diseases like rheumatoid factor.

The specificity of RDTs targeting pLDH (OptiMAL) is reportedly higher (> 95 %). This is probably because the body eliminates pLDH quicker (within a week) than HRP-2.

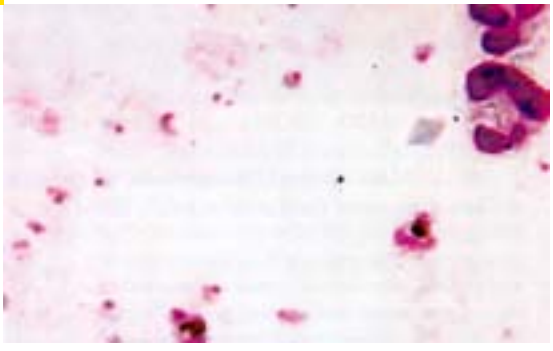
Advantages of RDTs over microscopy

- Simpler to perform. Health workers with minimal skills can perform RDTs within a short time, as they require less training.

Table: Comparison of methods for diagnosis of *Plasmodium* infection in blood.

Parameter	Microscopy	Dipstick HRP-2	Dipstick pLDH
Sensitivity (parasites/· L)*	50	> 100	> 100
Diagnosis	All malaria species Other diseases.	*P.falciparum* only	*P.falciparum* and *non-falciparum*
Parasitaemia or parasite density	Yes	Crude estimation	Crude estimation
Parasite stages	Yes	No	No
Time for result	30-60 min.	15 min.	15 min.
Skill level	High	Low	Low
Equipment	Microscope Reagents… etc	Kit only	Kit only
Cost/test	Low	Moderate	Moderate

** The lowest level of parasites in blood that can be detected.*



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Severe Malaria. P.F. ring forms and late trophozoites with pigment seen in a thick smear. (Photo: K. Silamut, Wellcome unit, Thailand).

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- Quick to perform. They are the tools of choice in malaria outbreaks because a large number of people can be diagnosed and treated within a short period of time.
- Logistically easy to implement and maintain.
- Microscope cannot detect less than 10^{8} parasites in the body; RDTs can if HRP-2 or pLDH is still remaining in the circulation.

Disadvantages of RDTs

- RDTs are not quantitative (unlike microscopy): they cannot provide information regarding parasite density and stages of development of parasites. Therefore, RDTs are not suitable for antimalarial drug studies (follow-up studies).
- RDTs that detect both *P. falciparum* and non-P.*falciparum* cannot distinguish between *P.vivax, P.ovale* and *P.malariae* and cannot diagnose mixed infection as well.
- Interpretation of the result can be difficult.
- The current price range is US$ 0.5-3 per test; even at US$0.30-0.50 per test, these assays would not be affordable for most malaria control programmes without external assistance.

As any other diagnostic tools, microscopy and malaria rapid tests offer both advantages and disadvantages in different perspectives. It is necessary to understand the characteristics and limitations of any RDTs in order to set up a proper protocol of use.

SMRU "¦wcce;/ rvpce;? *(Photo: SMRU)*

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The Problem of Presumptive Diagnosis and Treatment of Malaria

Lucy Phaipun, SMRU

This article is a true story of a little girl who suffered due to presumptive treatment of malaria.

Naw Eh Say was a 5-year old girl, who lived just across the Moei river, on the Karen side in Mun Ru Chai, with her grandparents. As she had been suffering from fever, headache, and vomiting and stomach pain for some days, her grandparents took her to the cross-border team community health workers. They made a presumptive diagnosis of malaria and gave her quinine for 3 days. Less than 20 minutes away from this place, a rapid test for checking *P. falciparum* as well as free treatment were available 7 days a week.

After 3 days, when Naw Eh Say's condition did not improve, they made the short trip across the river to have a blood test by Paracheck. The result of the Paracheck was quickly and strongly positive. Naw Eh Say was given oral artesunate, which she took with her grandfather's help and luckily she did not vomit.

The nurse on duty was worried about the condition of the child because she had passed urine only once in the last 24 hours. The nurse had been trained to double check the PF result with a malaria smear when the Paracheck was quickly and strongly positive. The child was sent to Maw Ker

Tests done

The first smear (H0) result was PFT 170/1000RBC with pigment present. Six (H6) hours later the smear result was PFT 169/1000RBC with pigment. At hour 12 (H12) the smear result was PFT 168/1000RBC with pigment and at 24 hours (H24) the smear result was PFT 25/1000RBC with pigment.

Treatment given

On the basis of the hour 12 smear with no significant decrease in the parasitaemia, the child was given an IV dose of artesunate of 1.2 mg/kg. After 48 hours her fever went down and Naw Eh Say started to feel better.

Naw Eh Say was given a total of 7 days of supervised artesunate and mefloquine and made a complete recovery. Her blood count dropped during the week and oral iron and folic acid were given to treat her anaemia.

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Thai patient house, where she could be more closely observed by a medical team.

This story highlights the problem of presumptive diagnosis and treatment. Although the presumption was correct, the treatment was not appropriate - it almost killed the child. Oral quinine is not well-tolerated, poorly absorbed when there is vomiting and not the treatment of choice for patients with uncomplicated hyperparasitaemia. Compliance with this regimen is poor. Incomplete treatment increases the chance of drug resistance and creates health problems for the patients as the malaria is not cured. Gametocytes produced by these patients are more transmissible and hence the community is put to further risk of malaria as they continue to be the source of the host to vector transmission.

Should we be using presumptive diagnosis and treatment?

The problem worldwide for diagnosis of malaria is that relying on clinical signs and symptoms results in low levels of correct treatment. The current practice of giving presumptive antimalarial treatment to febrile children living in malarious areas results in considerable over-treatment. In Southeast Asia the rate of malaria transmission is low and the proportion of children who present with fever but who do not have malaria is likely to be high.

The use of presumptive treatment for all children with signs of the highest sensitivity, i.e., history of fever in the absence of diarrhoea (94%) or headache (83%) – would lead to considerable over-treatment; 58-87% of our non-malaria patients would have received antimalarial drugs. This would increase the unnecessary side-effects and costs and could result in inadequate management of other infections. Using drugs unnecessarily and having antimalarial drugs present in the blood (often at subtherapeutic levels, i.e., at a concentration of drug which does not kill the parasites) for prolonged periods creates "drug pressure" which accelerates the spread of drug resistance.

On the other hand using more specific algorithms – such as history of fever with anaemia (specificity 99%), palpable spleen or liver (97%), or nausea (82%) – to reduce over-treatment, would result in a large number of patients not receiving treatment when they are in fact positive.

If we tried using the clinical features of

A study was conducted in Shoklo Camp in 1993 among 1,527 children. Any child who came to the clinic with fever was asked what their symptoms were and the signs & symptoms were recorded systematically. All children had a malaria smear. The proportion of children with each symptoms (headache, muscle or joint pain, nausea, vomiting, diarrhoea etc) and signs (temperature, pulse rate, respiratory rate, clinical anaemia, spleen and liver rates etc) were compared with 3 categories of children - infected with *P. falciparum* or *P. vivax* or no malaria. The outcome of the study was that there was no single symptom or sign or group of symptoms and signs that could be used to reliably predict malaria. Only about one-fourth (·) of the fevers were due to malaria and only 12% or about one-tenth (1/10) were due to *P. falciparum* (including mixed infections).

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history of fever with headache, in the absence of cough or history of fever, with fever confirmed – there would be prescription of antimalarials to over a quarter of the non- malaria febrile episodes and nearly half of the children with malaria, including potentially life threatening infections that would NOT be treated. Undiagnosed falciparum malaria in this area would increase morbidity and possibly mortality from malaria and would increase the spread of highly drug-resistant strains of *P. falciparum*.

The other important lesson to be learned from this study was that **no symptoms or signs could help the clinician predict *P. falciparum* infections compared to *P. vivax* infections.** A safe choice for presumptive treatment has to include a drug that covers *P. falciparum* infection. As artesunate and mefloquine combination treatment is reserved for slide or rapid test confirmed cases of malaria, in an effort to prevent developing resistance to the artemisinins, quinine (and teteracycline in children over 8 years) is the only available option. As mentioned before compliance to the 7-day regimen required for cure is poor.

For Southeast Asia, where malaria transmission is low, we should not be using presumptive diagnosis. Clinical criteria cannot be relied on and malaria should be confirmed by laboratory methods such as microscopy or rapid tests. If a microscope and malaria smear is not available, then the rapid tests (see other article on rapid tests) offer a high sensitivity and specificity for reliably diagnosing malaria. They are also portable and simple to use.

P. falciparum has managed to develop resistance to every antimalarial apart from the artemisinins (artesunate, artemether). In other words, we have one highly effective drug left before we face untreatable malaria. It has been shown that providing communities with the ability to provide early diagnosis and treatment with an artemisinin combination therapy, can reduce malaria transmission in this part of the world. This has an enormous impact on the health and economics of the community. Although initial outlay for provision of this service may seem expensive, the long-term benefit to the community by decreasing malaria far outweighs that initial cost.

In conclusion, presumptive treatment for malaria should be the exception and not the rule. The rapid tests are very convenient where microscopes cannot be used. The cost of the test should not be a problem as funding may be available for their purchase.

This article is a true story and the information given later in the article is based on published information from two studies conducted on the Thai-Burmese border.

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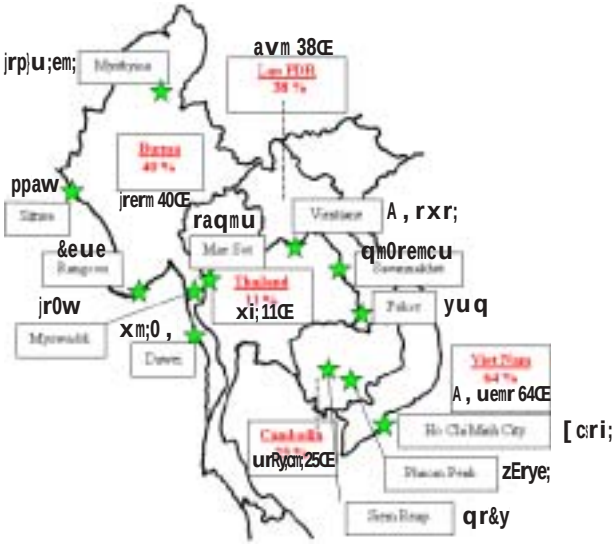


Fake Artesunate in Southeast Asia: A Murderous Trade

Stephane Proux, S.M.R.U

This article will discuss briefly the availability of fake artesunate and its effect on malaria patients in Southeast Asia.

Fake drugs accounted for 5 % to 15 % of the US$317 billion worldwide sales of pharmaceutical products in the year 2000. All kind of drugs such as antibiotics, asthma medicine, and anti-inflammatories are counterfeited; AIDS drugs, Viagra and antimalarials are no exception. This trade is especially flourishing in the Indian subcontinent, China and in Southeast Asia. Although it generates a large amount of money, it also encourages drug resistance and kills an unknown number of people.

Artesunate, in combination with slower acting antimalarials, is the recommended treatment for *Plasmodium falciparum* malaria in several countries of Southeast Asia. The recent distribution of counterfeit artesunate tablets in the region has killed patients and caused great public health concern.

In order to assess the extent of the problem, artesunate tablets were collected in Burma (Myanmar), Cambodia, Viet Nam, Lao PDR and Thailand. Tablets were tested for authenticity (genuineness) in two ways:

(1) Using a validated, simple and inexpensive Fast Red TR dye technique.

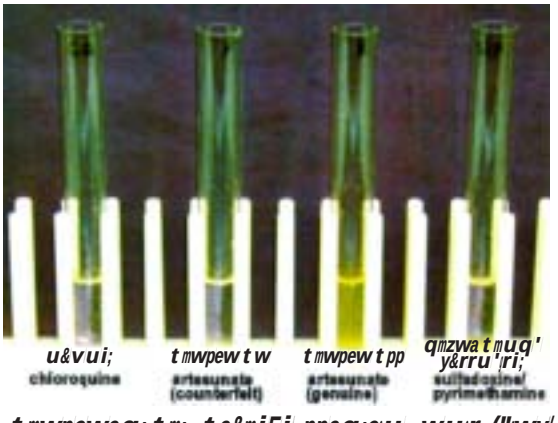
Fast Red TR dye technique: The test is based on a coloured reaction between an alkali-decomposition product of artesunate and the Fast Red TR salt: ***a yellow color indicates genuine artesunate, no color indicates fake drug.***

(2) An independent observer (unaware of the dye test results) examined tablets appearance and their packaging to classify the sample as "genuine" or "fake".

Findings

A total of 104 samples of blisterpacks supposedly containing artesunate were obtained - 51 from Myanmar, 26 from Cambodia, 11 from Vietnam, 8 from Laos and 8 from Western Thailand. Ninety-five samples (91%) were labeled as manufactured by Guilin Pharma (China) or repackaged by Atlantic Pharmaceuticals (Bangkok, Thailand).

(1) After the dye test, thirty-nine (38%) of the artesunate samples bought from pharmacies and shops contained no



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Artesunate colorometric assay specificity. (Photo: Michael D. Green)

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artesunate. All these counterfeits were supposedly manufactured by Guilin Pharma. Fakes were found in all five countries (see map).

(2) The result of examining the packaging was in agreement with the dye test. By looking at the packaging one can predict fake from genuine, but this might not be a reliable examination as the counterfeit (false) packaging might improve in the future..The following were the findings:

- Fake and genuine artesunate tablets were similar in size and colour, but genuine artesunate tablets were more friable (easily broken into pieces) than the fakes.
- Fakes labeled as Guilin Pharma were cheaper than the genuine counterparts: fakes cost about 30 % and 45 % of the local price of the genuine artesunate in Cambodia and Myanmar, respectively.
- There were forged holograms on fake artesunate blisterpacks bought in Vietnam and Cambodia; those from elsewhere had no hologram.
- Forged holograms were distinctive with a crude, hand-tooled design lacking the multicoloured, refractile appearance of the genuine Guilin holograms (see photos).

This survey suggests that fake artesunate is a public health problem in Southeast Asia. National malaria programmes must monitor the authenticity of antimalarial drugs available through malaria programmes and directly from pharmacies, shops and the black market. ***The ingredients for the artesunate testing kit cost about US$ 0.02 per tablet compared with about 1 US$ for an adult treatment course of artesunate.***

In the absence of the dye test, examination of the tablets and packaging can be used as markers for counterfeit artesunate. However, the characteristics of fake are likely to change and the ingredients of antimalarials must be monitored frequently.

Public education with posters on how to detect fakes by their external appearance, as in Cambodia, backed by dye testing and quality assurance could have a major impact.

Intervention of the authorities in

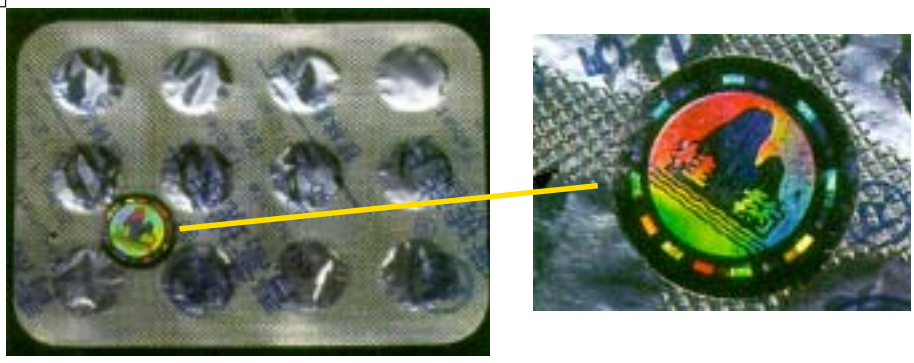
Summary of current predictors of counterfeit Guilin Pharma artesunate. (Keep in mind these might change with time)

In Cambodia and Vietnam:

1. Hologram forged (see picture): FAKE.
   If costs ≤ 1500 riels (Cambodian currency) per blisterpack: FAKE.
2. 'AS' logo on only one tablet face: PROBABLY FAKE.

In Myanmar:

1. If no hologram and manufactured after 1998: FAKE.
2. No Myanmar registration number on packet: FAKE.
3. If costs ≤ 200 Kyats (Myanmar currency) per blisterpack: PROBABLY FAKE.
4. 'AS' logo on only one tablet face: PROBABLY FAKE.
5. Crimped code on blisterpack: PROBABLY FAKE.
6. Six-digit manufacturing and expiry date codes on blisterpack: PROBABLY FAKE.



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Close-up of real artesunate with colourful hologram sticker.

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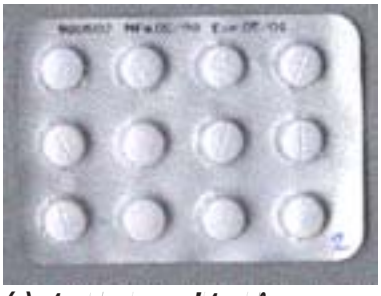
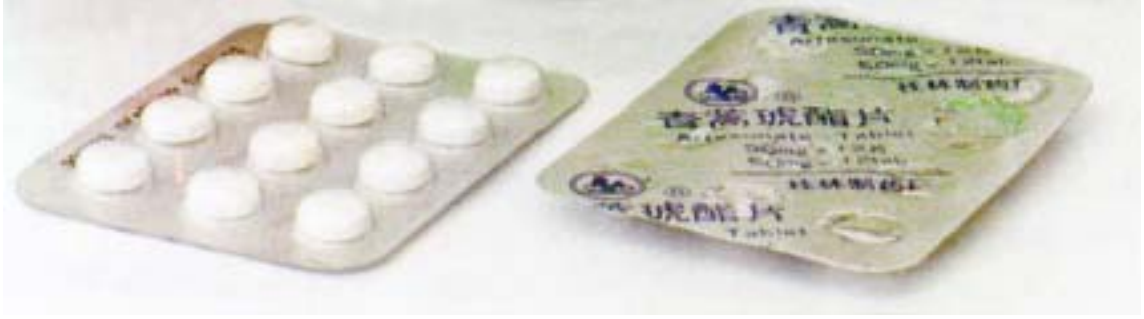
(a) Real Artesunate blister pack with hologram sticker on foil to distinguish it from fakes. (Photo: Dareen Campbell).

tppxu ta&mipvir ey;aoma&mijyejym;i , Ei/ aq;u' twtm; te;uyjri&y?
Close-up of fake artesunate with hologram sticker but less colourful than the original



(c) twp;epaq;u' twy?
(b) Fake artesunate.



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(c) Fake artesunate blister packs distinguished from the real artesunate because it does not have a metallic hologram sticker (Photo: Jan Rozendaal) [Source: Mekong Malaria Forum, issue no. 7, Dec 2000]

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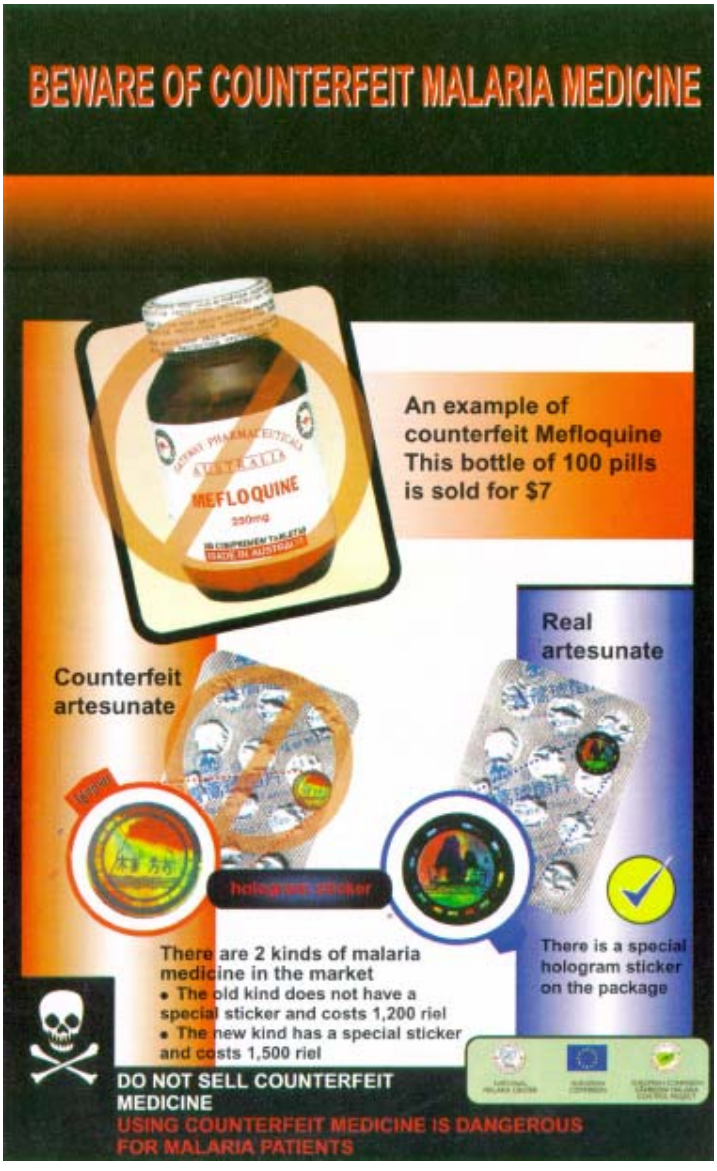
2/ Green MD **Ei tayi;tyjrm;/ iuzm; a&m*u tmwpewaq;tjzp a&mi;caeaom aq;rm;. pprer pr;oy&e ta&mijzi ppaq;en;/ "waq;0;Ei Z0aq;ynmpr;ppr *sme , 2000/ 24 ; 65- 70?**
3/ &Ze'a*sat/ uarBm'; , m;& iuzm;aq; twta , mirm;/ Lancet **2001/ tw 375/ pmrsuEm 890?**



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A poster for fake anitmalarial drugs in Cambodia. (Source: Mekong Malaria Forum, issue no. 7, Dec 2000)

combating this illegal business is crucial and can work for now, for example, in Cambodia fake artesunate and mefloquine are no longer seen.

This paper is adapted from an article published in the Lancet, Vol 357 June 16, 2001: "Fake Artesunate in Southeast Asia", by Paul Newton et al.

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3. Rozendaal JA. Fake antimalaria drugs in Cambodia. The Lancet 2001; Vol 357: 890.

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Important Issues Regarding Treatment of Malaria in Small Children

Lucy Phaiphun, SMRU

Lucy is the medic in charge of the SMRU Mawker Thai Malaria Clinic. This is a true story about one family who came to see her last year.

One Tuesday morning as I arrived at the clinic around eight o'clock, I saw a woman with three children waiting just outside of the door of the clinic. "Is everything alright?" I asked. "I am fine Thramu, but one of my children has been sick for 7 days," replied the woman. She could not come earlier as her village was very far away and she had to walk for the whole day to reach the clinic.

She said that she was alone with her children. Her husband died two months back. He had fever, headache, body pain, vomiting, tiredness and dizziness. He suffered from all these symptoms for about two weeks before he died. The day before his death his condition worsened and she tried to find someone to take him to Mawker Thai Clinic. But he died on the way. The cause of his death was malaria, she said.

Her son Pah Thu Di, appeared very sick. He was 5 years old and weighed 12 kg

On Examination:

His malaria smear showed PFT 20/1000 RBC+	PF Schizonts 3+PFG5/500WBC.
Hct was 25%,	Dextro 3.5,
Blood group O,	Temperature 39.8 C,
Spleen=4cm, Liver=3 cm,	No sign of dehydration.

She was very worried for her children. I did a malaria smear for all of them (including the mother) as they came from a malaria prevalent area. All of them were positive. I started giving the malaria treatment to the mother and the children.

I tookPah Thu Di to the patient house. I gave him 1/2 tablet of Paracetamol + sugar water. I tried to lower his temperature by applying cool water. I checked his fever again after half an hour. Before I started the malaria treatment, I asked his mother if he had malaria before and received malaria treatment in the last two months. The mother said that he had never had malaria before. I told her that there were a few simple rules that she had to follow.

She had to complete her son's treatment.

She had to stay at the clinic at least one hour after taking the malaria treatment.

If he vomited within one hour of taking the drug, he would be given another dose.

She agreed to this, so I started to treat him with **artesunate and mefloquine**.

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On day 0 I gave him artesunate 4mg/kg and he vomited 20 minutes later. I gave him IM plasil (metoclopramide) 0.2 mg/kg to control his vomiting. After twenty minutes, I washed him carefully and gave another full dose of artesunate. I waited for one hour and he did not vomit.

On day 1 I gave mefloquine one hour after giving artesunate because I was afraid he would vomit again as the mefloquine tastes very bad. When I gave him artesunate, he did not vomit until after one hour; but when I gave him mefloquine, he vomited after 45 minutes. I gave him the anti-vomiting drug again. Twenty minutes later I gave him mefloquine 7.5mg/kg (half dose) because he vomited more than half an hour after the first dose was given. As in half an hour some of the drug was already absorbed in the stomach, I did not repeat the full dose. He did not vomit that time.

On day 2 I gave him artesunate 4mg/kg with mefloquine 10mg/kg and I observed him carefully, but he did not vomit. The reason he did not vomit was because his fever had gone, and most of the malaria parasites had also been cleared from his blood.

I asked the mother to come back every two weeks for two months and she followed. Every time she came back, the child was better and this was because the child had received the right treatment with the right doses and when he vomited, the dose was repeated. I also gave him treatment for anaemia with ferrous sulphate, folic acid and mebendazole to deworm him. When the mother found her son was fine, she was very happy.

Treatment of falciparum malaria in very young children

Mefloquine and artesunate have been given to very young children (starting from 3 months old; body weight 4-5kg)

Artesunate is quite well-tolerated. The main problem is a very high incidence of

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The right way of giving medicine to very young children (Photo: SMRU)

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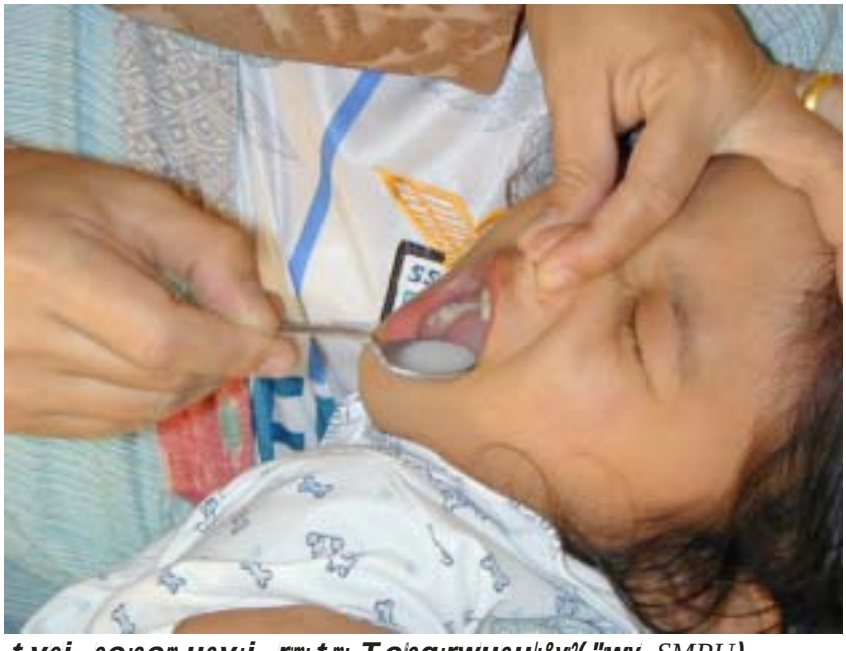
vomiting during the first hour after mefloquine intake in young children (up to 80% under 2 years).

Some children do not tolerate mefloquine. So do not repeat more than two times. Continue artesunate for a total of 7 days in such cases (4,2,2,2,2,2,2 mg/kg)

Recommendations for giving mefloquine

1. Reduce the fever.
2. Put the child in the mother's arms and wait until the child is calm. Explain to the mother the importance of her help.
3. Crush 1 tablet of mefloquine in 5cc of water and take the exact dose in a syringe. (for example: for 5 kgs 15mg/kg= 1.5cc).[consult doses table]
4. Give the medicine to the child with a syringe. Do not struggle with the child or pinch the nose.
5. Give a drink like sugar water or breast milk.
6. Observe for one hour.



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Wrong way of giving medicine to very young children (Photo: SMRU)

Key points:

1. Explain the importance of completing the full course of treatment.
2. Observe your patients carefully for one hour after giving the treatment.
3. If a patient vomits within half an hour, repeat the full dose; if between 30 minutes and one hour, repeat half of the dose.

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The Importance of Completing Antimalarial Treatment

Mya Ohn, Medic, SMRU

Completing treatment is very important for malaria.

Malaria causes a large number of mortalities in the world. More than one million people die from malaria every year, many of them children and pregnant women. This deadly disease is transmitted by the Anopheles mosquito. If there were no mosquitoes, there would be no malaria. But eliminating malaria from the world is impossible. So what can we do to prevent death from malaria? As there is a popular saying, 'prevention is better than cure', we have to try to prevent ourselves from being infected with malaria. It is important to seek medical advice after being infected with malaria.

Some people do not pay much attention when they have fever or symptoms of malaria. As the antimalarial drugs are easily available in the market, they just buy the medicine and treat themselves by taking 2 tablets of quinine and 2 tablets of paracetamol 2 times a day for 3 days. After that the fever or the symptoms might be gone. When they feel better, they think they are cured of malaria. Actually, they are not! The parasites can survive in the blood without showing any symptoms. The fever is very likely to come back in a few days later. **If the treatment is not taken properly, this can also lead to drug resistance that is very dangerous for the population.**

IRC

Always remember

If you are ill, never take antimalarial drugs by yourself. Go to the nearest malaria clinic or any health care centre. There, they will do a malaria smear for you to check whether you have malaria or not. If the malaria parasites are found in your blood, then you will be given anti-malarial drugs by the medic or nurse who is on duty. **You must complete the malaria treatment and this is very important.** Listen carefully to what the medic or nurse on duty explains. Ask questions if you don't understand and follow his or her instructions precisely.

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If you have fever and feel sick, go to the malaria clinic or any health care centre and test your blood for malaria. There you will have a correct diagnosis for malaria. If you are malaria positive then the medic on duty will give you the right treatment.

The choice of treatment to be given and for how many days depends on a number of factors such as, the condition of the patients, whether they are pregnant (if adult female) and if they have had mefloquine in the last 2 months.

Non-pregnant patients with uncomplicated falciparum malaria (PFT <4% red blood cells and no sign of severe malaria) can be treated with artesunate 4mg/kg/day for 3 days and mefloquine. At SMRU these days are marked as 0, 1 and 2. On Day 0 give artesunate alone. On Day 1 and Day 2, the same dose of artesunate can be given together with mefloquine 25mg/kg. Ideally, split the mefloquine into 2 doses (15mg/kg on day one and 10 mg/kg on day two). This will cause less vomiting. If possible, all drug administrations should be supervised by the medics to make sure the patients do not vomit in the first hour following drug intake.

If the patient is uncomplicated and hyperparasitaemic (PFT=4% RBCs), the recommended treatment is artesunate 4mg/kg on day 0 and 2mg/kg on day 1 to day 6 plus mefloquine 25mg/kg split into 2 as before and not given at the beginning when the patient is very unwell but afterwards on Day 5 and 6. A combination of artesunate and mefloquine works fast to make patients feel better and stops the transmission of falciparum malaria.

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Daw Shwe Mi's Lessons

Mya Ohn, Medic, SMRU

A woman with her two children and husband arrived at the malaria mobile clinic from Burma at about 10 am. Her name was Daw Shwe Mi and she was 36 years old. She was not pregnant and she never had malaria before. The two children aged 3 and 6 looked healthy. Daw Shwe Mi had fever, chills, tiredness, headaches, and body aches. She could eat and drink a little, and her condition was not too serious. The staff at the clinic did a malaria smear and the result was positive, showing PFT 10% of RBC with pigment. She was diagnosed as having uncomplicated hyperparasitaemia.

Before giving Daw Shwe Mi the treatment, the medic explained her condition clearly. He told her that she had to stay in the clinic for 7 days and he explained that it was important. Her parasite count was very high and she could develop severe malaria. The medics needed to check her haematocrit, blood sugar and do malaria smear every 6 hours to check that the parasite count was coming down. Supervised treatment is safest in these cases. If she refused to stay in the clinic, help could not reach her in time in the case of an emergency because her house was far from the clinic. After this explanation, the patient agreed to stay. Besides the treatment she was also provided with food.

On the first day of treatment the medic gave her artesunate 4mg/kg followed by artesunate 2mg/kg + mefloquine 15mg/kg on the next day and she felt better. Her fever had decreased and she could eat and drink very well.

One day later, when the medic came to give her medicication, the whole family had disappeared. Nobody knew where they had gone.

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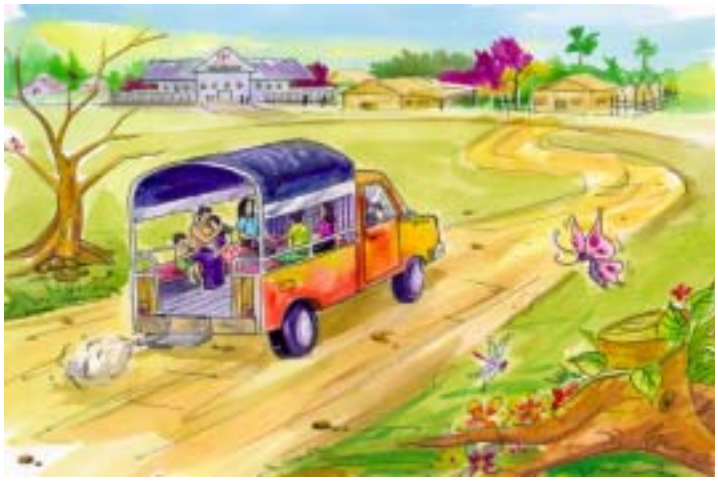

Six days laterDaw Shwe Mi came to the clinic again, but this time she was in a coma.

The nurse managed to get a taxi and sent her to the nearest hospital. When they did a malaria smear at the hospital, the result was found to be PF positive again. **This shows how important it is to complete the treatment.**

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If you do not finish the treatment, then the parasites will come back again. Also, if many people do not take their treatments properly, the parasites will become resistant to the drugs. Once there is drug resistance, it is very difficult to cure any patients.

It is very important to follow the instructions given by the clinician and complete the treatment. If you have a serious misunderstanding about how malaria is transmitted or what is the right treatment or anything else about malaria, you can always ask the medics or any medical staff. So do not be shy!

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Glossary

Adult Respiratory Distress Syndrome (ARDS):	A lung condition due to pulmonary oedema, which usually develops a few days after the initiating trauma. Also called *shock lung*.
Aggregate:	Combine
Aggressively:	Boldly, confidently.
Amenorrhoea:	Absence of menstrual period.
Cell-mediated immunity:	Immunity mediated by T lymphocytes either through release of certain enzymes or through action of direct cytotoxicity.
Compile:	Put together
Cytotoxicity:	The ability of an agent to destroy certain cells.
Dominant species:	Important/outstanding variety or category.
Diligent:	Attentive; persistent.
Ecological:	The relations between organisms and their environment.
Efficacy:	The ability to produce a desired effect: in the case of antimalarials it means the ability of the drug to produce a complete cure.
Embryo:	An organism in the earliest stage of development: in humans, from the time of conception to the end of the second month in the uterus.
Embryotoxicity:	An environmental or chemical agent that causes abnormal development of the embryo.
Empower:	To give power or authority; authorize; to enable or permit.
Enabling:	Empowering a person or corporation to do what he or it would otherwise be incapable of doing.
External intervening agencies:	Organizations not belonging to the government or locality; e.g. international NGOs, national NGOs.
Feasible:	Capable of being done.
Focal:	Pertaining to a focus.
Evidence:	Proof; an indication or sign.
Febrile paroxysm:	A sudden recurrence of intensification of fever.
Foetal anaemia:	Anaemia of the foetus inside the uterus.
Gametocytes:	A sexual form of the parasite that does not cause disease.
G6PD deficiency:	Glucose -6-phosphate dehydrogenase (G6PD) deficiency is the most common inborn error of metabolism. The deficiency may cause severe haemolytic crises in affected individuals.

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Haematocrit:	A tube with graduated markings used to determine the volume of packed red cells in blood specimen by centrifugation.
Hyperparasitaemia:	More than 4% of the red blood cells in a person's circulation contains parasites.
Hypnozoites:	The liver stage of the parasite.
Hypoglycaemia:	An abnormally diminished concentration of glucose in blood.
Impaired:	Weakened or damaged.
Interactions:	Reciprocal action or influence.
Perception:	Understanding.
Pilot implementation:	An experiment or trial undertaken prior to full-scale operation or use.
Merozoites:	The stage of the life cycle of malarial parasite where the para site re-enters the blood circulation from the liver.
Parasite clearance:	This is the time it takes from the start of antimalarial treatment for a positive malaria smear to becomnegative, i.e. until the parasites can no longer be detected in the person's circulation by malaria smear.
Parasitization:	Infection or infestation with a parasite.
Post-partum:	After childbirth or delivery.
Primigravida:	A woman pregant for the first time.
Profound:	Intense; extreme.
Promptly:	Action taken without any delay.
Rigor:	A chill; rigidity.
Relapse:	The return of a disease or condition after its apparent cessation. In case of fever - a relapse occurring before the temperature has reached a normal level.
Rationale:	A statement of reason.
Reciprocal:	Given in return; mutual.
Schizont:	Mature asexual form of the malarial parasite in the red blood cell.
Sporozoite:	The infectious stage in the life cycle of the malarial parasite.
Stakeholders:	Persons benefiting from or influenced by a programme, shareholders.
Trophozoite:	The stage where the parasite enters the red blood cell and feeds on the contents of the cell.
Teratogenicity :	An environmental or chemical agent that causes abnormal development of the foetus

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