

## Dealing with and preventing imported malaria due to *Plasmodium falciparum*

More than 4,000 cases of imported malaria due to *Plasmodium falciparum* are reported each year in France. Twenty patients die from this disease every year. At least two-thirds of the infected patients stay in hospital for an average of four days.

These figures illustrate the limits of a system which does not always prevent an avoidable disease from being contracted, does not always cure a curable disease, and the cost of which is detrimental to prevention.

How can this situation be improved?

- By making an earlier diagnosis. Indeed, for the medical community, malaria is a rare disease and thus potentially less well known than others: a physician may be confronted with a case every three years; two-thirds of the biological laboratories never see any in a year. Regular and recurrent information is necessary, more so since over two million travelers are exposed every year. These figures are constantly increasing.
- By strongly enhancing individual prevention, which is efficient against mosquitoes despite the constraints which are a source of travelers' non-compliance.
- By widely distributing clear and coherent chemoprophylaxis data adapted to the personal concerns of each individual.

### **Question 1: How can diagnosis be made earlier?**

According to data from the **Centre national de référence pour les maladies d'importation** (National Reference Center for Imported Diseases), the mean delay between onset of symptoms and diagnosis of imported malaria due to *P. falciparum* is three days. Malaria is a diagnostic and therapeutic emergency, given the unforeseeable risk of evolution to a severe form. Late diagnosis may be due to the traveler's or their relatives' negligence and/or to misdiagnosis when confronted with misleading forms. The suggested means for shortening these delays concern both travelers and healthcare providers.

### **The traveler's information is twofold:**

various sources of information are concerned (media, travel agents, pharmacists, committee for health education, etc.) and should alert travelers to the risk of contracting malaria;

– before the trip, a medical examination with a physician (GP, occupational medical doctor, specialist, Reference Center,...) should brief the traveler on prevention as well as on warning signs to be taken into account during the trip and for a few months afterward.

### **Training healthcare providers (clinicians and biologists)**

Knowing about epidemiology and clinical signs leading to the diagnosis must be an essential part of initial and continuing education. The prerequisite for coming to a diagnosis is to know about traveling in endemic zones. In 90% of the cases, imported malaria concerns patients who have traveled to tropical Africa for tourism, work, or a return to the native country. The frequency peak falls between July and October.

Over 90% of imported malaria cases are simple forms. Any fever after returning from an endemic zone should suggest the diagnosis, keeping in mind that misleading forms are frequent, especially in children: irregular fever, digestive disorders, abdominal pseudo-surgical emergency, flu syndrome.

Neurological signs, whether associated to fever and/or digestive disorders, suggest severe forms.

### **Biological proof for the diagnosis of malaria is an emergency**

Results must come within a maximum of two hours after contacting the clinician. Diagnosis depends on isolating the parasite in blood through an examination easily performed by any general purpose laboratory. Blood sampling must be performed immediately without waiting for shivering or a fever peak.

The blood smear technique is the most frequently used in unspecialized laboratories. It is fast and allows for a good identification of the species and determination of parasitemia. It can fail in the case of low parasitemia.

The reference and more sensitive examination is the “thick smear”, but its interpretation is more difficult.

Even though it is a rare diagnosis, permanent quality controls warrant a good reliability of the results. If the positive diagnosis is easy, the absence of parasitemia can only be proved after several biologists have carefully examined the slides.

To increase the sensitivity of the diagnosis in difficult cases, it is necessary to insist on taking into account the clinico-epidemiological context (role of the clinician-to-biologist interface) which encourages multiple examinations and possibly referral to a specialized laboratory. Indeed, the other techniques (QBC<sup>®</sup> malaria, detection of soluble antigen specific to *P. falciparum*) are hardly ever used in general purpose laboratories because of their cost and because they are not refunded by social security. In specialized laboratories, these techniques can either contribute to the immediate diagnosis of *P. falciparum*, or assist in a retrospective diagnosis. A thrombopenia below 150 giga/L is frequent and is a good marker within a clinical and epidemiologic context.

**The jury suggests the blood smear technique as a first-intention test for the biological diagnosis of malaria.**

### Question 2: How can emergencies be assessed and how should caregiving be organized?

#### **How relevant are the severity criteria defined by the WHO?**

Severe malaria is defined by the WHO through 10 criteria: coma, severe anemia (hemoglobin < 5 g/dl), renal insufficiency, severe respiratory distress syndrome, hypoglycemia, shock, bleeding and/or disseminated intravascular coagulation, tonic or clonic convulsions, metabolic acidosis, macroscopic hemoglobinuria. These criteria, defined within endemic zones, have not been validated on a non-immune population. Among the suggested criteria, the most relevant are, according to their frequency and prognostic value: coma, shock, acidosis, and pulmonary edema. The rate of parasitemia (> 5%) taken by itself is not a criterion of severity.

**Serious pediatric forms** are very rare in France. The frequency and the prognostic value of the severity criteria defined by the WHO have not been evaluated. The most important severity signs are neurologic (febrile convulsions, consciousness disor-

ders with risk of death in less than 24 hours and possibility of sequelae). Any febrile convulsion in a child coming back from an endemic zone will suggest a severe form of malaria. Witnessing a sign of clinical or biological severity must lead to the immediate transfer of the child to an intensive care unit. If no severity criterion is noted, treatment may be given in a general pediatric ward. Emesis, when isolated, has not proved to be a criterion of severity, but this condition may require parenteral treatment.

#### **To what extent can healthcare be ambulatory?**

Any suspected malaria is an emergency, whatever the initial status of the patient.

Non-severe forms of imported malaria account for 90% of *P. falciparum* malaria reported in France. This allows the GP to give complete ambulatory care with the following restrictions:

- the parasitology diagnosis must be known on the day of examination,
- non-severe form, no severity criterion,
- absence of digestive disorders,
- parasitemia must be inferior to 5%,
  - absence of sociocultural factors jeopardizing compliance with the treatment,
- absence of risk factors, such as: old age, splenectomy, pregnancy, underlying pathology especially when cardiological, people living alone,
- proximity of a hospital,
- medication available in a pharmacy and delivered to the patient for immediate ingestion,
- examination three and seven days after onset of treatment to follow up the evolution.

**In a young child**, the speed at which symptoms evolve and the frequency of digestive disorders can not allow complete ambulatory treatment.

#### **Where should the patient be referred?**

Besides complete ambulatory caregiving, patients are referred either to the emergency ward or reference ward (after a telephone conversation with one of the ward's senior physicians).

In the emergency unit, caregiving should never be delayed. A written protocol for caregiving in malaria, well publicized and updated, must be easily accessible. Diagnosing malaria must immediately lead to a curative treatment. Noting severity criteria makes referral to an ICU mandatory.

Uncomplicated forms should be monitored in a hospital unit. A minimum of 24 hours is recommended to ensure patient compliance and absence of adverse reaction to treatment. Outpatients' GPs should be informed of the necessity of monitoring the evolution of the disease by an examination on the seventh day.

### Can malaria that is biologically unconfirmed be treated?

The jury considers that treatment should be given if clinical suspicion is strong enough, even when no severity criterion is noted, and even if a first smear is considered as negative or if biological results are not available.

Reexamination of the slides and a new smear are then necessary, eventually with a more sensitive biological technique.

### Question 3: Treatment and monitoring protocol in uncomplicated forms

#### Definition and goals of caregiving

An uncomplicated form of *P. falciparum* malaria is an acute episode of malaria presenting no severity criterion. In this form, the patient should always recover.

**Choosing an antimalarial drug** depends on available medication, its potent effect on the plasmodial strain, its speed of action, its toxicity, the terrain, and compliance to the treatment.

In practice, only three products are commonly used: quinine, mefloquine, and halofantrine.

The choice will be based on the benefit/risk ratio of each of these three products.

#### Remarks and recommendations on the use of available antimalarial drugs

Their efficacy should currently be regarded as nearly constant and comparable to one another. Resistance is rare and geographically limited.

One is chosen according to its side effects. None of the available treatment is innocuous. All present potentially severe adverse effects, either because of an intrinsic toxicity or because of misuse.

Halofantrine presents a lethal risk of cardiac complication. The jury regrets the absence of pertinent pharmaco-vigilance data for halofantrine.

Complications due to mefloquine are essentially neuropsychiatric and can be severe. Their frequency is rather high (1 out of 200 to 1 out of 1,700 curative treatments).

Quinine presents lethal complication risks only in the case of administration mistakes when used intravenously. Quinine per OS is usually well tolerated. Difficulty in complying with oral treatment may lead to therapeutic failure. Strictly respecting dosage, administration directions, and contraindications warrants its safety of use.

### The benefit/risk analysis leads the jury to make the following recommendations for adults:

– to prefer quinine or mefloquine in first-intention treatment; the choice is linked to strict compliance, to specific contraindications, and to the socioeconomical context;

– to use halofantrine only with extreme caution.

The atovaquone/proguanil combination is an alternative to current treatments; its use remains to be specified.

Simultaneous or recurrent use of antimalarial medication requires caution.

#### Treatment protocol:

##### • Quinine:

– per OS 8 mg/kg of quinine 3 times a day for 7 days;  
– IV 8 mg/kg of quinine diluted in glucose serum at 5% and administered in slow infusion during 4 hours, 3 times a day, or in continuous infusion over 24 h.

A per OS secondary treatment is possible with quinine or mefloquine.

##### • Mefloquine:

– 25 mg/kg in 2 or 3 intakes separated by 6- or 12-hour intervals.

##### • Halofantrine:

– 24 mg/kg in 3 intakes separated by 6-hour intervals, not at mealtimes;

a second course must be undertaken on the seven day to prevent relapse; in this case, the cardiac toxicity risk is enhanced.

#### Particular cases

• Pregnant women: quinine is the only safe molecule.

• Malaria contracted in multiple resistance zones (specific zones in Southeast Asia and Amazonia).

– Quinine: IV or per OS during 7 days, combined with doxycycline 100 mg every 12 hours (non-government approved indication) for 7 days or with clindamycin 10 mg/kg every 8 hours (non-government approved indication) for 7 days; arthemeter: available only with nominal temporary government approval.

#### Should chemoprophylaxis be continued after treatment?

The risk of reviviscence from erythrocyte forms is countered by the schizonticide curative treatment, provided it is complete. There is no reason to suggest further treatment with a prophylactic objective.

#### Following up and monitoring treatment

A clinical follow-up on days three and seven after onset of treatment is recommended.

## Healthcare for children

Three drugs may be used:

- halofantrine: 24 mg/kg in 3 intakes with a 6-hour interval,
- mefloquine: 2.5 mg/kg in 2 or 3 intakes with a 6- or 12-hour interval,
- quinine: 8 mg/kg 3 times a day for 7 days.

Currently, the benefit/risk ratios of the various drugs are not comparable in the child and the adult.

Halofantrine is the most commonly used medication in France in pediatrics because of its adapted galenic presentation and because children comply well. Taking into account contraindications and monitoring the electrocardiogram probably limit the risk of cardiac complication. The jury does not wish to change this therapeutic standpoint, unless new data come from pharmacovigilance centers.

Mefloquine and quinine are two efficient drugs, provided their intake is monitored and there are no digestive disorders. A large-scale assessment of mefloquine use remains to be carried out. The jury would like galenic forms of oral parenteral quinine adapted to these age groups.

### **Question 4: Treatment and monitoring protocol in severe forms?**

Healthcare in severe malaria is an emergency, both in adults and children. Any severe form of malaria must be treated in an ICU.

The term 'severe form of malaria' is used for pernicious malaria, neuromalaria, cerebral malaria, and the severe form.

Intravenous quinine treatment is administered as soon as malaria is suspected.

The clinician must refer the patient to the ICU when confronted with one of the following symptoms: consciousness and/or behavior disorders, decrease in blood pressure, respiratory anomalies, increase of lactate levels, metabolic acidosis, renal insufficiency.

### **Treating severe forms**

Injectable quinine must be available in every hospital center. To avoid any administering mistake, only one commercial presentation should be available; the total concentration in quinine base (or alkaloid base) must be indicated on the ampule. The quinine dose to be administered is expressed in quinine base when the pharmacy product contains a quinine salt (Quinoforme®) or in alkaloid base when quinine is associated to other active princi-

ples (Quinimax®). Two products are currently available:

- Quinimax® 125 mg of alkaloid base per milliliter, 1.2 and 4 mL ampoules;
- Quinoforme® 219 mg of quinine base per milliliter, 2 mL ampoule.

Administration protocol is as follows: a primary dose at 17 mg/kg of quinine in 4 hours, followed by a maintenance dose at 8 mg/kg every 8 hours, either in continuous (electric syringe), or in 4-hour infusions.

The goal is to reach rapidly and maintain a quinine level between 10 and 15 mg/L.

The switch to oral quinine is made as soon as possible. The total treatment course is seven days. Suggesting the switch for prophylactic purposes is not justified.

When it is suspected that strains are less sensitive to quinine (specific zones in Southeast Asia and Amazonia) a combination with doxycycline (100 mg IV every 12 hours, non-government approved indication) or, in case of contraindication to tetracyclines, a combination with clindamycin (10 mg/kg IV every 8 hours; non-government approved indication) is recommended. Artemether is exceptionally indicated in the case of true resistance or strict contraindication to quinine.

Empiric antibiotherapy is justified if a bacterial infection is suspected.

### **Clinical and biological surveillance**

The narrow therapeutic index range requires an early assessment of initial dosage validity. For risk patients (hepatic and/or renal insufficiency, children, and pregnant women, etc.), further measuring of the quinine level may be indicated.

Measuring the quinine level is performed only from the third day onward. If the patient's state does not improve, day three parasitemia and measuring the quinine level will help treatment failure be understood and allow the dosage to be modified accordingly.

The hypoglycemic risk, enhanced in children and pregnant women, calls for a consequent IV supplementation of glucose and monitoring of glycemia every 4 hours. Electrocardiograms must be performed regularly.

### **Adjuvant treatments**

Corticoids are contraindicated. Plasma exchange, preventive anticonvulsants, and heparin are of no interest. Indications of vascular volume, of extra-renal clearance, and of curative anticonvulsants are those commonly used in ICU.

**Table I.** Prophylaxis in the adult.

<b>Group 1 countries</b>	Chloroquine 100 mg/d, every day
<b>Group 2 countries</b>	Chloroquine (100 mg/d) + proguanil (200 mg/d) used separately or in combination (Savarine®)
<b>Group 3 countries</b>	Mefloquine 250 mg, 1/week
Zones where resistance is found (specific zones in Southeast Asia and Amazonia) and/or contraindication or intolerance to mefloquine	Doxycycline 100 mg/d (monohydrated salt), not government approved

**Table II.** Prophylaxis in children.

Active principle	Presentation	Dosage	Comments
Chloroquine	syrup 25 mg/5 mL fractionable 100 mg tablets	< 8.5 kg: 12.5 mg/d 9-16.5 kg: 25 mg/d 17-33 kg: 50 mg/d 33.5-45 kg: 75 mg/d	Beware of accidental intoxication
Proguanil	100 mg tablets	< 8.5 kg: 25 mg/d 9-16.5 kg: 50 mg/d 17-33 kg: 100 mg/d 33.5-45 kg: 150 mg/d	
Mefloquine	50 mg tablets	15-20 kg: 50 mg 1/week 21-30 kg: 100 mg 1/week 31-45 kg: 200 mg 1/week	Contraindicated under 15 kg (for prophylaxis) and in case of previous convulsions

### **Question 5: How to choose chemoprophylaxis correctly?**

Most malaria cases in France occur in patients who do not use prevention against mosquito bites, and/or have not received adequate chemoprophylaxis.

Protection against mosquitoes is that which offers the best benefit/risk ratio. They are efficient as soon as night falls and are especially useful for young children. They are based on wearing ample clothing which cover as much of the body as possible, correctly using repellents and efficient insecticides (with caution in children and pregnant women), and setting up repellent-impregnated mosquito nets whenever possible.

### **How can availability of chemoprophylaxis and compliance be improved?**

Chemoprophylaxis completes the protective measures against mosquitoes.

General practitioners and pediatricians must be the key people in preventing malaria. Adapted and personal advice is given during the medical examination.

Counseling centers for travelers are reference structures, Telephone counseling should be given only to physicians. The pharmacist also has an informative role to play. Travel agents should only warn travelers.

Physicians' training and information should be improved. Healthcare managers and experts should have as a priority the creation of an easily accessible consensual national data bank. This data should be freely accessible to physicians.

Vital information for prescribing chemoprophylaxis must be exhaustive. Some information concerns the traveler; its aims are to assess contraindications, the risks of possible drug interactions, and the socioeconomic possibility of access to care. Other information concerns the journey (zones visited or crossed, altitude, season, length and material conditions of the stay), and its objective is to assess the real exposure risk.

### **Is chemoprophylaxis always necessary?**

A list of countries for which chemoprophylaxis is of no use (group 0 = no *P. falciparum* malaria) is compiled every year by the *Conseil Supérieur d'Hygiène Publique de France* (Superior Council for

Public Health in France). A census of large cities and areas for which there is no exposure risk, even though they are not listed in group 0, should be available. The jury considers that, for all other destinations:

- for a length of stay shorter than seven days, chemoprophylaxis is always necessary in zones where the exposure risk is high; in zones where the risk is low, the need for chemoprophylaxis must be discussed according to the conditions of the stay and the possibility of access to care when returning home.
- for a length of stay longer than or comprising seven days, chemoprophylaxis is always necessary.

### What products and dosages are recommended?

Chemoprophylaxis must be started the day before departure for the following drugs: chloroquine, proguanil, and doxycycline. For mefloquine, two dosages are given, one 10 days before and the other three days before departure (test doses).

- **Healthy adults** (*table I*)
- **Specific cases**
  - **Pregnant women:** a pregnant woman should travel to an endemic zone only if absolutely necessary. Only chloroquine and proguanil may be used.
  - **Children** (*table II*): infants and children should be taken to an endemic zone only if absolutely necessary.
  - **Migrant populations:** when they return to their native country, they should benefit from the same chemoprophylaxis as other non-immune people.

### How long should chemoprophylaxis last?

For stays shorter than three months, chemoprophylaxis should be maintained in endemic zones and for four weeks after returning from that zone. For longer stays (over three months), or for expatriates, chemoprophylaxis must be maintained as long as possible. Travelers will be advised to consult a local physician rapidly so as to assess the validity as well as the benefit/risk ratio of chemoprophylaxis.

The jury does not see any reason to limit the prophylactic use of mefloquine to three months.

People having received a seven-day quinine-based curative treatment (mefloquine or halofantrine) do not need any complementary chemoprophylaxis once back from the endemic zone, provided there is no new exposure risk.

### Using second-hand treatment

Second-hand treatment should be given only to isolated travelers who are more than 12 hours away from a healthcare institution.

The traveler must absolutely be advised by a physician, even when self-treatment is used.

The jury considers that the only molecules to be used are (in order of preference): oral quinine, mefloquine, and a pyrimethamine-sulfadoxine combination. A doxycycline and quinine combination is recommended when there is a risk of polychemosistance.