MALARIA PROPHYLAXIS IN THE FRENCH ARMED FORCES : EVOLUTION OF CONCEPTS

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ABSTRACT • Malaria is still a serious public health problem in the world and control remains a major priority for the approximately 25.000 French troops deployed, mostly on permanent assignment, in malaria transmission regions. Epidemiological surveillance of malaria provides data necessary to assess morbidity, monitor changing patterns of *Plasmodium falciparum* drug-sensitivity, and evaluate the efficacy of malaria control measures. About 540 cases were observed in 1999 for an incidence of 4.1 p. 100 men.year. Since 1991, strong emphasis has been placed on prophylaxis. In addition to vector control measures and individual protection against mosquito bites (impregnated bednets, protective clothing, application of repellents, and indoor insecticide spraying), drug prophylaxis has been recommended using a combination of 100 mg of chloroquine and 200 mg of proguanil chlorhydrate (CQ+PG) in a single capsule manufactured by the French Health Army Service. Initially this policy led to a significant decrease in malaria cases among French soldiers. However the incidence of malaria rose in 1995 and 1996. This recrudescence was attributed to poor compliance with chemoprophylaxis and to the declining efficacy of the CQ+PG combination. In response to these problems, a new policy was implemented especially in countries where cycloguanil-resistant *Plasmodium falciparum* incidence rate is increasing. The new chemoprophylactic regimen calls for a personal prescription of mefloquine. Doxycycline monohydrate is used in case of mefloquine contra-indication or intolerance. Combination of CQ+PG delivered in a single capsule remains a suitable chemoprophylactic regimen in Sahel countries as well as Horn of Africa..

KEY WORDS • Malaria - Chemoprophylaxis - *Plasmodium falciparum* - Army.

PROPHYLAXIE DU PALUDISME DANS L'ARMEE FRANÇAISE : EVOLUTION DES CONCEPTS

RESUME • Le paludisme reste un problème majeur de santé publique dans le monde et la prévention constitue toujours une priorité pour le service de santé des armées françaises qui déploient chaque année environ 25 000 militaires, dont la plupart en mission longue durée, dans des zones à forte transmission de paludisme. La surveillance épidémiologique du paludisme dans les armées permet de préciser l'importance de la morbidité, de suivre l'évolution des chimiosensibilités de *Plasmodium falciparum* aux antipaludiques et d'étudier l'efficacité des actions de lutte. Avec environ 540 cas signalés, l'incidence de paludisme en 1999 était de 4.1 p. 100 hommes.année. Depuis 1991, le service de santé a mis l'accent sur la lutte antipaludique. En plus des dispositions de lutte antivectorielle et de protection individuelle (les moustiquaires de lit imprégnées d'insecticide, les vêtements protecteurs, les insectifuges cutanés, et les insecticides en aérosol), chaque soldat a bénéficé d'une chimioprophylaxie utilisant 100 mg de chloroquine base et 200 mg de chlorhydrate de proguanil dans une seule gélule conditionnée par le Service de santé des armées. Dans un premier temps, cette stratégie a réussi à faire baisser significativement l'incidence du paludisme. Cependant le taux a augmenté de nouveau en 1995 et 1996 probablement à cause de l'inobservance du régime de chimioprophylaxie et d'une diminution de l'efficacité de l'association chloroquine-proguanil. Pour répondre à cette situation, une nouvelle stratégie a été développée et mise en place, surtout dans les régions où l'on a constaté une augmentation de la résistance de *Plasmodium falciparum* au cycloguanil. Le nouveau régime repose sur la méfloquine en prescription personnalisée. En présence d'une contre indication ou d'une intolérance, le monohydrate de doxycycline est utilisé. L'association chloroquine (100 mg +proguanil (200 mg) délivrée en une seule capsule reste indiquée dans les pays du Sahel et de la corne de l'Afrique.

MOTS-CLES • Paludisme - Chimioprophylaxie - *Plasmodium falciparum* - Armée.

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With 2.3 billion persons exposed i.e. more than 40 % of the world population and close to 2 million deaths, mostly in Africa (WHO), malaria remains the most serious parasitic endemy at the beginning of this millennium. It also is one of the main preoccupations for Western Armed Forces regularly called to intervene in this part of the world. Thus, more than 25 000 French troops were stationed in malarious

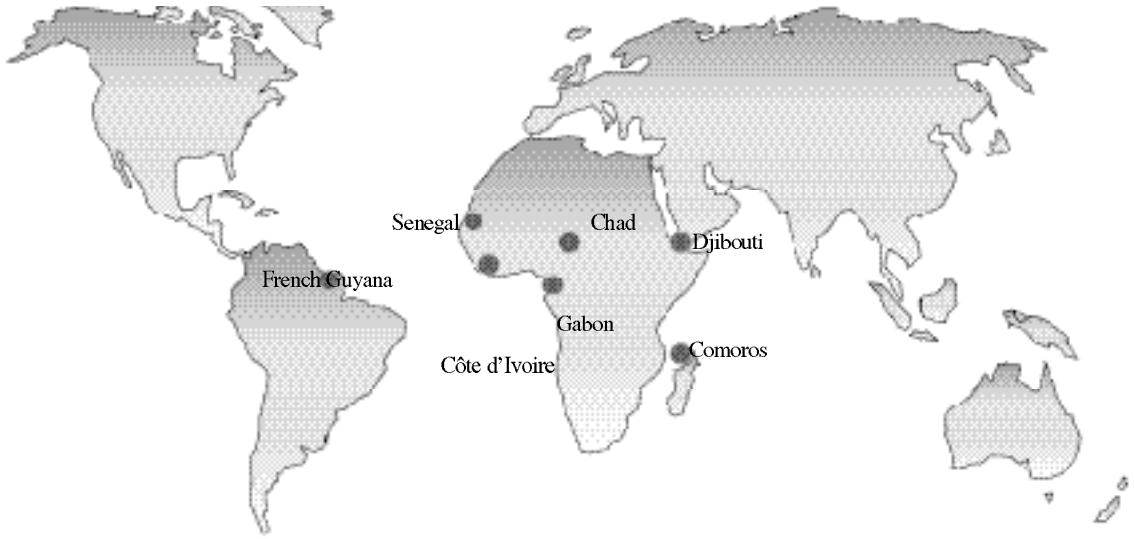

Figure 1 - Countries where French Forces are stationed.

regions in 2000 and 540 cases were reported i.e. a 4.1 % incidence rate per man and per year (1). Those figures are to be compared with the data provided in 1999 by the Imported Diseases Reference Center reporting 3 500 malaria cases with 40 deaths in France (2). This underlines the significance of the fight against malaria which is currently based on three different modes of action : diagnosing and treating the disease at an early stage, attempting to eradicate malaria vectors, and chemoprophylaxis. The latter extensively changed over the last 20 years as the chemoresistance of *Plasmodium falciparum* changed in those countries where French Forces were exposed.

RISKS OF MALARIA EXPOSURE

French forces operating in tropical regions are stationed in chloroquine resistant zones (Fig. 1). The risk of disease transmission in those countries concerned vary according to the length of stay, the endemic malarious zone and the forces operational conditions.

Length of stay includes short stays (< 1 month) i.e. short missions. This involves army personnel spending a few days on a mission or Air Force personnel flying regular rotations for those regiments based in tropical zones ; intermediate stays (4 to 6 months) mainly involving companies including 140 to 160 troops that are replaced every 4 months ; long stays (> 6 months) involving expert military personnel detached to foreign governments or international organizations.

Most countries in the tropical zone suffer chemoresistant *Plasmodium falciparum* infections. The risk of *Anopheles* transmission must be evaluated prior to departure and depends whether the personnel concerned shall be staying in cities or the country as well as upon the geoclimatic conditions encountered.

Transmission areas are divided as follows (3) :

- areas with a short transmission period (1 to 2 months/year) during the rain season. These are mostly sahel countries including Chad, Mauritania, Niger as well as Horn of Africa countries including Sudan, Somalia ;

- areas where transmission is permanent with seasonal increases. This includes savanna countries in Sub-Saharan Africa (Senegal, Mali, etc.) ;

- areas where transmission is permanent and regular throughout the year. This occurs mainly in Sub-equatorial Africa (Gabon, Côte d'Ivoire, etc.) and East Africa (Comoros) where vector transmission is high during the annual rain season.

Malaria transmission is lower in cities than country and significant mainly in sub-urban areas.

South America presents a different picture with maximum transmission in local rural zones. This is particularly the case in French Guyana with troops based in Cayenne and Kuru training in the Amazonian forest. Malaria is constantly evolving throughout those countries and the chemoprophylaxis schedules are reviewed and modified every year.

Those stays defined above excepted, French Armed Forces are sometimes called to intervene for humanitarian missions, policing operations or to safeguard French nationals in countries facing inner conflicts. This was the case over the last few years in Rwanda, Central African Republic, Congo, and more recently Côte d'Ivoire. Troops depart rapidly in this case and the prevention as well as sensitization advice given to the personnel concerned is naturally limited. Chemoprophylaxis must then be adapted to operational conditions.

MALARIA PROPHYLAXIS FEATURES

Malaria prophylaxis is based on a number of measures associating protection against mosquitoes, chemoprophylaxis and presumptive fever therapy.

Mosquito protection is the first line of defense against malaria. This includes individual protection (impregnated clothing and using repellents) as well as spraying insecticides

inside and outside housing accommodations. It must be noted that spraying insecticides and using impregnated bednets with deltametrine, in particular, is a remarkably efficient protection. *Anopheles* larvae sites including rusty food cans, old tires, drying water pools etc. must be eliminated and mosquito grids are to be secured to windows. Applying those measures stricto sensu helped considerably reduce the number of malaria cases in French forces stationed in heavy transmission areas overseas.

Until 1990, chemoprophylaxis was chloroquine-based with daily prescription of one Nivaquine® tablet including 100 mg of chloroquine base. Yet, the number of cases increased considerably in 1989 and 1990, and the annual incidence rate rose from 2 to 10.8 per 100 men per year (250 cases in 1986 *versus* 1 120 cases in 1989).

Considering those figures, the Armed Forces Medical Corps set up as from 1991 a new chemoprophylactic therapy associating 100 mg of chloroquine and 200 mg of proguanil in a same capsule administered daily (4, 5). This capsule named *Gélule Antipaludique du Service de Santé des Armées* (GAPSSA) was well tolerated, had the same plasma concentrations as both ingredients taken separately and induced few side effects. (6). The number of cases was thus significantly reduced while mosquito protection measures were reinforced. The incidence rate dropped to 3.3 per 100 men in 1993 without any modification in the number of personnel or conditions of stay.

In 1996, it was noted epidemiologically, thanks to *in vitro* testing and plasma dosage, that GAPSSA efficacy has dropped significantly, and *Plasmodium falciparum* was increasingly resistant to cycloguanil. At the same time, genetic studies demonstrated a mutation of 108 codon in the *Plasmodium* strains tested and this evidenced the development of a resistance gene for dihydrofolate reductase (7, 8).

A second, alternative chemoprophylaxis consequently proved necessary. Mefloquine was not retained for operational troops because of potential neurological and neurosensory toxicity, and doxycycline was selected instead (9, 10). The latter was successfully used in 1994 in the French forces serving with the United Nations in Cambodia and its malaria chemoprophylaxis efficacy has been demonstrated in several studies conducted during humanitarian missions in Zaire or Timor by Australian forces. Two additional studies were then conducted by the French Armed Forces Medical Corps. The first in 1996 with a sample including 441 troops and the second in 1998 and 1999 with a sample including 522 troops (11, 12). Their objectives were to study the efficacy, compliance and tolerance of various doxycycline formulations compared to the chloroquine-proguanil association. It was demonstrated that, whatever its formulation (hyclate capsules or monohydrate tablets), doxycycline 100 mg/day is more efficacious than the chloroquine-proguanil association although hyclate presented many adverse digestive reactions and was often discontinued. Monohydrate on the other hand was better tolerated than the chloroquine-proguanil association.

The new doxycycline galenic formulation made available as quickly disintegrating multi-particle tablets coated with a gastric soluble excipient was better accepted transitwise than other compact forms. The concentration of the ingredient was lower in the esophagus as a result of intragastric disaggregation and compliance subsequently improved. However, South East Asia excepted, doxycycline monohydrate has not yet received any marketing authorization for malaria prophylaxis ; consequently, it is not extensively used in French forces and mainly limited to some specific applications including operational troops rapidly dispatched to heavy transmission zones (Intertropical Africa, Amazonian regions etc.), intolerance or mefloquine contra-indications.

Prior to departing for endemic malarious zones, travelers must be informed that drug prophylaxis is not complete and they can have malaria even though they are strictly complying with their chemoprophylaxis. Fever in subjects staying for long periods must be treated presumptively without waiting for *Plasmodium* identification with blood smears. This therapy is to include an efficient drug against potentially chloroquine resistant strains and its administration shall be preceded by a medical consultation. Mefloquine and halofantrine have been extensively used in this indication. However, QTc lengthening in most of treated patients, severe ventricular arrhythmia such as *torsades de pointes* and several cardiac deaths have been recorded over the last few years, and halofantrine is no longer up to its initially enthusiastic expectations. Considering those adverse reactions and since it is frequently impossible to perform an electrocardiogram prior to therapy delivery in tropical areas, halofantrine is no longer prescribed as presumptive fever therapy or in a radical cure upon return as it was recommended in 1991 (13). Furthermore, halofantrine is also contra-indicated whenever mefloquine is administered beforehand, mainly as a chemoprophylactic, and if the patient is being treated with diuretics, laxatives, class-1 antiarrhythmics agents, sotalol, bepridil, melleril, astemizole, known to lengthen QT interval (14).

Thus, the drug currently recommended in stand-by treatment is quinine hydrochloride (Quinimax®), 25 mg/kg/day administered orally for 5 days. The place of fixed artemether/benflumethol (Coartem®) or atovaquone/proguanil (Malarone®) associations remains to be determined.

CURRENT CHEMOPROPHYLACTIC STRATEGY

This strategy is conditioned by the level of *Plasmodium falciparum* resistance in those countries where French forces are exposed.

Thus, in East Africa and the Horn of Africa, in particular, and in those sahelian countries (Chad, Mauritania, Mali) where chloroquine resistance is low, the chloroquine-proguanil association remains in force. In West Africa (Senegal), this association is still being used but the regular increase in the level of *Plasmodium* resistance shall involve a mid-term modification of the chemoprevention schedule.

In sub-equatorial African countries (Gabon, Côte d'Ivoire, Comoros), the first line chemoprophylaxis is mefloquine delivered in a personal prescription for operational troops or for scheduled missions of intermediate duration (4 to 6 months). Doxycycline monohydrate recently licensed in malaria chemoprophylaxis in indicated whenever mefloquine is bad tolerated or contra-indicated.

In other African countries and upon extended stays (> 6 months, resident military personnel) chemoprophylaxis is customized and based on the recommendations issued by the French Upper Council for Public Health and Safety (*Conseil Supérieur d'Hygiène Publique de France*) (2).

Whenever troops are rapidly sent for operations and conflicts overseas without sufficient preparation, doxycycline monohydrate is preferred to mefloquine. The former is limited in this indication by a chemoprophylaxis delayed for ten days after the first ingestion as well as potential neurosensory and psychiatric effects that may prove counter-productive for troops in action. Those prophylactic choices are part of an evolving strategy that is likely to change at any time, particularly if the encouraging results obtained with tafenoquine, a structural primaquine analogue, are confirmed (15).

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