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MOLECULAR EPIDEMIOLOGY OF MALARIA IN CAMEROON. XXI. BASELINE THERAPEUTIC EFFICACY OF CHLOROQUINE, AMODIAQUINE, AND SULFADOXINE-PYRIMETHAMINE MONOTHERAPIES IN CHILDREN BEFORE NATIONAL DRUG POLICY CHANGE

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Abstract. The availability of epidemiologic data on drug-resistant malaria based on a standardized clinical and parasitological protocol is a prerequisite for a rational therapeutic strategy to control malaria. As part of the surveillance program on the therapeutic efficacy of the first-line (chloroquine and amodiaquine) and second-line (sulfadoxine-pyrimethamine) drugs for the management of uncomplicated *Plasmodium falciparum* infections, non-randomized studies were conducted in symptomatic children aged less than 10 years according to the World Health Organization protocol (14-day follow-up period) at 12 sentinel sites in Cameroon between 1999 and 2004. Of 1,407 children enrolled in the studies, 460, 444, and 503 were treated with chloroquine, amodiaquine, or sulfadoxine-pyrimethamine, respectively. Chloroquine treatment resulted in high failure rates (proportion of early and late failures, 48.6%). Amodiaquine was effective at all study sites (proportion of failures, 7.3%). Sulfadoxine-pyrimethamine therapy was less effective than amodiaquine ($P < 0.05$), with failures observed in 9.9% of patients. Chloroquine is no longer a viable option and has been withdrawn from the official drug outlets in Cameroon. Amodiaquine and, to a lesser extent, sulfadoxine-pyrimethamine monotherapies are still effective in Cameroon, but further development of resistance to these drugs should be delayed by the novel strategy using artemisinin-based combination therapy. Our findings indicate that amodiaquine is the most rational partner for artesunate. Studies on the efficacy of artesunate-amodiaquine combination are currently being undertaken at several sites in the country.

The first reported cases of chloroquine-resistant *Plasmodium falciparum* infections in Cameroon occurred in non-immune expatriates under chemoprophylaxis who visited or were residing in Limbé or Douala, coastal cities in the western part of the country, in 1985–1986.[1–3] Subsequent studies on the response of Cameroonian patients and asymptomatic school children to chloroquine therapy had confirmed the emergence and spread of chloroquine-resistant *P. falciparum* in other parts of the country during the late 1980s and early 1990s.[4–7] Despite the fact that these clinical studies had been useful to detect and follow the evolution of chloroquine-resistant malaria, the results are not directly comparable since the studies had been conducted according to a nonstandardized protocol or the now outdated 7-day test developed by the World Health Organization (WHO).[8] Nonetheless, the clinical observations are supported by *in vitro* surveys conducted during the same period.[9–13]

Since 1994, the WHO has been developing and updating a standardized protocol for the evaluation of therapeutic efficacy of first-line and second-line antimalarial drugs.[14–16] Unlike the former standard 7-day and 28-day tests,[8] which required a daily parasitological examination for the first 7 days (followed by a weekly parasitological examination for the 28-day test) in asymptomatic carriers or patients followed in a malaria-free zone, the new standardized test defines a set of inclusion criteria and requires a minimum number of clinical and parasitological follow-up examinations for at least 14 days. Furthermore, the interpretation of results takes into account both clinical and parasitological responses. Although there is no *in vivo* test for drug resistance that is devoid of pitfalls, the majority of malaria experts consider the current WHO protocol for the evaluation of therapeutic efficacy during the 28-day follow-up to be practical and useful to guide the national antimalarial drug policy, in particular in areas where transmission is intense and reinfection is common. The important merit of the WHO protocol is that the results from different investigators working in various epidemiologic contexts are comparable.

Cameroon is one of the first countries that has adopted the new WHO protocol for the evaluation of therapeutic efficacy of antimalarial drugs.[17–20] As part of the national surveillance program of drug-resistant malaria, we applied the WHO protocol to evaluate the efficacy of chloroquine (first-line drug in Cameroon until 2002), amodiaquine (alternative first-line drug until 2004), and sulfadoxine-pyrimethamine (second-line drug until 2004) administered as monotherapy in symptomatic children from 1999–2004. The results of our monitoring allowed the selection of amodiaquine as the most suitable partner of artesunate on a rational basis. Furthermore, blood samples collected as part of the clinical studies constitute our primary source of field isolates of *P. falciparum* for the molecular analysis of resistance genes.

MATERIALS AND METHODS

Study sites. Clinical studies were conducted at 12 different localities situated in different geographical and epidemiologic strata in Cameroon (Figure 1). The country may be roughly divided into the northern savannah region and the southern forest region (Table 1). The sahelian climate in the far north (Maroua) is characterized by a long dry season lasting ≥ 7 months (November–June) and a short rainy season (July–

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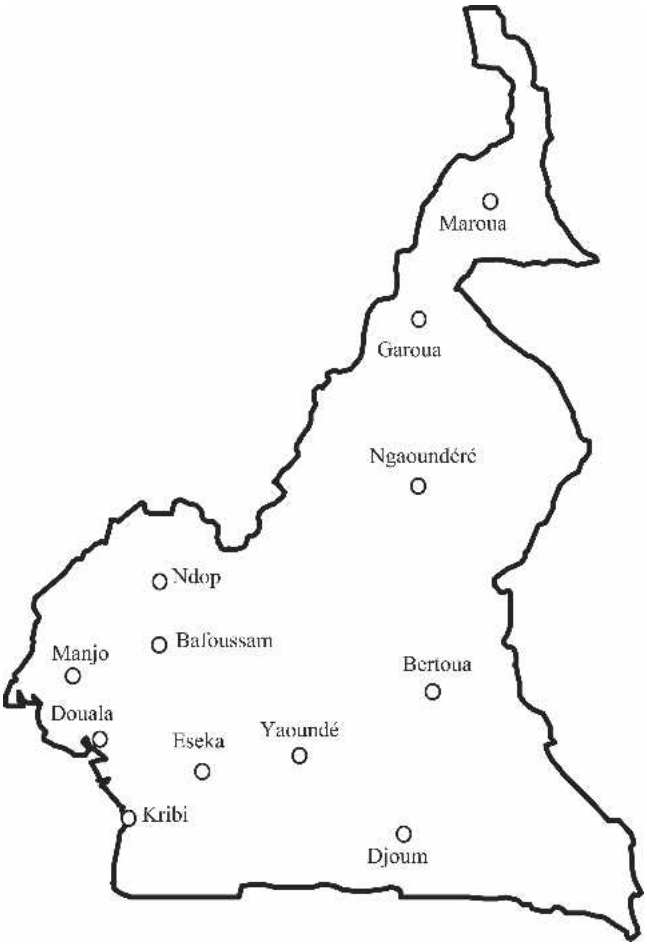

FIGURE 1. Sites of clinical studies in Cameroon.

October) with low precipitation (400–900 mm). The Sudanese-type tropical climate in the north (Garoua and Ngaoundéré) is also characterized by 2 seasons, a relatively shorter dry season lasting about 3–6 months and longer rainy season (March–November in Ngaoundéré) with heavier precipitation (900–1,500 mm), as compared with the far north. The Guinea-type equatorial climate in the southern, central, and eastern regions is characterized by fairly constant temperatures, abundant rainfall (1,500–2,000 mm), and 4 distinct seasons: 2 rainy seasons (March–May, September–November) and 2 dry seasons (December–February, June–August). The Cameroonian-type equatorial climate in southwestern coastal region and western highlands is characterized by fairly constant temperatures and 2 seasons: a short dry season (November–March) and a long rainy season with abundant precipitation (2,000–10,000 mm). In general, malaria transmission is intense and continuous throughout the year in coastal, southern, central, western, and eastern regions, with peak seasons corresponding to the rainy seasons. By contrast, malaria transmission is seasonal in the north.

At each study site, a joint mobile team of Institut de Recherche pour le Développement (IRD)–Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale (OCEAC) and the local health authorities and their personnel organized the clinical studies. Dispensaries or district hospitals were selected on the basis of the mean number of consultations of patients with fever presumably due to malaria > 50 per month and the presence of a sufficient number of health personnel, adequate diagnostic facilities, and hospital beds.

Patients. Children were enrolled after free and informed consent of the parents and/or legal guardians if the following inclusion criteria were met: age less than or equal to 10 years old (generally less than 5 years old in areas of intense transmission; up to 10 years old in western highlands and in the sahel), fever (either history of fever within the past 24 hours or fever at the time of consultation [i.e. rectal temperature ≥ 38.0°C]), parasite density ≥ 2,000 asexual *P. falciparum* parasites/μL of blood (without other *Plasmodium* species), and hematocrit ≥ 15%.[14–16] Children with signs and symptoms associated with concomitant infectious diseases, severe malnutrition, or danger signs defined by the WHO (e.g., inability to feed, sit, or stand up, repeated vomiting, convulsion, altered state of consciousness) were excluded.

The WHO protocol has undergone several modifications between 1994 and 2003, partly due to the difficulties in setting the same inclusion criteria for different epidemiologic situations.[21] These changes, together with the heterogeneity of transmission patterns in Cameroon, explain why slightly different inclusion criteria were used in some of our studies. The priority age group in areas of intense transmission in Africa is less than 5 years of age, but all age groups may be included in areas of low transmission. In our study, the upper age limit was arbitrarily set at 10 years of age. Earlier WHO protocols allowed the inclusion of patients with either a history of fever within the past 48 hours or axillary temperature range between 37.5°C and 39.5°C at the time of consultation, whereas the 2003 protocol requires fever at the time of consultation, without any upper limit of body temperature. In our studies, some smear-positive children who were afebrile at the time of consultation and to whom antipyretics were given before consultation were included. The 1994 protocol sets the lower and upper limits of parasitemia to 500 and 250,000 asexual parasites/μL of blood, respectively. The 1996 protocol sets the limits between 2,000 and 100,000 asexual parasites/μL of blood. According to the 2003 protocol, the lower and upper limits are 1,000–2,000 and 100,000–200,000 asexual parasites/μL of blood, respectively, depending on the intensity of malaria transmission. In our studies, patients with ≥ 2,000 asexual parasites/μL of blood were included, without any upper limit as long as there were no danger signs. The measurement of hematocrit (or hemoglobin) was required by the 1994 and 1996 protocols to limit patient inclusion to those with hematocrit > 15%. Hematocrit measurement is optional in the 2003 protocol. In our studies, hematocrit was measured in every included patient. Few patients with a low hematocrit (≥ 12%) were included. The studies were approved by the Cameroonian National Ethics Committee and the Cameroonian Ministry of Public Health.

Treatment and follow-up. Most of our studies were nonrandomized. Chloroquine was administered at a total dose of 25 mg/kg body weight (10 mg base/kg body weight on days 0 and 1, and 5 mg base/kg body weight on day 2). Amodiaquine was administered at a total dose of 30 mg base/kg body weight (10 mg base/kg body weight on days 0, 1, and 2) as either oral suspension (Flavoquine®; Hoechst Marion Roussel) or tablets. Sulfadoxine-pyrimethamine (25 mg/kg body weight sulfadoxine and 1.25 mg/kg body weight pyrimethamine) was

administered in a single dose. Paracetamol (30 mg/kg body weight/day) was administered to all patients.

The patients were followed on days 1, 2, 3, 7, and 14 at either health centers or home. Parents whose children developed fever or required other medical attention between days 4 and 6 and between days 8 and 13 were strongly advised to return to the health care center. Clinical and parasitological examinations were performed during each follow-up visit. Likewise, each dose was administered under supervision during the visits. Patients were observed for at least 30 minutes. If vomiting occurred within 30 minutes, another dose was administered. Patients with repeated vomiting were excluded from the study and treated with parenteral quinine followed by oral quinine. Patients who failed to respond to the assigned drug were treated with oral quinine (25 mg/kg body weight/day for 5 days).

Data interpretation. The lot quality assurance sampling (LQAS) method was used to calculate the sample size for studies between 1999 and 2001, which included the assessment of chloroquine.[15] The sample size was calculated to be 63, with the confidence level (1-α) and power (1-β) set at 95% and 80%, respectively. The lower and upper limits for treatment failure rates were fixed at 12.5% (i.e., acceptable therapeutic efficacy if failure rate is $\leq$ 12.5%) and 25% (i.e., unacceptable therapeutic efficacy if the failure rate is $\geq$ 25%), respectively. A major advantage of the LQAS method is that it allowed an early termination of the study if a high proportion of patients failed to respond to chloroquine. This ethical consideration was important for studies conducted in southern and central Cameroon, where previous studies have suggested that chloroquine is ineffective. In the studies on amodiaquine and sulfadoxine-pyrimethamine between 2002 and 2004, the minimum sample size was set at 50, with the anticipated prevalence of therapeutic failure of 15%, confidence level of 95%, and precision of the estimated prevalence of 10%.[16] The expected prevalence of clinical failure was based on an earlier study.[20]

The clinical and parasitological response of each patient was classified according to the 2003 WHO protocol:[16] (i) early treatment failure (ETF), danger signs or severe and complicated malaria on days 1–3 with positive smear, parasitemia on day 2 > parasitemia on day 0, parasitemia on day 3 $\geq$ 25% of parasitemia on day 0, or positive smear and fever on day 3; (ii) late clinical failure (LCF), danger signs, or severe and complicated malaria on days 4–14 with positive smear, or positive smear and fever on days 4–14; (iii) late parasitological failure (LPF), positive smear on day 14 without fever; and (iv) adequate clinical and parasitological response (ACPR), negative smear on day 14, with or without fever.

Results were expressed as the percentage of patients' response corresponding to one of the 4 possible responses. It is generally considered that failure rates (ETF + LCF + LPF) should be < 15% for a drug to be a viable option. Drugs with failure rates > 25% may be said to be ineffective. Such high failure rates are a strong indication for a change in drug policy. However, it must be emphasized that a single study performed at a sentinel site may not warrant a change in drug policy. A sufficient amount of clinical and parasitological data collected over several sites and over a period of time is required before a rational decision can be made. Part of the results on amodiaquine (N = 62 enrolled patients) and sulfadoxine-pyrimethamine (N = 64) in Hévécam in 2001 was published in our previous work.[22] These data were included in the present study to describe the global situation of the epidemiology of drug-resistant malaria in Cameroon.

Proportions were compared between groups by the χ^2 test. The mean hematocrit values on day 0 and day 14 were compared by the paired t test. The level of significance was set at 0.05. Data were analyzed by the Epi-Info software.

RESULTS

A total of 1,407 patients were included in the studies. Of these patients, 460, 444, and 503 were assigned to chloroquine, amodiaquine, or sulfadoxine-pyrimethamine treatment groups, respectively. A total of 73 patients (5.2%; 24, 19, and 30 from chloroquine, amodiaquine, and sulfadoxine-pyrimethamine treatment groups, respectively) were either lost to follow-up (mostly due to unscheduled trip with the parents) or excluded (self-medication, repeated vomiting without other danger signs). The clinical and laboratory characteristics of the patients on day 0 are summarized in Table 2.

The studies conducted in 1999–2000 included both patients with a history of fever within the past 24 hours and patients with fever at the time of consultation. From 2001, only patients with fever at the time of consultation were enrolled. Chloroquine treatment resulted in high overall failure rates (ETF + LCF + LPF, 48.6%) (Table 3). In addition, 4 of 9 studies were terminated before reaching the calculated sample size of 63 patients due to high failure rates. Chloroquine was ineffective in central, southern, eastern, and western regions of the country. Although the number of study sites was limited, there seemed to be a gradient, with decreasing failure rates towards the sahelian north (from 38% in Ngaoundéré to 20% in Garoua and 16% in Maroua). The inefficacy of chloroquine has led us to suspend all clinical studies on this drug from 2002.

Amodiaquine was highly effective in all study sites. The overall cure rate (i.e., ACPR) was 92.7% on day 14 (Table 4). Most of the failures were due to LPF. In Yaoundé, amodiaquine efficacy was evaluated in 1999 and 2003. There was no indication of change in the efficacy of the drug between these two time periods (P > 0.05). Compared with amodiaquine, sulfadoxine-pyrimethamine, the second-line drug, was less effective (P < 0.05), with 47 of 475 (9.9%) patients failing to respond to the treatment (Table 5). Close to half of these patients (20 of 47 failures; 43%) required an alternative treatment on or before day 3 due to ETF. For all drugs evaluated in this study, a comparison of treatment outcome in patients with a recent history of self-medication and in those who denied recent self-medication with antimalarial drugs did not show any significant difference (P > 0.05). Sulfadoxine-pyrimethamine efficacy was evaluated in Yaoundé in 1999 and 2003 (difference in failure rates not statistically significant, P > 0.05) and in Hévécam in 2001 (no failure) and 2004 (11.1% failure), but further studies with a larger sample size from the same sites are required to confirm this tendency.

Hematocrit was measured on both day 0 and day 14 in 728 children treated with either amodiaquine or sulfadoxine-pyrimethamine and in 297 children treated with chloroquine. The mean hematocrit increased by at least 5–6% (P < 0.05) in most studies on amodiaquine and sulfadoxine-pyrimethamine (data not shown). In contrast, most studies on chloroquine

TABLE 1
Geographic description of the study sites in Cameroon

Study site	Type of climate	Major characteristics
Far northern region		
Maroua	Sahelian	Provincial capital of the Far North (150,000 inhabitants) 1,250 km north of Yaoundé
Northern region		
Garoua	Sudanese-type tropical climate	Urban site (270,000 inhabitants) 1,050 km north of Yaoundé
Ngaoundéré		Urban site (207,000 inhabitants) 750 km north of Yaoundé
Central, southern, eastern regions		
Yaoundé	Guinea-type equatorial climate	Capital city (1,000,000 inhabitants), average altitude of 760 m above sea level
Bertoua		Urban site (100,000 inhabitants) within a transition zone between the tropical rain forest and savannah type of forest, 350 km to the east of Yaoundé
Eséka		Small town (22,000 inhabitants) 140 km southwest of Yaoundé
Djoum		Small town (15,000 inhabitants) 280 km southeast of Yaoundé
Western region		
Bafoussam	Cameroonian-type equatorial climate	City (260,000 inhabitants) in the western highlands, about 300 km northwest of Yaoundé
Ndop		Rural area (170,000 inhabitants) situated on a plain with natural lakes and irrigated agricultural lands, 60 km east of Bamenda, the principal city in the northwestern province, and 450 km northwest of Yaoundé
Coastal region		
Douala	Cameroonian-type equatorial climate	Largest city (2,000,000 inhabitants) often referred to as the "economic capital," 270 km west of Yaoundé
Hévécam*		Group of 15 villages (23,000 inhabitants) 40 km from Kribi and 340 km southwest of Yaoundé
Manjo		Small town (50,000 inhabitants) situated within a valley surrounded by 3 mountain ranges, 350 km northwest of Yaoundé

* The area is commonly referred to as "Hévécam" due to the presence of a company exploiting the hevea plantation. It is not an administrative term given to the locality.

showed either a significant increase (mean hematocrit > 5% on day 14) or slight but statistically non-significant increase in mean hematocrit. Children responding with LCF, but not LPF, showed no significant improvement ($P > 0.05$) in hematocrit.

DISCUSSION

Our studies show that chloroquine has become ineffective, particularly in southern, central, eastern, and western Cameroon. The drug remained relatively more effective in the northern regions. However, the failure rates of 16–38% during the short, 14-day follow-up period in these latter regions imply that chloroquine cannot be relied upon for a long-term drug policy and should be abandoned.[23] The high prevalence of chloroquine resistance found in our studies is in agreement with previous studies conducted in adults and children aged > 5 years in Yaoundé using the standard 1996 WHO protocol.[17–19] Based on the available clinical data,[4–7,13,19,24–26] it may be concluded that, since the first detection of chloroquine resistance in 1985 in Cameroon, it took less than 15 years for the drug to become ineffective in most parts of the country. The actual delay between the emergence of chloroquine resistance and its spread over the entire country to the extent of becoming ineffective is difficult to estimate because of the lack of comparable clinical data collected regularly from several sentinel sites. Based on the evidence of our studies, the Cameroonian Ministry of Public Health has suspended the importation of chloroquine into the country in 2002 and implemented a phased withdrawal of the drug from all government-controlled and official private outlets.

Amodiaquine administered as monotherapy has been an effective alternative first-line drug in Cameroon since the late 1980s.[6,7,13,25,27,28] More recent clinical studies, including those described in the present series of studies, confirm that the drug remains highly effective in Cameroon, even in chloroquine-resistant areas.[20,29] At least part of the reason may be related to the fact that amodiaquine has not been extensively distributed throughout the country in the 1990s and chloroquine-resistant malaria has often been treated with quinine. Serious concerns have been raised on the potential hepatic and hematological toxic effects of amodiaquine after repeated and regular intake, as in the past practice of weekly prophylaxis for non-immune travelers.[30] However, when the usual dose of amodiaquine is administered for treatment, the risk for toxic reactions is limited, and side effects are mild and

TABLE 2
Clinical and laboratory characteristics of enrolled children on day 0

Study site (year, treatment group*)	n	Age mean ± SD (range) months	Sex ratio (M:F)	Hematocrit mean ± SD (range) %	Parasitemia geometric mean and range† per μL of blood	Proportion of rectal temperature ≥ 38°C %	Proportion of self-medication, antimalarials %	Proportion of self-medication, antipyretics %
Yaoundé 1999 AQ	75	26.7 ± 16.5 (6–60)	1.14	33.2 ± 9.5 (20–37)	24,700 1,440–127.000	80.0	54.7	—
Yaoundé 1999 SP	67	22.5 ± 15.6 (5–60)	1.16	27.0 ± 5.7 (14–40)	20,000 2,340–140,000	83.6	64.2	—
Eséka 1999 CQ	18	22.7 ± 15.7 (6–54)	2.00	28.3 ± 5.5 (20–37)	20,400 2,160–92,000	94.4	61.1	—
Eséka 1999 AQ	60	22.7 ± 14.7 (5–60)	1.00	28.1 ± 6.2 (15–38)	15,000 2,400–154.000	83.3	61.7	—
Bertoua 1999 CQ	69	26.9 ± 16.6 (5–67)‡	1.23	29.5 ± 5.8 (15–41)	25,500 1,870–200,000	78.3	53.6	—
Douala 1999 CQ	21	34.0 ± 17.4 (7–60)	1.10	30.0 ± 4.1 (20–37)	13,900 2,140–77,000	90.5	28.6	52.4
Ndop 2000 CQ	69	32.0 ± 26.6 (4–90)‡	0.86	28.6 ± 5.8 (20–45)	16,500 (2,020–150,000)	94.2	31.9	34.8
Bafoussam 2000 CQ	39	35.9 ± 25.6 (7–97)‡	1.60	26.8 ± 5.6 (17–39)	15,100 3,000–100,000	97.4	43.6	51.3
Bafoussam 2000 AQ	67	41.8 ± 31.1 (5–115)‡	0.75	25.1 ± 4.9 (15–36)	12,300 2,030–140,000	97.0	53.7	52.2
Maroua 2000 CQ	73	43.0 ± 28.2 (6–108)‡	0.97	27.7 ± 6.7 (15–40)	38,800 2,000–220,000	100	26.0	60.3
Hévécam 2001 CQ	35	39.8 ± 21.8 (5–80)‡	0.65	28.5 ± 4.6 (19–36)	23,100 2,580–135,000	100	27.3	66.7
Hévécam 2001 AQ	62	35.2 ± 20.3 (4–75)‡	1.10	28.3 ± 4.5 (15–39)	12,200 2,000–160,000	100	29.5	45.9
Hévécam 2001 SP	64	36.0 ± 20.5 (5–89)‡	0.94	28.0 ± 3.9 (17–36)	9,620 2,050–114,000	100	17.7	35.5
Djoum 2001 SP	66	26.4 ± 18.7 (4–60)	0.91	27.0 ± 6.2 (12–37)§	24,900 2,100–228,000	100	29.5	44.3
Garoua 2001 CQ	66	46.1 ± 24.2 (8–105)‡	1.17	29.9 ± 4.8 (17–39)	47,300 2,800–220,000	100	53.8	78.5
Ngaoundéré 2001 CQ	70	46.6 ± 54.4 (4–115)‡	2.24	32.3 ± 12.4 (18–45)	22,200 2,090–300,000	100	41.2	73.5
Manjo 2002 SP	69	27.9 ± 31.2 (6–63)‡	0.94	28.0 ± 6.4 (16–40)	23,100 2,600–260,000	100	26.6	48.4
Yaoundé 2003 AQ	64	28.2 ± 19.2 (3–60)	0.90	27.4 ± 5.7 (16–39)	28,000 2,100–220,000	100	52.4	81.0
Yaoundé 2003 SP	61	27.1 ± 16.1 (4–58)	1.54	27.8 ± 6.2 (15–40)	30,900 2,900–260,000	100	34.4	62.3
Bertoua 2003 AQ	58	26.7 ± 15.8 (6–58)	1.07	27.9 ± 5.2 (16–41)	20,000 2,000–250,000	100	45.9	89.2
Bertoua 2003 SP	57	26.9 ± 15.9 (6–58)	0.80	27.7 ± 4.6 (18–37)	25,100 2,830–200,000	100	55.6	88.9
Garoua 2003 AQ	58	52.3 ± 29.4 (8–106)‡	1.37	30.8 ± 4.1 (20–38)	30,500 3,000–300,000	100	56.8	100
Garoua 2003 SP	61	47.8 ± 26.5 (10–108)‡	0.93	30.6 ± 5.5 (20–40)	39,000 3,300–194,000	100	65.9	90.2
Hévécam 2004 SP	58	35.1 ± 16.8 (6–60)	1.70	31.0 ± 5.0 (19–40)	24,900 2,730–191,000	100	25.9	63.0

* CQ, chloroquine; AQ, amodiaquine; SP, sulfadoxine-pyrimethamine.
† The following number of patients had <2,000 or >100,000 asexual parasites/μL of blood: 3 and 2 in Yaoundé AQ 1999, 0 and 4 in Yaoundé SP 1999, 0 and 5 in Eséka 1999 AQ, 1 and 5 in Bertoua 1999 CQ, 0 and 4 in Ndop, 0 and 1 in Bafoussam AQ, 0 and 7 in Maroua, 0 and 4 in Hévécam 2001 CQ, 0 and 3 in Hévécam 2001 AQ, 0 and 1 in Hévécam 2001 SP, 0 and 7 in Djoum, 0 and 14 in Garoua 2001, 0 and 9 in Ngaoundéré, 0 and 4 in Manjo, 0 and 1 in both Yaoundé 2003 AQ and SP, 0 and 2 in Bertoua 2003 AQ, 0 and 3 in Bertoua 2003 SP, 0 and 10 in Garoua 2003 AQ, 0 and 9 in Garoua 2003 SP, 0 and 2 in Hévécam 2004 (none in Eséka 1999 CQ, Douala, Bafoussam CQ).
‡ The numbers of children aged >60 months old are 1/69 (1.4%) in Bertoua, 8/69 (11.6%) in Ndop, 5/39 (12.8%) in Bafoussam CQ, 15/67 (22.4%) in Bafoussam AQ, 20/73 (27.4%) in Maroua, 8/33 (24.2%) in Hévécam CQ, 13/61 (21.3%) in Hévécam AQ, 12/62 (19.4%) in Hévécam 2001 SP, 25/65 (38.5%) in Garoua 2001, 48/68 (70.6%) in Ngaoundéré, 5/64 (7.8%) in Manjo, 18/57 (31.6%) in Garoua 2003 AQ, and 16/58 (27.6%) in Garoua 2003 SP.
§ Two children with hematocrit values of 12% and 14% were included (adequate clinical and parasitological response on day 14).

transient. The drug is an effective therapeutic option in many African countries.[31] When patients were followed until day 28 after amodiaquine monotherapy in Hévécam, Cameroon, the failure rate increased to 10.2%, as compared with 3.3% on day 14.[22] In our previous studies based on the analysis of 3 polymorphic genetic markers, persistence or reappearance of parasitemia on or before day 14 after treatment with chloroquine, amodiaquine, or sulfadoxine-pyrimethamine was mostly due to recrudescence, whereas reinfection was common beyond day 14 in our study sites.[32,33]

Earlier studies had shown the 100% efficacy of sulfadoxine-pyrimethamine in a small number of patients who failed to respond to chloroquine after either a full prescribed course or self-medication at the time when the use of antifolate drugs was still limited in Cameroon.[4,5,34] However, a later study based on the 1996 WHO protocol has shown the failure rate of 12% in adults and children aged more than 5 years who had no recent intake of antimalarial drugs.[20] In the present study, in which many children with a recent history of self-medication with antimalarial drugs were enrolled, the overall

TABLE 3
Therapeutic efficacy of chloroquine in Cameroonian children, 1999–2001

Study site/Year	n Enrolled		n Lost-to-follow-up		ACPR		LPF		LCF		ETF	
	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever
Eséka/1999	16	18	0	0	2 (12.5%)	2 (11.1%)	5 (31.2%)	5 (27.8%)	5 (31.2%)	6 (33.3%)	4 (25.0%)	5 (27.8%)
Bertoua/1999	54	69	6	8	23 (47.9%)	30 (49.2%)	12 (25.0%)	14 (23.0%)	4 (8.3%)	7 (11.5%)	9 (18.8%)	10 (16.4%)
Douala/1999	19	21	1	2	6 (33.3%)	6 (31.6%)	0	1 (5.3%)	2 (11.1%)	2 (10.5%)	10 (55.6%)	10 (52.6%)
Ndop/2000	65	69	3	3	14 (22.6%)	17 (25.8%)	19 (30.6%)	20 (30.3%)	18 (29.1%)	18 (27.2%)	11 (17.7%)	11 (16.7%)
Bafoussam/2000	38	39	1	1	7 (18.9%)	7 (18.4%)	9 (24.3%)	10 (26.3%)	15 (40.5%)	15 (39.5%)	6 (16.2%)	6 (15.8%)
Maroua/2000	73	—	5	—	57 (83.8%)	—	2 (2.9%)	—	4 (5.9%)	—	5 (7.4%)	—
Hévécam/2001	35	—	2	—	9 (27.3%)	—	2 (6.1%)	—	14 (42.4%)	—	8 (24.2%)	—
Garoua/2001	66	—	1	—	52 (80.0%)	—	1 (1.5%)	—	11 (16.9%)	—	1 (1.5%)	—
Ngaoundéré/2001	70	—	2	—	42 (61.8%)	—	9 (13.2%)	—	15 (22.1%)	—	2 (2.9%)	—

ACPR, adequate clinical and parasitological response; LPF, late parasitological failure; LCF, late clinical failure; ETF, early treatment failure.
The term "with fever" indicates children with rectal temperature ≥ 38.0°C at the time of consultation on day 0. The term "without fever" refers to children who satisfied all inclusion criteria but not febrile at the time of consultation. These latter children had febrile episodes before consultation and often received antipyretic self-medication at home.

failure rate was 8%. Paradoxically, sulfadoxine-pyrimethamine, the second-line drug, was less effective than amodiaquine, an alternative first-line drug. However, sulfadoxine-pyrimethamine is still a viable option in Cameroon, especially if it is combined with a suitable drug partner to prolong its period of clinical utility and/or if its use is limited to a specific target population, such as for the intermittent preventive treatment in pregnant women.

Based on the results obtained from various sentinel sites in different epidemiologic situations in Cameroon, amodiaquine was officially selected as the most suitable component of artemisinin-based combination therapy (ACT) in 2004. Although chloroquine is still moderately effective in the far north during the 14-day follow-up period, its continued use restricted to this region is not possible since a single drug or drug combination is required for the implementation of a single national drug policy over the entire country. Furthermore, its failure rate is expected to be unacceptable beyond day 14. Artesunate-amodiaquine combination has been shown to be well tolerated and effective in African countries, including Cameroon (Basco, unpublished data).[35] These drugs mutually protect each other to delay the spread of drug-resistant malaria. The combination will be prescribed for the treatment of all cases of uncomplicated malaria in Cameroon, and the therapeutic scheme of first-line, second-line, and third-line drugs will no longer be applied. Sulfadoxine-pyrimethamine still has an important role to play in antimalarial chemotherapy in Africa, in particular for the intermittent preventive treatment during pregnancy. Artesunate-sulfadoxine-pyrimethamine is also an alternative ACT that

TABLE 4
Therapeutic efficacy of amodiaquine in Cameroonian children, 1999–2003

Study site/Year	n Enrolled		n Lost-to-follow-up		ACPR		LPF		LCF		ETF	
	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever
Yaoundé/1999	47	75	4	8	34 (79.1%)	58 (86.6%)	9 (20.9%)	9 (13.4%)	0	0	0	0
Eséka/1999	50	60	3	3	38 (80.9%)	47 (82.5%)	7 (14.9%)	7 (12.3%)	1 (2.1%)	1 (1.8%)	1 (2.1%)	2 (3.5%)
Bafoussam/2000	65	67	1	1	60 (93.8%)	62 (93.9%)	2 (3.1%)	2 (3.0%)	2 (3.1%)	2 (3.0%)	0	0
Hévécam/2001	61	—	0	—	58 (95.1%)	—	1 (1.6%)	—	2 (3.3%)	—	0	—
Yaoundé/2003	64	—	1	—	62 (98.4%)	—	0	—	0	—	1 (1.6%)	—
Bertoua/2003	58	—	4	—	52 (96.3%)	—	2 (3.7%)	—	0	—	0	—
Garoua/2003	58	—	1	—	56 (98.2%)	—	0	—	0	—	1 (1.8%)	—

ACPR, adequate clinical and parasitological response; LPF, late parasitological failure; LCF, late clinical failure; ETF, early treatment failure.
The term "with fever" indicates children with rectal temperature ≥ 38.0°C at the time of consultation on day 0. The term "without fever" refers to children who satisfied all inclusion criteria but were not febrile at the time of consultation. These latter children had febrile episodes before consultation and often received antipyretic self-medication at home.

TABLE 5
Therapeutic efficacy of sulfadoxine-pyrimethamine in Cameroonian children, 1999–2004

Study site/Year	n Enrolled		n Lost-to-follow-up		ACPR		LPF		LCF		ETF	
	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever	With fever	With or without fever
Yaoundé/1999	56	67	4	7	48 (92.3%)	55 (91.7%)	1 (1.9%)	1 (1.7%)	1 (1.9%)	1 (1.7%)	2 (3.8%)	3 (5.0%)
Hévécam/2001	64	—	0	—	64 (100%)	—	0	—	0	—	0	—
Djoum/2001	66	—	5	—	54 (88.5%)	—	3 (4.9%)	—	2 (3.3%)	—	2 (3.3%)	—
Manjo/2002	69	—	5	—	53 (82.8%)	—	2 (3.1%)	—	7 (11%)	—	2 (3.1%)	—
Yaoundé/2003	61	—	0	—	53 (86.9%)	—	2 (3.2%)	—	1 (1.6%)	—	5 (8.2%)	—
Bertoua/2003	57	—	4	—	48 (90.5%)	—	0	—	2 (36.8%)	—	3 (5.7%)	—
Garoua/2003	61	—	3	—	53 (91.4%)	—	0	—	2 (3.4%)	—	3 (5.2%)	—
Hévécam/2004	58	—	4	—	48 (88.9%)	—	1 (1.9%)	—	3 (5.6%)	—	2 (3.7%)	—

ACPR, adequate clinical and parasitological response; LPF, late parasitological failure; LCF, late clinical failure; ETF, early treatment failure.
The term "with fever" indicates children with rectal temperature ≥ 38.0°C at the time of consultation on day 0. The term "without fever" refers to children who satisfied all inclusion criteria but were not febrile at the time of consultation. These latter children had febrile episodes before consultation and often received antipyretic self-medication at home.

has been shown to be effective in Africa (Basco, unpublished data).[36] Regular surveillance of antimalarial drug efficacy using a standard protocol is an important component of malaria control that provides evidence-based data to implement, adjust, and modify the national drug policy to combat drug-resistant malaria.

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