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Dramatically decreased therapeutic efficacy of chloroquine and sulfadoxine-pyrimethamine, but not mefloquine, in southern Benin

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Summary

OBJECTIVE To evaluate the *in vivo* therapeutic efficacy of chloroquine (CQ), sulfadoxine-pyrimethamine (SP) and mefloquine (MQ) in children presenting with uncomplicated malaria in Benin.
METHODS Drug efficacy was tested according to the WHO *in vivo* 28-day protocol. For failures that occurred after 7 days of follow-up, paired pre- and post-treatment blood samples were genotyped at *msp1* and *msp2* loci to distinguish new infections and recrudescent strains. Children enrolled were randomly assigned to a therapeutic group (CQ, $n = 14$; SP, $n = 42$; MQ, $n = 44$). The number of CQ treatment was intentionally restricted after 1 month, as its use was considered to constitute a danger for children.
RESULTS Chloroquine and SP showed very high failure rates (85.7% and 50%, respectively), whereas MQ treatment was successful in 97.5%. The molecular tool allowed to re-evaluate two new infections previously considered as failures.
CONCLUSIONS Chloroquine should no longer be used to treat children presenting with *Plasmodium falciparum* malaria in Benin.

keywords *falciparum* malaria, chloroquine, sulfadoxine-pyrimethamine, mefloquine, drug efficacy, Benin

Introduction

In Benin, chloroquine (CQ) has long been the first line treatment for uncomplicated malaria in children and used for prophylaxis during pregnancy. The second line treatment was defined as sulfadoxine-pyrimethamine combination (SP). Since 1994, CQ and SP efficacies are under supervision by the Beninese National Malaria Control Program (NMCP). Armed with variable results of efficacies in the whole country, World Health Organization (WHO) recommendations and support of the international institutions, Benin decided in March 2004 to change its first-line treatment for uncomplicated malaria to artemether-lumefantrine (Coartem®) and to introduce SP as intermittent preventive treatment during pregnancy.

Since October 2005, the Beninese NMCP tries to institute these two drug regimens at the country level. However, despite the support of the international institutions, Benin continues to have insufficient quantities of both treatments to supply hospitals and smaller health centres. The unavailability of Coartem® is an international problem as the restricted production does not respond to the international demand. Furthermore, considering the high cost of this association, Benin needs a long-term support to sell the treatment in health centres at a reasonable cost in the whole country.

Although the use of SP as an intermittent preventive treatment during pregnancy has been recommended by the WHO and adopted by many countries in Africa (Hill & Kazembe 2006), its relatively low efficacy and the rapid spread of molecular resistance are worrying. Faced with the choice of SP for malaria prevention during pregnancy, and problems of availability and cost of artemether-lumefantrine, our team proposed, in agreement with the NMCP, a study to obtain basic *in vivo* efficacy rates in 2005 for SP and mefloquine (MQ) in a town of southern Benin. Not widely used and with very high efficacy rates reported in Africa (Tinto *et al.* 2001; Adam *et al.*

2004, 2005), MQ may constitute an interesting molecule in Benin for use alone or in combination for both pregnancy prevention and malaria treatment particularly because of its long half-life, its short treatment course and its availability. A 28-day follow-up including molecular techniques to confirm treatment failures was thus conducted in Ouidah, in children under 5-years old treated with CQ, SP or MQ for uncomplicated malaria.

Methods

Study area and population

The study was conducted in two health centres belonging to the health district of Ouidah. Located in the Atlantique province on the main road that links Nigeria to Togo, about 42 km west from Cotonou, Ouidah is a town of about 37 000 inhabitants. The first health centre, Kpasse, is part of the town of Ouidah, whereas the centre of Tokpa Dome is 22 km from the town centre in a rural area. Southern Benin is characterized by a sub-equatorial climate and a perennial malaria transmission with two malaria transmission peaks corresponding to the rainy seasons (April–July and mid-September–November), (Akogbeto *et al.* 1992). Children were enrolled between June and October 2005 if the following criteria were met: age between 6 and 59 months, clinical illness compatible with malaria, presence of fever (axillary temperature ≥37.5 °C) or history of fever within 24 h, pure *Plasmodium falciparum* infection with a parasite density of ≥2000 asexual parasites, and free, informed and written consent of the parent or guardian. Children were excluded if presenting any of the complications defined by WHO guidelines (WHO 2000), particularly neurological signs and hyperparasitaemia above 5%; if presenting with clinically evident concomitant infectious disease or a history of allergic reaction to CQ, SP and MQ; and if presenting a potential problem for the 28-days follow-up, e.g. living >10 km from the health centre. The study was approved by the Beninese institutional ethical committee.

Information to the population

The population was informed that a malaria study was taking place in their health centre with free antimalarial drugs. Kpasse health centre covers three districts of the town (9880 inhabitants registered in 2002) whereas Tokpa Dome health centre serves 18 villages (8930 inhabitants registered in 2002). Information was given through local radios, town criers and briefings organized in villages for mothers.

Clinical and parasitological diagnosis

Children presenting at the health centre with fever were clinically examined and the parent or guardian was questioned on the history of symptoms. If the child satisfied the inclusion criteria, a finger-prick puncture was made to prepare two thick and thin blood smears and three blood-blotted filter paper spots. The first smear was stained with 10% Giemsa for rapid diagnostic and 3% Giemsa was used to stain the second smear kept for later reading. All thick blood smears were examined against 500 leucocytes. Parasite densities were recorded as the number of parasites/μl blood, assuming an average leucocyte count of 8000/μl.

Treatment and follow-up of children

The children were randomly assigned to a therapeutic group to receive oral CQ (total dose of 30 mg base/kg body weight divided in three daily doses), a single oral dose of SP (25 mg/kg body weight of sulfadoxine + 1.25 mg/kg body weight of pyrimethamine) or oral MQ (total dose of 25 mg/kg body weight divided into three doses given 8–12 h apart). Paracetamol (total dose of 60 mg/kg body weight in three doses a day, repeated 2 days) and iron (ferrous fumarate, 100–300 mg/24 h for 7 days) were added to the antimalarial treatment. All doses of antimalarial treatment were administered under supervision and patients were observed for at least 30 min after ingestion. Children who vomited within 30 min received the same repeated dose. Children treated first with CQ or SP who presented a treatment failure received oral MQ; children presenting a failure after MQ treatment were treated with oral quinine; those exhibiting signs of danger during the follow-up were hospitalized in the paediatric unit at the reference hospital of Ouidah and treated with i.v. quinine.

Parent or guardian was asked to return the child to the health centre at days 1, 2, 3, 7, 14, 21 and 28, as well as any other day if the child was unwell. Clinical examination, blood smears and blood-blotted filter papers were performed at each visit. If a child did not appear, s/he was visited at home by a nurse.

DNA preparation and PCR amplification

At enrolment and during the follow-up, three drops of blood were blotted either on isocode® filter paper or on 3MM Whatmann paper. DNA was prepared by Chelex extraction, as previously described (Plowe *et al.* 1995). A fluorescent PCR analysed block 2 of the *msp-1* and of *msp-2* domains, as described (Jafari *et al.* 2004). Primers were: *msp-1* f-5′-CACATGAAAGTTATCAAGAACTTGTC-3′

(sense, fluorescein-labeled) and 5′-GTACGTCTAA-TTCCATTTGCACG-3′ (antisense); *msp-2* f-5′-GAAGGTAATTAAAACATTGTC-3′ (sense, fluorescein-labeled) and 5′-GAGGGATGTTGCTGCTC-CACA-3′ (antisense) (Genset SA Europe) (Ranford-Cartwright *et al.* 1993). Amplification products were processed in an ABI Prism 310 Genetic analyser (Perkin Elmer Applied Biosystems) and analysed using Genescan software (Applied Biosystems) (Jafari *et al.* 2004). Each genotype is characterized by its size and the area under the curve (AUC) of the peak corresponding to *msp-1* or *msp-2* PCR products. Each peak AUC is proportional to the quantity of PCR products of the corresponding allele, allowing a precise relative quantification of this genotype. Numbers and ratios of genotypes were quantified for the *msp-1* and *msp-2* loci in all samples. Genotypes representing <2% of the overall parasite population from a given sample were not considered.

Objective and outcomes

The main objective of this study was to measure the level of efficacy of CQ, SP and MQ in children presenting uncomplicated malaria. The primary endpoint was the proportion of children achieving a treatment success in each therapeutic group. Secondly, treatment failures were analysed as early, late parasitological or late clinical failures, according to the WHO *in vivo* protocol (WHO 2003). Finally, to ascertain whether *in vivo* test failures were true treatment inefficacy or reinfection, blood samples from enrolment and from the day of failure were genotyped and compared, as described in the previous section. Treatment failure was considered when both samples shared at least one allele. Reinfection was defined as the presence of additional allele(s) in the day of failure sample, as compared with enrolment, in the absence of any allele present in the pre-treatment sample.

Sample size

This trial was designed as a comparative study of the efficacy of two antimalarial drugs, SP and MQ. Our sample size was calculated only in these two arms, as the efficacy of CQ was supposed to be much lower, according to previous data (NMCP, unpubl. data). With a sample size of 45 patients in each study group, a cure rate of 90% with either drug regimen could be estimated with 10% precision, and a maximum allowable inferiority of 25% for SP compared with MQ could be detected with 80% power and 95% confidence, taking into account a withdrawal rate of up to 20%.

Randomization

Two computer-generated randomization lists were drawn up, one for each health centre (Tokpa Dome and Kpasse). At the beginning of the study, both lists were given to the nurses responsible for the enrolment of children. Children included in the study were sequentially assigned to a number corresponding to one of the three treatments in the randomization list.

Data analysis

To analyse treatment efficacy, distributions of quantitative and qualitative data according to treatment groups were respectively assessed by Kruskal–Wallis test and Fisher exact test. To compare treatment efficacies, failures were grouped. Treatments were compared both all together and two by two. In the molecular approach, the polymorphism of each *msp* locus was assessed by the number of different alleles obtained for all typed samples. The multiplicity of infection (MOI), or number of genotypes per infection, was calculated as the highest number of genotypes at any of the two *msp* loci. The Mann–Whitney *U*-test was used to compare polymorphism degree according to each *msp* marker, as well as MOIs. Data were analysed with the STATVIEW software (SAS Institute Inc., Cary, NC, USA) and BMDP (Los Angeles, CA, USA) statistical software.

Results

Enrolment

Enrolment took place between June and October 2005 and started after information on the study in districts and villages was given. As shown on Figure 1, a total of 100 children were enrolled, including 54 children from the rural centre of Tokpa Dome, and 46 from the urban centre of Kpasse. Analysis was conducted with 92 children as 8 (8.0%) were excluded for follow-up for no more than day 14 as they travelled before the end of their follow-up ($n = 5$), repeated vomiting after treatment administration ($n = 1$), or unjustified treatment change ($n = 2$). After 1 month the CQ group was interrupted when it included 14 children, as most treatment outcomes were failures and as the medical staff judged that the use of CQ put the children in danger.

All parameters were compared between children from each treatment group enrolled in the urban and rural health centres. In both health centres, clinical and parasitological parameters were similar at enrolment and during follow-up, as well as treatment efficacies. Consequently, children from both the urban and rural areas were joined together for analysis. As shown in Table 1, all parameters

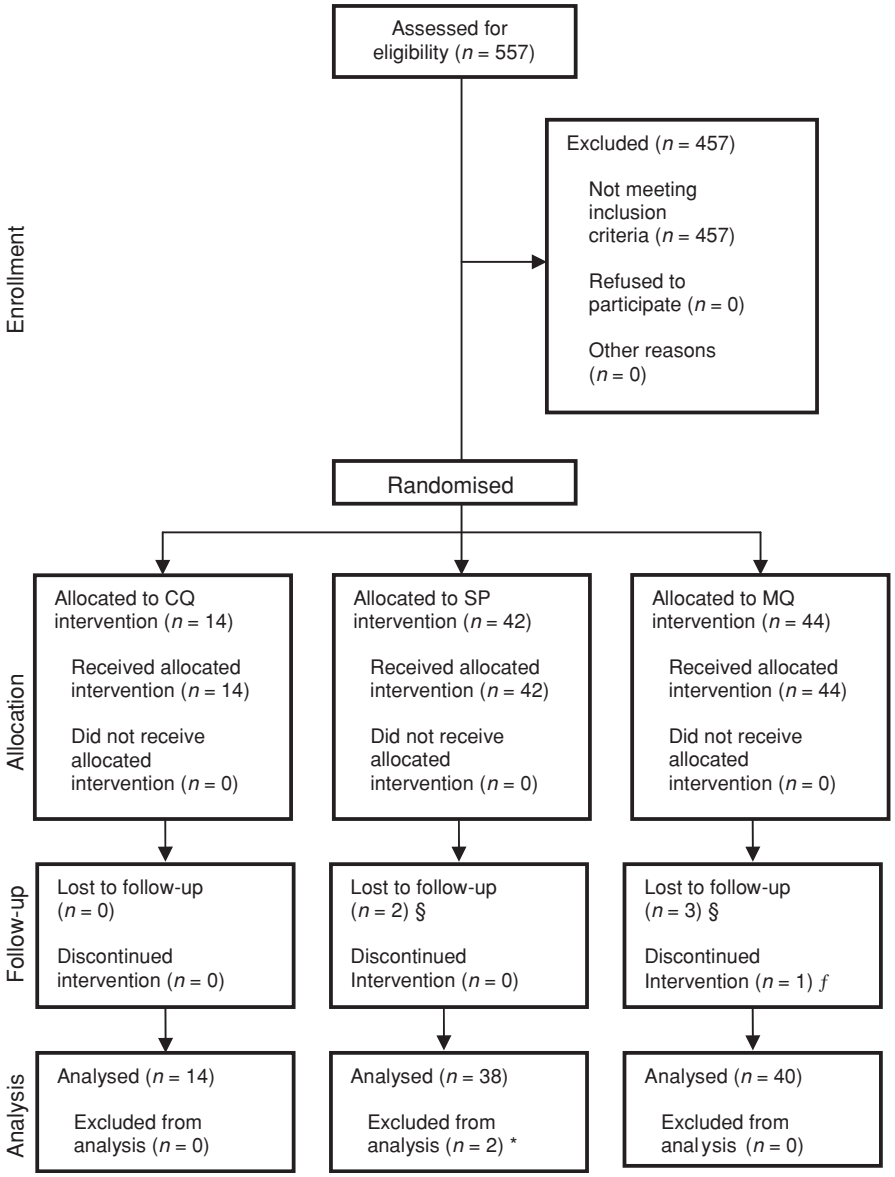

Figure 1 Phases of the randomized trial including chloroquine (CQ), sulfadoxine-pyrimethamine (SP), mefloquine (MQ) treatment groups of children aged 6–59 months, Ouidah, Benin, 2005. §Five children were lost and could not complete follow-up after day 14; *f*one child repeatedly vomited after the second dose of treatment; *two treatment outcomes were misinterpreted.

were similar at enrolment between treatment groups, except axillary temperature that was lower in children from the CQ group.

Treatment efficacy

As shown in Table 2, MQ was the sole effective drug. Two treatment failures occurred at day 28 in the group of children treated with this drug. CQ and SP presented respectively 85.7% (95% CI 57.2–98.2) and 52.6% (95%CI 35.8–68.5) failures. In both treatment groups, failures were mostly early ones as 50.0% (95% CI 31.1–78.9) and 68.4% (95% CI 43.5–87.4) failures occurred before day 3 (early failures, ETF). Late failures in the CQ group were all clinical failures, whereas SP treatment led to both parasitological and clinical late failures (LPF, LCF),

Table 1 Clinical and parasitological characteristics of children at enrolment according to the treatment received (CQ, SP, MQ), Ouidah 2005

Parameter*	CQ ($n = 14$)	SP ($n = 42$)	MQ ($n = 44$)	*P*-value
Age (mean ± SE) (months)	39.9 (±5.0)	28.3 (±2.6)	27.2 (±2.3)	NS
Sex ratio (F/M)	6/8	15/27	22/22	NS
Wt (mean ± SE) (kg)	12.1 (±0.7)	11.0 (±0.4)	10.6 (±0.4)	NS
Axillary temperature (mean ± SE) (°C)	38.2 (±0.2)	38.9 (±0.1)	39.3 (±0.2)	0.002
GMPD (95% CI), per μl of blood	24 054 (9805–59 012)	46 863 (31 183–70 428)	33 769 (22 707–50 220)	NS

CQ, chloroquine; SP, sulfadoxine-pyrimethamine; MQ, mefloquine; NS, not significant.
*SE, standard error; F, female; M, male; GMPD, geometric mean parasite density; CI, confidence interval.

Table 2 *In vivo* efficacy of CQ, SP and MQ treatments of non-severe *Plasmodium falciparum* malaria attacks in children from Benin in 2005

Parameter	CQ ($n = 14$)	SP ($n = 38$)	MQ ($n = 40$)	*P*-value
In vivo treatment response [no. (%, 95% CI) of children]*				
ACPR [no. of reinfection]	2 (14.3, 1.8–42.8) [0]	19 (50.0, 33.4–66.6) [1]	39 (97.5, 86.8–99.9)†[1]	<0.0001
ETF	6 (42.85)	13 (34.2)	0	
LCF	6 (42.85)	3 (7.9)	0	
LPF	0	3 (7.9)	1 (2.5)	
Total failures	12 (85.7, 57.2–98.2)	19 (50.0, 33.4–66.6)	1 (2.5, 0.06–13.2)	
Occurrence of danger signs [no. (%) of children]	2 (14.3)	3 (7.9)	0	ns
Parasitological clearance by day 3 in the ACPR group [no. (%) of children]	2 (100.0)	9 (47.4)‡	37 (94.9)	0.0008
Mean axillary temperature (±SE) on day 3	37.3 (±0.1)	37.1 (±0.1)	37.0 (±0.1)	ns
Presence of gametocyte on day 7 or later§ [no. (%) of children]	2 (28.6)	19 (76.0)	13 (32.5)	0.001

CQ, chloroquine; SP, sulfadoxine-pyrimethamine; MQ, mefloquine.
*Treatment response is divided into adequate clinical and parasitological response (ACPR), early treatment failure (ETF), late clinical failure (LCF) or late parasitological failure (LPF).
†One child treated with MQ was monitored until day 21 only.
‡Two parasite densities by day 3 are missing.
§Follow-up stopped by day 3 not included; CQ, $n = 7$; SP, $n = 25$; MQ, $n = 40$.

and one LPF occurred after MQ treatment. Danger signs occurred in some children treated with both CQ or SP. In the adequate clinical and parasitological response group, as shown in Table 2, after administration of the initial dose, 3 days were enough for CQ and MQ to achieve parasite clearance in 95–100% of children (2/2 and 37/39 in CQ and MQ groups, respectively), whereas more than half of the children treated with SP were still parasitemic by day 3 (Fisher's exact test, $P = 0.0008$). By day 3, axillary temperature was similar in the three groups. Furthermore, gametocytes were detected between day 7 and 28 much more frequently in children treated with SP (19/25) than in CQ and MQ treated children (2/7 and 13/40, respectively, Fisher's exact test, $P = 0.001$). For all three treatments, no adverse effect was mentioned by any parent during the 28-day follow-up.

Molecular approach

Blood spotted on isocode® filter papers and conserved as recommended by the supplier, poorly dried and DNA extraction was problematic. Conservation and drying of blood on Whatman 3MM paper was easier, and DNA extraction was managed successfully (results not shown). Paired samples (enrolment and failure) from the 11 children presenting a failure after day 7 were studied (in Table 2, two late failures occurred between day 4 and 7), including one sample typed at two parasitological failure points (day 14 and 28). Despite difficulties with extraction, genotyping of both *msp1* and *msp2* was achieved for respectively 20/23 and 22/23 samples. The high polymorphism rate in both markers allowed the distinction between reinfections and recrudescent strains.

Polymorphism was higher for *msp2* than for *msp1* (Mann–Whitney *U*-test, $P < 0.0001$). The mean number of alleles (±SE, min–max) was respectively 3.1 (±0.4, 1–8) and 6.6 (±0.6, 2–12) for *msp1* and *msp2*. Based on both *msp* markers, the mean MOI at enrolment (±SE, min–max) was 6.5 (±0.8, 2–11). MOI was similar in pre- and post-treatment samples. Mean MOI (±SE) measured at enrolment was slightly higher in the rural area (8.0 ± 1.1) compared with the urban area (5.3 ± 1.0), Mann–Whitney *U*-test, $P = 0.08$). Among the 11 paired samples tested, nine were confirmed as treatment failures, whereas two cases were due to a reinfection and reconsidered as a treatment success (see Table 2). Both reinfections were recorded by day 28. The new infection that occurred after SP treatment was combined with fever, unlike the other one recorded in the MQ group. All failures due to recrudescent allele(s) contained both pre-treatment alleles and additional alleles. Both new infections were previously included as LCF and LPF, respectively, after SP and MQ treatments. Thus, after adjustment of the results of treatment efficacies, the rates of treatment success were respectively 14.3% (95% CI 1.8–42.8), 50.0% (95% CI 33.4–66.6) and 97.5% (95% CI 86.8–99.9) for CQ, SP and MQ (Table 2). Adjusted efficacies were highly different when compared all three together (Fisher exact test, $P < 0.0001$) or two by two (Fisher exact test, $P < 0.0001$ for CQ *vs.* MQ and SP *vs.* MQ; $P = 0.02$ for CQ *vs.* SP).

Discussion

Chloroquine, SP and MQ treatment efficacies were assessed 28 days after treatment in children aged 6 months–5 years in Ouidah, southern Benin. All children treated with MQ were cured by day 28, except one late failure and one new infection. CQ and SP efficacies were extremely low as 85.7% and 50.0% of the outcomes were failures, as would be expected after their use as first- and second-line treatments for many years. Interestingly, late failures were all clinical failures after CQ treatment, but not SP treatment. Although parasitological failures might eventually become clinical failures after a few hours or days, asymptomatic failures show the role of immunity in limiting parasite growth and disease severity. SP treatment was also characterized by a delayed parasite clearance and a large majority of treated infections producing gametocytes. Although our results include a limited number of participants ($n < 50$ in each treatment group), efficacy rates are statistically highly different and conclusions about the consequences of the use of such antimalarial treatments are obvious. Such a study leads to specific results for an area, a population and a transmission rate. However, in many African countries, the use of CQ and SP has been promoted for years, and most people still use CQ at home.

Published data on treatment efficacy in Benin are rare and mainly focus on CQ efficacy. CQ-resistant *falciparum* malaria was first notified in non-immune visitors in 1986 and 1987 (Le Bras *et al.* 1986; Rosenheim *et al.* 1987). Djivoh *et al.* (1988) assessed a low rate of *in vivo* failure after CQ treatment in Zou province (60–260 km north of Ouidah) (Djivoh *et al.* 1988). Fluctuations in the frequency of CQ-resistant strains were shown between 1980 and 1989, and resistance was mainly localized to the region of Cotonou, an observation explained by a high illegitimate CQ distribution (Chippaux *et al.* 1990). In 2002, the Beninese NMCP observed 15.0–61.3% treatment failures with CQ and 3.3–45.9% with SP in under-fives followed-up for 14 days (unpubl. data). Efficacy rates depended on the place of the study, with higher efficacy in North Benin. Southern Benin is densely populated, the Atlantique province being the most crowded, and is an important trade place in West Africa, where illegitimate distribution of drugs is common. This area is also characterized by a higher malaria incidence, probably caused by its humid climate and marshy landscape. All these results show that resistance rate to both drugs increased dramatically in southern Benin since the 1990s and reached dangerous limits in 2005. We fully agree with the Beninese NMCP to change the national malaria treatment policy.

The high efficacy of MQ *in vivo* in southern Benin is a very important point for this area where CQ, SP and quinine have long been the sole antimalarial drugs administered in public health centres. The use of MQ, alone or in combination, could be considered as a temporary measure to get round the unavailability of arthemeter-lumefantrine. Pharmacy prices are similar for both treatments, but MQ is available and locally distributed by two pharmaceutical companies. MQ has proven its high efficacy in Africa through assays carried out in Sudan (Adam *et al.* 2004, 2005) and with tourists returning from West Africa (Matteelli *et al.* 2005), who achieved cure rates of 92.5–98.5%. One study carried out in Malawi reported a worrying failure rate in 1998, as 22% of treatments failed parasitologically during the 14-day follow-up (MacArthur *et al.* 2001). In this study, MQ was administered at the dose of 15 mg/kg recommended by WHO for areas without known MQ resistance, and increased post-treatment plasmatic doses of MQ were associated with higher level of therapeutic success. This demonstrates that an appropriate dosage regimen of MQ is required for achieving optimal efficacy of the drug. In the Sudan and West Africa studies, adverse side-effects including vomiting, nausea, dizziness and sleep disturbances were reported in 25–65% of the patients after MQ

treatment. Patients enrolled in both studies were adults unlike the under-fives we followed, for whom no adverse effect was mentioned. Adverse effects constitute a drawback for MQ treatment in adults, but it appeared to be well tolerated by children enrolled in our study. All these results reinforce the idea that the use of MQ in Benin may be suitable to avoid serious malaria attacks in children because of CQ or SP inefficacy, while Coartem® is not yet available in health centres at affordable prices.

As recommended by WHO, most African countries where CQ-resistance has spread, are switching to artemether-lumefantrine. The choice seems motivated by both efficacy and coformulation. Of note, ACT efficacy is reliant on the efficacy of the partner drug (Durrani *et al.* 2005, Int art study group 2004). According to our results, MQ constitutes a serious candidate for ACTs in Benin, and probably in most sub-Saharan African countries. Reported efficacies for artemether-lumefantrine are very high in West Africa (Koram *et al.* 2005; Meremikwu *et al.* 2006) and augur well for the use of this combination in Benin. However, as all other antimalarial drugs, the efficacy of artemether-lumefantrine will need to be followed once its use will become effective in Benin. Indeed, the introduction of this combination in Zanzibar led to rapid emergence of treatment failures with genetic evidence for selection of lumefantrine-resistant parasites (Martensson *et al.* 2005; Sisowath *et al.* 2005).

In Benin, the quality of malaria treatment for children is also hampered by the small number of people attending public health centres. Our study began with difficulty prior to the active information performed in districts and villages served by the two health centres chosen for the study. A report on countrywide demographic and health survey in 2001 concluded that distance to health centres (42% of answers in the whole country), high cost of drugs (42%), lack of medical employees (25%), lack of medical equipment (24%), high cost of consultation (16%), bad reception by medical staff (12%) and lack of essential drugs (10%) were the main problems that prevented people from attending (public or private) health centres (INSAE & ORC Macro 2002). The most quoted parameters, distance to health centre and cost of drugs, both remind us that poverty reduction is the key to improve the health status of people living in developing countries, a heavy work for the Beninese government and international institutions. Furthermore, CQ has been extensively used for years in Benin in self-medication as both preventive and curative treatment (Kiniffo *et al.* 2000). It is now very important to educate the population on the low efficacy of CQ to avoid the onset of complicated malaria because of delayed use of an effective treatment.

Msp genotyping showed a high degree of polymorphism in the samples tested. However, paired samples characterized by this approach were all treatment failures, and thus were not representative of *msp1* and *msp2* polymorphism in the place of the study. The technique allowed the reevaluation of two failures because of new infections, a not insignificant part of the failures studied with a molecular tool (18.2%). Interestingly, all failures were partly as a result of new alleles, in line with the high polymorphism of malaria infections in the area.

Conclusions

In conclusion, the rate of CQ and SP resistance in southern Benin is very worrying and the use of other molecules for curative malaria treatment constitutes an urgent and vital need for Beninese children. Problems of availability of efficient antimalarial drugs create a highly dangerous situation. In many other African countries where national policy has been based on CQ and SP for years, and/or where an overwhelming majority of people is still using CQ at home, there may be a similar problem.

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Efficacité thérapeutique limitée de la chloroquine (CQ) et de la sulfadoxine-pyrimethamine (SP), mais pas de la méfloquine, dans le sud du Bénin

OBJECTIF Evaluer l'efficacité thérapeutique *in vivo* de la chloroquine (CQ), de la sulfadoxine-pyriméthamine (SP) et de la méfloquine (MQ) chez les enfants présentant un paludisme simple au Bénin.

MÉTHODES L'efficacité des médicaments a été étudiée *in vivo* pendant 28 jours selon le protocole de l'OMS. Pour les échecs survenus après 7 jours de suivi, des échantillons de sang appariés prélevés avant et après traitement ont été génotypés au niveau des loci *msp1* et *msp2* afin de distinguer les nouvelles infections des souches recrudescentes. Les enfants enrôlés ont été aléatoirement affectés à un groupe thérapeutique (CQ, $n = 14$; SP, $n = 42$; MQ, $n = 44$). Le nombre de traitements à la CQ a été intentionnellement limité après un mois car son utilisation a été considérée comme dangereuse pour les enfants.

RÉSULTATS CQ et la SP ont démontré des taux d'échec très élevés (85,7 et 50% respectivement), tandis que le traitement à la MQ était efficace dans 97,5% des cas. L'outil moléculaire a permis de réévaluer deux nouvelles infections précédemment considérées comme des échecs.

CONCLUSIONS La chloroquine ne devrait plus être utilisée pour traiter les enfants présentant un paludisme simple à *P. falciparum* au Bénin.

mots clés paludisme falciparum, chloroquine, sulfadoxine-pyriméthamine, méfloquine, efficacité du médicament, Bénin

Dramática disminución de la eficacia terapéutica de cloroquina y sulfadoxina-pirimetamina, pero no mefloquina, al sur de Benin

OBJETIVO Evaluar la eficacia terapéutica *in vivo* de la cloroquina (CQ), la sulfadoxina-pirimetamina (SP) y la mefloquina (MQ), en niños con malaria no complicada en Benin.

MÉTODOS Se evaluó la eficacia de los medicamentos siguiendo el protocolo *in vivo* de 28-días de la OMS. Para fallos que ocurrieron después de 7 días de seguimiento, se genotiparon los genes *msp1* y *msp2* en muestras de sangre pareadas antes y después del tratamiento, para distinguir nuevas infecciones de cepas recrudescentes. Los niños incluidos fueron asignados de forma aleatoria a un grupo terapéutico (CQ, $n = 14$; SP, $n = 42$; MQ, $n = 44$). El número de tratamientos con CQ fue intencionalmente limitado después de 1 mes, puesto que se consideraba que su uso entrañaba un riesgo para los niños.

RESULTADOS CQ y SP presentaron unas tasas de fallo muy altas (85.7 y 50% respectivamente), mientras que el tratamiento con MQ fue exitoso en un 97.5%. La herramienta molecular permitió reevaluar dos infecciones nuevas, previamente consideradas fallos.

CONCLUSIONES No se debería continuar utilizando la cloroquina para tratar niños con malaria por *P. falciparum* en Benin.

palabras clave malaria *falciparum*, cloroquina, sulfadoxina-pirimetamina, mefloquina, eficacia medicamentos, Benin