

# Increasing antimalarial drug resistance in Uganda and revision of the national drug policy

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## Summary

Chloroquine (CQ) resistance was first documented in Uganda in 1988. Subsequent surveillance of antimalarial drug resistance, conducted by the Ugandan Ministry of Health and several research organizations, suggests that resistance to CQ is now widespread, reaching critical levels in many areas of the country. In June 2000, the Ministry of Health held a National Consensus Meeting to evaluate the available drug efficacy data and review the national antimalarial drug policy. After extensive debate, the combination of CQ + sulfadoxine–pyrimethamine (SP) was chosen to replace CQ as the first-line treatment of uncomplicated malaria as an interim policy. This review evaluates the *in vivo* drug efficacy studies conducted in Uganda since 1988 and issues confronted in revision of the drug policy. The Ugandan experience illustrates the challenges faced by sub-Saharan African countries confronted with rising CQ resistance but limited data on potential alternative options. The choice of CQ + SP as a provisional policy in the absence of prerequisite efficacy, safety and cost-effectiveness data reflects the urgency of the malaria treatment problem, and growing pressure to adopt combination therapies. Surveillance of CQ + SP treatment efficacy, collection of additional data on alternative regimens and active consensus building among key partners in the malaria community will be necessary to develop a rational long-term antimalarial treatment policy in Uganda.

**keywords** *Plasmodium falciparum*, malaria, drug resistance, drug policy, Uganda

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## Introduction

Malaria remains one of the most serious global health problems and a leading cause of morbidity and mortality in Uganda (Uganda Ministry of Health, unpublished data). Appropriate case management, focusing on prompt treatment with effective antimalarial drugs, is the foundation for malaria control throughout sub-Saharan Africa. For decades, chloroquine (CQ) was the mainstay of antimalarial therapy, but the emergence of *Plasmodium falciparum* resistance to CQ has challenged control efforts (Campbell 1991). In East Africa, the level of CQ resistance has risen steadily over the last 20 years, with recent studies indicating that CQ fails to clear parasites in up to 50–80% of patients (Brandling-Bennett *et al.* 1988; Sexton *et al.* 1988; Watkins *et al.* 1988; Bayoumi *et al.* 1989; Fowler *et al.* 1993; Premji *et al.* 1993; Wolday *et al.* 1995). Despite rising levels of resistance, CQ has remained the

first-line antimalarial in many African countries because of its low cost, lack of toxicity and observed clinical efficacy in many semi-immune patients (Hoffman *et al.* 1984; Brandling-Bennett *et al.* 1988; Barat *et al.* 1998). However, the spread of CQ resistance has been temporally associated with increased malaria-related morbidity and mortality in Africa, highlighting the urgent need to change antimalarial drug policy (AMDP) (Trape 2001).

The level at which CQ resistance is considered unacceptable is not well-defined. Criteria based on parasitological resistance, cost-effectiveness analyses, haematological response and duration of clinical improvement have been proposed (Sudre *et al.* 1992; Bloland *et al.* 1993; Schapira *et al.* 1993). More recently, it has been suggested that CQ should be abandoned when clinical failure rates reach 25% (Bloland *et al.* 1998). High-level CQ resistance has already forced several African countries, including Malawi, Kenya and Tanzania, to

change to sulfadoxine–pyrimethamine (SP) for first-line treatment of uncomplicated malaria (Bloland *et al.* 1993). In Uganda, CQ resistance appeared years later than in neighbouring East African countries and was first documented in 1988. Since 1988, antimalarial drug efficacy in Uganda has been monitored by several research organizations and the Malaria Control Programme (MCP) of the Ministry of Health (MoH). In 1998, the MCP developed sentinel surveillance sites in collaboration with the East African Network for Monitoring Antimalarial Treatment (EANMAT), selecting the sites based on location, malaria endemicity and population density. Studies conducted since 1996 at these sites and others, suggest that CQ resistance has risen to critical levels in Uganda, indicating a need to change drug policy.

Revising a national AMDP is a complex task and countries have approached changes cautiously (Bloland & Ettling 1999). Limited drug efficacy data, variable methodology of studies, a lack of consensus on when to change therapy and the absence of an obvious alternative regimen complicate policy decision making (Shretta *et al.* 2000). A key step in changing drug policy is identifying which drug should replace CQ as first-line treatment of malaria. Agents currently under consideration in Uganda include SP, amodiaquine (AQ), artemisinin derivatives (AS, artesunate), chlorproguanil–dapsone (CD, or lapdap) and combinations of these agents (Table 1). Unfortunately, certain disadvantages to each of these agents exist and the optimal alternative to CQ remains unclear.

In this paper, we review the data on antimalarial drug resistance in Uganda collected between 1988 and 2001 and the National Consensus Meeting to review the AMDP convened by the Uganda MCP in June 2000. We discuss the outcome of this meeting and future challenges ahead for Uganda and other African countries in monitoring drug resistance and formulating drug policy. The Ugandan

experience illustrates the difficulties and complexities in the development of a rational treatment policy in the era of CQ resistance.

## Methods

### Data collection

We searched the published and unpublished literature, and consulted with the MoH and other experts on malaria in Uganda, to identify all *in vivo* drug efficacy studies conducted in Uganda since 1988. *In vitro* and molecular studies were not included in the review. The following information was noted for each study: location, date of study, age range of patients, inclusion criteria, treatment evaluated, sample size, length of follow-up and method of outcome assessment. The malarial endemicity (holo-, hyper-, meso- or hypoendemic) and population density (urban or rural) for the location of each study was obtained either from the original documents or from the MoH. In addition, we reviewed the following documents provided by the MoH: *Background paper for the national consensus meeting to review antimalarial policy in Uganda* (June 2000), *Report on the national consensus meeting for the review of the AMDP for Uganda*, and *Implementation of the new antimalarial treatment drug policy: Plan of action* (November 2000). These documents were reviewed to identify decisions made and positions taken by the MoH.

### Statistical analysis

Data were entered into a computerized database (Microsoft® Access 2000) and verified to identify data entry errors. The number of treatment failures (parasitological resistance and/or clinical failure) listed by authors in the original documents was entered into the database. For two

**Table 1** Antimalarial agents available for first-line treatment of uncomplicated malaria

Drug	Type	Advantages	Disadvantages
CQ	4-aminoquinoline	Inexpensive, safe and widely available	Widespread CQ resistance
SP	Antifolate, fixed combination	Reasonable cost, simple dosing and widely available	Concern about therapeutic lifespan, potential toxicity (severe cutaneous reactions)
AQ	4-aminoquinoline	Reasonable cost and currently available	Concern for cross-resistance with CQ, potential toxicity (blood dyscrasias, hepatotoxicity)
AS	Sesquiterpene lactone	Rapidly acting, highly effective, well tolerated, decreased gametocytemia and may decrease transmission	Expensive, availability limited, recrudescence with monotherapy or short courses, possible neurotoxicity
CD	Antifolate, fixed combination	Effective, short half-life = less drug pressure	Not available until 2002, potentially limited useful therapeutic lifespan

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studies, MoH (1994, unpublished data) and Mpeka and Ndeezi (1996, unpublished data), the original documents were unavailable and data were obtained from MoH documents. For studies in which the number of patients failing treatment was not stated, this number was calculated by multiplying the total number of patients and the percentage of resistance listed. Studies were stratified for comparison as follows: date of study (conducted between 1988 and 1995 *vs.* after 1996), age range of patients (<5 years *vs.* ≥5 years) and location (urban *vs.* rural).

**Results**

We identified 13 drug efficacy studies conducted in Uganda between 1988 and 2000. Studies were divided into two groups, those conducted between 1988 and 1995 and those conducted after 1996, to reflect the change in study design and shift in treatment outcome assessment that occurred after 1996. Studies performed prior to 1996 generally followed the WHO 1973 recommendations for assessment of therapeutic efficacy of antimalarials, enrolling both asymptomatic patients and those with uncomplicated disease and measuring parasitological resistance at 7 days of follow-up as the primary outcome (Table 2). Since 1996, most studies have been conducted according to the guidelines released by the WHO in 1996, enrolling symptomatic patients and using clinical response 14 days after treatment as the primary outcome measurement (Table 3). The three studies that did not follow this pattern were

excluded from the evaluation in an attempt to simplify comparisons. This included the MoH study conducted in 1993, which assessed parasitological outcome after 14 days in symptomatic children, the study by Ndyomugenyi and Magnussen conducted in 1998 (Ndyomugenyi & Magnussen 2000), which assessed parasitological outcome after 7 days in asymptomatic school children, and the study by Priotto *et al.* conducted in 1999–2000 (unpublished data), which assessed parasitological outcome only. The remaining 10 studies were conducted in 14 districts around Uganda (Figure 1) representing all levels of malaria endemicity (36% holoendemic, 14% hyperendemic, 50% mesoendemic, 7% hypoendemic). Three study sites were considered urban (Kampala, Jinja and Mbarara) for all studies conducted in these areas, as was the study conducted in an urban section of Hoima, as specified (Table 2) (Ndyomugenyi & Magnussen 1997). Studies conducted in the other sites were classified as rural. In the study by Kamugisha *et al.* (1994), the age range of study subjects was not specifically stated. Because asymptomatic school children and symptomatic children and adults were included in the trial, the subjects were considered to be ≥5 years of age.

By comparing the combined results of studies conducted from 1988 to 1995 with those conducted since 1996, it can be estimated that parasitological (RI–RIII) resistance to CQ in Uganda has increased from 25% (147 of 581) to 54% (358 of 663). Since 1996, clinical failure following treatment with CQ was documented in

**Table 2** Antimalarial drug efficacy trials: 1988–95

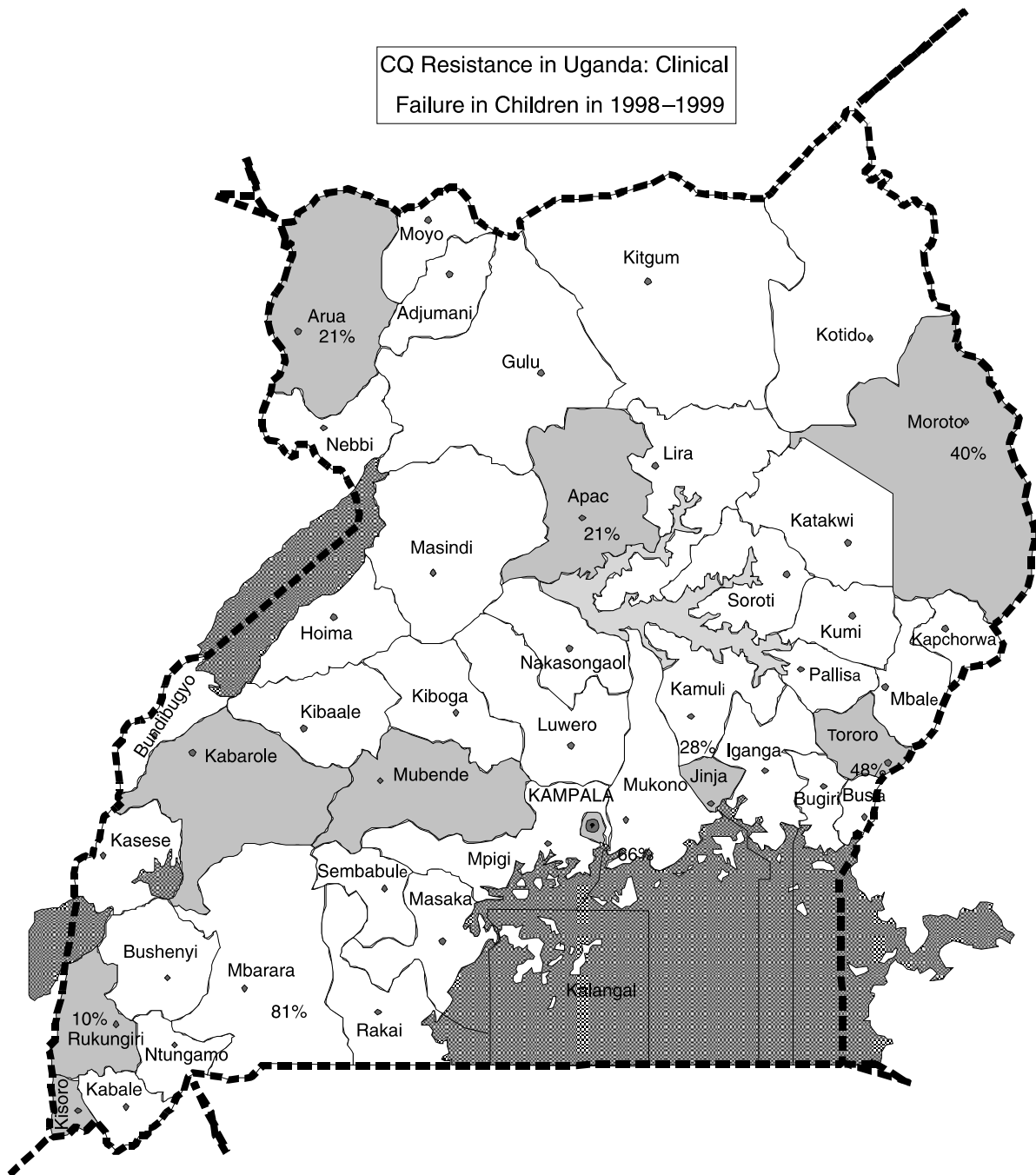
Year of study	Source	Method of outcome assessment	Age range (years)	Location	CQ		SP	
					N	Parasitological resistance (%)	N	Parasitological resistance (%)
1988	Nevill <i>et al.</i> (1995)	WHO 1973	5–15	Kampala	43	17 (39)	16	0
				Jinja	35	8 (23)	15	0
				Masaka	37	14 (38)	22	0
				Masindi	31	9 (29)	15	0
				Kasese	28	6 (21)	18	0
				Arua	36	1 (3)	36	0
1992	Kamugisha <i>et al.</i> (1994)	WHO 1973	Not stated	Kabarole	239	39 (16)	134	6 (4)
1993	MoH*	MoH protocol	<5	Kampala	50	6 (12)	50	1 (2)
				Apac	50	1 (2)	50	0
				Tororo	50	4 (8)	50	0
1995	Ndyomugenyi and Magnussen (1997)	WHO 1973	7–10	Hoima urban	64	37 (58)	77	0
				Hoima rural	68	16 (24)	71	3 (4)

\* Original documents not available. Excluded from final results. N represents the no. of patients who completed study follow-up.

**Table 3** Antimalarial drug efficacy trials: 1996-2000

Year of study	Source	Method of outcome assessment	Location	Age range (years)	CQ			SP		
					N	Parasitological resistance (%)	Clinical failure (%)	N	Parasitological resistance (%)	Clinical failure (%)
1996	Mpeka & Ndeezi 1996*	WHO 1994	Jinja	0.5-5	52	19 (36)	6 (12)	35	2 (6)	2 (6)
1996	Kilian <i>et al.</i> (1997)	Modified WHO 1996	Bundibugyo	0.5-5	60	24 (40)	20 (33)	38	5 (13)	2 (5)
			Kabarole	≥5	41	0	0	31	3 (10)	2 (6)
			holoendemic	0.5-5	60	46 (77)	35 (58)	29	2 (7)	1 (3)
			Kabarole	≥5	48	17 (35)	15 (31)	29	0	0
			hypoendemic	≥5	50	4 (8)	3 (6)	-	-	-
1998	EANMAT/MoH	Modified WHO 1996	Arua	0.5-5	59	-	14 (24)	51	-	5 (10)
			Jinja	0.5-5	25	-	7 (28)	35	-	2 (6)
			Moroto	0.5-5	56	-	27 (48)	52	-	6 (12)
			Apac	0.5-5	53	-	11 (21)	53	-	9 (17)
			Moroto	0.5-5	19	-	3 (16)	14	-	2 (14)
			Rukungiri	0.5-5	41	-	4 (10)	47	-	0
			Tororo	0.5-5	63	-	30 (48)	68	-	13 (19)
1998	Ndyomugenyi and Magnussen (2000)†	WHO 1973	Hoiima urban	4-10	55	21 (38)	-	8	0	-
			Hoiima rural	4-10	47	13 (28)	-	84	1 (1)	-
1998	Epicentre 1998 (Legros <i>et al.</i> 1998)	WHO 1996	Mbarara	0.5-5	53	-	43 (81)	64	-	16 (25)
1998-99	Dorsey <i>et al.</i> (2000)	Modified WHO 1996	Kampala	0.5-5	141	117 (83)	87 (62)	-	-	-
				≥5	117	63 (54)	33 (28)	-	-	-
1999	Kanya <i>et al.</i> (2001)	Modified WHO 1996	Kampala	0.5-5	51	49 (96)	39 (76)	45	15 (33)	5 (11)
				≥5	43	19 (44)	12 (28)	48	13 (27)	5 (10)
1999-2000	Staedke <i>et al.</i> (2001)	Modified WHO 1996	Kampala	0.5-5	-	-	-	72	19 (26)	10 (14)
				≥5	-	-	-	59	15 (25)	3 (5)
1999-2000	G. Priotto, personal communication†	Parasitological failure at 14 days	Mbarara	0.5-5	-	-	-	154	68 (44)	-

\* Original documents not available. † Excluded from final results. N represents the no. of patients who completed study follow-up.



**Figure 1** Chloroquine resistance in Uganda: clinical failure in 1998-99. The proportion of chloroquine-treated children (aged 0.5-5 years) with clinical failure (early or late treatment failure) documented at study sites around Uganda during 1998 and 1999.

389 of 1032 (38%) of evaluated patients, and was higher in children under the age of 5 years [44% (326 of 733)], than in older patients [21% (63 of 299)]. CQ resistance

was more common in urban areas: before 1996, parasitological failure was noted in 44% (62 of 142) of urban *vs.* 19% (85 of 439) of rural patients. Similarly,

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after 1996, CQ-treated patients in urban areas were more likely to fail therapy [parasitological resistance: 66% (267 of 404), clinical failure: 47% (227 of 482)] than were patients in rural areas [parasitological resistance: 35% (91 of 259), clinical failure: 29% (162 of 550)].

Sulfadoxine-pyrimethamine resistance is less common in Uganda. Of SP-treated patients evaluated since 1988, parasitological resistance was documented in 11% (83 of 790) and clinical failure was observed in 11% (83/770). However, SP resistance, as measured by parasitological resistance in studies conducted before 1996 and those conducted since, increased from 2% (nine of 404) to 19% (74 of 386). Clinical failure following SP treatment was also more common in children [12% (73 of 603)] than in older patients [6% (10 of 167)]. Although parasitological resistance to SP was higher in urban than in rural areas [17% (64 of 367) *vs.* 4% (19 of 423), respectively], levels of clinical failure after SP treatment were similar [urban: 12% (43 of 358) *vs.* rural: 10% (40 of 412)].

Few studies evaluated the efficacy of alternatives to CQ and SP (Table 4). AQ appears to be effective when used alone or in combination with SP. In the one study that evaluated AQ prior to 1996, no resistance was documented. More recently, parasitological resistance to AQ monotherapy was observed in 21 of 131 (16%) AQ-treated patients, and clinical failure documented in nine of 131 (7%) patients. The combination of AQ/SP, evaluated in one study conducted in Kampala, was highly effective [parasitological resistance: 10% (14 of 138), clinical failure 3% (four of 138)]. The combination of SP and AS was more effective when AS was given for 3 days than as a single dose (parasitological resistance 15% *vs.* 39%, respectively) (Table 4).

**Discussion****Antimalarial drug efficacy in Uganda**

Chloroquine resistance appears to be widespread and increasing in Uganda. Studies conducted between 1988 and 1995 demonstrated wide variability of CQ parasitological resistance, with levels ranging from <5% to >50%. More recent studies suggest that parasitological resistance to CQ has increased and that clinical failure following CQ treatment is common throughout Uganda. Not surprisingly, CQ appears to be least effective in children and in urban areas (Dorsey *et al.* 2000).

A meta-analysis of available studies would be the ideal method of combining these drug efficacy data. However, comparison of available drug efficacy studies and interpretation of results was complicated by variation in study design, including eligibility criteria for study subjects, length of follow-up and method of outcome assessment. Because only limited information was available for several studies, a complete statistical meta-analysis was not possible. Thus, we have attempted to demonstrate proportions of treatment failure, recognizing that combining highly heterogeneous results is problematic. It is particularly difficult to compare levels of parasitological resistance measured in studies conducted before 1996 with those conducted later. Earlier studies, which included asymptomatic patients and limited follow-up to 7 days, may have been less likely to detect antimalarial resistance than later studies. Additionally, a greater proportion of patients assessed prior to 1996 resided in rural areas (439 of 581, 76%) while the majority assessed after 1996 were from urban areas (404 of 663, 61%). This shift from rural to urban predominance likely impacts the trend of parasitological resistance. Thus, comparing levels of parasitological resistance detected before and after 1996 may give a false

**Table 4** Assessment of alternative antimalarials in Uganda

Year of study	Source	Method of outcome assessment	Location	Drug	Age range (years)	Parasitological resistance		Clinical failure	
						N	Per cent	N	Per cent
1992	Kamugisha <i>et al.</i> (1994)	WHO 1973	Kabarole	AQ	Not stated	94	0	-	-
1999-2000	Staedke <i>et al.</i> (2001)	Modified WHO 1996	Kampala	AQ	0.5-5	69	15 (22)	69	7 (10)
					≥5	62	6 (10)	62	2 (3)
				AQ + SP	0.5-5	86	11 (13)	87	3 (3)
					≥5	51	3 (6)	51	1 (2)
1999-2000	G. Priotto, personal communication	Parasitological failure at 14 days	Mbarara	AS (1 day) + SP	0.5-5	116	45 (39)	-	-
				AS (3 days) + SP	0.5-5	117	18 (15)	-	-

N represents the no. of patients who completed study follow-up.

impression of rising levels of resistance, and results should be interpreted with caution. In addition, although studies conducted since 1996 used similar protocols, there were slight variations in inclusion criteria and outcome classification that may limit comparability. However, despite the limitations of available studies, the level of clinical failure after treatment with CQ is above the critical threshold of 25% in many areas. The WHO (2000) guidelines for assessment and re-evaluation of AMDP based on the level of clinical failure in first-line therapy provide the following reference points for different levels of action: 0–5% (grace period), 6–14% (alert), 15–24% (action) and >25% (indication for drug policy change). Certainly, the summary estimate of 38% clinical failure following CQ treatment in Uganda, indicates a need for policy change.

Data indicate that resistance to SP has developed in Uganda, even reaching the 'alert' and 'action' stages in some areas. SP, a synergistic combination of a dihydrofolate reductase inhibitor (pyrimethamine) and a dihydropteroate synthetase inhibitor (sulfadoxine) has generally been the preferred second-line antimalarial treatment in Africa. However, the useful therapeutic lifespan of SP may be limited by the rapid emergence of resistance (Nzila-Mounda *et al.* 1998). In Kampala, AQ remains efficacious, despite high-level CQ resistance. Use of AQ in Uganda has been somewhat limited because of concerns over toxicity and potential cross-resistance with CQ (Olliaro *et al.* 1996). Serious adverse events, including blood dyscrasias and hepatotoxicity, have been associated with AQ chemoprophylaxis in travellers (Phillips-Howard & West 1990). But, despite concerns over drug safety, the expanding problem of antimalarial drug resistance in Africa has renewed interest in AQ as an alternative to CQ. Recent studies suggest that AQ is efficacious and safe when used for treatment of malaria, even in areas of high CQ resistance (Olliaro *et al.* 1996; Brasseur *et al.* 1999; van Dillen *et al.* 1999; Gorissen *et al.* 2000; Staedke *et al.* 2001). In Kampala, the combination of AQ + SP appears to be highly effective, however, this combination has not been widely evaluated and overall, data on alternatives to CQ and SP, is extremely limited.

### Revision of the national AMDP

Minimizing malaria-associated morbidity and mortality is the primary goal of a national AMDP. To accomplish this, safe, effective, affordable antimalarial drugs must be provided in a manner that promotes rational drug use and limits the development of drug resistance. To ensure the adequate delivery of effective antimalarial therapy, drugs must be widely available in the community. However, unrestricted access to drugs and inappropriate drug use

may increase drug selection pressure and promote the spread of resistance. A national AMDP must attempt to strike a balance between these two conflicting issues. In 1999, WHO/Africa Regional Office (AFRO) created guidelines for developing, implementing and updating AMDP in Africa. These guidelines recommend that drug efficacy, cost, potential for cross-resistance, side-effect profile, estimated therapeutic lifespan and acceptability, must all be considered in the context of developing a national AMDP. The local epidemiological situation, health-seeking behaviour, capacity of the health care system to implement changes, and an analysis of the cost and cost-effectiveness of various alternatives, should also be considered. Unfortunately, adequate data on several of these factors, particularly alternative agents, cost-effectiveness of policy options and the potential impact of policy change, are lacking in many African countries, including Uganda.

At the Uganda National Consensus Meeting, held in June 2000, all available data were presented and discussed, following WHO guidelines. Particular information gaps included the cost and cost-effectiveness of alternative agents, acceptability of alternative treatments, care-seeking behaviour and health worker practice. During the meeting, several primary issues were extensively debated including: (1) geographical variation of levels of CQ resistance, (2) possibility of a regional AMDP for Uganda, (3) use of SP as a first-line agent given evidence of emerging resistance and concern for the useful therapeutic lifespan, and (4) use of antimalarial drugs in combination, particularly CQ + SP and AQ + SP. The final recommendation reached by members of the committee was that provisionally, CQ should remain the first-line antimalarial in areas where clinical resistance to CQ is <25% (with SP or AQ remaining second-line therapy), but that a combination of CQ/SP should replace CQ as the first-line treatment in areas where CQ resistance is >25% (with quinine as second-line).

The choice of CQ/SP as a provisional policy was a difficult compromise, and was made based on the assumption that this combination would offer improved efficacy over CQ monotherapy and potentially delay the spread of SP resistance. Although both components of the combination have an acceptable safety record, CQ/SP had not been studied in Uganda at the time the policy was formulated. The fact that CQ/SP was ultimately chosen reflects the lack of available data on potential alternative therapies, including combination regimens and a reluctance to abandon CQ, particularly given evidence for low level CQ resistance in some areas. It was also recognized that regional implementation of a dual first-line therapy policy presented significant challenges, given that the resistance pattern for the entire country was not known. As a result,

the original policy decision was amended in November 2000, and the CQ/SP combination was recommended for use in all areas of Uganda, regardless of baseline CQ resistance.

### Combination therapy

The strategy of combining antimalarial agents has been advocated as an approach to improve therapeutic efficacy and delay the development of drug resistance (White 1999). Countries faced with rising CQ resistance and few alternative antimalarials are increasingly considering combination regimens and certain combinations (e.g. CQ/SP) are already commonly used outside government guidelines. Limited available studies suggest that CQ/SP provides more rapid resolution of symptoms and improved treatment efficacy when compared with SP alone (McIntosh & Greenwood 1998). However, it is unclear if substantial benefit will be gained from the CQ/SP combination if resistance to either agent already exists. In an ongoing trial conducted in Kampala, the addition of CQ to SP improved parasitological outcome compared with SP alone (CQ/SP *vs.* SP,  $P = 0.0026$ ), but showed only a trend towards improved clinical outcome ( $P = 0.053$ ). (Gasasira *et al.* 2001).

Members of EANMAT recently prioritized the following antimalarial combinations for future evaluation: AQ + SP, AS + AQ, AS + SP, CD + AS, CD + AQ, and coartemether (artemether/lumefantrine) (William Watkins, personal communication). In Kampala, data from three studies (Dorsey *et al.* 2001; Gasasira *et al.* 2001; Staedke *et al.* 2001), suggest that the combination of AQ/SP, both affordable antimalarials that are currently available in Uganda, is a highly effective regimen. However, enthusiasm for widespread use of this regimen in Uganda has been limited, particularly by toxicity concerns. Although serious adverse events have been described with use of both AQ and SP, short-term treatment with both agents appears to be much safer than long-term chemoprophylaxis (Sturchler *et al.* 1993; Olliaro *et al.* 1996). However, in areas of intense transmission, where frequent episodes of clinical malaria may require repeated therapy, repeated use of antimalarials will be needed (Olliaro *et al.* 1996). Additional evaluation of AQ/SP and larger studies of drug safety will be needed to better assess the risk associated with routine use of these drugs.

In South-east Asia, the use of artemisinin-containing combinations has been a successful strategy for treatment of multidrug resistant malaria (Price *et al.* 1996; Nosten *et al.* 2000). Artemisinin compounds are rapidly acting and substantially decrease the parasite biomass soon after administration, promoting rapid clinical recovery, and decreasing the likelihood that parasites may develop and/or

perpetuate drug resistance (White 1999). The combination of AS (3 days) + SP has been shown to be highly effective in areas of Africa with relatively low-level resistance to SP (von Seidlein *et al.* 2000; Dorsey *et al.* unpublished data). However, in Mbarara, Uganda, where parasitological resistance in SP-treated children was 44%, the AS (3 days) + SP combination was only 85% effective in clearing parasites at 14 days of follow-up (Gerardo Priotto, personal communication). In addition, drug cost currently remains an obstacle for widespread use of artemisinin derivatives in Africa. Other combination options include CD + AS or AQ, but CD is not yet available and there is concern that increased SP use and rising levels of resistance may endanger the therapeutic lifespan of this new drug. Two coformulated antimalarial combinations, atovaquone/proguanil (Malarone) and artemether/lumefantrine (coartemether) are currently available, but again, high cost currently precludes their use in Africa.

Despite the success of combination therapy in South-east Asia, and the hope that this strategy provides for Africa, there are vast differences in epidemiology, socioeconomics and approach to malaria case management between the two regions (Bloland *et al.* 2000; Wongsrichanalai *et al.* 2000). Although combination antimalarial therapy is likely to provide greater therapeutic efficacy than monotherapy in areas of rising drug resistance, it remains to be seen if this strategy will have the same impact in Africa as in South-east Asia. There remains concern about the potential risk of adverse events with alternative drugs when used alone or in combination with other antimalarial agents. In Uganda, fevers are routinely treated at home with antimalarial drugs obtained in the community or private sector (Strategy for Home-based Management of Fever/Malaria in Uganda, MoH, WHO, UNICEF, June 2001). Formal health care is typically sought only if initial treatment fails, and empirical treatment is common. Drug use is often unregulated, and inappropriate and frequent use of antimalarial drugs is likely to occur (Bloland & Ertling 1999). Although the benefits of using highly effective combination therapy for treatment of malaria in Africa are likely to be substantial, the potential risks of toxicity and promotion of drug resistance must be considered carefully.

### Future directions

Uganda now faces the challenge of implementing the provisional CQ/SP treatment policy. However, the effective therapeutic lifespan of the CQ/SP combination is likely to be short and active preparation for future policy changes will be required. The need for an efficient multisite surveillance system for monitoring antimalarial drug efficacy in Uganda has been recognized. The infrastructure

established by the MoH/EANMAT exists but may require further strengthening. In response to this need, a collaborative project involving members of the Uganda MoH, the Makerere University Institute of Public Health, the University of California School of Public Health, and the Makerere University – University of California, San Francisco malaria research collaboration has been established with the purpose of building public health capacity and developing a malaria surveillance network in Uganda. The primary goals of this project are to conduct anti-malarial drug efficacy studies, to monitor malaria-associated morbidity and mortality, and to establish a pilot system to evaluate for possible antimalarial-related adverse drug events. This project, an alliance of the malaria research community and public health institutions, will remain affiliated with the EANMAT network and all data collected will be transferred to the MoH and National Drug Authority and be made available for policy-making decisions. The Ugandan experience in revising the national AMDP indicates that additional data on the efficacy, safety, cost-effectiveness and provider/consumer acceptability is crucial for rational drug policy development. In addition, as evidenced by the Kenyan experience (Shretta *et al.* 2000), consensus building among key policy-makers appears to be essential in order to translate available data into an optimal AMDP. Heightened interest in the national AMDP and recent collaboration among the malaria community offers hope for the future of malaria control in Uganda.

### Conclusions

Uganda has reached a crossroad. Faced with rising levels of CQ resistance and inadequate data on alternative regimens, the combination of CQ/SP was selected for first-line treatment of uncomplicated malaria. The choice of CQ/SP, despite limited information about this combination, reflects the reluctance to abandon CQ, the lack of available data on appropriate alternatives and a desire to use combination therapy to combat the growing problem of drug resistance. CQ/SP is expected to be an interim solution to the malaria treatment dilemma in Uganda. Our experience has highlighted the urgent need for additional data on the efficacy, safety and cost of alternative antimalarial regimens, particularly combination therapies. Members of the malaria community in Uganda have begun to take the necessary steps to prepare for a longer-term solution. Through active surveillance of CQ/SP and other potential combination regimens, monitoring for antimalarial drug safety, and evaluation of operational issues of combination antimalarial therapy, a body of necessary data will be generated for use in future policy-making decisions.

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