Tropical Medicine and International Health

VOLUME 8 NO 10 PP 860–867 OCTOBER 2003

The efficacy of antimalarial monotherapies, sulphadoxine–pyrimethamine and amodiaquine in East Africa: implications for sub-regional policy

The East African Network for Monitoring Antimalarial Treatment (EANMAT)

Summary Between 1998 and 2001, Kenya, Uganda, Tanzania, Zanzibar, Rwanda and Burundi changed antimalarial drug policy, in the face of widespread chloroquine resistance. The new first-line treatment is either sulphadoxine–pyrimethamine (SP) monotherapy, or a combination of SP with either chloroquine or amodiaquine. Two national malaria control programmes, Burundi and Zanzibar, have decided upon amodiaquine-artesunate as their first-line treatment, although SP will continue to fill this role until the new policy can be implemented. Given the broad uniformity of parasite chemoresistance in the six countries, The East African Network for Monitoring Antimalarial Treatment (EANMAT) has focused attention on, and worked towards, a sub-regional antimalarial drug policy, where the evidence base would be the entire portfolio of network *in vivo* test results. Currently, there are several different antimalarial drug policies within the EANMAT area: the intention is to eventually replace this plethora of policies with a single, sub-regional policy based upon combination therapy. Currently, successful malaria treatment depends primarily upon the efficacy of SP, and of amodiaquine, which is either a component of first-line treatment, or the second line drug. This report addresses the results of WHO *in vivo* tests on these two monotherapies within the network. Results are analysed to assess the evidence for change in parasite susceptibility over time; the range of susceptibility to each drug within countries, and the implications of test results on policy.

keywords East African Network for Monitoring Antimalarial Treatment, antimalarial drugs, sulphadoxine–pyrimethamine, amodiaquine, drug resistance, drug policy

Introduction

Developing an appropriate national drug policy in Africa for a common disease, such as malaria, is a complex task. This is particularly true for countries faced with insidious debt, poorly financed health systems and drug budgets, and growing threats posed by multi-drug resistant falciparum malaria. For over 50 years, chloroquine (CQ) was the mainstay of malaria treatment and control, providing effective, affordable and widely available therapy across the continent. The demise of CQ as a reliable treatment for malaria in Africa, and the precipitous decline in the efficacy of the most feasible alternative drug, sulphadoxine–pyrimethamine (SP); in East and Southern Africa has led to considerable debate over the future of malaria case-management (World Health Organization 2001a). Effective, affordable treatment options are limited, and national decision makers have, until recently, lacked adequate comparative data on the options. The Roll Back Malaria movement hopes to reduce by 50% deaths from malaria by the year 2010 (Alnwick 2001). However, this ambitious goal is unlikely to be attained without radical approaches to the management of clinical disease. The monitoring of treatment efficacy is of primary importance to this endeavour.

The East African Network for Monitoring Antimalarial Treatment (EANMAT) was founded in 1998 to provide reliable and current estimates of malaria treatment efficacy. The network is composed mainly of staff from national malaria control programmes (NMCPs) of participating sub-regional ministries of health. A description of the network's historical development has been reported elsewhere (East African Network for Monitoring Antimalarial Treatment 2001). Each country decides which treatments should be monitored, according to their respective antimalarial drug policies. At the end of the 1990s, options for first-line therapy after CQ included SP and amodiaquine (AQ) for most of the countries in the sub-region. In this paper, we present the temporal and spatial comparative efficacy data for these two

mono-therapeutic options across East Africa and discuss the possible interpretation of these data for future sub-regional drug policy.

Methods

The geographical extent of the network

The EANMAT started with three member countries: Kenya, Tanzania (mainland) and Uganda. Rwanda joined the network in 1999, Burundi in 2001. Zanzibar, a semi-autonomous region within the United Republic of Tanzania, has its own Ministry of Health and malaria control programme, which operates independently of the mainland. The inclusion of Zanzibar in 2001 extended coverage of the WHO/AFRO East Africa and Great Lakes epidemiological block, with the exception of Eritrea and Ethiopia. Each country has selected between two and eight sentinel sites, reflecting the diversity of malaria transmission and human settlement in each country (EANMAT 2001).

The WHO *in vivo* test

The central tool of all network monitoring is the WHO *in vivo* test (World Health Organization 1996). This is a test of clinical efficacy, designed to estimate the outcome of malaria treatment over a 14-day period: a time chosen primarily for practicability in Africa. If the patient's condition deteriorates in the first 4 days, or if parasitaemia fails to decline at the prescribed rate, the outcome is early treatment failure (ETF). Presence of parasitaemia and fever after 4 days is recorded as late treatment failure (LTF). If the clinical condition of the patient meets standard criteria, including the presence of either parasitaemia or fever (but not both) up to day 14, the test outcome is an adequate clinical response (ACR). The current version of the WHO test employs the Lot Quality Assurance Method (LQAS) sampling system in calculating sample size. This method has the advantage of providing a simple estimate of treatment failure rate with a small number of patients (as low as 16) and was designed to minimize fieldwork. However, few monitoring tests have been conducted on this basis: more usually the data are interpreted as if a traditional sample size calculation had been conducted. The next version of the test will recommend a traditional sample size calculation, and analysis of data by the life table method (World Health Organization 2002). EANMAT tests support this finding: in no case has a monitoring test been terminated at low patient recruitment by using LQAS analysis, and patient numbers in tests have averaged 50, but with a wide variance (SD = 15). This implies that test teams have either not regarded the LQAS method as appropriate, or have not fully understood the methodology, or have preferred the assurance of a test result based upon larger numbers of patients. Both the current and modified tests emphasize treatment efficacy in children less than 5 years of age. The rationale is that even in populations with low acquired immunity, younger children often have a less favourable response to antimalarial drugs than older children and adults. In the EANMAT tests, all patients were within the 6–65 month age range; 89% aged 6–59 months.

The WHO *in vivo* test was developed in 1996 and has recently been reviewed, following 5 years of use (World Health Organization 2002). The most significant change is the addition of a new outcome – late parasitological failure (LPF) defined as the presence of parasitaemia at day 14 without fever or clinical symptoms. LPF describes the common occurrence, with a failing drug, where parasitaemia is initially cleared but returns later without accompanying clinical symptoms at day 14. This new category acknowledges the importance of separating asymptomatic but parasitaemic patients (LPF) from aparasitaemic patients, especially at the end of the follow-up period, as a high proportion of the former are known to progress to clinical malaria within a month (Brandling-Bennett *et al.* 1988; Mutabingwa *et al.* 2001). If this modification is adopted by control programmes, it will be important for NMCPs to realize that the new classification will reduce the estimated efficacy of the tested drug because patients who would have been previously classified as ACR will be classified as LPF.

The EANMAT tests only provide information on treatment efficacy, although it is accepted that the important criterion for policy change is treatment effectiveness (WHO Secretariat to the RBM Partnership 2002). Treatment effectiveness is a broader concept than efficacy, and comprises compliance, safety and side effects, affordability, availability and potential for widespread use, in addition to the efficacy of the treatment. Thus, tests of treatment effectiveness would provide policy makers with more comprehensive information than the simple *in vivo* efficacy test. Similarly, as the WHO test uses pharmacopoeial quality drug, in contrast to the multiplicity of sub-standard preparations often found on the market, it has been pointed out that the test provides no information on the influence of drug product variability on malaria treatment. However, until a standardized effectiveness test is available (which might also incorporate variability in product quality) NMCPs and policy makers will continue to rely on treatment efficacy, based upon pharmacopoeial quality drugs, as the main method of evaluating antimalarial drug policy.

In the studies reported here, test drugs were supplied to the national teams through the EANMAT office in Nairobi, which purchases and maintains a stock of pharmacopoeial quality treatment drugs. With each drug consignment the agent provides an analytical report from the Department of Pharmaceutical Sciences, Edinburgh[1]. For the first 3 years of monitoring, a second analysis on each batch of drug was conducted at the National Quality Control Laboratory, Nairobi. Agreement between these two analyses has been good: in future, a single assay at NQCL, Nairobi, or other accredited National Quality Control Laboratory will be acceptable, provided appropriate technology is available (currently, this does not include assays for artemisinin-containing dosage forms).

After every monitoring test, data from the individual patient clinical record forms (CRFs) are transferred to computer at the NMCP office, and the test results summarized. The summary does not include individual patient details, so patient confidentiality is assured. Once cleared by the NMCP manager, this summary is e-mailed to the EANMAT office in Nairobi, where the network manager assembles country data into the EANMAT database. From this point, data are in the public domain, and available on the EANMAT website http://www.eanmat.org).

Informing policy change

Before considering the EANMAT monitoring exercises, it is necessary to define the 'criteria for changing treatment policy', which these tests complement. These criteria have been proposed by WHO and WHO/AFRO as the basis for changing antimalarial drug policy. The first category, where total treatment failure (the sum of ETF and LTF) is <5%, is called the 'grace period'. Here, with a view to the longer-term future, the collection of baseline data is advocated, to establish trends and to build consensus. When total failure reaches the 6–15% range, an 'alert period' commences, where the control programme needs to define the alternative treatment, initiate mechanisms for the change over process, attempt forecasts of the change point and costs of change, and promote advocacy for change. At 16–24% failure, the scheme defines an 'action period' where, if prior steps have been effected, the control programme can focus on the operational plan for drug replacement, and detailed cost and operational considerations. This scheme is now contained within the WHO recommendations for the use of antimalarial drugs (World Health Organization 2001a,b).

[1] Department of Pharmaceutical Sciences – A Department of the Pharmaceutical Society of Great Britain, which analyses formulations on a commercial basis.

Results

In 1999, at the start of monitoring, CQ was the first-line treatment in the public sector in Tanzania and Uganda. Kenya had already changed from CQ to SP in 1998, essentially on the basis of non-EANMAT data from WHO *in vivo* tests, although early EANMAT tests supported this decision (Shretta *et al.* 2000; EANMAT 2001). Table 1 shows the degree and extent of CQ resistance throughout the sub-region in the late 1990s.

The response of each country was to accelerate the monitoring of both SP and AQ efficacy. AQ has long been studied in east Africa as a potential alternative to CQ (Watkins *et al.* 1984), and is attractive on the basis of cost, availability, clinical experience and comparative efficacy. By January 2000, the EANMAT newsletter reported the completion of the first round of testing: Kenya had tested six of eight sentinel sites, Uganda seven of eight and Tanzania six of eight (EANMAT 1999). By covering 19 of the 24 sentinel sites, the first round of monitoring provided profiles of CQ, SP and AQ efficacy which were broadly representative for the sub-region as a whole, although no tests had been carried out in Rwanda, Zanzibar or Burundi at this stage because they were not part of the network. By early 2003, a total of 49 monitoring tests for SP, in 2604 patients, had been carried out in the EANMAT area, and 38 tests, in 1969 patients for AQ. The mean number of patients per test was 53 for SP and 52 for AQ.

The results have been analysed to compare treatment efficacy profiles before, and after 2000 (Tables 2 and 3 and Figures 1 and 2). For SP, the proportion of sites in the 'alert' phase increased from five of 17 (29%) pre-2000 to 13 of 32 (41%) post-2000 ($P = 0.44$). Of greater concern, the proportion of sites where treatment failure exceeded 25% increased from one of 17 (6%) pre-2000 to seven of 32 (22%) post-2000 ($P = 0.15$) (Table 2). Figure 1 shows the range of SP efficacy in the sub-region, and that the initial tests, conducted before 2000, were predictive of the more comprehensive pattern revealed by subsequent tests, including the occasional out-lying result. The AQ test data implies a different rate of development of resistance to this treatment. The proportion of sites in the 'alert' phase pre- and post-2000 remained the same at one of seven and two of 31, respectively ($P = 0.46$). The proportion of sites with total treatment failure in excess of 25% was one of 31 post-2000, not statistically different to the pre-2000 value of zero of seven ($P = 0.82$).

Table 1 Chloroquine efficacy, EANMAT area, in patients aged 6–59 months, 1998–2000

Sentinel site	Date	Number of patients	ACR %	ETF %	LTF %	Total clinical failure rate (%)
Kenya/Busia	February 1999	44	36	5	59	64
Tanzania/Masasi	March 1999	62	69	22	9	31
Tanzania/Mlimba	January 1999	71	29	32	39	71
Uganda/Apac	June 1999	55	80	13	7	20
Uganda/Arua	June 1998	60	77	10	13	23
Uganda/Jinja	June 1998	22	68	23	0	23
Uganda/Kabarole	June 1999	16	44	25	31	56
Uganda/Rukungiri	June 1999	49	90	10	0	10
Uganda/Tororo	June 1999	62	55	18	27	45
Rwanda/Nyarurema	October 1999	59	42	46	12	58
Rwanda/Rwaza	October 1999	54	46	13	41	54
Rwanda/Kivumu	February 2000	54	81	15	4	19
Zanzibar/Kivunge	April 2000	74	39	47	14	61
Zanzibar/Micheweni	April 2000	78	40	35	25	60

Table 2 Sulphadoxine–pyrimethamine (SP) treatment efficacy in East Africa before and after 2000

	Percentage of sites showing ETF + LTF ≥ 15%		Percentage of sites showing ETF + LTF ≥ 25%		Median (%) ETF + LTF (range)		Average % ACR (combined national data from all sentinel sites)	
	Pre-2000	2000 and after	Pre-2000	2000 and after	Pre-2000	2000 and after	Pre-2000	2000 and after
Uganda	28.0 (2/7)	0.0 (0/4)	0.0 (0/7)	0.0 (0/4)	12 (3–19)	6.5 (2–10)	89.3	93.8
Kenya	25.0 (1/4)	42.8 (6/14)	0.0 (0/4)	21.4 (3/14)	9 (3–18)	8.5 (0–52)	90.3	84.9
Tanzania (mainland)	33.4 (2/6)	40.0 (2/5)	16.7 (1/6)	0.0 (0/5)	9 (1–34)	11 (5–19)	86.9	88.5
Zanzibar	–	0.0 (0/2)	–	0.0 (0/2)	–	9 (5–13)	–	91.2
Rwanda	–	66.7 (2/3)	–	66.7 (2/3)	–	35 (12–36)	–	72.3
Burundi	–	75.0 (3/4)	–	50.0 (2/4)		27 (9–49)		71.8

Table 3 Amodiaquine (AQ) treatment efficacy in East Africa before and after 2000

	Percentage of sites showing ETF + LTF ≥ 15%		Percentage of sites showing ETF + LTF ≥ 25%		Median (%) ETF + LTF (range)		Average % ACR (combined national data from all sentinel sites)	
	Pre-2000	2000 and after	Pre-2000	2000 and after	Pre-2000	2000 and after	Pre-2000	2000 and after
Uganda	–	33.4 (1/3)	–	0.0 (0/3)	–	4 (0–14)	–	93.9
Kenya	33.4 (1/3)	0.06 (1/15)	0.0 (0/3)	0.06 (1/15)	13 (0–16)	3 (0–36)	90.3	94.0
Tanzania (mainland)	0.0 (0/4)	0.0 (0/5)	0.0 (0/4)	0.0 (0/5)	3.5 (1.5–4.3)	4 (0–11)	96.7	94.6
Zanzibar	–	0.0 (0/2)	–	0.0 (0/2)	–	3.5 (5–7)	–	94.4
Rwanda	–	0.0 (0/6)	–	0.0 (0/6)	–	0 (0–2)	–	99.3
Burundi	–	–	–	–	–	–	–	–

Discussion

The EANMAT monitoring has provided evidence of decreasing efficacy of SP across the sub-region. The problem is most acute in the western countries Rwanda and Burundi, where SP failure rates exceed the critical 25% value at most sentinel sites. SP failure rates are also high in the areas of high population density surrounding

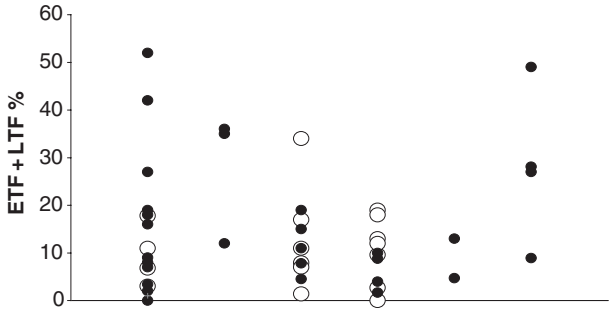

Figure 1 EANMAT: SP total clinical failure (ETF + LTF) by country pre-2000 (○) *vs.* 2000 and after (●).

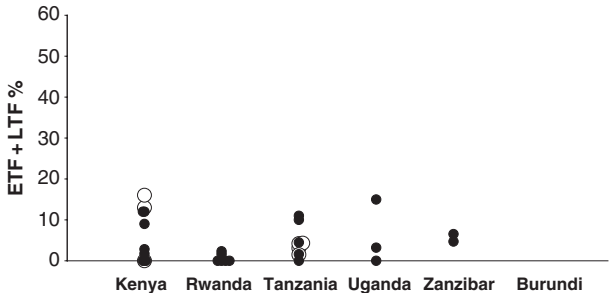

Figure 2 EANMAT: AQ total clinical failure (ETF + LTF) by country pre-2000 (○) *vs.* 2000 and after (●).

Lake Victoria. These results are an immediate cause for concern for Kenya and Tanzania, where SP is the first-line treatment, and for Uganda, which has opted for the SP/CQ[2] combination. Compared with the 14 SP tests in Kenya post-2000, the data are weak for both Uganda and Tanzania mainland (three and five tests, respectively), and may not be sufficiently representative. For example, although none of the Tanzanian sentinel sites has returned a combined clinical failure rate for SP > 25%, a recent study at Muheza has reported SP failure well above this level (Mutabingwa *et al.* 2001). It is accepted that the characteristics of malaria can vary widely in space as well as time, which complicates the selection of a practicable number of representative sentinel sites. In a future paper, we shall try to assess how effectively the EANMAT sentinel sites have represented changes in treatment efficacy.

In general, SP resistance increases in severity from east to west across the sub-region. Rwanda and Burundi have responded with immediate changes in antimalarial drug policy: Rwanda from CQ to SP/AQ[3] in December 2001 and Burundi from CQ to SP as an interim policy in June 2001. More recently, Burundi has replaced SP with AQ/AS[4] as first line treatment, and implementation will start in July 2003.

Kenya has witnessed a marked change in SP efficacy at some sites, but not at others. In comparison with the 1999 pattern, the SP failure rate in 2000 increased significantly at the western sites Kisumu (11–42%) and Bondo (3–27%), and remained just under 20% in Kirinyaga and at Kibwezi. In comparison, SP was highly effective at the coastal sites Kwale and Lamu. In 2001, SP monitoring was not repeated at Bondo and Kisumu, because of these high failure rates. Estimation of the SP treatment failure varied considerably in Kibwezi (from 18% in 2001 to 52% in 2002) and in Kisumu (from 42% in 2000 to 3.4% in 2002).

Tables 2 and 3 indicate fundamental differences in the rate of emergence and spread of parasite resistance to SP and AQ. For SP, the molecular basis of resistance is well documented. The two essential controlling factors are the long elimination half-life of the two drugs, together with the small number of mutations in the parasite *DHFR* and *DHPS* genes which separate the states of complete chemosensitivity and complete chemoresistance (Watkins & Mosobo 1993; Watkins *et al.* 1997). The selection process accelerates once parasites have been selected which have the ability to survive treatment (Hastings *et al.* 2002). The EANMAT Uganda team, using *in vivo* test data from seven of their sentinel sites, has carried out the first empirical study of the relationship between intensity of transmission and evolution of drug resistance. SP failure rates were correlated with intensity of transmission, independent of drug use, suggesting that SP resistance spreads faster in areas of high transmission (Talisuna *et al.* 2002). This will be a seminal finding, if the pattern holds true in wider studies in the EANMAT area: one anomaly is that the countries with the highest rates of SP resistance, Rwanda and Burundi, are also the countries with collectively the lowest endemicities. Further, although caveats are necessary, the Ugandan study has provided the first empirical support for the occurrence of intrahost competition as a component of the resistance selection process – a critical issue if the predictive modelling of resistance progression is to be of use in public health (Hastings 2003).

Taken together, these facts confirm the short 'Useful Therapeutic Life' for SP monotherapy predicted for Africa (Watkins & Mosobo 1993), and previously experienced in South East Asia. AQ, however, is proving to be a very different matter. AQ is a pro-drug, producing metabolites with short half-lives, and there are other factors related to

[2] SP/CQ – CQ 10 mg/kg daily for 3 days with a single dose of SP on the first day.

[3] SP/AQ – AQ 10 mg/kg daily for 3 days with a single dose of SP on the first day.

[4] AQ/AS – a regimen of AQ 10 mg/kg plus artesunate 4 mg/kg daily for 3 days.

chemical structure and mechanism of action (O'Neil *et al.* 1998) which may explain a resistance selection process significantly slower than that of SP. AQ has a 4-amino-quinoline structure, similar to that of CQ which probably involves a multigenic resistance mechanism. The maintenance of AQ efficacy, which EANMAT surveillance has documented, supports the choice of AQ as a partner drug for interim strategy combinations (SP/AQ) and in artemisinin-containing combinations (ACTs) intended for long-term policy.

The EANMAT data have raised a number of questions to which explicit answers are not available within the WHO/RBM recommendations. Is it acceptable to continue to monitor the official first-line treatment at sites where clinical failure rates are known to be high? Kenya has decided against this for SP in Bondo and Kisumu. When should a country change antimalarial drug policy? Should change be initiated when one site, more than half, or all the sites report clinical failure exceeding the nationally agreed change point? This question has caused concern on several occasions in the past. CQ was retained in Kenya on the basis of high sensitivity at one site, Turkana, where drug use patterns, malaria endemicity and vector characteristics were not representative of the country as a whole (Clarke *et al.* 1996). For the time being, drug policies in Africa are not practicable at levels below a national consensus. So it is relevant to ask whether change should be implemented early, when only a small fraction of the population is at risk (the 'first site' scenario) or only at a later stage, when risk rises for a higher proportion of the susceptible population (the proportional, or 'all site' scenario). There are inherent problems in designing a national antimalarial drug policy (Shretta *et al.* 2000), and these are amplified at the sub-regional level. Nevertheless, building a framework for a sub-regional antimalarial drug policy remains a worthwhile target for a network like EANMAT, and the question posed above is applicable to sub-regional, as well as to national data. An EANMAT-RBM meeting in Kampala, October 2001 attempted to formulate a sub-regional policy, but found it to be premature, although member states accepted the innate potential of collective network data for this purpose (EANMAT 2002). Comparisons at this level, based upon the six country database would be more powerful, and more accurate, than those using individual national databases. For example, from the EANMAT database, 22% of monitoring sites have an SP clinical failure rate >25%. At the sub-regional level, this should be a clear mandate for change from SP monotherapy. This move could be achieved more quickly if the member states were to agree (despite political difficulties) that this treatment was no longer acceptable for east Africa. In fact, there is an inescapable parallel between this figure of 22% of sites with unacceptable SP failure, and the equivalent figure for CQ in 1998/1999 (41%; Table 1), which finally led to policy change. A sub-regional agreement on malaria treatment, based upon network rather than country data, would also present a unified, collective argument for donor support, e.g. in applications to the Global fund for AIDS, TB and Malaria (GFATM).

The WHO/AFRO framework for treatment change, based on monitoring results, is a very important tool. However, the categories were proposed as examples, rather than absolute criteria for the sequence of stages preparatory to policy change. The EANMAT countries have tended to adopt the framework *in toto*, without considering the applicability to different antimalarial drugs. One particular problem is that the WHO categories of response (grace; alert; action and change), and the specific change points were proposed with CQ in mind. The emergence of CQ (and AQ) resistance has been a comparatively slow process compared with that of SP resistance. The change points, as instruments of the national malaria control strategy, need to be defined in relation to the anticipated rate of development of resistance for a specific drug, and the consequences of failure in terms of case management. With the benefit of hindsight, change points for SP should have been set at lower percentages, to accommodate adequate warning for the NMCP and a time frame within which appropriate action might reasonably have been taken. In contrast, it is the generalized framework, with arbitrary change points, that has been adopted. While it is too late to make these revisions for SP in east Africa, this matter needs to be addressed by countries which have changed to SP/CQ or SP/AQ, as it will influence the frequency of testing, and the NMCP response to resistance rates. The change points should be re-considered by any country intending to adopt SP monotherapy as an interim measure in central or western Africa.

Another problem is whether the agreed change point, expressed as a percentage clinical failure, is appropriate to all populations at risk, e.g. whether a change point deemed suitable for districts with high malaria endemicity is equally applicable to districts where malaria is highly seasonal, or epidemic. Should the non-immune populations of the east African highlands, for example, be asked to bear a clinical failure rate in the WHO test of 25% before changing to a more effective treatment? This should be considered in relation to the emerging evidence that highland epidemics in east Africa are more a function of drug resistance than of the changes in malaria endemicity resulting from global warming (Hay *et al.* 2002).

What is clear to all participating members of EANMAT is that affordable options for first-line therapy are already

inadequate. Current SP resistance levels are no longer compatible with effective malaria treatment, and pose a real threat to malaria control. Further, as the WHO test does not inform on treatment failure beyond 14 days, it is apparent that the estimates of resistance from these tests must be significantly lower than the real rates of treatment failure which malaria patients in east Africa are suffering. AQ resistance is less severe, and is not increasing so rapidly. However, the presence of low-level AQ resistance in the EANMAT area should provide a warning of the dangers implicit in widespread use of AQ monotherapy. Since 1999, there has been a growing interest in the potential of combination therapy (White *et al.* 1999) within the countries of the network. Two RBM meetings have addressed the importance of combination therapy (CT) to antimalarial drug policy development (World Health Organization 2001a,b), and there has been regular discussion of the scientific basis of CT at EANMAT secretariat meetings – Rwanda, Uganda and Zanzibar have adopted CT as the basis of their antimalarial drug policy.

In this paper, we have provided a summary of the efficacy tests conducted within the EANMAT network, since 1999, to evaluate SP and AQ monotherapies. We have started the process of evaluating the impact of treatment monitoring on the development of national, and eventually sub-regional antimalarial drug policy. Currently, countries within the network are evaluating existing or new policies, and the degree to which CT is providing improved treatment for malaria. Subsequent reports will concentrate on the adoption of CT, both as 'interim' and as 'long-term' strategy, and an evaluation of the strengths and weaknesses of the EANMAT operation as a tool for policy change.

Acknowledgements

The monitoring tests were conduced by EANMAT national teams, working within the NMCPs of the member countries. In Tanzania, research institutes undertake the role of the national team, and we gratefully acknowledge the work of malaria researchers from the Muhimbili University College of Health Sciences (MUCHS), Dar es Salaam; the National Institute of Medical Research (NIMR), Amani; The Bugando Medical Centre (BMC), and the Kilimanjaro Christian Medical Centre (KCMC), Moshi. We gratefully acknowledge assistance from the Kenya Medical Research Institute (KEMRI) to the Kenya national team. Funding for the EANMAT project has been provided by the Department for International Development (DfID) of the British Government. Bob Snow is a Wellcome Trust Senior Fellow (no. 058992), and Bill Watkins is a Wellcome Trust Resettlement Fellow (no. 056305): they are grateful to the Wellcome Trust, London, for research and personal support.

References

Alnwick D (2001) Meeting the malaria challenge. *Africa Health* **September** (Suppl.), 18–19.

Brandling-Bennett AD, Oloo AJ, Watkins WM, Boriga DA, Kariuki DM & Collins WE (1988) Chloroquine treatment of falciparum malaria in an area of Kenya of intermediate chloroquine resistance. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **82**, 833–837.

Clarke D, Odialla H, Ouma J *et al.* (1996) A malariometric survey in Turkana District, Kenya: chemosensitivity *in vivo* of *Plasmodium falciparum* infections and identity of the vector. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **90**, 302–304.

East African Network for Monitoring Antimalarial Treatment (1999) EANMAT: Chairman's Column. *EANMAT Newsletter* **2**, 1–2.

East African Network for Monitoring Antimalarial Treatment (2001) Monitoring Antimalarial Drug Resistance within National Malaria Control Programmes (NMCPs): the EANMAT experience. *Tropical Medicine and International Health* **6**, 1–8.

East African Network for Monitoring Antimalarial Treatment (2002) RBM-EANMAT – a sub regional antimalarial drug treatment policy dialogue meeting, Kampala, 25/26 October 2001. *EANMAT Newsletter* **5**, 4–5.

Hastings IM (2003) Malaria control and the evolution of drug resistance: an intriguing link. *Trends in Parasitology* **19**, 70–73.

Hastings IM, Watkins WM & White NJ (2002) The evolution of drug-resistant malaria: the role of drug elimination half-life. *Philosophical Transactions of the Royal Society B* **357**, 505–519.

Hay SI, Rogers DJ, Randolph SE *et al.* (2002) Hot topic or hot air? Climate change and malaria resurgence in African highlands. *Trends in Parasitology* **18**, 530–534.

Mutabingwa T, Nzila A, Mberu E *et al.* (2001) Chlorproguanil-dapsone for treatment of drug-resistant falciparum malaria in Tanzania. *Lancet* **358**, 1218–1223.

O'Neil PM, Bray PG, Hawley SR, Ward SA & Park BK (1998) 4-Aminoquinolines – past present and future: a chemical perspective. *Pharmacology and Therapeutics* **77**, 29–58.

Shretta R, Omumbo JA, Rapuoda B & Snow RW (2000) Using evidence to change antimalarial drug policy in Kenya. *Tropical Medicine and International Health* **5**, 755–764.

Talisuna AO, Langi P, Bakyaita N *et al.* (2002) Intensity of malaria transmission, antimalarial drug use and resistance in Uganda: what is the relationship between these three factors? *Transactions of the Royal Society of Tropical Medicine and Hygiene* **96**, 310–317.

Watkins WM & Mosobo M (1993) Treatment of *Plasmodium falciparum* malaria with pyrimethamine-sulfadoxine: selective pressure for resistance is a function of long elimination half life.

Transactions of the Royal Society of Tropical Medicine and Hygiene **87**, 75–78.

Watkins WM, Sixsmith D, Spencer HC *et al.* (1984) Effectiveness of amodiaquine as treatment for chloroquine-resistant *Plasmodium falciparum* infections in Kenya. *Lancet* **i**, 357–359.

Watkins WM, Mberu EK, Winstanley PA & Plowe C (1997) The efficacy of antifolate antimalarial combinations in Africa: a predictive model based on pharmacodynamic and pharmacokinetic analyses. *Parasitology Today* **13**, 459–464.

White NJ, Nosten F, Looaresuwan S *et al.* (1999). Averting a malaria disaster. *Lancet* **353**, 1965–1967.

WHO Secretariat to the RBM Partnership (2002) 'Implementation of new antimalarial treatment policies in Africa'. *Discussion Paper for the RBM Partner's Meeting*, 26–28 February 2002, WHO, Geneva.

World Health Organization (1996) *Assessment of Therapeutic Efficacy of Antimalarial Drugs for Uncomplicated Malaria in Areas with Intense Transmission*. WHO/MAL/96.1077, WHO, Geneva.

World Health Organization (2001a) *The Use of Antimalarial Drugs: Report of a WHO Informal Consultation*, 13–17 November 2000. WHO/CDS/RBM/2001.33, WHO, Geneva.

World Health Organization (2001b) *Antimalarial Drug Combination Therapy: Report of a WHO Technical Consultation*, 4–5 April 2001. WHO/CDS/RBM/2001.35, WHO, Geneva.

World Health Organization (2002) *Monitoring Antimalarial Drug Resistance: Report of a WHO Consultation, Geneva*, 3–5 December 2001. WHO/CDS/RBM/2002.39, WHO, Geneva.

Authors (Members of the EANMAT Secretariat)

Dr B. Rapuoda, Division of Malaria Control, Ministry of Health, Nairobi, Kenya. E-mail: eanmat@africaonline.co.ke

A. Ali, National Malaria Control Programme, Zanzibar. E-mail: Abdullah1964@hotmail.com

Dr N. Bakyaita, National Malaria Control Programme, Kampala, Uganda. E-mail: natsbach@hotmail.com

Dr T. K. Mutabingwa, National Institute of Medical Research, Tanzania & Gates Malaria Partnership, LSHTM, London. E-mail: ekmuta@ud.co.tz

Dr A. Mwita, National Malaria Control Programme, Dar es Salaam, Tanzania. E-mail: nmcp@raha.com

Dr C. Rwagacondo, Programme National de Lutte Contre le Palidisme, Kigali, Rwanda. E-mail: pnlp@hotmail.com

Dr V. Mugisha, Directorate of Epidemiology & Public Hygiene, Ministry of Health, Kigali, Rwanda. E-mail: vnmugisha@hotmail.com

Dr S. Staedke, Department of Medicine, San Francisco General Hospital, University of California, San Francisco. E-mail: staedke@itsa.ucsf.edu

Prof. R. W. Snow, University of Oxford, UK and KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya. E-mail: Rsnow@wtnairobi.mimcom.net

Dr W. M. Watkins, Department of Pharmacology & Therapeutics, University of Liverpool, UK. E-mail: bwatkins@btinternet.com (corresponding author).

Prof. Umberto D'Alessandro, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium. E-mail: udalessandro@itg.be