Tropical Medicine and International Health

VOLUME 6 NO 11 PP 891–898 NOVEMBER 2001

Monitoring antimalarial drug resistance within National Malaria Control Programmes: the EANMAT experience

The East African Network for Monitoring Antimalarial Treatment (EANMAT)

Summary The National Malaria Control Programme (NMCP), organized within the Ministry of Health (MoH), is an essential component for the planning, execution and coordination of malaria control activities. As effective case management remains the mainstay of malaria control in almost every African country, antimalarial drug resistance is a major barrier to the implementation of effective malaria control policies. In order to function effectively, these units must have an efficient surveillance system which can provide reliable and current estimates of the severity of drug resistance. Without this information, it is impossible for the MoH to design and promote a rational antimalarial policy, but because of limited resources, especially of people and expertise, most NMCPs have been unable to initiate and manage such a system. The need for collaborative partnerships between the MoH and the research community prompted the establishment of the East Africa Network for Monitoring Antimalarial Treatment (EANMAT). EANMAT has attempted to bring together the complimentary skills of malaria researchers and MoH staff in four east African countries. After 3 years of operation, data generated by EANMAT have been used to review and modify national malaria treatment policies in Kenya, Uganda, Rwanda and Tanzania. This new approach, which forges a closer working relationship between the research and policy communities, has effectively built capacity around the complex of surveillance, interpretation and use of evidence within a policy environment. The added-value of this approach is that the research community has learned to appreciate the constraints of policy development, and that the control community has established the need to build capacity and ownership of research evidence. Networks similar to EANMAT should be encouraged elsewhere in Africa to engender similar partnerships: to assist the development of rational treatment policies, and thus more effective malaria chemotherapy leading to significant lowering of malaria morbidity and mortality.

keywords case management, drug resistance, monitoring resistance, EANMAT

correspondence Dr T. K. Mutabingwa, National Institute for Medical Research, Amani Centre, P.O. Box 4, Amani-Tanga, Tanzania. E-mail: tkmuta@ud.co.tz or tk.mutabingwa@lshtm.ac.uk

Introduction

Clinical malaria accounts for the greatest burden virtually upon all health services across sub-Saharan Africa. With the inception of the Roll Back Malaria (RBM) initiative, National Malaria Control Programmes (NMCPs), charged with the responsibility for effective case-management, have a renewed importance within the Ministry of Health (MoH). In east Africa, however, rapid emergence of resistance to the widely available and cheap antimalarial drugs chloroquine and sulphadoxine–pyrimethamine (SP) are seriously threatening this central pillar of malaria control.

Since the early 1980s, drug-resistant *Plasmodium falciparum* has increasingly limited the provision of adequate treatment. This is often manifested in subtle ways which are only apparent when treatment is accompanied by detailed follow-up over several weeks – the rationale for formal monitoring of treatment efficacy. Resistance to chloroquine is now so widespread in eastern and southern Africa that some authorities have questioned whether there is any continuing role for this drug. The choice of a replacement has been dictated primarily by economic considerations, and until very recently SP was generally considered the only practicable and affordable alternative. As a result, SP is replacing chloroquine in east and central Africa: a process now characterized by the

rapid selection and spread of parasite resistance to SP. For example, within 5 years of the first reports of SP-resistance in Muheza district, Tanzania (Ronn *et al*. 1996; Trigg *et al*. 1997), parasitological failure at day 7 following SP treatment in children is now 45%, rising to 61% after re-treatment (Mutabingwa *et al*., unpublished observation). Muheza is, perhaps, the most SP-resistant location in East Africa, but similar results have been recorded elsewhere. At Kilifi on the Kenya coast, parasitological failure at day 7 has risen from 2% in 1993–1995 to 20% in 2000 (Nzila *et al*. 2000). It is this alarming rate of change of SP efficacy which has highlighted the inadequacies of treatment monitoring within NMCPs, and provided the drive for novel approaches which are typified by the East Africa Network for Monitoring Antimalarial Treatment (EANMAT) project.

Problems faced by NMCPs in obtaining epidemiological information on drug resistance

A surveillance system for monitoring drug resistance is really only useful if it is sustained over time and is representative of the patterns of drug use, ecology and demographic characteristics of the region. These systems require expertise in drug sensitivity testing, considerable time and resources, and a competent governing body to coordinate programme operations. Unfortunately, most NMCPs lack the necessary expertise and facilities: they are understaffed, and they operate under limited and restrictive budgets. In consequence, NMCPs have relied upon information from National Research Institutions or other external research groups to provide the field-based evidence necessary to guide policy. There are several important limitations to this arrangement. First, the research evidence may be varied and fragmented: a plethora of different test methods has been common, making comparisons difficult even within a country, and test sites have varied, reflecting the transient and often short-term interests of the research group, rather than the national need for sustained and regular surveillance of treatment efficacy. As a result, the researchers have often failed to agree on the status of resistance and the resulting input into policy development has been fragmented. Secondly, communication has been notoriously inadequate between the research and operational spheres. Some have considered the scientific community a traditionally poor communicator of 'evidence' to the control and policy sector, while equal blame has been attached to public sector weaknesses in retrieving relevant data from the public domain. In part, these are general, institutional problems: research institutes have not clarified the reporting structure by which operationally important findings are made known to government, and individual researchers, in using the scientific literature as their sole means of communication, have often been unaware that crucially important data were not reaching the executive branches of government. The ownership of research evidence, in the past firmly anchored within the scientific community's domain, has probably had a negative impact on communication, and on the subsequent generation of broad-based responses to the problems of drug-resistant malaria. There have been critical delays in access to information for those charged with responding to the situation, and a mistrust of the evidence itself which is rooted in a lack of participation in its generation. Where MoH have commissioned research studies in an attempt to address this impasse, the results have frequently been ineffectual because of the differing priorities and agendas of the research groups and their time-limited engagement in the process.

These combined constraints have impacted upon the efficient collection, dissemination and use of drug sensitivity results in many countries. A recent analysis of the policy transition from chloroquine to SP in Kenya exemplifies these difficulties (Shretta *et al*. 2000).

Addressing the problems

For many years there have been calls to use research-developed or evidence-based platforms to guide policy. As many pleas have been made to develop essential health research agendas through partnerships between MoH and Research Institutions. Partnerships can maximize resources and provide stronger guarantees that research findings will be translated into practice. Indeed, partnerships form one of the guiding principles behind the new RBM movement. and yet, there are few examples in east Africa where these partnerships have been created to identify research needs, undertake the research and move it into policy dialogue. One explanation for this failure may be the degree of labour, patience, good-will and time required to sustain the initiation of the partnership from scratch. Collective agreements upon common goals, defining ownership of evidence, etc., are not, of themselves, that difficult to achieve in the context of African malaria chemotherapy. The problems are apparent, and common across wide swathes of the continent. But the partnership process needs to grow out of a comprehensive appreciation of the commonality and urgency of the problem by the potential partners at the NMCP level. Achieving cooperation amongst groups with differing styles and agendas is hard work, and requires time to ensure trust, and the fullest involvement by all concerned. It must be a 'bottom–up' rather than a 'top–down' process: it will not work by

Table 1 Stages in the development of EANMAT

Landmark agreements or levels of technical competence achieved	Dates
1. Basic network aims and objectives. Formation of secretariat representing Kenya, Uganda, Tanzania. MoH support for network confirmed by three countries	February–July 1997
2. Standardization of test methodology and field manual. Number and location of sentinel sites (SS). Confirmation of National Team Leaders and TOT workshop. Composition of National Monitoring Teams (NTs). Project and budget proposal submitted to DFID. First and second secretariat meetings: draft testing timetable. Newsletter started	July–December 1997
3. Start of monitoring in all three countries ('first round'). Start of DFID funding (March 1998). QC of test drugs. Continued secretariat meetings in Nairobi. Funding routes established to NTs	1998
4. Computer data entry program. Some SS start 'second round' testing. Rwanda joins EANMAT. EANMAT data used by Kenya and Tanzania Drug Policy meetings. EANMAT constitution finalized. Secretariat meetings rotate by country. '1st round' tests complete throughout network: 'second round' completed at some SS. Start of registration of EANMAT as international NGO	1999
5. First 'Internal Evaluation' of project. First 'Output to Purpose' Review (OPR). EANMAT data used by Uganda Drug Policy meeting. EANMAT registered as an NGO. Computer-entry of results completed by Uganda. Plans for EANMAT gene bank. Network Manager appointed	2000
6. Development of policy for project extension and modification post-March 2002: new role for secretariat. First publication of EANMAT data summary in newsletter	2001
7. Completion of first budget period (March 2002). DFID project and finance reports	2002

TOT – Training of Trainers; DFID – Department for International Development: the aid arm of UK Government; QC – Quality Control; NGO – Non-governmental Organization.

imposition on an NMCP which does not see very clearly the advantages which can be gained.

Experience within the EANMAT project has taught that the network needs to be built in stages. We are not suggesting that this is the ideal way forward: merely that a staged development, ensuring acceptability at progressive levels of organization, has achieved reasonable success in the EANMAT model. Stages of development for EANMAT, and the time frame, are shown in Table 1.

EANMAT: a model for the development of subregional partnerships in monitoring efficacy of malaria treatments?

The EANMAT was founded in response to a clearly recognized need. The concept was first explored in February 1997, at an evening social event following a 'malaria day' at the annual NIMR[1] scientific conference in Dar es Salaam (EANMAT 1998). Thus the initiative came from scientists and public health experts, who recognized the essential similarities of antimalarial drug resistance throughout the countries of east Africa, and the need to maximize a concerted response by pooling scarce resources. The advantages of this approach have spread beyond the founding partners: Rwanda joined the network in 1999, and it is hoped that Burundi will soon follow. At that first unofficial meeting, the vision was a network which would enable regular monitoring of treatment outcome for the commonly used (first and second line) antimalarial drugs, upon which rational antimalarial treatment policies could be based. The past problems of communication and ownership were openly addressed, and consensus quickly reached on the central role of the MoH, in terms of general ownership, implementation of output and political support for a supra-national programme. A coordinating secretariat was seen as essential, both for project organization, and also, importantly, to provide a subregional, malaria-specific scientific focus.

In the first 4-year phase the secretariat, representing the NMCPs of the constituent countries, has been crucially important to network organization. Formal meetings are held every 3 months, the location rotating by country. These EANMAT meetings, convened around the common problem of drug resistance, are the only regular meetings of the subregional NMCP managers and their staff. As such they also provide a forum for national MoH programme staff and research scientists to

[1]NIMR – National Institute of Medical Research, Republic of Tanzania.

discuss wider issues related to the practical problems of malaria control.

At a technical level, the 14-day WHO *in vivo* test (WHO/MAL/96.1077) was adopted as the standard EANMAT test: a priority if data were to be compared both within and between countries. The test is conducted in children under 5 years of age suffering from uncomplicated falciparum malaria and living in areas of year-round malaria transmission. The WHO protocol was re-written as an 'EANMAT Field Manual', more suitable for staff at the peripheral health units identified as network 'sentinel sites'. This manual was a basic tool for the Training of Trainers (ToT) workshop (Table 1) which prepared the 'national team leaders' for the job of selecting and training their own 'national teams' in-country. Each national team comprises eight staff (four clinical, four parasitological background) trained in the WHO test methodology and selected as appropriate from either the NMCP or research institute(s). All countries have eight 'official' sentinel sites (except Rwanda with four), based within peripheral health units and chosen by the national team/NMCP to be representative of the local range of ecological and epidemiological conditions. Most countries have one or two extra sentinel sites whose activities are funded outside EANMAT, referred to as 'additional sentinel sites' (Table 2, Figure 1). Important criteria in this selection

Table 2 Location and typology of EANMAT sentinel sites within the east Africa subregion

Country	Number on map	Sentinel site	Rounds of tests done	Typology
Kenya	1	Busia	2	Border, perennial endemic
	2	Makueni	2	Semi arid, seasonal endemic
	3	Kirinyaga	2	Irrigation, seasonal endemic
	4	Kisumu	2	Urban, perennial endemic
	5	Lamu	2	Island, seasonal endemic
	6	Bondo	2	Lakeside, perennial endemic
	7	Kwale	1	Coastal, seasonal endemic
	8	Nandi	0	Highland, epidemic prone
	9	(Garissa)	0	Arid, epidemic prone
Tanzania	10	Mkuzi	2	Valley-rural, perennial endemic
	11	Chamwino	1	Semi arid, seasonal endemic
	12	Masasi	1	Highland, perennial epidemic prone
	13	Mlimba	1	Rural, perennial endemic
	14	Butimba	1	Lakeside, perennial endemic
	15	Kyela	1	Border, perennial endemic
	16	Kigoma	1	Lakeside, border, perennial endemic
	17	Kibaha	0	Urban, perennial endemic
	18	(Micheweni-Pemba)	1*	Island, perennial endemic
	19	(Kivunge-Zanzibar)	1*	Island, perennial endemic
Uganda	20	Arua	2	Rural, perennial endemic
	21	Jinja	2	Urban, perennial endemic
	22	Moroto	2	Rural, seasonal endemic
	23	Mubende	2	Rural, perennial endemic
	24	Apac	2	Rural, perennial endemic
	25	Rukungiri	2	Highland, epidemic prone
	26	Tororo	2	Urban, border, perennial endemic
	27	Kabarole	2	Rural, seasonal endemic
	28	(Kampala)	0	Urban, seasonal endemic
Rwanda	29	Rwaza	1	Highland, epidemic prone
	30	Mashesha	1	Border, perennial endemic
	31	Rukara	1	Urban, perennial endemic
	32	Kivumu	1	Highland, border, epidemic prone
	33	Kicuriro	1	Urban, perennial endemic
	34	Busoro	1	Rural, border, perennial endemic

Sites in brackets are additional Sentinel Sites for respective countries. Round of test = testing at least the first and second line antimalarial drugs once a year. Additional sites with 1* = recently introduced, tested only Chloroquine because of low recruitment, although the initial intention was to also test sulphadoxine–pyrimethamine (SP).

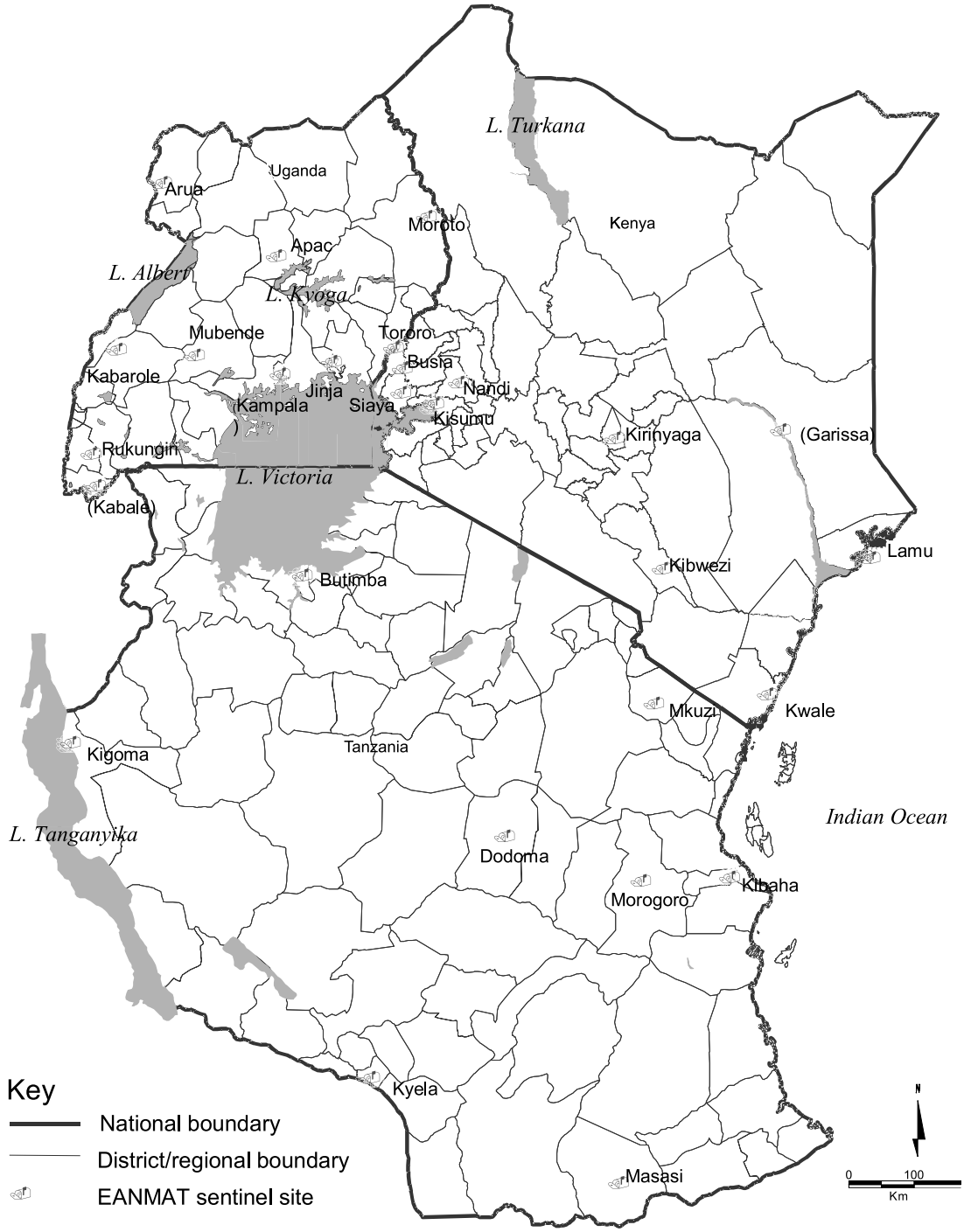

Figure 1 East African network for monitoring anti-malarial treatment sentinel sites

process were transmission intensity, population density, accessibility of the health centre, the special case of national borders, geographical spread, and the need for the sentinel site to have a defined catchment area, and a stable population with limited in- and out-migration. Testing is carried out during the peak malaria transmission season

and patients are included according to the inclusion or exclusion criteria stated in the WHO Manual. The data generated classifies patients into three categories of early treatment failure (ETF), late treatment failure (LTF) or adequate clinical response (ACR), all of which are clearly defined in the Manual.

A minimum of four trained staff is required by the EANMAT protocol for each test site (one clinical officer, two nurses, and one microscopist), and the MoH try to ensure that this pertains. Before each monitoring test, a 2-day training/re-training workshop of sentinel site staff is conducted by two members of the national team (one clinician, one parasitologist), and there is further training during the test itself. In the first 2 years of the project, 18 of 24 (75%) sentinel sites had tested at least one drug and 41 separate drug tests had been conducted. As the test procedures became established and monitoring teams gained experience, attention was given to other issues: standardization of data records, computerized data entry, quality control of test drugs, and protocols for internal and external controls on the monitoring process. Of particular importance and advantageous to participating countries, test drugs are centrally 'quality controlled' and thereafter issued to testing sentinel sites. Every national team manages its own national data base, and provides summarized data to the MoH and the secretariat. It was envisaged that the EANMAT secretariat would meet with policy makers from all member countries once every 2 years, to discuss the policy implications of the data, and this has been accomplished (Table 1). At the two and a half year stage, EANMAT's successes and failures were summarized in the September 2000 newsletter (EANMAT 2000)[2]. A 'first round' of tests has been completed at 80% of sites using current first and second line antimalarial drugs. EANMAT has an agreed constitution, and has been registered as an international NGO. The network has a working arrangement with the African region of the World Health Organization (WHO/AFRO), is recognized as the first network to become functional within the AFRO programme, and is seen as a credible model by RBM for similar networks, both within AFRO and in other regions (Dr P Ringwald, Dr B Nahlen, Dr K Mendis, WHO, Geneva, personal communications). In 1999 the network expanded to include Rwanda, and the indications are that Burundi will join soon.

[2]The EANMAT newsletter is available to any interested person or institution – send an e-mail to the EANMAT Network Manager, Mr Andrew Wamari at eanmat@africaonline.co.ke or download a copy from www.kmis.org.

Using EANMAT within policy dialogue

Most importantly, treatment efficacy data generated by EANMAT have been used in the evaluation and modification of antimalarial treatment policies in all member states. In Kenya, EANMAT data strengthened the decision to change from chloroquine to SP (a decision taken before EANMAT became operational), while in Uganda (June 2000), Rwanda (February 2001) and Tanzania (May 1999), data presented at National Consensus meetings for policy review proved to be decisive. The 10th secretariat meeting, in Entebbe, Uganda, was run sequentially with a Uganda MoH meeting to review antimalarial drug policy: the meeting chairman, Professor Francis Omaswa, Director General for Health Services, strongly supported the sequential meeting concept, and suggested that this should become an annual event. Every effort will be made to build on this type of collaboration. At each national policy debate, the EANMAT national team leader presented the scientific evidence generated from the sentinel sites to the broad stakeholder audience. The scientists provided technical advice when required, but to all intents and purposes the centre of gravity of the scientific platform for each policy dialogue was squarely within the MoH arena. To this end the historical suspicions of scientific data were broken.

Limitations

There have been setbacks as well as achievements. The prolonged drought of 1998–1999 in east Africa dramatically lowered malaria transmission at many sentinel sites, and delayed the testing programme. In the early stages of the network, there were delays in routing money from funding agency to NMCP and monitoring teams, although this problem has now been resolved. The network newsletter, designed to inform peripheral MoH staff of general network results and developments has not been reaching sentinel sites, although it has become a useful means of keeping other, widely dispersed members of the network in touch. But we are concerned that peripheral staff should not feel excluded or neglected, and other means of maintaining communication are being explored. Deficiencies were uncovered at the mid-term internal and external reviews, common problems being inadequately filled case report forms (CRFs), misclassification of the outcome of the test, and CRF-to-database transcription errors. Perhaps this has been the major stumbling block in balancing the expectations of the research community on one side and the control community (MoH and NMCPs) on the other. However, considering that MoH staff at sentinel sites was new to treatment efficacy monitoring,

these deficiencies were no more than expected, and they are being rectified as the national teams gain in proficiency. Another drawback was the rate at which trained staff was transferred away from the sentinel sites, despite prior assurances from the MoH. While this necessitated remedial training of the new staff to bridge the gap, polite reminders to the MoH have improved the situation. When staff are permanently stationed they should be capable after repeated rounds of tests, and able to work with a minimum of supervision. This will greatly increase the testing capacity of each national team and the degree of independence of the teams from the secretariat. Anticipating this eventual outcome, the EANMAT secretariat is preparing for a modified role in the next phase. As the individual country teams become proficient in all aspects of the monitoring system, there will be no further need of 'micromanagement' by the secretariat. Paradoxically, rather than signalling a successful end of the network, we believe that this new phase highlights unique opportunities for additional impact on the evidence-to-policy continuum. The secretariat will continue, if requested, to moderate country-level activities (i.e. countries would opt-in to this 'service' if needed), and it will always serve subregional needs for a malaria discussion forum, library of monitoring results and other network data, and other core roles such as the gene bank repository. It is essential that these critical and hard-won gains are consolidated and assured. But new foci of secretariat activity could well develop in research areas which are important to antimalarial treatment policy: the field testing of novel treatments, or treatment strategies; identifying factors contributing to the emergence and rapid spread of resistance, mechanisms of resistance, and the economic implications of resistance and policy change.

To date, EANMAT successes have outweighed the failures. The partnership with the MoH has contributed to beneficial attitude changes, and the impact of EANMAT on the development of antimalarial treatment policies in Kenya, Uganda, Rwanda and Tanzania may prove to have been significant.

Conclusion

Neighbouring countries in Africa often share similar problems with drug-resistant malaria, yet lack the resources to mount their own comprehensive monitoring system. In this situation, the EANMAT experience suggests that country response can be optimized by pooling resources, and sharing experience and data through a small (three–five countries) network. These networks are practicable, given a few basic provisos: motivation at the NMCP level; commitment from the respective 'National Teams' and their MoH, and, very importantly, a 'bottom–up' rather than 'top–down' staged development. Creating partnerships between the research and control communities demand new ways of working. Practically, this requires the research community to adopt a more technical role and to devolve ownership to those who must assume the ultimate responsibility for evidence-based platforms. This may not be easy for the traditionally academic scientist, nor for the entrenched, highly suspicious MoH. Nevertheless we believe that manageable monitoring networks brokered between the MoH and national research groups provide the only way forward if research evidence on drug sensitivity is ever going to impact upon national policies.

Acknowledgements

EANMAT acknowledges financial support from the Department for International Development (DFID) of the British Government, without which the network would not have taken off. We are grateful for the recognition and political support from the Ministries of Health of the participating countries. Research and academic institutions in each of the four participating countries and partner institutions from the North willingly provided the required technical expertise. The co-operation of the staff at the sentinel sites and communities within the catchment area, which ensured successful testing, is highly appreciated. Mr AM Noor of Kenya Medical Research Institute/Wellcome Trust Collaborative Programme helped with producing the map of EANMAT sentinel sites.

References

East Africa Network for Monitoring Antimalarial Treatment (1998) EANMAT: origins and 'start-up'. *EANMAT Newsletter* **1**, 1–3.

East Africa Network for Monitoring Antimalarial Treatment (2000) EANMAT – internal and external evaluation: the past, present and future. *EANMAT Newsletter* **3**, 1–20.

Hyde JE (1990) The dihydrofolate reductase-thymidylate synthetase gene in the drug resistance of malaria parasites. *Pharmacology and Therapeutics* **48**, 45–59.

Nzila AM, Mberu EK, Sulo J *et al.* (2000) Towards an understanding of the mechanism of pyrimethamine–sulfadoxine resistance in *Plasmodium falciparum*: genotyping of dihydrofolate reductase and dihydropteroate synthase of Kenyan parasites. *Antimicrobial Agents and Chemotherapy* **44**, 991–996.

Ronn AM, Msangeni HA, Mhina J, Wernsdorfer WH & Bybjerg IC (1996) High level of resistance of *Plasmodium falciparum* to sulfadoxine–pyrimethamine in children in Tanzania.

Transactions of the Royal Society of Tropical Medicine and Hygiene **90**, 179–181.

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.

Trigg JK, Mbwana H, Chambo O, Hills E, Watkins W & Curtis CF (1997) Resistance to pyrimethamine–sulfadoxine in *Plasmodium falciparum* in 12 villages in NorthEast Tanzania and a test of chlorproguanil-dapsone. *Acta Tropica* **63**, 185–189.