Journal of Pharmacy and Bioresources
Vol. 1 no. 1, pp. 51-60 (September 2004)

Journal of
PHARMACY AND
BIORESOURCES

Responses of *Plasmodium falciparum* infections to antimalarial drugs in north eastern Nigeria – Part 1: 1988 - 1995.

Norman B. Molta[1*], Ismaila M. Watila[2] and Stephen Oguche[3]

[1]*Dept. of Biological Sciences, University of Maiduguri, P.M.B. 1069, Maiduguri. Nigeria. (Current address: Unit of Parasitology & Entomology, Department of Zoology, Faculty of Natural Sciences, University of Jos, Jos. Nigeria.)*
[2] *Department of Paediatrics, State Specialist Hospital, Maiduguri. Borno State, Nigeria.*
[3] *Dept. of Paediatrics, University of Maiduguri Teaching Hospital, P.M.B. 1414, Maiduguri. Nigeria.*

Received 19th April 2004; Revised, accepted 16th July 2004

Abstract

The responses of *Plasmodium falciparum* strains to different antimalarial drugs were assessed in the north east of Nigeria, using a modified version of the World Health Organization (WHO) extended *in vivo* field test protocol from 1988 to 1995. The sensitivity of the strains to chloroquine phosphate varied from a delayed clearance of parasitaemia, through Type-RI resistance or recrudescence to asymptomatic Type-RII resistance. Chloroquine was still clinically efficacious against *P. falciparum* malaria and continued to play a major role in reducing malaria-related morbidity. However, parasitological failure rates were on the increase as demonstrated in Damboa, where a 1.3-fold increase occurred in D7 failure rate over a 7-year period, from 18.7% in 1988 to 24.5% in 1995. This highlighted the need for continued monitoring of the performance of the drug against the parasites, in addition to evaluating the efficacy and tolerability of new products. Second-line drugs, particularly the combinations of pyrimethamine and sulphadoxine (SD-Pyr, Fansidar®), and pyrimethamine and sulfalene (SL-Pyr, Metakelfin®) were clinically and parasitologically efficacious, producing 100% and 97.1% cure rates, respectively. Self-medication, non-compliance with treatment regimens (particularly for multiple dose therapy), sub-standard or even fake drugs/products, in addition to parasite resistance were identified as factors compounding the treatment of *P. falciparum* malaria.

Keywords: Antimalarial drugs; *Plasmodium falciparum*; North Eastern Nigeria; 1988 – 1995.

Introduction

Malaria, caused by *Plasmodium* species is a significant health problem and by far the most important vector borne disease (Curtis, 1996). About 300 - 500 million people experience clinical episodes and 1.4 - 2.6 million deaths occur annually due to this disease with 80 - 90% of these being in tropical Africa (WHO, 1993). The disease has its greatest impact on the poor people of this part of the world (Nabarro, 1999).

Malaria control in Africa is largely based on presumptive treatment of fever cases using anti-malarial drugs (Trape and Rogier, 1996; Breman and Campbell, 1989). However, this approach is faced with several

* Corresponding author. *E-mail address*: nbmolta@yahoo.com or moltan@unijos.edu.ng *Tel.*: 0803 4549004

inherent problems. First, although fever is the most recognizable feature of clinical malaria, many *P. falciparum* cases in endemic areas do not present with measurable temperature elevations (Rogier *et al.*, 1996; Smith *et al.*, 1995, 1994). Second is the development, spread and intensification of parasite resistance to chloroquine (the cheapest and most widely available first line drug) and other antimalarials, including combination drugs (Sowunmi *et al.*, 1996; Molta *et al.*, 1993; Olliaro and Trigg, 1995). Third is the high cost of development and production of new effective drugs that are unaffordable to poor rural dwellers who are the ultimate consumers in developing countries.

Because of these problems, there are renewed efforts to evolve radically different strategies for controlling malaria. The new alternative methods under exploration include the genetic manipulation of vectors using "loaded" transposons or symbiotic rickettsia-like organisms to drive parasite inhibiting construct into the wild population (Zeng *et al.*, 1997; Collins and James, 1996; Collins, 1994; Curtis, 1994; Kidwell and Ribeiro, 1992). The goal of this approach is to reduce mosquito vector competence by inhibiting sporogonic development at an appropriate stage. Specific intentions include:

(i) inhibition of exflagellation in the midgut
(ii) inhibition of penetration of gut-wall by ookinete
(iii) encapsulation and / or melanization of oocysts on gut wall, and
(iv) reduction/inhibition of sporozoite survival in the salivary glands of adult mosquitoes. Efforts are also continuing towards the development of an effective vaccine against malaria (Greenwood, 1997; Leach *et al.*, 1995) despite the setbacks experienced with SPf66 (Alonso *et al.*, 1996, 1994; D'Allessandro *et al.*, 1995).

The problem of increasing antimalarial drug resistance of *Plasmodium* species, notably *P. falciparum* prompted the study reported in this article. This paper presents data generated in the north east of Nigeria from 1987 to 1995, to determine the susceptibility of *P. falciparum* to some common antimalarial drugs, particularly chloroquine. The period marked the first phase of the antimalarial drug efficacy studies in Nigeria. The studies reported were joint efforts between the National Malaria and Vector Control Division of the Nigerian Federal Ministry of Health (NMVCD/FMOH) and the African Child Survival Initiative - Combating Childhood Communicable Diseases (ACSI-CCCD) of USAID programme. These investigations followed unconfirmed, but nonetheless disturbing reports of malaria treatment failure from various parts of the country (Daniel and Molta, 1989; Molta *et al*, 1991; Molta *et al.*, 1993).

Experimental

Study area. Susceptibility of *P. falciparum* to various antimalarial drugs was assessed at more than 7 sites scattered across the north east (Zone D of the Primary Health Care system) of Nigeria (Table I). The area begins from the forested 800-mm annual rainfall belt to the south and spreads northwards into the dry sahelian environment with maximum rainfall of 500 mm annually. It shares borders with Niger and Chad Republics to the north and Cameroon to the east and comprises of Adamawa, Bauchi, Borno, Gombe, Jigawa, Kano, Taraba and Yobe states. It had a population of 2.4 million (NPC, 1991), and majority of the inhabitants live in rural communities where malaria is highly endemic. The entire population is at risk of infection (Salako, 2002) and, like in other parts of the country, at least 50% of the people experience one clinical attack every year. The geographical variation of the area has significant influence on the epidemiology of malaria.

Selection of sites for the antimalarial efficacy study was a joint effort by the National Malaria Therapy Surveillance team in the zone and the respective states Ministry of Health, particularly the Epidemiological Units. Guiding factors in site selection included: (i) records of high endemicity and transmission of malaria, (ii) relatively large human population to allow enrollment of the minimum number of patients for a full study, and (iii) accessibility.

Subject selection and enrollment. To qualify for enrollment, the following criteria, initially defined by Khoromana *et al* (1986), Breman *et al* (1987) and FMOH/CCCD (1987a, b) had to be met:

(i) age not less than 6 months and not above 5 years
(ii) pure *P. falciparum* infection with at least 1,000 asexual parasites per µl (ap/µl.) of whole blood
(iii) absence of any obvious concurrent infection or sign of nervous dysfunction
(iv) ability to take oral medication.
(v) no history of antimalarial ingestion in the last 7 days often confirmed by negative Dill-Glazko urine test for 4-aminoquinolines (Lelijveld and Kortmann, 1970). This test was initially mandatory, but later became optional since it is known to produce false positives or even false negatives if drugs other than aminoquinolines had been ingested.
(vi) declared consent by parents/guardians to comply with follow-up requirements.
(vii) residence within close proximity to the study centre.

All studies, except those conducted at Maiduguri in 1991 and Damboa in 1995, involved children aged 6 months to 5 years. Subjects were randomly screened (except in the Maiduguri study of 1991 where those with clinical symptoms of malaria were selectively examined) by microscopic examination of thick and thin blood samples obtained from finger pricks and stained in 2% or 4% Giemsa solution diluted in phosphate buffer of pH 7.3.

Essential data on enrolled subjects included: names of both parents (father and mother), home address for possible visit, weight, axillary temperature, clinical presentation and parasite counts. In addition, records of vomiting, diarrhoea and pruritus were kept.

Medication / Treatment. Since this study was initially designed to investigate the efficacy of chloroquine as first line drug in the treatment of uncomplicated malaria, this drug was studied in all sites. It was administered orally, either as tablet or syrup, at the standard dose of 25 mg/kg spread over 3 days (i.e. 10 mg/kg on D0, 10 mg/kg on D1 and 5 mg/kg on D2) (WHO, 1973).

The combination of sulphadoxine/ pyrimethamine (SD-Pyr) was assessed at Hadejia and Tafawa Balewa and sulphalene/ pyrimethamine (SL-Pyr) at only Tafawa Balewa. These drugs were administered as single-dose treatments based on weight (rather than age, which could be unreliable) i.e. 5-10 kg, ½ tablet; 10-20 kg, 1 tablet of 500 mg sulphadoxine and 25 mg pyrimethamine as recommended by the manufacturers.

Assessment of drug efficacy against infections. A minimum of 31 enrollable patients was required for a full study based on the sequential analysis of Dixon and Massey (1957). This was necessary to identify a success rate of 99% at the 95% confidence level and a failure rate of no less than 10% at 90% confidence level (Breman *et al.*, 1987). Responses of the parasites to drugs by D2, D7, and D14 were used as basis for determining the efficacy of each drug. In addition, clinical responses to therapy were assessed by monitoring body temperature, diarrhoea, vomiting, etc. A D2 parasitological failure was considered to have occurred if asexual parasite count on D2 was equal to or exceeded 25% of the D0 count (i.e. parasite clearance did not exceed 75% by D2). In

addition, the mere presence of asexual parasites in blood samples on D7 and/or D14 signified parasitological failure.

Results and Discussion

Baseline data on malaria in the North-East of Nigeria. Out of the 6,285 subjects screened at various sites, 3,725 (59.3%) were positive for malaria infection. *P. falciparum* was the predominant species (constituting at least 90% of infections) causing human malaria in the north east of Nigeria. *P. malariae* occasionally occurred and usually in mixed infections with *P. falciparum*. *P. ovale* was extremely rare and appeared mainly in the southern fringes of the zone.

P. falciparum infection was highest at Damboa (66% - 76% infection rates during the high transmission season). Here, gametocyte rate was 2.7% i.e. 43 out of 1,602 subjects. The lowest infection rate occurred at Kumo (19%), during the low transmission months of April/May (Table 2). Seasonal variation in the prevalence of malaria was clearly depicted in Tafawa Balewa; 36.7% infections during the dry season compared to 63.6% in the rainy season of 1989 (Table II).The level of parasitaemia in Damboa during 1995 showed significant positive correlation (r_s= 0.929, N=7, $p<0.01$) with occurrence of fever (axillary temperature ≥ 37.5°C). Less than 10% of subjects with parasite density lower than 1,000 ap/µl, while at least 80% of those with more than 100,000 ap/µl were febrile. The overall fever rate was 14.3%. Asymptomatic infection constituted at least 12.2% among those with 1,000 ap/µl or higher parasite densities.

The geometric mean parasite density (GMPD) on D0 was highest at Damboa (13,676 ap/µl.), during the 1988 study and lowest at Baissa (5,656 parasites/µl.). GMPDs for asymptomatic cases with more than 1,000 ap/µl were 3,687 ap/µl, Baissa; 5,609, Damboa; 6,384, Tafawa Balewa; and 3,441, Hadejia.

Generally, patient enrollment rates were rather low, about 6.9% in Damboa (1995) and 14.9% in Baissa (1988). Extensive screening of subjects was therefore undertaken in order to enroll the minimum required numbers. As an exception to this pattern, a high enrollment rate (58.8%) was however, recorded in Maiduguri in 1991 among patients presenting with signs/symptoms of malaria.

Parasitological responses of P. falciparum to chloroquine therapy. *P. falciparum* parasitaemia was rapidly cleared following chloroquine therapy, giving an overall reduction of 91.8% by D1 and 97.8% by D2 (Table IV). Most strains of the parasite in the north east were thus fully sensitive to the drug. However, strains with reduced sensitivity as well as resistant ones had already emerged (Molta *et al.*, 1992, 1993) in this geographically vast area. Thus, low - moderate levels of D2 (8.6%), D7 (20.1%) and D14 (4.1%) therapeutic failures were recorded. D2 or early failure occurred at Baissa (6.7%), Damboa (6.8%, in 1995, but not in 1988) and Maiduguri (11.8 - 14.6%).

D7 failure was recorded in all study sites, the highest rate being at Maiduguri (25.5%) and the lowest at Tafawa Balewa (5.4%). At Damboa, D7 parasitological failure increased from 18.7% in 1988 to 24.5% in 1995 demonstrating reduced sensitivity of *P. falciparum* to chloroquine in this area. Records of D14 responses were incomplete due to either change of protocol or failure of patients to appear for follow-up, but available data showed low recrudescence (Type-RI and asymptomatic RII resistance) rates at Baissa (9.3%) and Damboa (6.1%).

Clinical responses of P. falciparum malaria to chloroquine therapy. Baseline (D0) average body temperature of enrolled subjects was 37.6°C. The highest mean value (38.2°C) was recorded at Hadejia, while Baissa had the lowest (37.0°C)(Table V). Generally, body temperatures declined to an

overall average of 36.7°C on D1, and further to 36.5°C on D2, where the values remained up to D14. Like the average body temperatures, fever rate was highest at Hadejia (66.7%) and lowest at Baissa (20%) prior to administration of chloroquine (Table VI). There was re-appearance of fever by D7 in some subjects at Baissa (4.7%) and Tafawa Balewa (9.1%). In these patients, fever had previously disappeared by D2.

Incidence of vomiting on D0 was highest in children at Hadejia (38.9%) and lowest at Baissa (20.1%). Vomiting rates declined to between 4 and 12% in all subjects at various sites within 24 hours following chloroquine treatment. However, total disappearance of vomiting was only achieved at Hadejia on D2. In all other centres, the proportion of patients vomiting increased marginally on D2 over the D1 rates, before making a further decline and stabilising thereafter.

Like vomiting, diarrhoea responded rapidly to chloroquine therapy. The highest incidence of diarrhoea on D0 occurred at Baissa (34.9%) while the fewest cases were in Tafawa Balewa (18.9%). As was the case with vomiting, only at Hadejia was total clearance of diarrhoea achieved (again on D2 and remained so to D14). In Damboa, the number of those suffering from diarrhoea remained virtually constant after the first 24 hours (i.e. D1) of chloroquine treatment, until D2 when nearly half of the cases were cleared. The responses were better in other sites.

Chloroquine was well tolerated going by the incidence of pruritus. The highest incidence of 13.5% on D1 occurred at Tafawa Balewa, while the lowest rates were in Baissa (3.4%) and Damboa (3.8%). The pattern of response was different for each study centre. Thus, there was no uniformity in chloroquine tolerance among subjects at different study sites.

Responses of P. falciparum malaria to combination drugs. SD-Pyr demonstrated high parasitological and clinical efficacy against *P. falciparum* malaria in the area. About 88% reduction of GMPD occurred within 24 hours, from 13,989 ap/µl on D0 to 1,721 on D1, following ingestion of this drug. A reduction of 98% in parasite density was achieved by D2 (GMPD = 245), and of 99% by D3 (104 ap/µl.). Parasites were completely cleared from peripheral circulation by D7 and remained so to D14. Thus, *P. falciparum* in the north east was fully sensitive to the combination of sulfadoxine-pyrimethamine. The performance against *P. falciparum* malaria was even better with MSP combination in Damboa (1995), where chloroquine-resistant strains (CRPF) had been confirmed in 1988.

Like SD-Pyr, the combination of pyrimethamine with sulphalene showed good efficacy against the parasites, achieving 88.6%, 97.6% and 98.2% overall reductions of parasite density among the patients by D1, D2 and D7 respectively. However, there was 2.9% parasitological failure. Parasites in this subject multiplied from 133 ap/µl on D7 to 2,389 ap/µl by D14. This increased parasitaemia was effectively treated with SD-Pyr. Thus, a clear case of recrudescence was established with SL-Pyr.

These data on susceptibility of *P. falciparum* to various antimalarial drugs confirmed the presence, as well as increasing prevalence and intensity of chloroquine-resistant *P. falciparum* (CRPF) in the north east. Baissa and Damboa, where Type-RI and asymptomatic Type-RII were found, could have been newly established foci (Bruce-Chwatt, 1986) of chloroquine resistance. In Damboa, CRPF rate had a near 1½-fold increase in less than a decade. On the other hand, parasites at Hadejia and Tafawa Balewa showed only reduced sensitivity, with delayed clearance of parasitaemia following chloroquine therapy. Perhaps, more

importantly, chloroquine was still clinically efficacious against falciparum malaria in the area. These evidences provide sufficient justification for the continued use of this drug in reducing malaria-induced morbidity in the north east. In fact, Trape (1999) noted that, despite high levels of resistance in some areas, chloroquine remained the first line treatment for malaria attack in most African countries.

Table 1. Sites used in the study of antimalarial responses of *Plasmodium falciparum* in north eastern Nigeria during 1988 – 1995.

Study Site	Location	Year of Study	Drug Used
Baissa (Taraba State)	Lat. 7° 12' N Long. 10° 38' E	1988	Chloroquine
Damboa (Borno State)	Lat. 11° 42' N Long. 11° 48' N	1988, 1995	Chloroquine
Tafawa Balewa (Bauchi State)	Lat. 9° 46' N Long. 9° 29' E	1989	Chloroquine, SD-Pyr, SL-Pyr
Hadejia (Jigawa State)	Lat. 12° 27' N Long. 10° 03' E	1990	Chloroquine, SD-Pyr
Maiduguri (Borno State)	Lat. 11° 40' N Long. 13° 05' E	1988*, 1991	Chloroquine
Kumo (Gombe State)	Lat. 9° 58' N Long. 11° 20' E	1989*	Chloroquine
Dadin Kowa (Gombe State)	Lat. 10° 17' N Long. 11° 50' E	1989*	Chloroquine

SD-Pyr = Sulfadoxine/pyrimethamine; SL-Pyr = Sulfalene/pyrimethamine; * = Incomplete study

Table 2: Malaria infection rates at various sites in north eastern Nigeria.

Study site	Year/Period	No. screened	No. positive for *Plasmodium*	Percent infection
Baissa	1988 (March)	769	363	47.2
Dadin Kowa	1989 (May)	290	114	39.3
Damboa	1988 (Nov/Dec)	619	433	70.0
	1995 (Sept.)	1,451	960	66.2
	1995 (Dec.)	846	642	75.9
Hadejia	1990 (Sept.)	740	499	67.4
Kumo	1989 (May)	257	48	18.7
Maiduguri	1987 (Nov.)	165	41	24.8
	1991 (April/June)	104	60	57.7
	1991 (Aug/Sept)	105	54	51.4
Tafawa Balewa	1989 (May/June)	343	126	36.7
	1989 (Sept/Oct.)	700	445	63.6
TOTAL		6,285	3,725	59.3

Table 3: *Plasmodium falciparum* parasitaemia and frequency of febrility in North-Eastern Nigeria.

Parasite density (per μl)	No. of cases	No. febrile	Percent febrile
0*	691	-	-
Less than 1,000*	1,340	79	5.9
1,000 – 4,999	160	38	23.8
5,000 – 9,999	82	29	35.4
10,000 – 24,999	83	44	53.0
25,000 – 49,999	40	29	72.5
50,000 – 99,999	26	10	62.5
100,000 – Above	24	20	83.3
TOTAL	1,745	249	14.3

Total excludes numbers of cases without detectable parasitaemia; * Data generated only from Damboa, Borno State.

Table 4: Parasitological failures of chloroquine against *Plasmodium falciparum* infections.

Study site	Year	No. cases enrolled	Parasitological failure rate (%)		
			D2	D7	D14
Baissa	1988	54	6.7	20.9	9.3
Damboa	1988	35	0.0	18.7	6.1
	1995	110	6.8	24.5	ND
Maiduguri	1991 Apr/June	33	14.6	25.5	ND
	1992 Aug/Sept	34	11.8	11.8	0.0
Tafawa Balewa	1989	41	0.0	5.4	0.0
Hadejia	1990	42	0.0	25.0	0.0
TOTAL		349	8.6	20.1	4.1

ND - Not determined

Table 5: Changes in mean body temperatures of *falciparum* malaria patients following chloroquine therapy.

Study site	D0 (°C)	D1 (°C)	D2 (°C)	D7 (°C)	D14 (°C)
Baissa	37.0	36.8	36.8	36.5	36.4
Damboa (1988)	37.2	36.5	36.2	36.3	36.2
Damboa (1985)	38.1	36.8	36.5	36.5	-
Tafawa Balewa	37.4	36.5	36.4	36.6	36.7
Hadejia	38.2	36.9	36.5	36.4	36.4
Maiduguri	37.8	36.8	36.5	36.4	36.7
Overall Average	37.6	36.7	36.5	36.5	36.5

Table 6: Frequency of fever in *Plasmodium falciparum* malaria patients treated with chloroquine in the north east of Nigeria.

Study site	D0 (%)	D1 (%)	D2 (%)	D7 (%)	D14 (%)
Baissa	20.0	12.2	0.0	4.7	2.3*
Damboa (1988)	32.4	9.1	0.0	0.0	0.0
Damboa (1985)	49.1	16.7	5.7	5.9	0.0
Tafawa Balewa	28.8	0.0	0.0	9.1	0.0
Hadejia	66.7	14.6	3.6	0.0	0.0
Maiduguri	58.8	23.5	2.9	2.9	0.0
Overall Average	42.7	12.7	2.0	3.8	**

* No detectable parasites. ** Uncertain due to incomplete follow-up.

Chloroquine resistance has been associated with increased morbidity and mortality in malaria endemic areas of the tropics and sub-tropics (Bloland, 2001; Trape, 1999). Therefore, the emergence, spread and intensification of *P. falciparum* resistance to this drug necessitate the identification of effective alternatives (second line drugs) as well as the development of new products with novel properties (Olliaro and Trigg, 1995). In this regard, it is significant that the combinations of SD-Pyr or SL-Pyr demonstrated high efficacy against the strains of *P. falciparum* in this part of Nigeria. The single case of early recrudescence (Type-RI resistance) recorded with SL-Pyr in Tafawa Balewa could be attributable to malabsorption of the drug or other metabolic factors in the patient, or to actual resistance features in the parasite. The methodology adopted in this study excluded vomiting and under-dosing as possible factors for this observation, but did not include confirmation of plasma concentration of the drug.

Although, the levels of susceptibility of *P. falciparum* to chloroquine and other antimalarial drugs were investigated in this first phase of antimalarial therapeutic efficacy

studies, the actual duration of clinical respite following treatment was not quantified. Besides, only in Damboa was the performance of chloroquine re-evaluated after some time interval (7 years) to determine the trend of therapeutic response. Furthermore, haematological responses following treatment with these antimalarial drugs were not carefully evaluated during this phase of the studies. These issues are of crucial importance in formulating antimalarial drug policy (Howard and Kuile, 1994; Bloland *et al.*, 1993) and are addressed in the second phase of our studies.

Self-diagnosis and self-medication were found to occur at considerable proportions (Molta *et al.*, 1995) at various sites: Dadin Kowa (7%), Kumo (47%), Hadejia (38%), Maiduguri (48%) and Tafawa Balewa (23%). A much higher rate (54%) has been reported from Calabar (Ezedinachi and Ejezie, 1990). These figures might well be under-estimates of the true magnitude and may be related to the availability of the drugs as well as the awareness of the signs and symptoms of the disease. Thus, significant proportions of members of various communities treat themselves of malaria without consulting the designated public health facilities. This emphasizes the need for proper health education on correct treatment regimens, implications of non-compliance with correct dosage regimens, and prompt treatment using effective drugs. The new roll-back-malaria (RBM) initiative stresses the need for prompt and effective treatment of malaria in curtailing morbidity and mortality attributable to this disease (Nabarro, 1999). The initiative has resolved that at least 60% of those suffering from malaria should have prompt access to and be able to use correct and affordable treatment within 24 hours of the onset of symptoms. This may involve home treatment of the disease (Nabarro, 1999).

Standardization of procedure and a clear definition of criteria for evaluating therapy outcome are essential in drug efficacy and tolerability studies. Protocols that run for 14 days (Khoromana *et al.*, 1986; Daniel and Molta, 1989) and beyond (WHO, 1973) have the inherent difficulty of distinguishing between re-infection that happens very commonly in endemic areas, and the initial inoculum of parasites. This problem is compounded in the African setting, especially in field situations, by lack of facilities for genetic fingerprinting. Moreover, patients' compliance with follow-up requirements diminishes with time following the start of treatment, especially when clinical relief has been achieved. On the other hand, protocols of short duration e.g. 7 days, are unable to differentiate between reduced sensitivity (as observed in Hadejia and Tafawa Balewa) and recrudescence or late treatment failure. Therefore, a balanced protocol is needed for ascertaining the true therapeutic status of any antimalarial drug.

Other unresolved issues relating to antimalarial efficacy studies include: (i) The haematological changes associated with antimalarial drug treatment. (ii) The exact role of immunity in drug performance against parasites. (iii) The level of resistance at which changing from one antimalarial drug to another will be required. Howard and Kuile (1994) and Bloland *et al.* (1993) recommend that the use of a drug be discontinued in any area where RII/RIII resistance to it exceeds 25%. However, heterogeneity in responses of parasites, even within a single zone like the north east of Nigeria, to any given antimalarial drug complicates the formulation and implementation of the relevant policy. iv. Whether the withdrawal of a drug, against which parasites have developed high-grade resistance, from an area could restore susceptibility to the drug. v. Possible methods of enhancing *P. falciparum* susceptibility to chloroquine using compounds that inhibit the

resistance mechanisms. vi. Also, the possibility of developing antimalarial products of African origin as a step towards self-reliance and for the purpose of affordability is a matter of priority.

Acknowledgements

Funds, materials and other forms of support for this work were provided by the NMVCD/FMOH, Lagos and the ACSI-CCCD, Nigeria. Special gratitude to: Dr. O.J. Ekanem (formerly, Chief Consultant Malariologist of Nigeria), Dr. J. Weisfeld (formerly of the CCCD, Nigeria), all Colleagues (Drs. H.I. Daniel and T.I. Otu; Professor N.M. Gadzama, J.O. Ameh, A.A. Abah, J.T. Waba and Z. Tukur) on the National Malaria Therapy Efficacy Surveillance Network (NMTSN), the managements of the Ministry of Health in various states of the north east; and the University of Maiduguri/University of Maiduguri Teaching Hospital. The tremendous help rendered by the different Executive Councils of Akko, Damboa, Hadejia and Tafawa Balewa LGAs is highly appreciated.

References

Alonso P.L., Smith T.A., Armstrong-Shellenberg J.R.K., Kitua A.Y., Masanja H., Hayes R., Hurt N., Font F., Menendez C., Kilama W.L., and Tanner M. (1996); Duration of protection and age-dependence of the effects of the SPf66 malaria vaccine in African children exposed to intense transmission of *Plasmodium falciparum*. *J. Inf. Dis.*, 174: 367-372.

Alonso P.L., Smith T.A., Armstrong-Shellenberg J.R.K., Masanja H., Mwankusye H., Urassa H., Bastos de Azevedo I., Chongela J., Kobero S., Menendez C., Hurt N., Thomas M.C., Lyimo E., Weiss N.A., Hayes R., Kitua A.Y., Lopez M.C., Kilama W.L., Tuescher T., and Tanner M. (1994); Randomized trial of efficacy of SPf66 vaccine against *Plasmodium falciparum* malaria in children in southern Tanzania. *Lancet*, 344: 1175-1181.

Bloland P.B. (2001); Drug resistance in malaria. World Health Organization, Geneva. WHO/ CDS/ CSR/ DRS/ 2001.4; 27pp .

Bloland P.B., Lakritz E.M., Kazembe P.N., Were J.B.O., Steketee R., and Campbell C.C., (1993); Beyond chloroquine: implications of drug resistance for evaluating malaria therapy efficacy and treatment policy in Africa. *J. Inf. Dis.*, 167: 932-937.

Breman J.G. and Campbell C.C. (1989); Combating severe malaria in African children. *Bull. World Health Organization*, 66: 611-620.

Breman J.G., Gayibor A., Roberts J.M., Sexton J,D., Agbo K., Miller K.D., Karsa T., and Murphy K. (1987); Single dose chloroquine therapy for *Plasmodium falciparum* in children in Togo, West Africa. Am. J. Trop. Med. Hyg., 36(3): 469-473.

Bruce-Chwatt L.J. ed. (1986); *Chemotherapy of malaria*. WHO Monograph Series No. 27; Geneva.

Collins F.H. (1994); Prospects for malaria control through the genetic manipulation of its vectors. *Parasitology Today*, 10(10): 370-371.

Collins F.H. and James A.A. (1996); Genetic modification of mosquitoes. *Science and Medicine*, 3(6): 52-62.

Curtis C.F. (1994); The case for malaria control through control by genetic manipulation of its vectors. *Parasitology Today*, 10(10): 371-374.

Curtis C.F. (1996); Detection and management of pyrethroid resistance in relation to the use of impregnated bednets against malaria vectors. *2nd Intern. Cong. Insect Pests in the Urban Environment*, Edingburgh; pp.281-384.

Daniel H.I. and Molta N.B. (1989); Efficacy of chloroquine in the treatment of malaria in children under five years in Baissa (Gongola State, Nigeria). *Ann. Trop. Med. Parasitol.*, 83: 331-338.

D'Alessandro U., Leach A., Drakeley C., Bennet S., Olaleye B.O., Fegan G.W., Jawara M., Langerok P., George M.O., Targett G.A., and Greenwood B.M.,. (1995); Efficacy trial of malaria vaccine SPf66 in Gambian infants. *The Lancet*, 346: 462-467.

Dixon W.J. and Massey Jr. F.J. (1957); *Introduction to Statistical Analysis*, 2nd Edition. McGraw-Hill, New York, pp.304-317.

Ezedinachi E.N.U. and Ejezie G.C. (1990); Current concepts on the prevention and treatment of malaria in West Africa. *Postgraduate Doctor Africa*, 12(2): 26-32.

FMOH/CCCD (1987a); Protocol for evaluation of drug therapy for *Plasmodium falciparum* infection. Misc. Publ. Nig. Fed. Min. Hlth., Lagos, Nigeria.

FMOH/CCCD (1987b); Protocol for surveillance of drug therapy for *Plasmodium falciparum*. Misc. Publ. Nig. Fed. Min. Hlth., Lagos, Nigeria.

Greenwood B.M. (1997); What can be expected from malaria vaccine? *Ann. Trop. Med. Parasitol.* 91(1): S9-S13.

Howard P.P. and Kuile F.T. (1994); Childhood malaria in Africa. *Africa Health*, 16(2): 10-12.

Khoromana C.O., Campbell C.C., Winima J.J. and Heymann D.L. (1986); *In vivo* efficacy of chloroquine treatment for *Plasmodium falciparum* in Malawian children under five years of age. *Am. J. Trop. Med. Hyg.*, 35: 465-471.

Kidwell M.G. and Ribeiro J.M.C. (1992); Can transposable elements be used to drive disease refractoriness genes into vector populations? *Parasitology Today*, 8(10): 325-329.

Leach A., Drakeley C.J., D'Alessandro U., Fegan W., Bennet S., Ripley Ballou W., Targett A.T., and Greenwood B.M. (1995); A pilot safety and immunogenicity study of the malaria vaccine SPf66 in Gambian infants Parasite *Immunology*, 17: 441-444.

Lelijveld J. and Kortmann H. (1970); The eosin colour test of Dill and Glazko: a simple test to detect chloroquine in urine. *Bull. Wld Hlth Organ.*, 42: 477-479.

Molta N.B., Watila I.M., Gadzama N.M., Muhammad K.K., Ameh J.O. and Daniel H.I. (1991); Chloroquine therapy of *Plasmodium falciparum* in Damboa, Borno State. *Annals of Borno*, 8/9: 224-214.

Molta N.B., Daniel H.I., Watila I.M., Oguche S.O., Otu, T.I., Ameh J.O. and Gadzama N.M. (1992); Efficacies of chloroquine, pyrimethamine/ sulphadoxine and pyri-methamine/sulphalene against *P. falciparum* in north eastern Nigeria. *J. Trop. Med. Hyg.*, 95: 253-259.

Molta N.B., Daniel H.I., Oguche S.O., Watila I.M. and Otu T.I. (1993); Malaria treatment failures in north eastern Nigeria. *Nig. J. Parasitol.*, 14: 21-26.

Molta N.B., Watila I.M. and Gadzama N.M. (1995); Malaria-related hospital attendance, admissions and deaths in five selected surveillance centres in north eastern Nigeria. *Res. J. Sc.*, 1(1): 102-110.

Nabarro D. (1999); Introducing the global partnership to roll back malaria. *Proc. MIM Afr. Mal. Conf.*, March 14-19, Durban, South Africa. pp.27-33.

NPC (1991); Nigerian National Population Census: Preliminary Statistics.

Olliaro P.L. and Trigg P.I. (1995); Status of antimalarial drugs under development. *WHO Bull. OMS.*, 73: 565-571.

Rogier C., Commenges D. and Trape J.F. (1996); Evidence for an age-dependent pyrogenic threshold of *Plasmodium falciparum* parasitaemia in highly endemic populations. *Am. J. Trop. Med. Hyg.* 54(6): 613-619.

Salako L.A. (2002); National Malaria Day – "Malaria awareness walk, 2002". *J. Mal. Afr. Trop.*, 1(1): 6-7.

Smith T., Shellenberg J.A. and Hayes R. (1994); Attributable fraction estimates and case definition for malaria in endemic areas. *Stat. Med.*, 13: 2345-2358.

Smith T., Hurt N., Teuscher T. and Tanner M. (1995); Is fever a good sign for clinical malaria in surveys of endemic communities? *Am. J. Trop. Med. Hyg.*, 52(4): 306-310.

Sowunmi A., Oduola A.M.J., Ilesanmi A.O. and Salako L.A. (1996); Open comparison of artemether and mefloquine in uncomplicated *Plasmodium falciparum* hyperparasitaemia in children. *Ann. Trop. Paed.*, 16: 5-9.

Trape J.F. (1999); Impact of drug resistance on morbidity and mortality in malaria infections in Africa. *Proc. MIM Afr. Mal. Conf.*, Durban, South Africa; pp36-42.

Trape J.F. and Rogier C. (1996); Combating malaria morbidity and mortality by reducing transmission. *Parasitology Today*, 12(6): 236-240.

WHO (1973); *Chemotherapy of malaria and resistance to antimalarials*. WHO Technical Report Series No. 529, Geneva.

WHO (1993); World malaria situation in 1991. *Weekly Epidemiol. Rec.*, 68: 245-252.

Zeng L., Cornel A.J., Wang R. (1997); Quantitative trait loci for refractoriness of *Anopheles gambiae* to *Plasmodium cynomolgi* B. *Science*, 276: 425-428.