FIGHTING A MOVING TARGET: MALARIA *THE PAINS AND THE GAINS*

AN INAUGURAL LECTURE,
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UNIVERSITY OF IBADAN

FIGHTING A MOVING TARGET: MALARIA
THE PAINS AND THE GAINS

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By

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The Vice-Chancellor, Deputy Vice-Chancellor (Administration), Deputy Vice-Chancellor (Academic), The Registrar and other Principal Officers, Provost of the College of Medicine, Dean of the Faculty of Basic Medical Sciences, Deans of other Faculties and Postgraduate School, Dean of Students, Distinguished Ladies and Gentlemen.

As I stand here before you all today to deliver this inaugural lecture on behalf of the Faculty of Basic Medical Sciences, College of Medicine, I feel highly humbled and filled with awe of God for His divine love, grace, faithfulness and goodness. He has continued to surprise me at every turn in my life right from my childhood up to this point. He indeed makes things beautiful in His time.

It is indeed an honour and a privilege to deliver the third inaugural lecture from the Department of Pharmacology & Therapeutics, the first having been delivered by my dear teacher, Prof. D.T. Okpako in 1988 and the second by Prof. Akintunde Sowunmi my immediate predecessor as Head of Department of Pharmacology & Therapeutics in 2008. Professor Okpako's lecture was titled "Good Drugs do not grow on Trees or do they?" while Prof. Sowunmi's Lecture was titled "In Pursuit of the Deadly Foe (malaria parasite)". The title of my lecture today is "Fighting a moving Target; Malaria - the Pains and the Gains".

The title of my lecture was inspired by the permanently changing epidemiological scenario of this parasitic infection, the uncanny ability of the causative organism to undergo mutation in a survival bid and the nature/direction of what God has in His kindness enabled me to research into as my contributions to the fight against this deadly parasite. Indeed there have been many triumphs (the gains) and disappointments (the pains) in the fight to control and possibly eradicate this infection.

Preamble

Pharmacology is derived from Greek words (Greek φάρμακον, *pharmakon*, "poison" in classic Greek; "drug" in modern Greek; and -λογία, *-logia*_"study of"/"knowledge of") – (study of drugs). Pharmacology is thus the branch of medicine and biology concerned with the study of drug action. A drug can be broadly defined as any man-made, natural, or endogenous (within the body) molecule which exerts a biochemical and/or physiological effect on the cell, tissue, organ, or organism. More specifically, it is the study of the interactions that occur between a living organism and chemicals that affect normal or abnormal biochemical function. The divisions within the discipline include Clinical Pharmacology, Neuropharmacology, Psychopharmacology, Pharmacogenetics, Pharmacogenomics, Pharmaco-epidemiology, Toxicology, Theoretical Pharmacology, Behavioral Pharmacology and Environmental Pharmacology, among others. Pharmacologists are also involved in molecular modelling of drugs, and the use of drugs as tools to dissect aspects of cell function.

I will now zone into defining the sub-specialization of Clinical Pharmacology. Clinical pharmacology is the science of drugs and their clinical uses. It is underpinned by the basic science of pharmacology, with added focus on the application of pharmacological principles and methods in the real world. It has a broad scope, from the discovery of new target molecules, to the effects of drug usage in whole populations. Clinical pharmacology connects the gap between medical practice and laboratory science. The main objective is to promote the safety of prescription, maximize the drug effects and minimize the side effects. Clinical pharmacologists usually have a rigorous medical and scientific training which enables them to evaluate evidence and produce new data through well designed studies. Clinical pharmacologists must have access to enough outpatients for clinical care, teaching, education and research.

The intellectual content of the discipline of clinical pharmacology ranges from basic principles of pharmaco-kinetics and pharmacodynamics to the design and execution of clinical drug trials. The specialized knowledge that results from clinical pharmacology studies should be applied to the everyday evaluation and treatment of patients with clinical problems related to all aspects of drug therapy.

Mr. Vice-Chancellor Sir, distinguished ladies and gentlemen, I will be presenting to you today some of my research endeavours primarily in the field of malaria chemotherapy which includes its diagnosis, drug treatment and management. My academic career has also taken me through other areas such as global health, biomedical ethics, therapeutic drug monitoring of seizure disorders and treatment of hypertension, amongst others. Why malaria? My interest is multipronged—personal, community and global.

Introduction

Malaria is undoubtedly an ancient disease. A disease resembling malaria has been noted for more than 4,000 years dating back to 2700 BC in China where ancient writings refer to symptoms now commonly associated with malaria. Few diseases in history have been as widely spread, poorly understood, and long fought as malaria. The name itself evokes centuries of misunderstanding—a misnomer that comes from an old Italian construction *"mala aria"* that means *"bad air"* demonstrating the misunderstanding of malaria transmission. People once thought it was caused by swamp gasses, since it seemed to be prevalent in wet, marshy places. One of the early gains over malaria was in the 20th century when it was discovered that mosquitoes are the primary vectors of malaria transmission to humans (fig. 1).

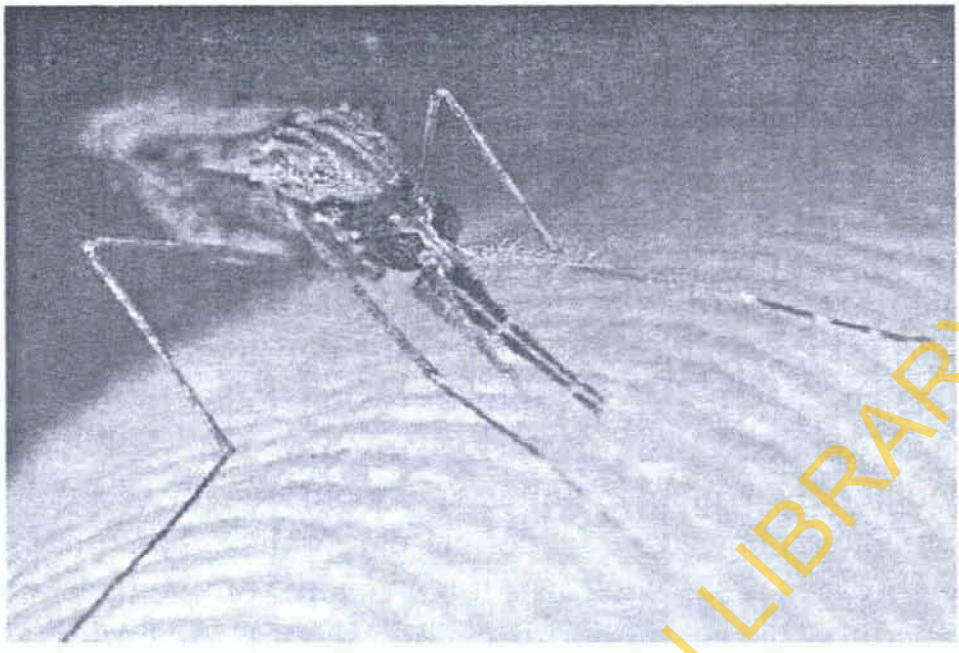


Fig. 1: Mosquito having a blood meal

Malaria has shaped history in peace and war. It has also played major roles in religion. Until the 20th century, malaria was a major cause of disability and death not only in tropical Africa, but also in South East Asia, China, Europe and the Americas (fig. 2). Malaria was eliminated from the United States of America only in 1951! In 1955, the WHO began a malaria eradication effort. It was focused on house spraying with residual insecticides, antimalarial drug treatment, and surveillance. There was substantial gain from this effort. Malaria was successfully eliminated in temperate regions and areas with seasonal transmission. Some countries such as India and Sri Lanka had sharp reductions in the number of cases, followed by increases to substantial levels after efforts ceased. The pains were more in some areas. Other nations had negligible progress (such as Indonesia, Afghanistan, Haiti, and Nicaragua). Most of sub-Saharan Africa was excluded from the eradication campaign.

The emergence of drug resistance in the parasite, widespread resistance to available insecticides, wars and massive population movements, difficulties in obtaining sustained funding from donor countries, and lack of community participation made the long-term maintenance of

the 1955 eradication effort unachievable. Completion of the eradication campaign was eventually abandoned—a major pain. Until recently, the goal of most national malaria prevention and control programmes and most malaria activities conducted in endemic countries is to reduce the number of malaria-related cases and deaths. To reduce malaria transmission to a level where it is no longer a public health problem has been the goal of what is called malaria control. Recent increases in resources, political will and commitment have led again to discussion of the possibility of malaria elimination and, ultimately, eradication.

Fig. 2: Distribution of malaria around the world (2013)

Source: WHO 2012

The Burden of Malaria

The burden of malaria is enormous. About 3.3 billion people are at risk of malaria world-wide and about 216 million cases occur annually. 81% of these cases occur in Africa with about 655,000 deaths in one year (WHO 2011). 91% of malaria deaths occur in the African subregion and 86% of the victims are children <5years. Six countries—Nigeria, DRC, Burkina Faso, Mozambique, Cote d'Ivoire and Mali, account for 60%,

or 390,000, of malaria deaths. Malaria accounts for 1 in 4 deaths in Africa (World Malaria Report 2011).

Sequelae from severe malaria include cognitive impairment, behavioural disturbances, spasticity, epilepsy as well as visual, hearing, and speech impairments. Apart from illness (morbidity) and death (mortality), malaria imposes a heavy economic, emotional, developmental and technological burden on the citizens and nations of endemic regions.

Some Recent Gains: (World Malaria Report 2013)

Between 2000 and 2012, malaria mortality rates decreased by 45% across all age groups and by 51% in under-five year old children. Global malaria incidence also fell by 29%. This translates to an estimated 3.3 million deaths averted between 2001 and 2012. These improvements are attributed to human interventions, including greater use of insecticide treated bed nets, indoor residual spraying, rapid diagnostic tests, and artemisinin-based combination therapies.

Pathogenesis of Malaria

Malaria is caused by infection of parasites of the genus *Plasmodium,* which are obligate intracellular protozoa. Only five of over 300 species of *Plasmodia* known to date are pathogenic to man. These are the original well known four: *Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale* and *Plasmodium vivax*. It is now well established that the monkey malaria *Plasmodium knowlesi* not only infects man but also causes severe disease (William et al. 2011). Reports of *P. knowlesi* infections have been from the forested regions of South-East Asia.

Mosquitoes of the genus *Anopheles* transmit the infection to man. *Anopheles* mosquitoes breed in warm humid climate in relatively clean pools of water such as marshes, puddles and irrigation water. In rural areas in the wet tropics, *Anopheles* can breed in any water filled foot- and hoof-prints as well as plant stems making larval control in the tropical rain forest an uphill task. Only female mosquitoes bite and the protein in the blood meal is used to produce a batch of eggs.

In the mosquito, there are four larval stages and a short pupal stage before emergence of the adult. In the warm tropical climate, the whole process from egg to adult takes a little more than one week but longer at lower temperatures. We must also keep in mind that mosquitoes do not require visas and customs clearance for international travel. Anopheles mosquitoes regularly stow away on airplanes taking off from malaria endemic areas and have become well known agents of transmission of airport malaria especially during the summer months when they bite innocent citizens of temperate climates whose only offense is living very near international airports. Other modes of transmission include through transfusion of infected blood and transplantation of infected organs. Occasionally, malaria is transmitted through the placenta to the unborn baby and by accidental inoculation in the laboratory during parasite culture procedures or through needles when main-line addicts share needles.

When an individual has been inoculated with plasmodium parasites, a variety of clinical effects may follow:

Infection → asymptomatic parasitemia → acute uncomplicated illness → severe malaria → death

Many factors influence the disease manifestations of the infection and the likelihood of progression to the last two categories. These factors include the species of the infecting parasite, the level of innate and acquired immunity of the host, and the timing and efficacy of treatment, if any.

The Life Cycle of the Malaria Parasites

The life cycle of the malaria parasite is summarized briefly in figure 3—the life cycles of the species are very similar (fig. 3).

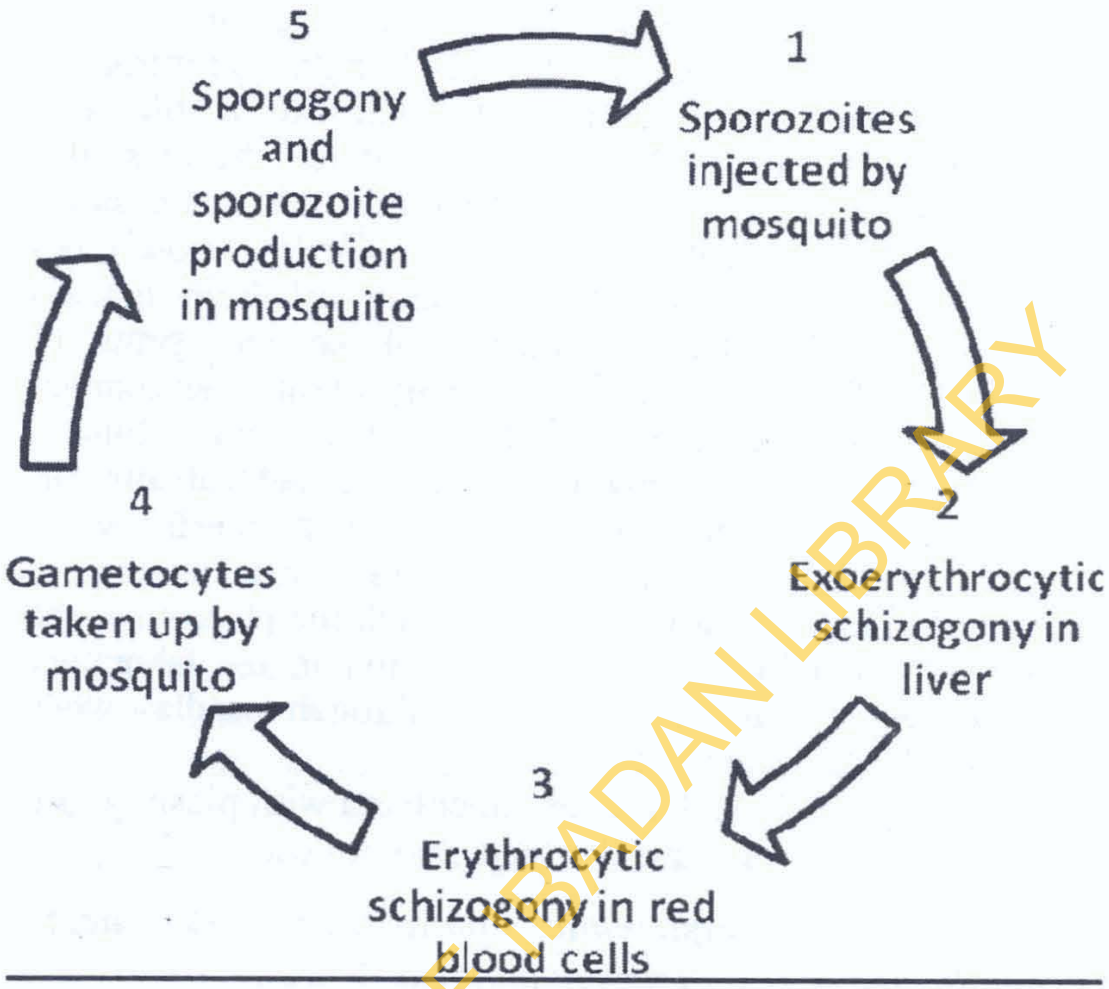


Fig. 3: Schematic life cycle of Plasmodium spp. (After Cox Parasites & Vectors 2010)

Infection begins when

(1) Sporozoites, the infective stages, are injected by a mosquito and are carried around the body until they invade liver hepatocytes.

(2) In the liver, the sporozoites undergo a phase of asexual multiplication (exoerythrocytic schizogony) resulting in the production of many uninucleate merozoites. These merozoites flood out into the blood and invade red blood cells.

(3) In the red blood cells, they initiate a second phase of asexual multiplication (erythrocytic schizogony) resulting in the production of about 8-16 merozoites which invade new red blood cells. This process is repeated almost indefinitely and is responsible for the

disease, malaria. As the infection progresses, some young merozoites develop into male and female gametocytes that circulate in the peripheral blood.

(4) The gametocytes are then taken up by a female anopheline mosquito when it feeds.

(5) Within the mosquito, the gametocytes mature into male and female gametes. Fertilization occurs and a motile zygote (ookinete) is formed within the lumen of the mosquito gut, the beginning of a process known as sporogony. The ookinete penetrates the gut wall and becomes a conspicuous oocyst within which another phase of multiplication occurs resulting in the formation of sporozoites that migrate to the salivary glands of a mosquito and are injected when the mosquito feeds on a new host.

Malaria Control

Malaria is an entirely preventable and treatable disease, provided the currently recommended interventions are properly implemented. These interventions include;

(1) Vector control through the use of insecticide treated nets (ITNs), indoor residual spraying (IRS) and, in some specific settings, larval control;

(2) Chemoprevention for the most vulnerable populations, particularly pregnant women and infants in the form of intermittent preventive treatment (IPT);

(3) Confirmation of malaria diagnosis through microscopy or rapid diagnostic tests (RDTs) for every suspected case; and

(4) Timely treatment with appropriate antimalarial medicines (according to the parasite species and any documented drug resistance).

Clinical and Laboratory Diagnosis of Malaria

Accurate and prompt diagnosis is pivotal to effective disease management. A very high index of suspicion is needed to consider malaria as a possible diagnosis in symptomatic

patients. The first symptoms of malaria are nonspecific and similar to those of other febrile illnesses such as acute respiratory tract infections, pneumonia, meningitis, viral hepatitis and many other viral illnesses such as measles (prodromal phase), viral hemorrhagic fevers (Chikungunya, West Nile, Marburg and even the dreaded Ebola). The story of Mr. Sawyer, the Liberian-American is still fresh in our minds. He was first treated as a case of malaria. Simple fatigue or exhaustion could be misdiagnosed as malaria especially in semi-immune adults in whom malaria is infrequent. The confirmation of the diagnosis of malaria can only be done by laboratory identification of the parasite or its product. This is because contrary to general belief, malaria has no clinical signs and symptoms that are diagnostic of it. I am sure that many people in this august audience will find this odd if not actually disagreeable. However, that is the true situation of things. Clinical presentation in each case depends on a complex interplay of several factors which include the age of the patient, parasite density, level of natural or acquired immunity, previous exposure to malaria and other clinical conditions peculiar to the individual patient (White 1997; Wensedorfer and Payne 1991).

Plasmodium, the causative agent for malaria is an obligatorily intracellular unicellular organism—either in the red cell (erythrocyte) or in the liver cell (hepatocyte), depending on the phase of its cycle in man. *P. falciparum* malaria infected erythrocytes also sequester in the micro-capillaries of vital organs, interfering with microcirculatory flow and host tissue metabolism. The pathophysiology of malaria results from three main sources: destruction of erythrocytes, liberation of parasite and erythrocyte materials into the circulation, and reaction of the host to these events. These parasite products, like endotoxin, induce activation of the cytokine cascade.

Cells of the macrophage-monocytes series and possibly the endothelium are stimulated to release cytokines, TNF, IL-1 and later other pro-inflammatory cytokines such as IL-6 then IL-8. Since blood circulates to all organs in the body, it is not difficult to understand that malaria is a multi-organ disease and so it can present in a myriad of ways. Indeed

malaria can be called the great mimicry! A case of malaria presenting as myocardial infarction has been reported (Sulaiman, Ismail, et al. 2014).Time of starting treatment and facilities available for management are crucial in determination of prognosis.

By convention, clinical malaria is classified into two types (WHO 1990):

(1) Acute uncomplicated malaria (mild disease) – the sort that you all encounter every day.
(2) Severe and complicated malaria.

It is important to distinguish these two types of presentation for appropriate management. Cases of severe malaria constitute the subset of patients (mainly children) (fig. 4) who run the risk of dying within a short time interval. Mortality from severe malaria is estimated between 10 and 40% in excellent centers. Untreated, death is inevitable in patients with severe malaria.

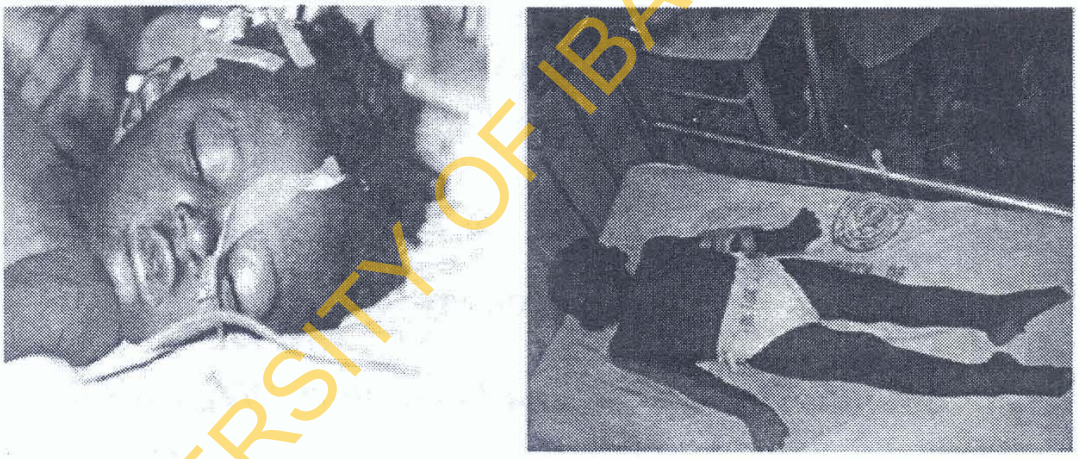


Fig. 4: Children suffering from severe malaria

Prompt access to accurate diagnosis of malaria following onset of symptoms is central to effective and rational treatment. In a major paradigm shift from conventional presumptive treatment, the WHO now recommends prompt parasitological confirmation of ***all suspected cases*** of malaria before treatment (WHO 2010). ***The era of treatment without making a diagnosis has passed and such practices should be regarded as unethical.***

My Contribution to Malariology

Mr. Vice-Chancellor Sir, the main trust of my research efforts is malaria in children and pregnant women, the sub-segments of the population of malaria endemic areas that take the brunt of the infection. I have also researched into the interphase of HIV and malaria. My research into malaria is a holistic one which covers many areas of the field of study in an effort to contribute in some meaningful way to the control of this parasitic infection. This I have done in collaboration with many other researchers locally and internationally and also in active collaboration with the Malaria Control Units of both the State and Federal Ministries of Health in Nigeria. As a result, many of our research findings have been incorporated into policy for the benefit of citizens in malaria endemic areas in general and Nigeria in particular. My research focus can be broadly summarized into five subgroups.

(1) Clinical and laboratory diagnosis of malaria;
(2) Chemotherapy of malaria;
(3) Malaria during pregnancy;
(4) Community perception and management of malaria;
(5) *Preclinical evaluation of antimalarial compounds in* animal model.

I will now proceed to elaborate on my research efforts.

My Contribution to Clinical and Laboratory Diagnosis of Malaria

Malaria presenting as Psychosis

- We reported a case of malaria presenting as psychosis in a 15-year-old male from a high socio-economic class. He presented with fever, aggressive behaviour, poor sleep and mixed affective and schizophreniform symptoms. Evaluation revealed the presence of *Plasmodium falciparum* in his blood film. The behavioural changes occurred in association with fever and *P. falciparum* parasitemia on two other occasions. The symptoms resolved promptly

following anti-malarial treatment. The child was followed up for two years. Prophylaxis with daily proguanil prevented recurrence of the illness throughout the follow-up period. The patient subsequently went abroad to a malaria free environment to continue his education (Sowunmi, Ohaeri, and Falade 1995).

Gastrointestinal Manifestation of Malaria

Although fever is the hallmark of malaria infection, vomiting, diarrhea and epigastric pain are not uncommon presenting symptoms and signs of malaria in childhood and sometimes precede the onset of fever.

- We reported the gastrointestinal manifestations of acute symptomatic uncomplicated falciparum malaria in 184 consecutive children aged from 6 months to 15 years (Sowunmi, Ogundahunsi, et al. 2000). Vomiting was the most common, and epigastric pain the least common presenting symptom. Peripheral parasite density was higher in children who were vomiting than in those who were not. There was no relationship between the density of peripheral parasitaemia and the duration of gastrointestinal symptoms at presentation. All gastrointestinal symptoms cleared within 3 days after instituting antimalarial therapy

Lack of Specificity of Presumptive Diagnosis of Malaria

- This was aptly demonstrated in a publication by Ajayi, Falade, and Kale (2009). In that report, we demonstrated extremely low specificity (22.2%) of mothers' diagnoses of malaria. The study was conducted in rural southwestern Nigeria between March 2004 and October 2005 in two rural districts of Ona-Ara.

Non-microscopic Diagnosis of Malaria

Mr. Vice-Chancellor Sir, microscopic evaluation of stained blood smears remains the gold standard for laboratory confirmation of malaria. In competent hands, microscopy is a

cheap diagnostic tool which allows for identification of the causative organism, quantification of the parasite load, speciation of parasite type and a rational follow-up of patients to identify treatment failure versus other causes of fever. However, microscopy of malaria parasites is tedious, time consuming, requires electricity to power functional microscopes, good quality reagents and competent technical personnel. Few as the challenges of microscopy may appear to be, they are quite daunting in environments like ours. Electricity is at best erratic, functional microscopes are too few to go round, quality of reagents in the Nigeria market is highly variable and competent technical personnel are few and far between. The limit of detection is also an issue. This makes malaria rapid diagnostic tests (RDT) the most viable option for programmatic deployment especially in resource limited regions. Without doubt, molecular diagnosis of malaria is the most accurate with its very low limit of detection but it requires high technology, expensive equipment and reagents, highly trained manpower and stable electricity supply; all of which make it unsuitable for routine use in developing countries and for field application.

- For my MSc project, I evaluated the *in vitro* activity of *Plasmodium falciparum* specific lactate dehydrogenase (pLDH) in plasma (PS), parasitized red blood cells (PRBC) and culture supernatant samples (CSS). pLDH activity was determined quantitatively and qualitatively using an antibody capture technique with 3-acetyl pyridine adenine dinucleotide (APAD) and OptiMAL® dipstick respectively. The sensitivity and specificity of OptiMAL® strips for detecting pLDH activity in PRBC samples during *in vitro* culture was 100% while the level of false negative result was 6.7% ($\leq$0.048mOD/min). The predictive value of a positive result by OptiMAL®strips is 93.3% (Falade 2001). There was a stage specificity of pLDH production which may have implications on the effect of antimalarial drugs targeting pLDH. This is the basis for

one of the malaria RDTs, and pLDH is being explored as an antimalarial drug target.

- We also evaluated the sensitivity and specificity of two RDTs—Cyscope® mini (fluorescent microscope with rechargeable battery) and Paracheck-*Pf*® (HRP-2 RDT) (fig. 5), using expert microscopy of Giemsa-stained thick blood films as reference. Paracheck-*Pf*® has a high sensitivity (86.21%) and specificity (82%) compared to Cyscope® mini which had a sensitivity of 91.3% but a very low specificity of 16.6%. Paracheck-*Pf*® may be a good diagnostic tool for field studies (Rabiu et al. 2012).

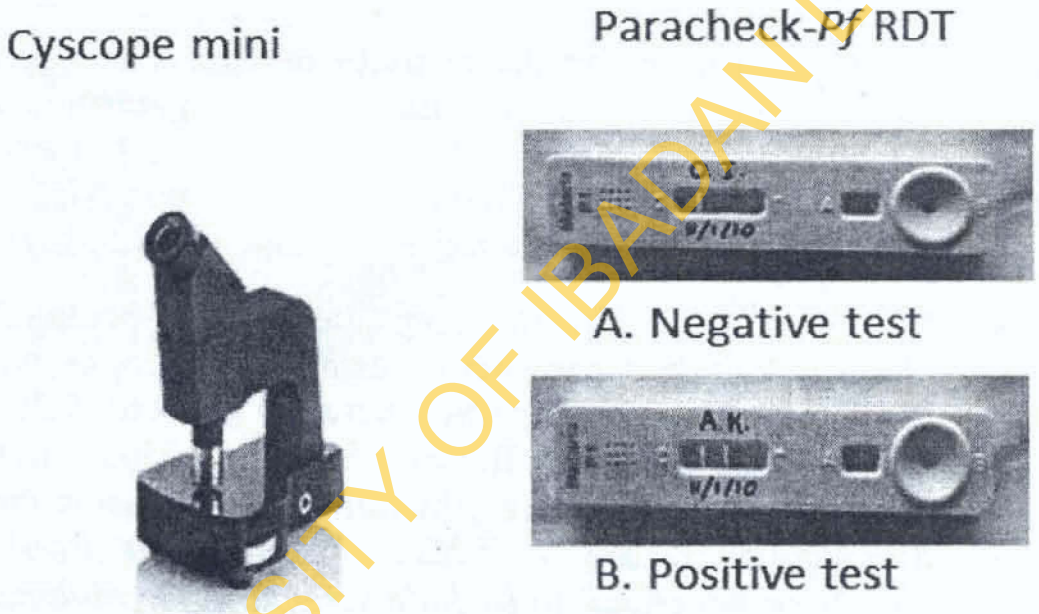


Fig. 5: Two types of rapid diagnostic test – Cyscope mini and Paracheck RDT

Mr. Vice-Chancellor Sir, it is well established that HIV +ve persons are prone to many infections which can be bacterial, mycobacterial, viral, fungal or parasitic. Thus, febrile illnesses occur frequently among HIV +ve patients. These febrile episodes are often treated presumptively as malaria in endemic areas.

- We reported a malaria parasite prevalence rate of only 19.1% by microscopy and RDTamong HIV +ve adults receiving antiretroviral therapy at the PEPFAR supported AIDS Prevention Initiative in Nigeria, UCH, Ibadan.
- We also reported high sensitivity and specificity of Paracheck RDT (90.9% and 90.3% respectively) at parasite densities ≥200/μl, and was thus found to be a useful malaria diagnostic tool facilitating appropriate clinical management among HIV-infected adult patients presenting with a febrile illness (Falade, Adesina, et al. 2013).

The value of parasite based diagnosis of malaria was again brought to the fore in a study evaluating malaria parasitemia among healthy blood donors at the University College Hospital Ibadan. In Nigeria, as in most of sub-Saharan Africa, blood donors are not routinely screened for malarial infection.

- We reported that one of every five (20.2%) potential blood donors had parasitemia using microscopic and RDT methods with densities between 34 and 6,289 asexual parasites/μl (mean 544/μl). This was significantly higher during the rainy season than in the dry season (27.3% v. 5.5%; ρ=0.0001). ***It would clearly be beneficial to include screening for malaria parasitemia in the routine screening of potential blood donors in Nigeria, especially during the rainy season, when the risk of transfusion-transmitted malaria appears relatively high*** (Falade et al. 2009).

Chemotherapy of Malaria

Historical Perspectives

Early malaria treatments were first noted in China with the use of *Artemisia annua* (sweet wormwood; Quinghao plant) which contains the active ingredient artemisinin, which today has become the *'wonder'* anti-malaria drug (fig. 6). Quingahao was first noted in a document found in a tomb

dating from 168 B.C.while the first record of its use for malaria was made by Ge Hon in 341 AD. However this was as a local herbal remedy. The antimalarial qualities of *Artemisia annua* was established only in 1971. Artemisinin, the active ingredient was identified in 1972.

Artemisia annua plant

Structure of artemisinin

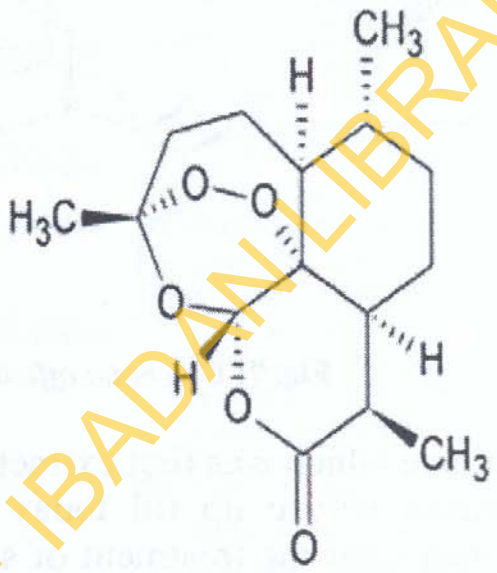
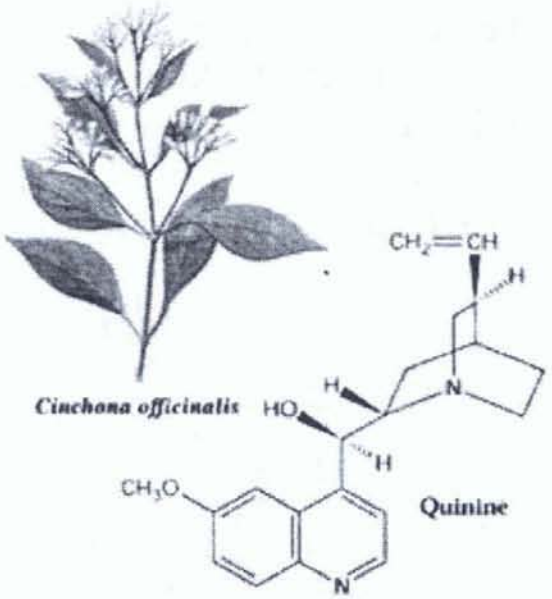


Fig. 6: Sweet wormwood plant and product

However, quinine was the first definitive drug used for malaria chemotherapy. Quinine is one of a number of active extracts from the bark of the Cinchona tree (fig. 7). Cinchona bark was further popularized by the Jesuit priests and it was the primary treatment for malaria throughout the mid-1600s to mid-1800s. The bark, which became known as Jesuit's powders, had a tremendous effect on the Catholic Church in Rome, a city notorious for malaria. For instance, during the conclave of 1623 that elected Pope Urban VIII, eight cardinals and thirty secretaries died of malaria. But once the Jesuits controlled cinchona, not a single cardinal died of malaria at subsequent conclaves (Pearl 1960).

The Cinchona plant



Cinchona tree

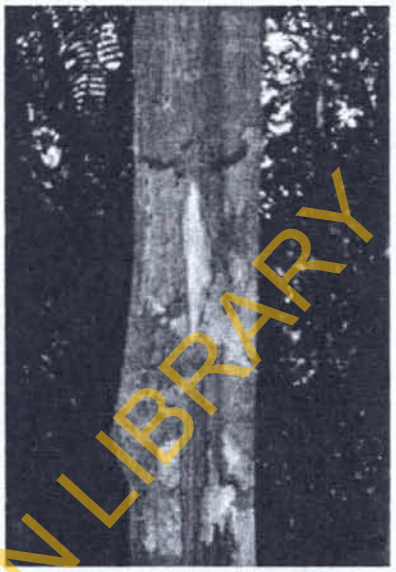


Fig. 7: *Cinchona officinalis* plant and product

Quinine which was first extracted from cinchona bark in 1820 remains in use up till today and was the drug of choice globally, for the treatment of severe malaria until 2011 when it was replaced by injectable artesunate. Quinine remains the recommended drug for the treatment of malaria during the first trimester of pregnancy as well as in special cases of drug resistant malaria when it is used in combination with another efficacious antimalarial drug. It is noteworthy that quinine in clinical use today is synthesized. Apart from artemisinins and quinine, other conventional antimalarial drugs in current clinical use are synthetics (table 1).

Table 1: History of Antimalarial Drugs

Drug	Date synthesized	Status	Comments
Pamaquine	1925	No longer in use	8-aminoquonline based but Toxic
Quinacrine (Mepacrine)	1930	No longer in use	Acrideine-ring based. Was standard antimalarial drug for Allied forces during World War II
Chloroquine	1934/1941 Germany/USA	Still in use	Used for radical cure of P. vivax and treatment of malaria in areas where the parasites are still sensitive
Amodiaquine	1948	Still in use	Part of ACT in combination with artesunate
Pyrimethamine & Proguanil	1950	Still in use	For chemoprophylaxis, IPT agent and combination therapy with other efficacious antimalarial drugs
Primaquine	1951	Still in use	Field tested during the Korean war. For radical cure of P. vivax and gametocidal for all other *Plasmodia* species.
Mefloquine	Late 1970s/early 1980s	Still in use	Oral formulation only. Used in combination with artesunate as part of a WHO approved ACT.
Pyronaridine	1970	Still in use	As part of an ACT in combination with artesunate. Not yet pre-qualified by WHO 2015/ 2016
Halofantrine (Halfan)	1988	Still in use	Withdrawn 2° to carditoxicity and intravascular haemolysis
Lumefantrine (*benflumetol*)	Early 1990	Still in use	As part of an ACT – Coartem™ (Artemether-lumefanthrine)
Atovaquone		Still in use	In fixed dose combination with proguanil. First licenced for use in the treatment of *Pneumocystis carinii* pneumonia in HIV patients. Currently deployed in the artemisinin resistance containment efforts.

Drug Treatment of Malaria

Prompt treatment with effective drugs is an essential component of malaria control strategies. The primary goal of treating malaria is to eliminate the parasite in the patient. Other benefits are the reduction of transmission rate, prevention of emergence and spread of resistance in the parasite. The WHO has recommended artemisinin-based combination therapies (ACTs) as first-line treatment forum complicated *P. falciparum* malaria since 2001 (WHO 2001). In the last ten years, most malaria-endemic countries including Nigeria (2005) changed their national treatment policies to ACTs. ***However, the malaria parasite has shown an almost limitless ability to develop resistance to all antimalarial drugs known to date especially when used as monotherapy.***

The emergence of resistance in the causative organism to antimalarial drugs is the greatest challenge to malaria chemotherapy. Antimalarial drug resistance has now become a major public health problem which hinders the control of malaria. The measurement of drug resistance in malaria is complex, as four different tools are used: *in vivo* efficacy studies, *in vitro* studies to measure intrinsic sensitivity of parasites, studies of molecular markers to identify mutations related to antimalarial drug resistance in the parasite genome and pharmacokinetic studies to characterize antimalarial drug absorption, distribution, metabolism and elimination in the body.

In a PLOS Publication of 2008, Newton et al. expressed the anxiety within the malaria research circles thus: *"Since 1998 the serious public health problem in South East Asia of counterfeit artesunate, containing no or sub-therapeutic amounts of the active antimalarial ingredient, has led to deaths from untreated malaria, reduced confidence in this vital drug, large economic losses for the legitimate manufacturers, and concerns that artemisinin resistance might be engendered."*

Mr. Vice-Chancellor Sir,

***P. falciparum* resistant to the artemisinins has emerged – this is a major tragedy and pain.**

Artemisinin resistance has been reported from Cambodia–Thailand border (most severe) as well as Myanmar–Thailand and China–Myanmar borders and one province of Viet Nam. Historically, South East Asia is the bedrock of antimalarial drug resistance. Occurrences to antimalarial drugs in SE Asia heralds subsequent events in the rest of malaria endemic areas. The WHO has put a very aggressive containment strategy in place to stop the spread of artemisinin resistance and ultimately eliminate malaria in the area. This is a wake-up call for us in Nigeria. Fake ACTs, irrational use of antimalarial drugs and poor adherence to even good drugs can only lead to emergence of drug resistant strains of *Plasmodium* and its consequences which entails much suffering from illness and death!

Drug resistance is defined as the ability of a parasite strain to survive or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the tolerance of the subject (WHO 1967). This definition was later modified to include the sentence: "The form of the drug active against the parasite must be able to gain access to the parasite or the infected erythrocyte for the duration of the time necessary for its normal action" (Bruce-Chwatt et al. 1986).

Treatment failure is not, however, always due to drug resistance, and many factors can contribute, mainly by reducing drug concentrations. These factors include incorrect dosage, poor patient compliance in respect of either dose or duration of treatment, poor drug quality and drug-drug interactions. Even after supervised administration of a full regimen of an antimalarial medicine, individual variations in pharmacokinetics might also lead to treatment failure because of poor absorption, rapid elimination (e.g. diarrhoea or vomiting) or poor biotransformation of pro-drugs.

Therapeutic efficacy studies conducted by the national malaria control programmes of Cambodia and Thailand were the first to show an increase in the proportion of patients who

were still parasitaemic on day 3, which indicates a change in the pattern of parasite susceptibility to artemisinins (fig. 8) and is probably the first stage of artemisinin resistance. An increase in the proportion of patients who were still parasitaemic on day 3 was also reported on the Myanmar–Thailand and China–Myanmar borders and in one province of Viet Nam; the situation in these other sites is less severe than on the Cambodia–Thailand border but merits careful monitoring and early response.

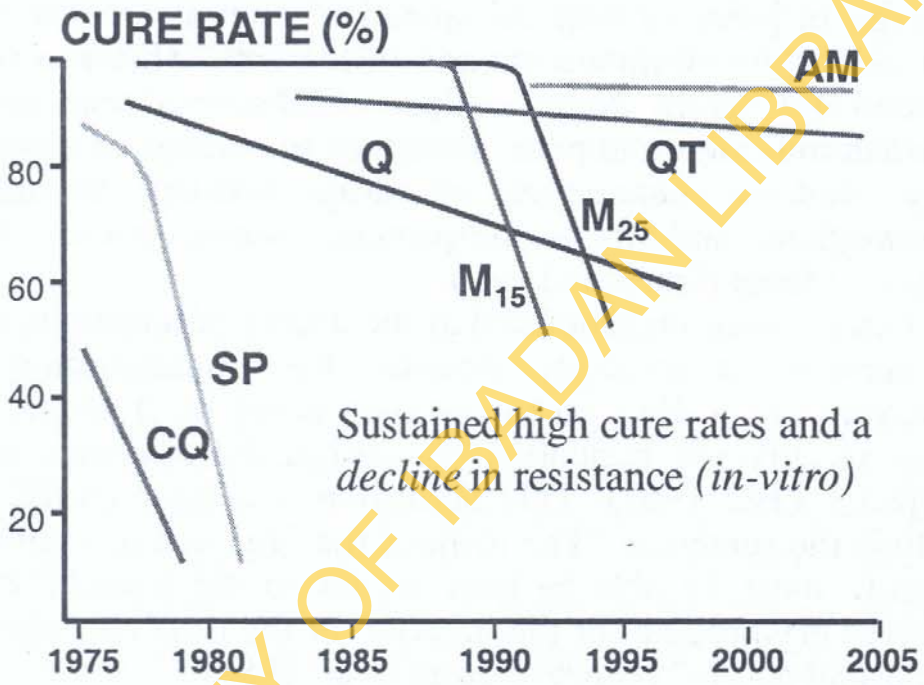


Fig. 8: Trends in antimalarial sensitivity in Thailand
(*Source*: White NJ)

Multidrug resistance of *P. falciparum* is seen when the parasite is resistant to more than two operational antimalarial compounds of different chemical classes and modes of action. Generally, the two classes first affected are the 4-aminoquinolines and the antifolates (diaminopyrimidine, sulfonamides). Drug resistance results in a delay or failure to clear asexual parasites from the blood, which allows production of the gametocytes that are responsible for transmission of the resistant genotype. The rise of anti-malarial drug resistance has changed the global epidemiology of malaria. Table 2 lists the implications for malaria control.

Table 2: Effects of Antimalarial Drug Resistance on Global Malaria Control

Disease burden	- The appearance of chloroquine resistance in Africa led to an increase in hospital admissions (Zucker et al. 1996). - Increasing mortality trends were found at community level (Trape et al. 1998; Korenromp et al. 2003). - Ineffective treatment causes anaemia and low birth weight (Björkman 2002) and renders the health of children and adults infected with *P. falciparum* or *P. vivax* more fragile (Tjitra et al. 2008). - Resistance to antimalarial drugs was implicated, at least partially, in malaria epidemics (Warsame et al. 1990). - Resistance to antimalarial drugs is associated with increased transmission (Price & Nosten 2001).
Economic cost	- Resistance to antimalarial drugs has increased the global cost of controlling the disease, including the cost of new drug development (Phillips & Phillips-Howard 1996). - Therapeutic failure requires consultation at a health facility for further diagnosis and treatment, resulting in loss of working days for adults, absence from school for children and increased cost to the health system (Talisuna, Bloland, D'Alessandro 2004).
Changes to distribution of malaria species	- The proportion of *P. falciparum* malaria has changed, such as an increase with respect to *P. vivax* (Dash et al. 2008).
Lack of access to high-quality treatment	- Ineffective treatment in the public sector due to resistance could lead to greater reliance of patients on the unregulated private sector, which in turn could increase the use of monotherapies or substandard and counterfeit medicines and increase the risk for drug resistance.

Chloroquine, a 4-aminoquinoline has been used extensively for the treatment and prevention of malaria since 1941. Unfortunately, resistance in the causative organism has rendered it virtually useless now. Table 3 shows the pattern of response to chloroquine and the ACTs which are the current

drugs of choice for the treatment of malaria in Nigeria. Apart from its anti-plasmodial properties, chloroquine has a wide therapeutic margin as well as potent analgesic (pain relieving), antipyretic (temperature lowering properties) and anti-inflammatory properties. These pharmacological properties made chloroquine a very useful drug in the treatment of malaria. These properties are also responsible for the reluctance of Nigerians to let go of chloroquine especially among the adult semi-immune population. Chloroquine will relieve joint pains, headache, malaise from any cause while the drug effect lasts. Even when used to treat laboratory confirmed malaria, the patients are relieved of the symptoms without clearance of the parasite. Chloroquine remained the drug of choice for the treatment of acute uncomplicated malaria in Nigeria until January 2005 when it was replaced by artemisinin-based combination therapy (ACT) in the National Treatment Guideline.

Table 3: Response Profile to Antimalarial Drugs in Nigeria before Policy Change

Zones	CQ (2003)	SP (2003)	AL (2004)	ASAQ (2004)
SE	3.7%	14.9%	100%	100%
SS	9.1%	8.5%	87%	82.5
NC	52.2%	82.7%	100%	96%
NW	77.3%	94.2%	100%	100%
SW	40.9%	75.6%	100%	100%
NE	50.8%	64.8%	100%	100%

CQ = Chloroquine, SP = Sulfadoxine/pyrimethamine
AL = Artemether/lumefantrine, ASAQ = Artesunate/amodiaquine

By 2004, the level of treatment failure to chloroquine 14 days after treatment had risen to between 50% and 94.3% in different parts of Nigeria while response to sulfadoxine-pyrimethamine was between 35% and 85%. Because of rampant treatment failure of chloroquine, we lost a huge number of children to malaria as they progressed to cerebral malaria and other forms of severe malaria, while adult patients remained symptomatic albeit at a lower grade, and this translated to increased morbidity and mortality. If we all think back, that was the period the diagnosis of *"typhoid"* was rampant and the use of alternative medicine became the norm. These situations arose because of failure of chloroquine to cure malaria. Artemether-lumefantrine and artesunate-amodiaquine are the ACTs of choice for the treatment of malaria in that order of preference in Nigeria (FMoH, Nigeria 2005). The national treatment guideline also made mention of the availability of other ACTs in the country.

Just as the treatment of acute uncomplicated malaria has evolved, so has the treatment of severe malaria. The drug of choice for the treatment of severe malaria in Nigeria was changed from parenteral quinine to injectable artesunate in line with WHO directives (FMoH 2011). These changes in the drug of choice for the treatment of malaria were based on very convincing pieces of evidence (fig. 9).

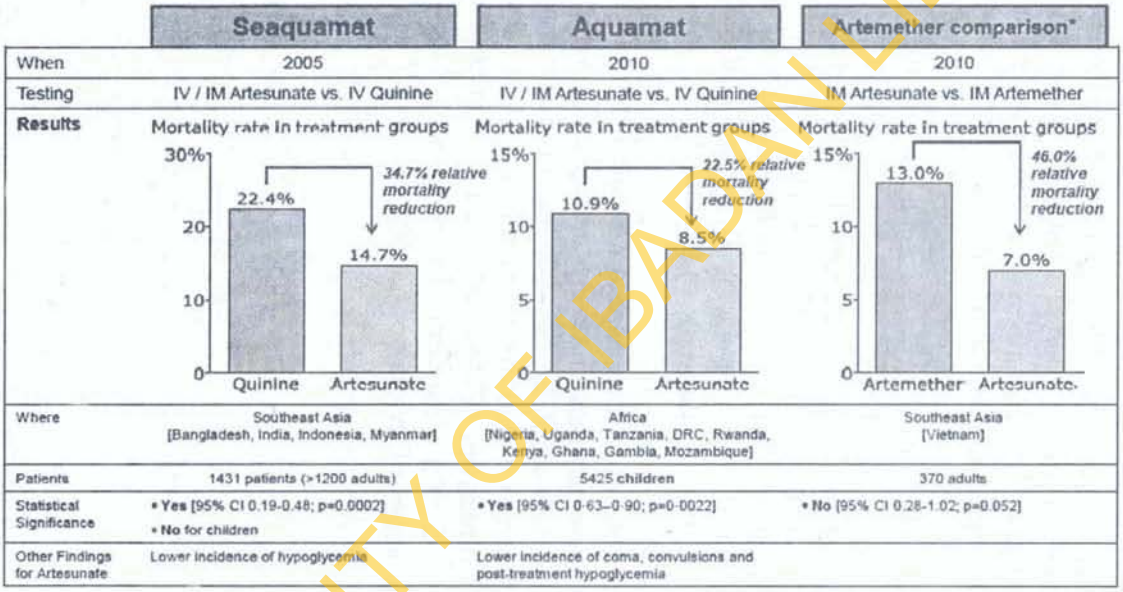


Fig. 9: Summary of studies showing Artesunate to be safer and more efficacious than Quinine in both adults and children in the treatment of severe malaria

* Results of trial not statistically significant

Source: ClinicalTrials.gov; WRAIR; EDCTP.org; Nick White

My Contribution to Knowledge on Malaria Chemotherapy

Mr. Vice-Chancellor Sir, my contribution to the chemotherapy of malaria includes evaluating the efficacy and safety of:

(i) Existing antimalarial drugs;
(ii) Combination of old molecules to prolong the clinical useful life of some antimalarial drugs and
(iii) Newer artemisinin-based combination therapy;
(iv) Evaluation of antimalarial properties of some Nigerian plants.

Pains

Studies on 4-aminoquinolines: Chloroquine and Amodiaquine

My first foray into studies on malaria chemotherapy started with a clinical trial which evaluated the comparative efficacy of halofantrine, chloroquine and sulfadoxine-pyrimethamine in Nigerian children. This study was funded by Glaxo-Welcome Pharmaceuticals.

- We reported the first clear evidence that chloroquine resistance had risen to unacceptably high levels in Ibadan, southwest Nigeria (65% at Day 14) ***thus drawing the attention of the National Malaria Control Division of the Federal Ministry of Health to a need for the review of the national treatment guideline*** (Falade et al. 1997). Despite mounting evidence, chloroquine remained a firm favorite in Nigerian public healthcare workers and lay public alike. Many people still swear by chloroquine even today.
- Pruritus (itching) is a major drawback to the use of chloroquine. We evaluated the profile of chloroquine induced pruritus among Nigerian children resident in Ibadan. We concluded that chloroquine-induced pruritus in this group of children evolved with increasing age and was associated with positive family history (Fehintola et al. 2004).

- We reported a strong association between gametocytaemia on day 7 and treatment failure. 92% of infections on day 7 also harbored T76 allele of *pfcrt*. This suggests that chloroquine resistant parasites may have a transmission advantage over chloroquine sensitive parasites (Happi et al. 2003; Happi et al. 2004)
- We also demonstrated the remarkable efficacy [>95% cure rate at Day 28] of amodiaquine (Camoquine™), another 4-aminoquinoline as monotherapy in the treatment of acute uncomplicated malaria including patients who had earlier failed chloroquine treatment (Sowunmi et al. 2001). ***This study confirmed the place of amodiaquine as a suitable companion drug in ACTs in Nigeria.***

Chlorpheniramine (Piriton™) and a number of other drugs without antimalarial properties have been shown to modulate/ enhance antimalarial property of chloroquine *in vitro*.

- We reported the clinical validation of this *in vitro* finding in studies carried out both in controlled clinical studies in the hospital (Sowunmi et al. 1997) and in the community (Falade et al. 2007) during which enhanced efficacy of chloroquine-chlorpheniramine combination in treating acute uncomplicated *P. falciparum* infection in children was clearly demonstrated.
- We also reported that the combination of amodiaquine plus chlorpheniramine was significantly more efficacious than amodiaquine alone in the treatment of acute uncomplicated falciparum malaria thus *suggesting that the combination could be a better alternative to amodiaquine alone as a companion drug in artemisinin-based combination therapies* (Falade, Michael, and Oduola 2008).

- ***This concept has been accepted and a fixed dose combination ACT formulation containing Artesunate-amodiaquine-chlorpheniramine – Artemoclo™ manufactured by Niemeth Pharmaceuticals, Nigeria Limited.*** The evaluation of Artemoclo™ is reported in published work (Falade et al. 2014). We compared the safety and efficacy of artemether-lumefantrine, artesunate-amodiaquine and artesunate-amodiaquine-chlorpheniramine (Artemoclo™). The three ACTs were efficacious and safe. Artemoclo™ resulted in better haematological recovery on day 2 and higher cure rates throughout the study period.

Studies on Anti-folates

Sulfadoxine-pyrimethamine (Fansidar™)

Sulfadoxine-pyrimethamine (SP) was used widely in sub-Saharan Africa as a result of emergence of resistance to chloroquine. Unfortunately, SP exerts a high selection pressure for resistance with point mutations on the dihydrofolate reductase (*dhfr*) and dihydropteroate synthase (*dhps*) genes in the *Plasmodium* with worsening degree of resistance as the number of mutations increase reaching a peak at quadruple mutation.

- We demonstrated declining sensitivity of *Plasmodium falciparum* to sulfadoxine-pyrimethamine from 100% (Ekanem et al. 1990), 98.1% (Sowunmi, Ohaeri, and Falade 1995) to 75.7% in 1997 (Falade et al. 1997). ***This led to the search for effective alternatives***.

Chlorproguanil-Dapsone (LapDap™)

We evaluated the safety and efficacy of Chlorproguanil-dapsone (LapDap) which selects resistance less readily than SP as a possible replacement for SP. Mr. Vice-Chancellor Sir, I led the Nigerian team in this 5-African country study. This study was funded by a grant from WHO/TDR.

- LapDap was significantly more efficacious than SP over all. However, both were at par in Nigeria. Both achieved reasonably high clinical and parasitological cure rate at D14. There were however treatment failures even at day 14 which is sub-optimal! (Alloueche et al. 2004).
- More importantly, the safety profile of LapDap among Nigerian children was of concern. The Nigerian team was the first to report severe intravascular haemolysis ***(a serious adverse event and a signaling issue)*** despite many publications of previous use in over 3000 patients who had received the drug in East Africa. ***This adverse effect profile led to the discontinuation of LapDap-Artesunate development.***
- We also reported cardiac rhythm disorders in the form of primary A-V block and occasional ventricular ectopic in a prospective electrocardiographic study, among Nigerian children who received LapDap (Ogunkunle et al. 2011). There was however no incidence of overt clinical intolerance or symptoms suggestive of cardiac malfunction in these patients throughout the period of treatment and follow-up.

Studies on halofantrine (Halfan™)

When halofantrine, a phenantrine methanol was introduced for malaria chemotherapy in 1988, it seemed to be the long awaited messiah in malaria chemotherapy! Halofantrine was available in oral formulation, pleasant tasting, cost was moderate and its dosage schedule was patient friendly – three doses in all at six hourly intervals and is all done in 12 hours.

- However, we reported a significant loss of efficacy of halofantrine leading to 12.5% treatment failure within five years of its introduction into Nigeria (Falade et al. 1997).
- We also reported significant cardiotoxicity (Sowunmi et al. 1998 & 2000) and intravascular haemolysis (Fehintola, Falade, and Sowunmi 2006). Although

fatal cardiac arrhythmias have been reported in adults in literature, we had no fatality in our studies. ***This adverse effect profile led to withdrawal of halofantrine from most pharmacopeia globally.***

Gains

Sequential Therapy for severe Malaria

Patients suffering from severe malaria run the risk of dying within a short time of onset unless they receive appropriate parenteral treatment. Unfortunately, malaria is more severe in the rural areas where manpower, syringes, water and electricity to sterilize equipment are often lacking.

- We compared two dose forms of artemisinin derivatives, dihydroartemisinin suppository (DHA) and intramuscular artemether (ART), in children 6 months to 10 years of age with moderately severe malaria for which oral therapy was not appropriate. Study volunteers received DHA or ART followed by a single oral dose of sulfadoxine-pyrimethamine on the third day. Days 14 and 28 parasitological cure rates were 100% and 96.2% versus 96.2% and 91.7% for children treated with DHA and ART, respectively. Both treatment regimens were efficacious and well tolerated (Falade et al. 2007).
- 60% of mothers and other caregivers of enrolled children were skeptical about the use of a suppository formulation during the informed consent procedure. However, the attitudinal disposition changed from skepticism to acceptance, followed by enthusiasm and finally request for information as to the source of purchase of the "antimalarial suppository drug" after 24 hours of initiating treatment. Parents and guardians were glad to know about the availability of antimalarial drug in suppository form that could be administered at home to children who were vomiting repeatedly or those who were simply uncooperative whenever they needed to take drugs. ***Pre-referral artemisinin suppository use for patients with severe***

malaria has been incorporated into malaria treatment guidelines both by the WHO and Nigeria (WHO 2010; FMoH 2011).

Combination Therapy for Malaria

Mr. Vice-Chancellor Sir, malaria parasites became unresponsive to the conventional monotherapies – chloroquine and sulfadoxine-pyrimethamine as a result of emergence and wide dissemination of drug resistant *P. falciparum*. This led to worsening morbidity and mortality as well as increased transmission of drug resistant infection. To stem the tide, the WHO in 2001 directed that combination therapy (CT) should replace prior monotherapies with strict definitions of what constitutes combination therapy—two or more efficacious drugs from different chemical classes used simultaneously and at full dosage. The rationale was that the components of the combination will kill different strains of parasites should they exist in the same patient being treated. Moreover, combination therapy had previously worked in tuberculosis, leprosy, cancer and HIV chemotherapy. Combination therapy in malaria can be artemisinin-based or non artemisinin-based. Artemisinin-based combination therapies (ACTS) are the preferred options because of the added property of the artemisinins in killing gametocytes. Coartem™ (artemether-lumefantrine) was the first fixed dose combination ACT to be pre-qualified by the WHO and as a result, most initial studies were done with Coartem™. Fixed dose combinations are preferred to loose combinations because the pill burden is less and adherence to therapy is remarkably better.

My Contribution to the Use of ACTs for Malaria

Coartem™, [artemether-lumefantrine (AL)] was first registered as a 4-dose regimen. While the four dose regimen of AL was effective, in terms of the 28-day cure rate, in regions where *P. falciparum* is not multidrug-resistant and patients are partially immune, this was not so in areas such as South East Asia where the parasite is drug-resistant, and a higher dose schedule was required.

- I was the Principal investigator for the Nigerian arm of an extensive three-African country study (Kenya, Tanzania and Nigeria) which evaluated the safety and efficacy of the 6-dose regimen of Coartem® in the treatment of malaria in African infants and children weighing between 5 and 25 kilograms. The study which was sponsored by the WHO/TDR was an in-patient study with detailed haematological and blood chemistry evaluation as well as population pharmaco-kinetic and electrocardiographic aspects. ***This study established the high efficacy and safety of the 6-dose regimen of AL in African children aged 5-25 kilograms. Data from this study was used for the registration of the 6-dose regimen with Swiss-medic for Coartem®. The 6-dose regimen is now the global standard for AL treatment of acute uncomplicated malaria. Data from this study also informed the choice of drugs that were evaluated by the National Malaria Control Program in choosing a replacement for chloroquine and SP*** (Falade et al. 2005).
- We also reported high cure rates and rapid resolution of parasitemia, fever, and gametocytemia in paediatric and adult patients in pooled data (Makanga et al. 2006; Makanga et al. 2011).
- We reported that the fat content of the African diet is adequate to achieve optimal efficacy with fixed-dose artemether-lumefantrine (Premji et al. 2008). This is a very significant report because lumefantrine, the companion drug in AL is highly lipophylic (depends on fat for absorption) and it is often recommended that AL be administered with milk. We however showed that all that is necessary is to administer AL soon after or during a meal in Africa.
- In an extensive review, Falade and Manyando (2009) reported the safety and tolerability from over 6,300 patients who had taken artemether-lumefantrine (Coartem®). We did not identify any neurological,

cardiac or haematological safety concerns following the use of AL. In addition, repeated administration was not associated with an increased risk of adverse drug reactions including neurological adverse events. ***We consider this finding very relevant for children living in areas with high malaria transmission rates who often receive many courses of anti-malarial medications during their lifetime***. This is very important as there was a lot of concern about the safety profile of lumefantrine, the companion drug in AL especially with regards to cardiotoxicity and intravascular haemolysis because lumefantrine belongs to the same chemical class as halofantrine.

- Continuous monitoring of the efficacy of ACTs in Nigeria has shown that the two commonly used ACTs in Nigeria – AL and ASAQ remain highly efficacious and safe (Falade et al. 2005; Falade, Ogunkunle, et al. 2008; Falade, Ogundele, et al. 2008; Ajayi, Falade, et al. 2008; Falade, Dada-Adegbola, et al. 2014).

Mr. Vice-Chancellor Sir, this I believe will be reassuring to all sub-segments of the Nigerian community as some medical practitioners and general public continue to report varied claims about the therapeutic efficacy of some of the recommended ACTs and the wisdom of some of the strategies for malaria control. These varied claims are not unconnected with the heritage of presumptive diagnosis, generally unreliable microscopy, fear of a disturbing truth from RDT results that malaria may just not be as common as we want to believe and the deceptive efficacy of chloroquine.

Monitoring selection and responding to emerging signs of drug resistance are critical tools for preserving efficacy of artemisinin combination therapies.

- In a collaborative study involving researchers from more than 50 institutions in 24 countries under the umbrella of the World-Wide Antimalarial Resistance Network, data for more than 7,000 patients were

analyzed to assess relationships between parasite polymorphisms in *pfcrt* and *pfmdr1* and clinically relevant outcomes after treatment with AL or ASAQ. Presence of the *pfmdr1* gene N86 and *increased pfmdr1* copy number were significant independent risk factors for recrudescence in patients treated with AL. AL and ASAQ exerted opposing selective effects on single-nucleotide polymorphisms in *pfcrt and pfmdr1*. (Venkatesan……et al. 2014).

Evaluation of Antimalarial Plants

Mr. Vice-Chancellor Sir, I did not research into orthodox antimalarial drugs only. As a result of a grant funded by MIM/TDR, I had the opportunity of working as a co-investigator in the Phytomedicine research group ably led by my sister and friend – Prof. Edith Ajaiyeoba. The grant was titled "Identification of potential antimalarial compounds from Nigerian phytomedicine compendium". The studies which went on for three years were conducted in three states, Oyo State, Benue State and Rivers State. Two LGAs, one rural and one urban were selected in each state. Atiba LGA (rural) and Itesiwaju LGA (urban) in Oyo state, Gboko (rural and Katsina Ala (urban) in Benue State while Kana LGA (rural) and Eleme LGA (urban) are located in Rivers state.

- The communities surveyed proffered different types of febrile illness which included yellow fever, typhoid fever, ordinary fever, rainy season fever and headache fever. Different herbal remedies are used in the treatment of each type. The four most frequently used plants for fevers in the LGAs in Oyo state were *Azadiracthta indica, Mangifera indica, Morinda lucida* and *Citrus medica* (Ajaiyeoba et al. 2003). In the middle belt, the most commonly used plants were *Azadiracthta indica, Ficus thonningii, Amona senegalensis and Cymbopogun citratus* (Ajaiyeoba et al. 2002; Osowole et al. 2005) while the most mentioned plants in Rivers State were *Azadiracthta*

indica, Cymbopogun citratus, Carica papaya, Psidium guajava (Ebong et al. 2005). Methods of preparation were similar and the oral route was the most frequently used route for administration of decoctions, powders etc. Incantations and offering of sacrifices were sometimes used, especially in Rivers State.

- In an observational study, the efficacy of eight different herbal remedies was investigated in Oyo (urban center) and Otu (rural center). Parasitemia was evaluated by microscopy to confirm diagnosis and evaluate efficacy. Only 62 of 163 of the children treated presumptively by the herbalists had patent parasitemia. The remedies were prepared and administered by the herbalists. They provided detailed descriptions of each of the 8 herbal remedies. *Gossypium arboretum, Anarcadium occiedentalis, Citrus medica, Phyllanthus amarus and Lippia multiflora* were the main ingredients in the efficacious remedies (Ajaiyeoba et al. 2004).
- We reported the *in vitro* anti plasmodial activity of seven methanol extracts of seven plants from seven plant families identified and selected from Gboko and Katsina Ala LGA in the Middle Belt zone of Nigeria. They were moderate to weak in their *in vitro* anti-plasmodial activity (Ajaiyeoba, ….., et al. 2005).

Malaria during Pregnancy & in the New Born

Ordinarily, adults living in malaria endemic areas acquire substantial immunity to malaria and we refer to this as semi-immunity. However, this semi-immune status is compromised during pregnancy and the pregnant woman is more susceptible to malaria than her non-pregnant counterpart with grave consequences for mother and child (fig. 10). This increased susceptibility of the pregnant woman to malaria results from a combination of immunological, hormonal and the unique ability of infected erythrocytes to sequester in the placenta (fig. 11).

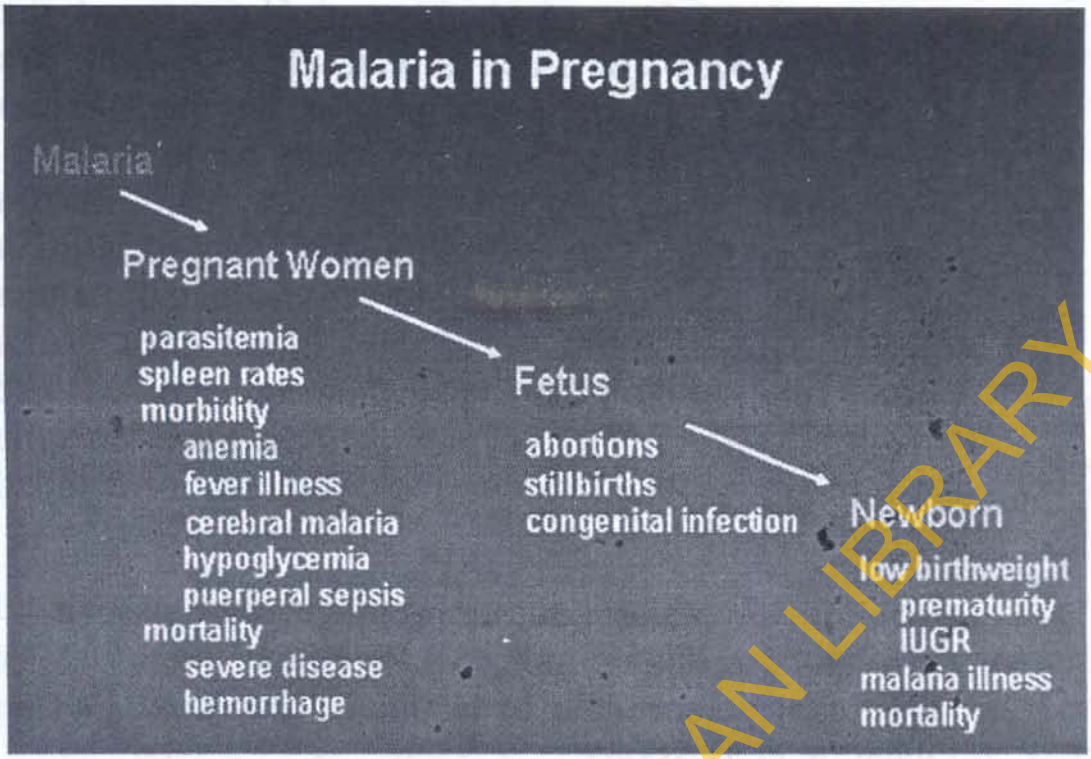


Fig. 10: Adverse consequences of malaria during pregnancy

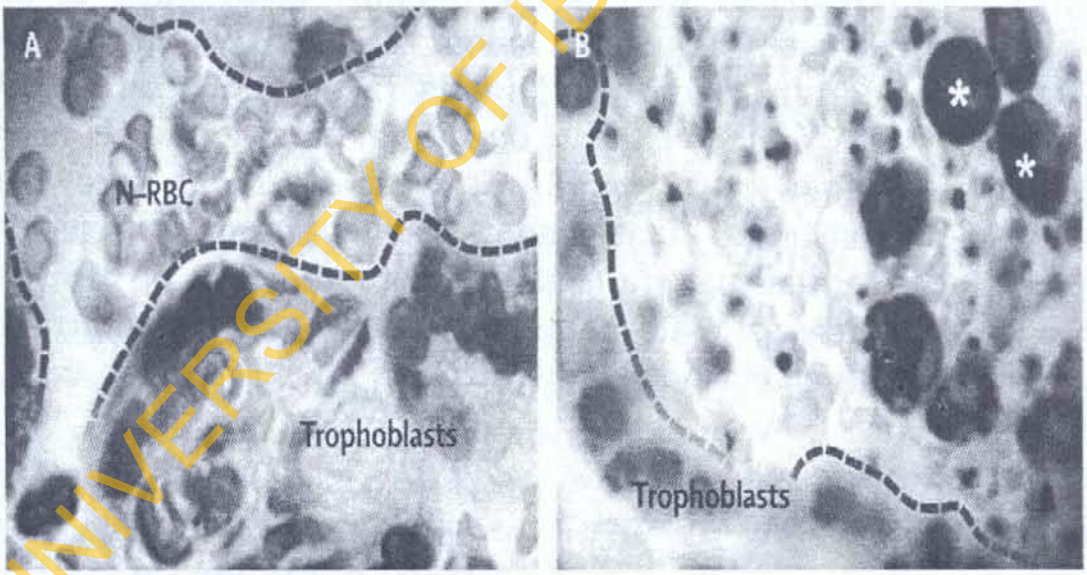


Fig. 11: Placenta tissue (A) normal and (B) malaria-infected women

My Contribution to the Body of Knowledge in Malaria in Pregnancy and the Newborn

In a series of publications which emanated from studies on a grant supported by a Cooperative Agreement between Boston

University and the Office of Health and Nutrition of the United States Agency for International Development, we reported on malaria during pregnancy at the peri-partum period in Nigeria. These publications were based on a12-month longitudinal study of 1875 mother-baby pairs from a multi-centre study from four geopolitical regions of Nigeria i.e. Ibadan, Ilorin, Kaduna and Enugu. We evaluated malaria parasitemia by ***expert*** microscopy of thick blood smears from the mother's peripheral blood, placenta, cord blood and baby's blood. Many of these publications have become important references. The following key findings were added to the body of knowledge:

- Symptomatic malaria during pregnancy was associated with early booking and malaria parasitemia was a significant determinant of anemia at booking (Falade, Olayemi, et al. 2008).
- We provided the first comprehensive national report on the incidence of congenital malaria as 5.1% (95/1875) in Nigeria as well as the monthly distribution of the occurrence of malaria among pregnant women in the peripartum period in Nigeria (Mokuolu et al. 2009) (fig. 12). Mean parasite density in parasitemic neonates was low (mean = 48/μL, range 8–200/μL).We also demonstrated that under the strict definitions of congenital malaria (within the first 7 days of life) the majority of the babies did not require additional treatment (Falade et al. 2007).

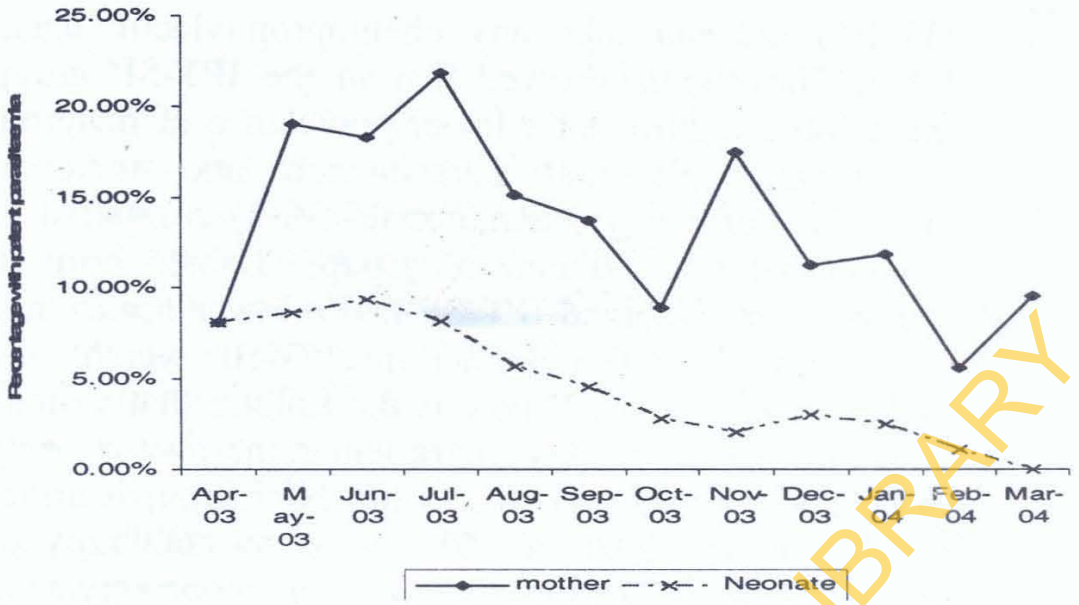


Fig. 12: Monthly prevalence of peripartum maternal and neonatal parasitaemia among pregnant women in Nigeria

- We also described the clinical features of congenital malaria in Nigeria. Less than 40% of parasitaemic neonates were symptomatic and they responded promptly to antimalarial therapy (Orogade et al. 2008).
- We reported that more than one in every five women had patent malaria parasitemia (maternal and/or placental) at delivery and that maternal age less than 20 years was the most important predisposing factor for malaria at parturition. The major consequences of malaria at parturition identified in our studies were *maternal anaemia*, *reduction in maternal hematocrit*, *reduction in mean birth weight* and a *higher proportion of LBW babies*. ***The findings of this study underscored the need for a focused and concerted effort to address the control of malaria during pregnancy in Nigeria*** (Mokuolu et al. 2009).
- We examined the effect of malaria prophylaxis in 983 parturient mothers over an 18-month period in St. Mary's Catholic Hospital, Eleta, Ibadan. Five hundred and ninety-eight mothers (60.8%) received IPT-SP, 214 (21.8%) received pyrimethamine (PYR) and 171

(17.4%) did not take any chemoprophylactic agent (NC). The results showed that in the IPT-SP group there was a significantly lower prevalence of maternal parasitemia, placental parasitaemia and maternal anaemia (defined as haematocrit <30%) compared to the comparator and control groups. Babies born to mothers who received IPT-SP had a lower occurrence of preterm deliveries, higher mean birth weight and higher hematochrit. Of note is the finding that women who received weekly pyrimethamine were only marginally better off than the NC group further confirming the lack of efficacy of monotherapy of pyrimethamine (Daraprim™) as a chemoprophylactic agent. ***The report concluded that SP-IPT is effective in preventing maternal and placental malaria as well as improving pregnancy outcomes among parturient women in Ibadan, Nigeria; providing evidence for the implementation of the IPT-SP strategy in reducing the national burden of malaria in pregnancy*** (Falade, Yusuf, et al. 2007).

- We reported on the use of malaria preventive practices among mothers delivering in a secondary hospital in Ibadan. Although 98.4% (956/972) used one form of anti-vector measure or another to prevent malaria, the use of ITN was very low 1.1% (11/972) among enrolled mothers (fig. 13). ***The report concluded that there is a need to pay concerted efforts to improve ITN usage rate in Nigeria*** (Yusuf, Falade, et al. 2008).
- We also reported that malaria was more frequent and severe among pregnant HIV +ve Nigerian women compared to HIV –ve counterparts and that CD4 count >250 cells/mm^3 was negatively correlated with malaria parasitemia. The HIV +ve women also have a lower KAP of malaria and a significantly larger proportion of them lacked knowledge of and do not use malaria preventive measures (Falade, Adesina, et al. 2010). ***Intervention in this vulnerable segment of the Nigerian population needs urgent attention.***

- We reported that malaria during pregnancy (N=983) results in symmetric foetal growth restriction and the effect is more marked among primigravid mothers and that neonates born to mothers with peripheral and/or placental malaria have significant lower birth weight, length, occiptofrontal circumference and ponderal indices, compared to those free of parasitemia (Falade, Tongo, et al. 2010).
- We also reported poor knowledge, low usage of IPT-SP (27.3% of 209 pregnant women) and poor adherence to the Directly Observed Therapy (DOT) scheme among pregnant women attending ANC in Primary Health Care facilities in rural Ekiti State, SW Nigeria (Akinyele et al. 2009). Findings of another study in Adeoyo State hospital Ibadan yielded similar findings (Olorunda, Ajayi, and Falade 2013). ***We concluded that concerted effort should be made to increase awareness of IP-SP among the public especially women of child bearing age and health care workers should be trained and monitored to ensure adherence.***

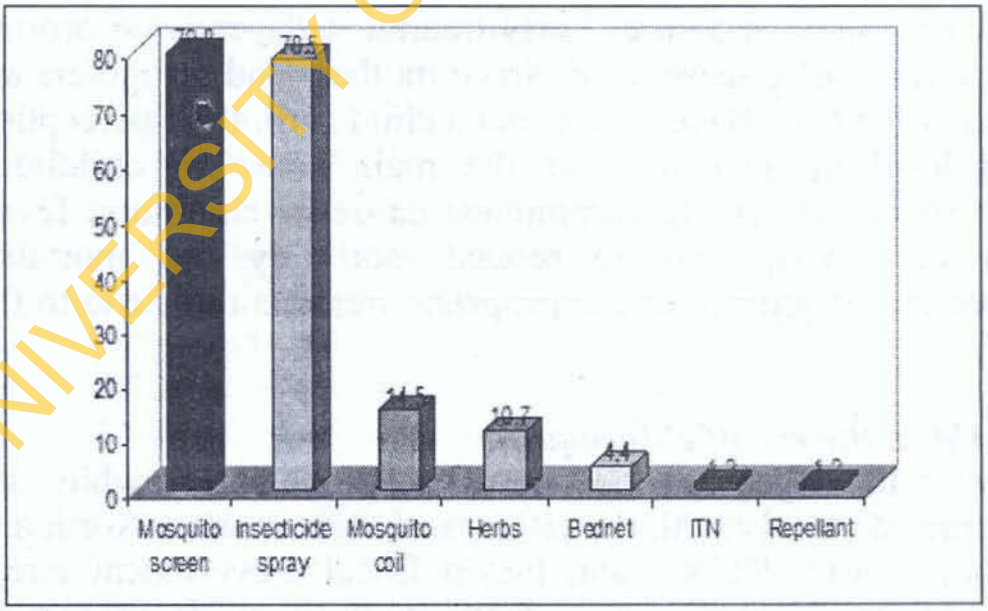


Fig. 13: Pattern of Anti-vector Measures (Percentage) Used by Parturient Women in Ibadan, South Western Nigeria

Community Perception and Management of Malaria

Mr. Vice-Chancellor Sir, in tandem with most infectious diseases, community involvement is absolutely essential if the malaria scourge is to be successfully controlled and/or eliminated. It is common knowledge that all childhood illnesses especially childhood fevers are first treated at home by the first and best known *"doctors"* – mothers. My research endeavours included substantial community work especially in the rural areas where children with malaria live.

- In a study at the General Out-patients Department of the University College Hospital, Ibadan, we reported that 87.7% (470/535) of febrile children brought to the out-patients clinic had received one form of treatment or the other before coming to the hospital while 46% had been presumptively treated for malaria by their mothers or other care givers. Only 15% used chloroquine correctly while only 3.6% of the children were brought in within 24 hours. ***The urgent need for involvement in home management of Nigeria was established*** (Ajayi and Falade 2007).

Early and appropriate case management is an important malaria control measure. Early treatment depends on prompt recognition of disease state. Since mothers and caregivers are usually the first to recognize that a child is ill, their perception and level of awareness of the main cause of childhood malaria, which is the commonest cause of childhood fever, can go a long way to reduce morbidity and mortality especially if prompt and appropriate treatment is close to the home.

HMM in the era of chloroquine

Over a three year period – 1999 to 2003 during which we interacted closely with the citizens of Ogbomosho (North and South), Orire, Kajola, and Iseyin Local Government Areas (LGA) we conducted an in-depth study titled "Incorporating Socio-cultural and Economic Characteristics of Mothers and Caregivers in the Home Management of Malaria (HMM) in

Children". The study was funded by a grant from the MIM/TDR. It was during this study that I had the privilege of cutting my milk teeth in community studies under the knowledgeable, gentle but firm tutelage of Prof. J.D. Adeniyi who we fondly call JD. I believe that one or two of my molars in community studies actually erupted successfully before the end of the project. Members of the HMM research team became one family. I want to seize this opportunity to say thank you to JD for the knowledge which you impacted so willingly and effortlessly, for caring and for nurture. The findings of that study which involved over 2000 citizens in the selected LGAs are reported in a series of publications.

- There was a wrong notion of causation of malaria in the study LGAs with too much sun and too much work being the two most mentioned. Malaria was perceived as a trivial illness – *"iba lasan"* unlike the other fevers which were appropriately named and so was handled with levity.
- Fathers play a very important role as decision makers in the HMM of malaria strategy and must be included in all programmes promoting HMM for success.
- Severe anaemia, convulsions and cerebral malaria cases which are the subset of children that die within a short interval of onset of illness are not perceived as complications of malaria and are thus preferentially treated by traditional healers (Falade et al. 2006).
- The enabling factors and challenges of the crucial role of the patent medicine sellers (PMS) in HMM included availability round the clock, credit facilities, patient friendliness and wrong dosing of chloroquine (>90% of cases) which was the drug of choice for treatment of malaria at the time of the study (Ajayi et al. 2003).
- A market survey showed that less than 10% of teaspoons available in the market in SW Nigeria could hold up to 5 millilitres of fluid with the result that prescriptions based on teaspoon measure were definitely under-dosed. The PMS association commissioned a plastic manufacturing company to make

disposable teaspoons that could measure 5 millilitres for distribution among its members. The added cost was less than one kobo per spoon because of the bulk order! (Ajayi et al. 2003).

- The key players in the HMM strategy were identified: mothers & fathers (primary) while the secondary targets were health workers, patent medicine sellers (PMS), traditional healers and policy makers at local and state government levels. Each of these groups was systematically targeted for intervention. Participatory workshops were organized through the various professional associations; collaborations were successfully established between healthcare workers, patent medicine sellers and traditional healers (Falade, Osowole, et al. 2004; Fawole et al. 2007-2008; Falade et al. 2008).

Although healthcare facilities serve as first line of care for some, most children are taken to the healthcare facility only when illness is severe or the clinical status of the child has deteriorated. It is thus important that health care facilities in sub-Saharan Africa have the capacity to diagnose and manage malaria of varying severity and drug sensitivity, as these healthcare facilities are the last resort.

- We reported that the healthcare facilities in the study LGAs were grossly under-equipped in manpower, training and materials to manage childhood malaria in the four selected LGAs (Falade et al. 2006). More recent experiences in Ona-Ara LGA, SW Nigeria, are not any different while it is worse in Katcha and Gbako LGAs in Niger State.

HMM in CQ era in Ona-Ara LGA

- We developed an easy to understand and follow treatment guideline for home management of malaria (HMM) in Ona-Ara LGA, SW Nigeria using a participatory approach. The aim was to produce clear, acceptable, and culturally relevant visuals that will

facilitate effective case management of malaria in children at the home level. Mothers, selected by community members from 11 communities in the LGA, research team members and a graphic artist developed the guideline in phases (fig. 14). A seasoned health educator (Prof. Oladimeji Oladepo) provided very useful comments. The guideline is in cartoon format with scripts in the local language – Yoruba (Ajayi, Oladepo, et al. 2009). This treatment guide was subsequently modified for ACT – artemether-lumefantrine use (fig. 15).

- We assessed the baseline and post-intervention knowledge, attitude and practice with household surveys conducted among mother trainers. We reported that the use of the guideline with adequate training significantly improved correctness of malaria treatment with chloroquine at home. ***Adoption of this mode of intervention is recommended to improve compliance with drug use at home*** (Ajayi, Falade, et al. 2007).

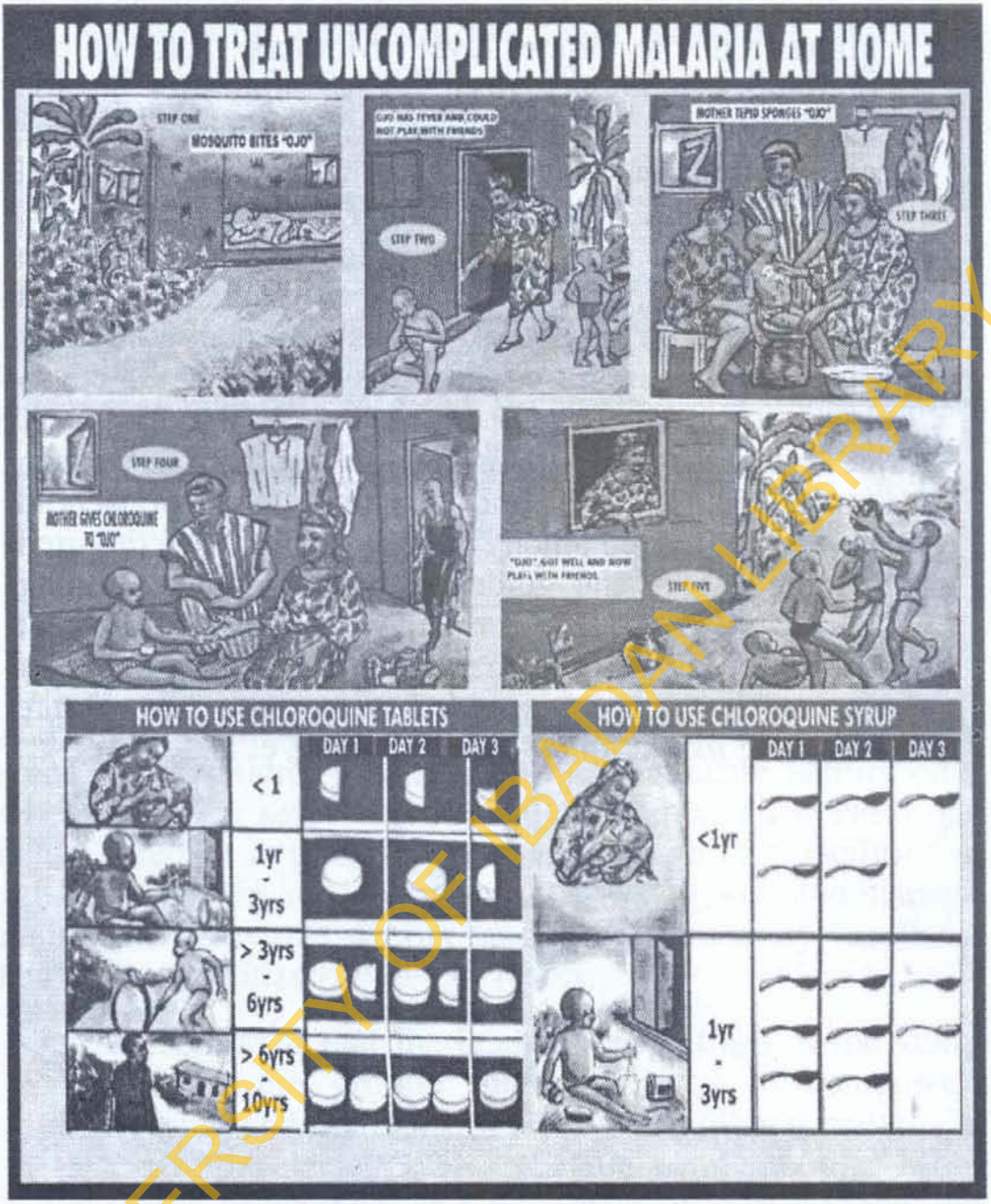


Fig. 14: Treatment guideline of HMM using chloroquine

Fig. 15: ACT – Artemether-lumefantrine treatment guideline used for HMM based on estimated age for weight

HMM in the era of ACT

In Nigeria, the use of chloroquine at home with its simple regimen has been shown to be largely incorrect. The regimen of ACT is however more complicated than that of CQ. We evaluated the feasibility of using ACT at the home level and determine community perception on its use as well as its effectiveness.The feasibility, acceptability and effectiveness of the new WHO policies on treatment of malaria were studied in rural southwestern Nigeria using operational research and quasi experimental designs. ***Findings from these studies were pivotal in the plan by the FMoH to scale***

up the use of ACT for HMM in Nigeria. The study which was funded by the WHO/TDR led to the publication of a series of journal articles.

The Gains

- In a before and after qualitative study using key informant interviews (KII) and focus group discussions (FGDs), we showed that the use of AL at home and community level is feasible with adequate training of community medicine distributors (CBD) and caregivers. Community members perceived AL to be effective thus fostering acceptability. ***The negative attitudes of the health workers and issue of incentives to CMDs need to be addressed for successful scaling-up of ACT use at community level*** (Ajayi, Falade, et al. 2008).
- We also reported the high acceptability of AL in rural communities in SW Nigeria. 97.6% (1019/1044) of the children treated with AL by the community medicine distributors (CMDs) received the correct dose. 80.2% (231/288) received prompt treatment at the correct dose and for the correct length of time. 98% percent of the caregivers perceived AL to be effective and none reported severe adverse events (Falade, Ajayi, et al. 2014).

Previous studies evaluating the safety and efficacy of AL have been hospital based under supervised therapy and strict protocol adherence. It is important to evaluate the safety and effectiveness of this new drug combination in the community under natural situation where the drug will be most often used.

- We reported high parasitological cure rate (PCR adjusted) greater than 90% in all sites (Nigeria, Ghana and Uganda), as well as very good adherence to correct treatment in terms of dose and duration between 81% to 97% of children treated with ACT in the context of

HMM. CMDs successfully learned to prepare blood films and another study using RDTs in the community is going very well as I give this lecture. ***This has added to the evidence base for HMM as a public health strategy as well as for scaling-up implementation of HMM with ACTs globally*** (Ajayi et al. 2008).

The Pains

- We also reported that age and educational background of caregiver were significantly associated with guideline use. Caregivers with primary education were 4 times more likely to use guideline compared with caregivers with no formal education. Guideline use reduced with increasing age and lower education (Akerele et al. 2011).
- The sustainability of these interventions was explored two years after the end of the intervention. Despite adoption of the HMM strategy by the government, AL supply to the PHCs where CMDs were to obtain their stock was erratic. CMDs resorted to treating children with paracetamol, sulfadoxine-pyrimethamine or chloroquine during stock outs which sometimes lasted many months. ***Laudable as the strategy is, HMM sustainability has been poor*** (Ajayi, Jegede, and Falade 2012).

Preclinical Evaluation of Antimalarial Compounds **in Animal Model**

- We reported the superior efficacy of Chloroquine in combination with promethazine (CQ + PZ) in the treated of gravid mice infected with *Plasmodium berghei* compared with chloroquine alone. Gestation outcome (weight of pups, was also better among gravid mice that received CQ + PZ compared to those treated with CQ alone (Oduola et al. 2004).
- We also reported that the antimalarial effect of chloroquine, artemether and methylene blue countered *P. yoelii*-induced oxidative stress in infected mice

leading to the elevation of enzymatic and non-enzymatic antioxidants in the host system (Nneji et al. 2013).

- We evaluated the antimalarial and antioxidant activities of the methanolic extract of *Nigella sativa* seeds (black cumin) in mice infected with *Plasmodium yoelli nigeriensis*. The methalonic extract of *Nigella sativa* was more effective than CQ in parasite clearance and, in the restoration of altered biochemical indices by *P. yoelli* infection. ***These results suggest that Nigella sativa seeds have strong antioxidant property and, may be a good phytotherapeutic agent against Plasmodium infection in malaria*** (Okeola et al. 2010).

Curcumin, a major yellow pigment and active component of *Curcuma longa Linn* (Turmeric), has been shown to possess anti-inflammatory and anti-cancer activities. Recent studies have indicated that curcumin inhibits chloroquine-sensitive and chloroquine-resistant *Plasmodium falciparum* growth in culture. However, the clinical use of curcumin has not been encouraging owing to its poor oral absorption. Extremely low aqueous solubility, extensive intestinal and hepatic metabolism, rapid elimination, rapid metabolism, high sensitivity to light and moisture have restrained the bioavailability of curcumin. Several strategies such as encapsulation in liposomes, biodegradable microsphere, cyclodextrin, hydrogels, polymeric nanoparticles, lipid-based nanoparticles (Aditya et al. 2012) and synthesis of analogues of curcumin are being developed to circumvent these pitfalls.

- We evaluated the *in vitro* and *in vivo* antimalarial activity of five curcumin analogues in our effort to discover novel antimalarial compounds from natural product. All the five curcumin analogues compounds tested were more active against *P. falciparum NF54* strain than the parent compound curcumin (Abiodun, Falade, et al. 2014, under review). Cyclopentanone analogue of curcumin (CPC) appears to be the most

active compound against chloroquine sensitive *P. falciparum* NF54 with absence of toxicity against the rat skeletal myoblast cell (L6 cell) (table 4). Furthermore, the *in vivo* antiplasmodial activity of the most active compound—cyclopentanone analogue of curcumin was evaluated in an animal model of *P. berghei* using Peter's four day suppressive test. The cyclopentanone analogue of curcumin at a dose of 200mg/kg demonstrated a significant suppression of parasite growth (75%) on day 4 post infection while chloroquine and artemether/lumefantrine had suppression of parasite growth of 90 and 100% respectively (fig. 16).

Table 4: *In vitro* Antiplasmodial Activity and Toxicity Assessment of some of Curcumin and Curmin Analogues

Compound ID	Fifty Percent Inhibitory concentration (IC50 μg/ml)		
	P. falciparum	Cytotox L6	S.I
Curcumin	1.87 ± 0.06	5.68 ± 0.51	3.0
Acyclic analog bisacetate	0.59 ± 0.05	1.11 ± 0.35	1.9
Acyclic analog	0.55 ± 0.07	0.73 ± 0.10	1.3
Cyclopentanone	0.35 ± 0.06	5.53 ± 0.7	15.8
Cyclohexanone	0.68 ± 0.16	2.55 ± 0.37	3.8
Cyclopentanonebis acetate	0.94 ± 0.07	32.35 ± 7.31	34.4
Chloroquine	0.0055 ± 0.002	-	-
Artesunate	0.0011 ± 0.00	-	-

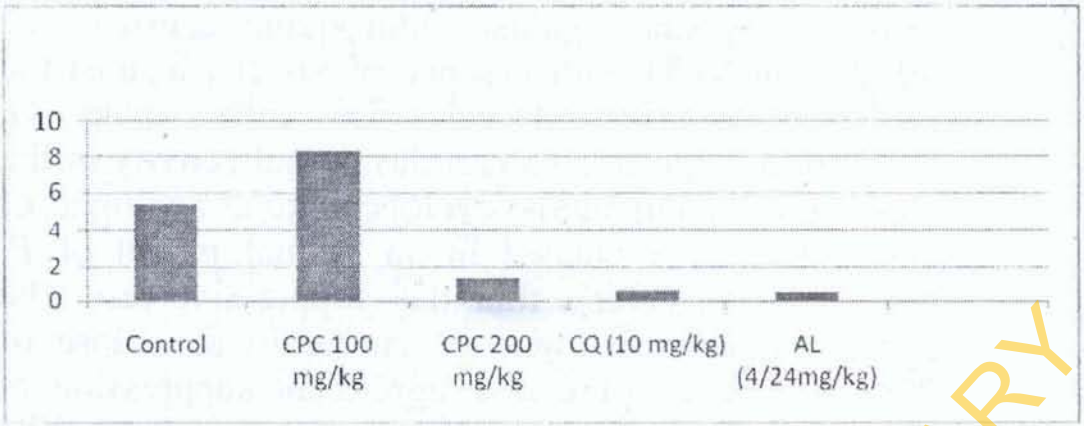


Fig. 16: Percentage parasitaemia on day 4 post-infection after treatment with cyclopentanone analogues of curcumin and standard antimalarial drugs

Some Other Assignments

(1) Global Health and Georesource Management in Africa- teleconferencing facility to the College of Medicine.
(2) Manual on Working as a Peer Educator on Malaria in the Workplace for NIBUCA.
(3) Development of a national malaria policy for Nigeria.

In Conclusion

Malaria has acquired the status of a pandemic, occurring all over the world. The toll exerted by malaria remains unacceptably high in Nigeria. Efforts at malaria eradication have gone a full circle since the mid-1950s and the world has a second chance. Global goodwill, technology, standard operating procedures and know-how are all in place, accessible and unprecedented.

Can it be done? The answer is a definite yes. However, it demands that **ALL** hands must be on deck. The **ALL** includes everybody in this hall today and those who are out there – individuals, communities, LGAs, state and national officials of Nigeria and other countries in the world. It calls for a multi-disciplinary and multi-sectorial approach. The efforts must be intense, coordinated, and sustained over a long time interval of many years. Resurgence will negate all the gains, and the pains will be worse than before the efforts

if we fail to do these. Given the human and material resources that God has endowed Nigeria with, there is no reason for Nigeria to be a high-burden country for malaria!

Recommendations

- Chloroquine has failed as an antimalarial drug and its use in that application should be laid to rest. If done properly, sensitivity may return after many years (decades).
- ***The era of treatment without laboratory confirmation has passed and such practices should be regarded as unethical. ACTs are now the drugs of choice for the management of acute uncomplicated malaria while injectable artesunate is the drug of choice for severe malaria. These should be adopted across board. Good quality RDTs are now available. Without definitive diagnosis, malaria data emanating from Nigeria will be only speculative and we will fail to know where we are with regards to malaria control, elimination and ultimately eradication. Remember – TEST, TREAT & TRACK MALARIA CASES (WHO 2012)***
- The emergence of artemisinin resistance in South East Asia is a wake-up call for us in Nigeria. Fake ACTs, irrational use of antimalarial drugs and poor adherence to even good drugs can only lead to emergence of drug resistant strains of *Plasmodium* and its consequences which entails much suffering from illness and death!. We thank God for NAFDAC and call for intensive and sustained surveillance.
- Healthcare facilities are grossly under-equipped in manpower, training and materials to manage childhood malaria and indeed many other health conditions.
- There is a need for healthcare workers to correct their negative attitudes towards the involvement of alternative healthcare providers in the home management of malaria.

- Mothers and other caregivers of children are usually the first to know that a child has a fever. Studies have consistently shown that the nearer home the treatment for malaria is received, the better the treatment outcome. ACT use in HMM is feasible, acceptable and effective. The HMM Strategy has been adopted in Nigeria; it should be strengthened and pursued with vigour. However, that is only possible if the health system itself is in a good shape. Nigeria has come of age to do just that.
- Availability of national and institutional funding for research and development is absolutely essential for the success in the fight against this moving target – The Malaria Parasite.

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Mr. Vice-Chancellor Sir, distinguished ladies and gentlemen, I thank you all for making time out to attend this lecture and for being such a wonderful audience.

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BIODATA OF
PROFESSOR CATHERINE OLUFUNK E FALADE

Catherine Olufunke Falade was born to the family of late Sir Jacob Adeniyi Falodun and Lady Felicia Bosede Falodun on the 25th of November 1952 both of Ire-Ekiti, Ekiti State. She received her primary education at St. Louis Catholic Primary School, Ado-Ekiti and her secondary education at St. Louis Catholic Secondary Grammar School in Ondo. Catherine graduated in Grade 1 from St. Louis Ondo as the best graduating student in her set. She started advanced level classes at Aquinas College Akure but left midway to take up the offer of admission to study medicine at the University of Ibadan. Catherine Falade graduated from the Faculty of Medicine, now College of Medicine, University of Ibadan in June 1975 with a Bachelor of Medicine: Bachelor of Surgery degree with Distinction in Paediatrics. She received both the Departmental and Glaxo prizes in paediatrics. Her first appointment on leaving the University was into the University College Hospital for house job. She spent the mandatory NYSC service year at the Jaja Health Service in the University of Ibadan following which she was appointed Senior House Officer into the residency program in the Department of Medicine at the University College Hospital, Ibadan. Catherine Falade transferred her services to the then General Out Patient's Department of the University College Hospital in October 1980 from where she was deployed to the Staff Medical Services on its creation. This was to afford her ample time to care for her family. She re-entered the residency program in 1986 which she completed in 1990.

Prof. Catherine Falade holds the Fellowships of both the National and West African Postgraduate Medical Colleges. In addition, she holds an MSc in Pharmacology & Therapeutics from the University of Ibadan. She was appointed Lecturer 1 into the Department of Pharmacology & Therapeutics, University of Ibadan in May 1994. She was promoted to the

grade of Senior lecturer on October 1, 1998 and to the grade of full professor on October 1, 2008.

She is an examiner for both the National and West African Postgraduate Medical Colleges. She is also an external examiner for many Nigerian Universities at undergraduate and postgraduate levels. Catherine Falade is a member of many learned societies including, the International Network for the Rational Use of Drugs (INRUD), Nigerian Medical Association, West African Society of Pharmacologists, The American Society for Tropical Medicine & Hygiene and a fellow of The Royal Society of Tropical Medicine & Hygiene UK.

Professor Falade has successfully supervised six resident doctors for the Fellowship of the Postgraduate Colleges, eight MSc. students and numerous Bachelor of Pharmacy students. She has also co-supervised two MPhil students on the MPH program. She is currently supervising two PhD students. Catherine Falade is currently the Head of the Department of Pharmacology & Therapeutics, a member of UI Senate and has served on numerous committees. Catherine Falade is a consultant Clinical Pharmacologist to the University College Hospital and a member of the Pediatric ACT Advisory Committee of Medicine for Malaria Venture (MMV). She was also a member of the International CDA Independent Data and Safety Management Committee. She is member of the Board of the Institute for Malaria Research & Phytomedicine, University of Port-Harcourt, Committee of experts on malaria, GSK, and the Catholic Home for the Needy. Catherine Falade is a member of the M&E committees of the National Malaria Control Program and only recently completed a major assignment in collaboration with two other consultants (Prof. Gbenga Mokuolu & Dr. Sam Awolola) to develop a National Malaria Policy Document. Prof. Falade has also been involved in writing a manual for peer educators on malaria in the workplace in collaboration with three other consultants – Prof. J.D. Adeniyi, Dr. Ogundeji and Dr. Dunni Arulogun. Catherine

Falade led the University of Ibadan/Nigeria arm of the Global Health & Georesource Management in Africa aspect of AESEDA, [Alliance for Earth Sciences, Engineering and Development in Africa], a multinational partnership with College of Earth and Mineral Sciences of the Penn State University, College Park, Pennsylvania, USA where she was a visiting scientist on two occasions. One of the outcomes of this partnership is the video teleconferencing centre at the College of Medicine, University of Ibadan. I want to thank professors Michael Adewunmi and Collin Airhihenbuwa for a very productive and pleasant time during my visits.

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Catherine is in conjugal bliss with Professor Kayode Falade and the union is blessed with six exceptional children and grandchildren.

NATIONAL ANTHEM

Arise, O compatriots
Nigeria's call obey
To serve our fatherland
With love and strength and faith
The labour of our heroes' past
Shall never be in vain
To serve with heart and might
One nation bound in freedom
Peace and unity

O God of creation
Direct our noble cause
Guide thou our leaders right
Help our youths the truth to know
In love and honesty to grow
And living just and true
Great lofty heights attain
To build a nation where peace
And justice shall reign

UNIVERSITY OF IBADAN ANTHEM

Unibadan, Fountainhead
Of true learning, deep and sound
Soothing spring for all who thirst
Bounds of knowledge to advance
Pledge to serve our cherished goals!
Self-reliance, unity
That our nation may with pride
Help to build a world that is truly free

Unibadan, first and best
Raise true minds for a noble cause
Social justice, equal chance
Greatness won with honest toil
Guide our people this to know
Wisdom's best to service turned
Help enshrine the right to learn
For a mind that knows is a mind that's free