CHAPTER 1

1.0 INTRODUCTION

1.1 Background to the study

Malaria is a disease caused by the parasite of the genus *Plasmodium*. The causative agents in humans are four species of *Plasmodium* protozoa: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae.* Of these, *Plasmodium falciparum* accounts for the majority of infections and is the most lethal.

Malaria is a common and serious tropical disease, which continues to be a huge public health problem throughout the world especially the developing countries. Worldwide prevalence of the disease is estimated to be in the order of 200 - 300 million clinical cases and over 1 million deaths each year (World Health Organisation (WHO), 1999). In many developing countries especially in Africa, malaria exacts an enormous toll on lives, in medical costs, and days of labour lost. It reduces economic productivity and academic performance due to absenteeism from places of work and schools for up to one week during each attack. This is particularly disturbing because the countries concerned are economically poor and/or underdeveloped. In Nigeria, it is a major cause of morbidity and it is still one of the major causes of hospital attendance according to the Federal Ministry of Health (FMOH), 2001).

Malaria is a curable disease if promptly and adequately treated and may present as uncomplicated (non-severe) or severe. Prompt and correct treatment of uncomplicated malaria is important to prevent progression to severe malaria, therapeutic failure and development of drug resistance. Control involves vector control, protection from bites, chemoprophylaxis and treatment of any infection that develops as it is now recognized that for many countries, vector eradication is unrealistic (Parfitt, 1999)

Drug therapy has played an important role in the fight against malaria. Drugs can be used for prevention as well as to cure but the falciparum parasite is developing resistance to drugs used against it. In addition, resistance to many insecticides used to prevent malaria has also been reported (White and Olliaro, 1996). Chloroquine is a first line drug in the treatment of malaria in Nigeria due to the fact that it is cheap, effective, safe, widely and readily available (Salako, 2002). Although there have been reports of chloroquine resistant falciparum malaria (CRFM) in Nigeria (Salako and Aderounmu, 1987; Ekanem *et al*., 1990; Oduola *et al*., 1992; Sowunmi and Salako, 1992; Ketiku, 1995, Sowunmi *et al*., 2000), chloroquine is still highly effective when proper therapeutic doses are given (Basco and Le Bras, 1990; Salako, 2002).

Rational use of drugs (RUD), according to WHO (1985), requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community. RUD includes appropriate prescribing, appropriate drug, appropriate

dispensing and appropriate use by patient. While irrational use of drugs is deviation from rational use of drugs which could be due to inappropriate prescribing, inappropriate dispensing or inappropriate use. Irrational use of drugs has consequences for the health and wealth of the individual patients as well as the community. It can result in wasted resources leading to increased health care costs and reduced availability of other vital drugs, it can also lead to increased morbidity and mortality.

Inappropriate dosage is a form of irrational use of drug that could be due to both inappropriate prescribing and dispensing. Inappropriate prescribing is a manifestation of irrational drug use behaviour when drugs are not prescribed in accordance with guidelines based on scientific evidence to ensure safe, effective and economic use. Inappropriate dosage is one of the factors responsible for therapeutic failure of chloroquine (Bjorkman and Phillips-Howard, 1990; Hellgreen *et al*., 1994; Gomes *et al.,* 1998). Substandard drugs also can contribute to inappropriate dosage and therapeutic failure. Increased benefits from chloroquine or slowing down in progression to resistance could be achieved by focusing on improving prescribing practices, improving drug quality and patient's compliance (Gomes *et al.,* 1998).

The steps involved in improving prescribing practices or drug use are to

1. measure existing practices and identify specific problems (quantitative).
2. understand why they occur (qualitative)
3. suggest possible actions to correct the problems (intervention).

Interventions implemented without gathering this information are likely to fail (Quick *et al.,* 1991).

1.2 Problem Statement

Chloroquine is the first line drug treatment for malaria in Nigeria. However therapeutic failure is on the increase in the management of uncomplicated malaria using chloroquine (Salako and Aderounmu, 1987; Ekanem *et al*., 1990; Oduola *et al*., 1992; Sowunmi and Salako 1992; Ketiku 1995, Sowunmi *et al*., 2000). This could be due to many factors including inappropriate prescribing, poor quality of drugs, poor patient compliance, resistance etc (Gomes *et al.,* 1998). However very little systematic research has been done to investigate these factors.

Development of new drugs and insecticides is a very costly process both in time and money. While waiting for new drugs to be discovered, developed and deployed, appropriate measures should be taken to safeguard the few compounds available (White and Olliaro 1996).

There have been published reports on prescription pattern of antimalarial and/or irrational prescribing or use of chloroquine (Taylor *et al.,* 1998; Tekobo *et al*.,2004) but no published reports on intervention to improve the chloroquine prescribing habits in public health facilities in Lagos State. Available literature reveals that studies on adequate dosage of chloroquine in management of malaria has been based on questionnaire administration and no reports of studies carried out on the prescription process of adequate dosage are currently available in literature. Consequently the present study was designed to investigate the prescribing pattern in the management of uncomplicated malaria in all Lagos State General Hospitals (LSGH) since it has been reported that resistance to some of the drugs or therapeutic failure, can arise from irrational prescribing.

1.3 Objectives of the study

The objectives are to

1. Conduct a situation analysis of the prescribing pattern of chloroquine in the management of uncomplicated malaria in Lagos State General Hospitals (LSGH).
2. Investigate the factors that influence the observed prescribing pattern of chloroquine in these health facilities.
3. Determine the quality of chloroquine dosage forms available in LSGH
4. Determine the cost effectiveness of chloroquine tablet and injection
5. Conduct an intervention in order to improve prescribing pattern
6. Compare the impact of two modes of educational intervention on chloroquine prescribing pattern of prescribers in LSGH.

1.4 Research Questions / Hypotheses

1.4.1 Research Questions

1. What is the prescribing pattern of chloroquine in Lagos State General Hospitals?
2. What are the factors responsible for the observed prescribing pattern?
3. Are there problems with the quality of the chloroquine formulations available in these hospitals?
4. Is chloroquine tablet more cost effective than chloroquine injection?
5. Is there any difference between correct dosage of chloroquine prescribed pre and post - intervention?
6. Is there any difference between correct dosage of chloroquine prescribed under the different modes of intervention?

7. Is there any difference in the correct dose of chloroquine prescribed between the different dosage forms?

1.4.2 Research Hypotheses

The following hypotheses were examined in this study

1. The percentage of prescriptions with correct dosage of chloroquine after the educational intervention will not be statistically different from before intervention.
2. The quality of the chloroquine formulations available in these hospitals meets the official recommended standard
3. Chloroquine tablet is more cost effective than chloroquine injection
4. The percentage of prescriptions with correct dosage of chloroquine in the plastic box intervention group is not statistically different from that in the poster intervention group.
5. There is no relationship between the dose of chloroquine and the different dosage forms of chloroquine prescribed

1.5 Significance of the study

This study is significant in the management of malaria in Nigeria especially Lagos State with a high population density. The findings will add to the body of knowledge in rational use of drugs and highlight the role of educational intervention in improving prescribing pattern. It might also assist in the documentation of the quality of chloroquine formulations available in Lagos State General Hospitals.

1.6.0 Theoretical framework

Theories from social and behavioural science can make an important contribution to the process of developing a conceptual framework for improving use of clinical practice guidelines and clinician performance and consequently, improved drug use (Moulding *et al*., 1999). It is impossible to exhaust the list of theories from social and behavioural science. There are five general theories from social and behavioural science that are relevant to this study. These are diffusion of innovation theory, health education theory, social influence theory, transtheoretical model of behaviour change and social ecology. Of these five theories, four of them are applicable to the present study and some details of these are given below.

1.6.1 Diffusion of innovation theory

Diffusion of innovation theory derives from communication theory and describes the process by which an innovation is communicated through certain channels over time to a member of a social system (Schramm and Lerner, 1978). This theory places an emphasis on the role of the change agents (Rogers and Shoemaker, 1971; Rogers, 1983). It involves an essentially rational conceptualization of behaviour where knowledge and attitude change alone are considered to lead to changed practice (Macdonald, 1992). It is believed that change in knowledge will lead to change in prescribing habit in this study.

1.6.2 Health education theory

A central tenet of health education theory is that behaviour change cannot take place without attention to gaps in both knowledge and skills (Green *et al*., 1980). Another tenet is that the positive impact of education is proportional to the degree of active

rather than passive participation of the learner. Thus, educative processes need to incorporate interactive, participatory elements as well as information provision. A reminder for appropriate care might be considered a reinforcing factor. It is believed that education plus a form of reminder will produce a positive change in the prescribing habit of the prescribers.

1.6.3 Social influence theory

Social influence theory emphasizes the role of others in decision making about behaviour, postulating that factors such as custom, habit, assumptions and beliefs of peers, prevailing practices and social norms shape the interpretation of information provided through education (Mittman *et al*., 1992). The perceived opinion of peers, opinion leaders, patients and other health professionals play a part in influencing the attitudes of individual practitioners (Hayward *et al*., 1996; Felch and Scanlon, 1997). Hence social influence based strategies for implementing guidelines might include academic detailing (personal visit by a trained person to physicians at their practice), group education, the use of opinion leaders and mass media education strategies such as publication in journals or campaigns (Conroy and Shannon, 1995). It is expected that group education of the prescribers at their different hospitals might influence their prescribing habits and use of guidelines reminder.

1.6.4 Transtheoretical model of behavioural change

The transtheoretical model of behavioural change, often referred to as the "readiness to change model" has a broader conceptualization of the factors which influence change. Prochaska and DiClemente, (1983), suggest that behaviour change is a continual process made of five main stages: 1) pre-contemplation 2) contemplation 3)

preparation 4) action, and 5) maintenance. In this study pre-contemplation refers to the stage when the prescribers have no intention to change their prescribing pattern probably because they are not aware of the fact that they are not prescribing rationally. At the contemplation stage they are being informed of their irrational prescribing and are considering changing. At preparation stage they are actually preparing to change their prescribing pattern after being informed of their irrational prescribing pattern. At the action stage they are actually changing their prescribing pattern and finally at the maintenance stage they have continued to prescribe according to the guidelines for over 6 months. Relapse can occur during action or maintenance where the individual relapses to the behaviour before the action stage. At relapse stage they are going back to their old prescribing pattern.

1.7 Conceptual Framework

The conceptual framework of this study is adapted from the International Network for Rational Use of Drugs (INRUD) framework for formative and intervention studies by Quick *et al.*, 1991 (Fig 1). The first stage is to define problems with drug use patterns which in this study is prescribing problem. This may be done through a prescription survey, review of drug management data or observation of a particular practice or event. The second stage is to identify motivating factors underlying causes of the problem (informational). This may involve qualitative investigational methods. The third stage is to package possible interventions to correct the specific problems. Each intervention must be monitored and evaluated to assess its impact. Evaluation of impact needs to be directed at the specific prescribing pattern or prescribing behaviour that the intervention is designed to affect.

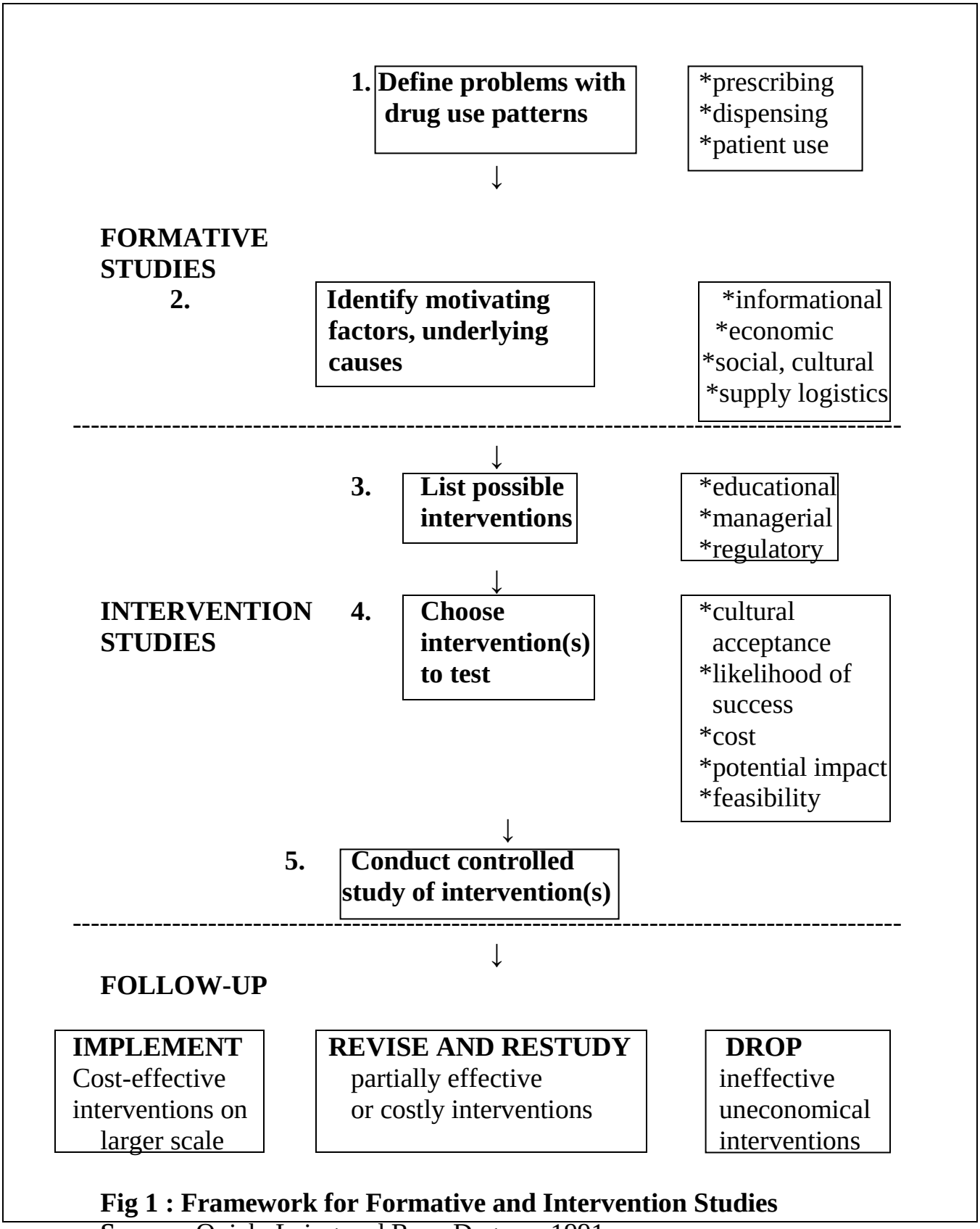

Fig 1 : Framework for Formative and Intervention Studies
Source: Quick, Laing and Ross-Degnan, 1991

CHAPTER 2

2.0 LITERATURE REVIEW

2.1 Malaria

Malaria is a disease caused by the parasite of the genus *Plasmodium*. Malaria is by far the world's most important tropical parasitic disease and kills more people than any other communicable disease except tuberculosis.

In many developing countries and in Africa especially, malaria exacts an enormous toll, on lives, medical costs and days of labour cost. It reduces economic productivity (performance) due to absenteeism from schools and places of work for up to a week during each attack of malaria.

The causative agents in humans are four species of Plasmodium parasites; *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae.* Of these, *P. falciparum* accounts for the majority of infections and is the most lethal. Malaria is a curable disease if promptly and adequately treated.

The Global Picture (WHO 1999)

- Worldwide prevalence of the disease is estimated to be on the order of 200 - 300 million clinical cases each year;
- 2400 million people are at risk;
- More than 90% of all malaria cases are in sub-Saharan Africa;
- Mortality due to malaria is estimated to be over 1million deaths each year;
- Almost 90% of all deaths occur in sub-Saharan Africa;
- The vast majority of deaths among are young children in Africa;

- It is responsible for the illness of one out of every 10 persons admitted to hospitals in Africa;
- High-risk groups are children under 5 years; pregnant women (especially 1st and 2nd pregnancy), non-immune travelers, persons entering endemic areas and the old

WHO's Global Malaria Control Strategy (WHO 1993)

1. Provisions of early diagnosis and prompt treatment for the disease;
2. Planning and implementation of selective and sustainable preventive measures, including vector control;
3. Early detection for the prevention or containment of epidemics;
4. Chemoprophylaxis or intermittent treatment in pregnant women;
5. Use of Insecticide treated nets;
6. Strengthening of local research capacities to promote regular assessment of countries malaria situations, in particular the ecological, social and economic determinants of the disease.

Malaria Situation in Nigeria (FMOH 2001)

- Malaria occurs throughout Nigeria in all the country's ecological zones (forest, coastal, mangrove, savannah and sahel);
- Mortality and morbidity patterns are the same throughout the country;
- The mosquito vectors which are largely responsible for transmission of malaria in Nigeria are *Anopheles gambiae, Anopheles arabiensis* and *Anopheles funestus* ;

- Malaria is characterized by a stable perennial, transmission in all parts of the country with greater intensity in the wet than in the dry season. This seasonal difference is more striking in the northern part of the country;
- *Plasmodium falciparum* is responsible for about 98% of all cases in the country and *P. malariae* usually occurs as a mixed infection with it;
- Malaria is the commonest cause of out-patient hospital attendance in all age groups in all parts of Nigeria and is among the 4 commonest causes of childhood mortality in the country;
- The nation loses over ₦132 billion from cost of treatment and absenteeism from work, schools and farms;
- Death in malaria usually results from severe complicated forms of which the most lethal is cerebral malaria. Malaria is a medical emergency if mortality is to be reduced significantly.

Current Strategy to Deal with Malaria in Nigeria

Current strategy is **control**

Control means a reduction in the morbidity and mortality from the disease to a level at which it ceases to constitute a major public health problem. Control strategies include:

- Case management, that is early diagnosis and access to prompt effective treatment within 24 hours of the onset of symptoms;
- Chemoprophylaxis in suitable groups like pregnant women (especially 1st and 2nd pregnancies), persons with sickle cell disease and non-immune visitors/residents and immune-compromised patients.
- Personal protection to reduce man-vector contact;

- Vector control appropriate to the prevailing epidemiological and socio-economic circumstances such as reducing breeding of mosquitoes through community mobilization to improve environmental sanitation. Such mobilization can to be supervised by Environmental Health officers.
- Health education;
- Surveillance, monitoring and evaluation;
- Operational research;

Treatment protocol

- ❖ Treatment of non-severe malaria with chloroquine base 25mg/kg body weight as shown in the Table I (FMOH 2001).
- ❖ Treatment of chloroquine-resistant malaria or patients with contraindication to chloroquine (BNF 2004)
  - A single dose of Sulphadoxine 500mg/Pyrimethamine25mg (Fansidar) or Sulphalene 500mg/Pyrimethamine 25mg (Metakelfin)
  - Quinine 10mg/kg body weight every 8 hours for seven days followed by sulphadoxine-pyrimethamine if quinine resistance is suspected; or doxycycline 200mg daily for 7 days if sulphadoxine-pyrimethamine resistant.
  - Mefloquine 20 –25 mg/kg (base) as a single dose (up to 1.5g) or preferably as 2 divided doses 6 - 8 hours apart.
  - Halofantrine 1.5g of halofantrine hydrochloride divided into 3 doses i.e. 500mg every 6 hours (on an empty stomach). Repeated after 1 week.

- Malarone^{R} (Proguanil with atovaquone); 4 'standard' tablets once daily for 3 days.
- Artemisinin and related compounds {Artemether – (Paluther^{R} inj); - Artesunate (Arsumax^{R} Tab), Dihydroartemisinin – (Cotecxin^{R} Tab), Artemether with lumefantrine - (Riamet^{R,}, Coartem ^{R})}

- Artemether Inj. 480mg over 3 days –80mg bd (Adult)
- Artemether Inj. 9.6mg/kg for 3 days i.e 3.2mg/day (Children)
- Artesunate tab 100m bd on day1, then 50mg bd from day 2 to day 5
- Dihydroartemisin tab 200mg on day1, then 100mg for 4-5 days.
- Riamet^{R} (artemether with lumefantrine); adults over 35kg 4 tablets initially followed by 5 further doses of 4 tablets at 8,24,36, 48 and 60 hours.

N.B. It is not necessary to give Fansidar or doxycycline after mefloquine, Halofantirine, Malarone^{R,} or Riamet^{R} treatment

Chemoprophylaxis

Pregnant women, initially chloroquine base 600mg (Day 1), 600mg (Day 2) and 300mg (Day 3); then followed by 300mg weekly. Intermittent Preventive Therapy (IPT) with sulphadoxine-pyrimethamine as one full treatment dose during the 2nd and 3rd trimester not later than one month before expected date of delivery.

Children and adults with sickle cell disease - Pyrimethamine 0.5mg/kg body weight once weekly; Proguanil 3mg/kg body weight once daily; Chloroquine, if instructed by a specialist, 5mg/kg body weight once weekly.

Non-immune visitors/residents - Chloroquine base 5mg/kg body weight (averagely 300mg once weekly for an adult) + Proguanil about 3.5mg/kg (averagely 200mg once daily for an adult) for up to 5 years. Mefloquine 250 mg weekly for up to 1year. Doxycycline 100mg daily for up to 2 years. Malarone 1 tablet daily for up to 3 – 6 months.

Control of malaria involves vector control, protection from bites, chemoprophylaxis and treatment of any infection that develops. It is now recognized that for many countries including Nigeria, vector eradication is unrealistic.

CQ TREATMENT OF NON – SEVERE MALARIA 1 Tablet = 150mg CQ base Syrup 1 tsp (5ml) = 50mg CQ base Injection: 3.5mg/kg 6 or 8 hourly until a total dose of 25mg/kg (1 amp (5ml) = 200mg CQ base; 1 ml = 40 mg CQ base)				
AGE (YRS)	**WEIGHT (KG)**	**1ST DAY**	**2ND DAY**	**3RD DAY**
< 1	< 9.9	½ Tab ◗ 7.5ml(1½tsp)	½ Tab ◗ 7.5ml(1½tsp)	¼ Tab ◔ 3.75 ml(¾ tsp)
1 – 3	10 - 14.4	1 Tab ● 15ml(3tsp)	1 Tab ● 15ml(3tsp)	½ Tab ◗ 7.5 ml(1½tsp)
4 - 6	14.5 -18.4	●◗ 1 ½ TABS	●◗ 1 ½ TABS	● 1 TAB
7 – 11	18.5 -34.9	●● 2 TABS	●● 2 TABS	● 1 TAB
> 12	> 35	●●●● 4 TABS	●●●● 4 TABS	●● 2 TABS

Table I: Treatment of non-severe malaria with Chloroquine (Extracted from FMOH 2001 recommendation)

2.2 Roll Back Malaria (RBM)

The Roll Back Malaria (RBM) Initiative is a creation of the World Health Organization (WHO). It was announced at the World Health Assembly in May 1998 by Dr G. Harlem Brundtland, the Director-General of WHO. RBM aims to coordinate global action to fight malaria and help governments reach their own individual targets to combat the disease in their country (TDR news, 1998).

RBM will provide overarching coordination of all efforts at malaria control; it will promote the development and better utilization of all tools for malaria control - old, new and future - as and where appropriate, and it will help strengthen the health sector, but it will be driven by the countries (TDR news, 1999)

Tools for malaria control that will be implemented through networking include, insecticide-treated bed-nets, rectal suppositories, the package of essential interventions for Care of the Sick Child, simple packaging of antimalarials to help ensure people take the proper course of treatment, improved referral for severe malaria by mothers and tradition healers, and training of drug suppliers in provision and counseling for safe use of antimalarials. Networking will also help ensure that locally produced antimalarials meet Good Manufacturing Practice standards and that favourable pricing structures for antimalarials are created for poor peoples, that epidemics are forecast better, and that drug and insecticide resistance are detected and their spread slowed. But will it work? One reason for a positive answer is that we know we can better control malaria with the tools at our disposal today, and this is without the new tools

that are on the horizon - vaccines, resistant mosquitoes, new drugs. We also know that there is capability for malaria research and control in endemic countries (TDR news, 1999).

One lesson learned in the 50s and 60s was that dedicated campaigns for eradication are not sustainable and that there is no one solution to fit all malaria situations - each situation is unique. That is why one of the first steps in RBM is for each country to carry out a situation analysis (of local malaria treatment and prevention practices, availability and quality of health care, etc) and needs assessment and, on the basis of this, incorporate actions for roll back malaria within health sector development.

Malaria should be rolled back in its own right through the strengthening of health services (TDR news, 1998). The two most important elements of ensuring that malaria won't appear again once rolled back are, firstly that the RBM project is going to address the weak aspects of the health sector. So the approach is not to circumvent a weak health sector, but to strengthen it and that is certainly important for sustainability. The second is that this operation is going to be driven by people in the endemic countries, and that is another very important aspect of making sure that there will be no relapse this time".

In 2000 April, the African Summit on Roll Back Malaria was held in Abuja. Thus, for the first time, many nations gathered together to discuss, plan, review and look for the way forward about the scourge of malaria.

Objectives of RBM

The goal of RBM is graded or progressive (WHO 2000). It does not pretend or assume that malaria could be eradicated at a go. It is hoped that by the year 2005:

- About 60% of malaria sufferers should have ready access to affordable and appropriate treatment;
- At least 60% of those at risk of malaria, particularly pregnant women, should benefit from the most suitable combination of personal and community protective measures;
- At least 60% of all pregnant women who are at risk of malaria, especially those in their first pregnancies, should have access to effective treatment.
- Malaria deaths should have reduced progressively by 50% by the year 2010.
- Deaths should have reduced by another 30% by the year 2015
- Deaths should have reduced by another 20% by the year 2025.
- By 2030, malaria will neither be a major contribution to mortality and morbidity nor of socio-economic consequences

Six elements of RBM:

There are basically six elements of the Roll Back Malaria programme. These are:

1. Rapid diagnosis and treatment,
2. Better multi-pronged protection using Insecticide Treated Nets (ITNs), chemoprophylaxis and environmental management,
3. Focused research to develop new medicines, vaccines and insecticides and to help epidemiological and operational activities,
4. Coordinated actions for strengthening existing health services, policies and providing technical support,
5. Evidence based decisions using surveillance, appropriate responses, and building community awareness,

6. Harmonized actions to build a dynamic global movement.

The role of the pharmacists in RBM

It is quite obvious that the pharmacist has a very important role to play in RBM since chemotherapy is one of the mainstay of malaria control. According to Mosanya (2001), the pharmacist should be actively involved in the following:

- Developing (with other health professionals) an antimalarial first aid kit fitted with equipment for simple diagnostic tests and affordable drugs for early treatment for every household especially the 'at risk' group.
- Improving antimalarial drug use all over the country and assessing the benefits of such improvements.
- Making visible efforts in public understanding of the value of ingesting the full regimen of antimalarials in order to achieve complete cure. Simple technologies (e.g.) blister packaging) should be developed to achieve compliance.
- Exerting more efforts to reduce the availability of fake or substandard drugs in the market
- Improving drug use through drug packaging, public information and assessment of quality of drugs
- Counselling mothers on home treatment of malaria which is one of the strategic activities of RBM in the communities
- Developing repositories which contain well-characterized parasites from treatment failures and successes. This takes into account the recognition of drug

distribution and use to monitor resistance (this requires an intersectoral collaboration).

- ❖ Ensuring sustainable quality assurance system. The overall goal is to guarantee a zero-defect product to the consumer and the communities
- ❖ Strengthening the consortium of pharmacology, pharmacy and pharmacognosy, traditional and herbal medicine centers doing clinical studies for the discovery, design and development of new antimalarial drugs
- ❖ Agreeing on what the pharmacists want for waiver of tax in order to bring down the cost of drugs.

2.3 Rational Use of Drug (RUD)

2.3.1 Rational Use of Drugs

The conference of experts on the rational use of drugs, convened by the World Health Organization (WHO) in Nairobi in 1985 defined rational use of drugs as follows: "rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community".

Irrational drug use occurs with poly-pharmacy, with the use of wrong or ineffective drugs, or with under-use or incorrect use of effective drugs. These actions have adverse impact on the quality of drug therapy, cost and may cause adverse reactions or negative psychosocial impacts.

Rational Drug Use includes the following criteria (Quick *et al., 1997)***:***

- Correct drug
- Appropriate indication (i.e. the reason to prescribe is based on sound medical considerations)
- Appropriate drugs, considering efficacy, safety, suitability for the patient and cost;
- Appropriate dosage, administration and duration of treatment;
- Appropriate patient (i.e. no contraindications exist and the likelihood of adverse reactions is minimal;
- Correct dispensing, including appropriate information for patients about the prescribed medicines;
- Patient adherence to treatment

The Prescriber:

The prescriber should follow a standard process of prescribing which starts with a diagnosis that defines the problem that requires intervention or management.

The therapeutic goal is then defined. The prescriber decides which treatment is required based on up-to-date drug and therapeutic information to achieve the desired goal for an individual patient. When the decision to treat the patient with drugs is made, the best drug for the patient is selected based on efficacy, safety, suitability and cost. The dose, route of administration and duration of treatment are determined, taking into account the condition of the patient. The prescriber should provide information to the patient about both the drug and the patient's condition. Finally, the

prescribers should decide how to monitor the treatment, after considering the probable therapeutic or adverse effects of treatment.

The Dispenser:

The 'dispenser' should make sure the drugs are dispensed to the patient in a safe and hygienic manner and makes sure that the patient understands the dosage and course of therapy by proper counselling of the patient.

The Patient

The patient should take the drugs and adhere to the dosage and course of therapy. Adherence occurs if the patient (and the community) understands and appreciates the value of taking specific drugs or specific indications.

2.3.2 Irrational Use of Drugs (Quick *et al*., 1997; WHO 2002):

Irrational use of drugs is deviation from rational use of drugs. Irrational use of drug occurs in all countries.

These include:

1. No drug needed: Use of drug when no drug is needed. Includes non-therapeutic uses of pharmaceuticals (e.g. using antimicrobials or antidiarrhoeals instead of oral rehydration solution (ORS) to treat acute diarrhoea in children).
2. Wrong drugs: Selecting wrong drugs for an indication (e.g. using tetracycline to prevent recurrence of rheumatic fever following streptococcal pharyngitis in children)
3. Ineffective drugs and drugs with doubtful efficacy (e.g. excessive use of multivitamin preparations or tonics);

4. Unsafe drugs: When unsafe drugs are prescribed/used the likelihood of adverse reactions outweigh the therapeutic effect (e.g. anabolic steroid for growth and appetite stimulation in children or athletes); dipyrone a drug banned in most developed countries is used indiscriminately for a large variety of minor ailments in Nigeria.

5. Under-use of available effective drugs: This occurs when needed medications are not prescribed or used (e.g. under-use of effective oral rehydration therapy for acute diarrhoea).

6. Incorrect use of drugs: This occurs when the length of treatment is short (e.g. two days' supply of antibiotics rather than the full course of therapy which is usually a minimum of 5 days). Another example is over-use of injections.

Factors Underlying Irrational Use of Drugs (Finer and Tomson 1992)

There are many interrelated factors influencing use of drugs. The prescriber, dispenser, patient, community and health system are all involved in the therapeutic process and all can contribute to irrational use in a variety of ways.

Prescriber Factors:

- Inadequate training
- Lack of continuing education which leads to outdated prescribing practices
- Poor role model - role models who are imitated may not prescribe rationally
- Inadequate and/or unreliable drug information by drug representatives
- Financial interest
- Heavy patient load

- Pressure to prescribe from peers, patients and drug representatives
- Incorrect generalization about the effectiveness or side effects of drugs
- Inappropriate desire for prestige

Dispenser Factors:

- Poor or inadequate training
- Heavy patient load
- Shortage of dispensing materials
- Lack of or inadequate supervision
- Low status of dispenser
- Poor remuneration
- Communication/counselling problems

Patient and Community Factors

- Non-compliance
- Communication skills of the prescriber and dispenser
- Cultural beliefs
- Short consulting time
- Lack of printed information
- Misleading belief of efficacy of certain drugs or routes of administration
- Patients' demands/expectations

Health System:

- Unreliable supply
- Drug shortages
- Expired drugs

- Availability of wrong or non-essential drugs

Inefficiencies in the Health system:

These lead to a lack of confidence in the system by the prescriber and the patient. It reduces the efficiency of the dispenser. The patient demands treatment and the prescriber feels obliged to give what is available, even if the drug is not the correct one to treat the condition or it can lead to out-of-stock syndrome. This will eventually lead to therapeutic failure.

Adverse Impact of Irrational Drugs Use (Hardon and le Grand, 1993; Quick *et al*., 1997; WHO 2002):

1. Impact on Quality of Drug Therapy and Medical care: Irrational drug use can jeopardize the quality of patient care and negatively influence the outcome of treatment. The likelihood of adverse drug reactions increases e.g. misuse of injectables being implicated in a high incidence of anaphylactic shock. Also over-dosage or under-dosage of antibiotics and chemotherapeutic agents leads to the rapid emergence of resistant strains of bacteria or malaria parasite.
2. Impact on cost: Over-use of drugs, even essential ones causes waste of financial resources by both patients and the health care system. Inappropriate or under-use of drugs at an early stage of a disease may also produce excess costs by increasing the probability of prolonged disease and eventually hospitalization.
3. Psychosocial Impact: The concept that there is a pill for every illness is harmful. Patients come to rely on drugs and this reliance increases the demand for them.

Some patients may demand unnecessary injections because they believe injectables work better than oral drugs.

2.3.3 Strategies to Promote Rational Use of Drugs (Quick *et al*., 1997)

Before attempting to change drug use, the scale of the problem should be assessed and quantified. The underlying reasons for the problem behaviours then need to be investigated. Quantitative and qualitative methods are used for assessing drug use. These will be dealt with extensively under drug utilization studies.

Developing a Strategy

Six steps to follow in developing a strategy to promote rational drug use are as follows:

Step 1: Identify the problem and recognize the need for action;

Step 2: Identify underlying causes and motivating factors;

Step 3: List possible interventions;

Step 4: Assess resources available for action;

Step 5: Choose an intervention or interventions to test;

Step 6: Monitor the impact and restructure the intervention

2.4.0 Drug Utilization Studies (DUS)

2.4.1 Drug Utilization Studies (DUS)

Drug utilization has been defined by the World Health Organization (WHO) as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (WHO 1977). This broad definition differs from the more narrow one which is “the prescribing,

dispensing and ingesting of drugs" (Conley, 1976). Studies of the process of drug utilization focus on the factors influencing and events involved in the prescribing , dispensing, administration and taking of medication According to the WHO definition, studies of drug utilization include not only studies of the medical and non-medical aspects influencing drug utilization, but also the effects of drug utilization at all levels. The general objectives of drug utilization studies are: "problem identification and problem analysis in relation to importance, causes and consequences; establishment of a weighted basis for decisions on problem solution; assessment of the effects of the action taken. These objectives are relevant to problems and decisions-making throughout the drug and health chain. The approaches may vary according to the purpose and the needs of the users which include the health authorities, drug manufacturers, the academic and clinical health professionals, social scientists, economists, the media and consumers (Lunde and Baksaas, 1988).

The ultimate goal of drug utilization research must be to assess whether drug therapy is rational or not. To reach this goal, methods for auditing drug therapy towards rationality are necessary (WHO 2003).

DUS embraces two main aspects, the process of drug utilization along the drug chain in the society, and how drug utilization relates to the effects of drugs used (Baksaas 1984). These studies can provide reliable information on the cost and effects (harmful and beneficial) of drugs. The information can be of a great use in the subsequent elaboration of pharmacoeconomic studies, or in the selection of problematic areas in which these studies may be applied.

Retrospective DUS gather information and detect problems in the population after they have occurred. Existing data are used, they are less expensive to carry out and can describe practices over a longer period of time. The retrospective studies used for health problems detection are the main basis to define objective, administrative and educational interventions with the aim of modifying and improving drug utilization patterns in accordance with previously established criteria (Brodie 1972).

Prospective DUS anticipate and avoid problems that might occur in a particular patient prior to consumption of the drug; e.g. when the drug is sold in the pharmacy (Erwin 1991). They are more expensive to carry out. They provide information about the treatment setting, diagnostic process, communication between heath providers and patients, or the time of consultation and dispensing (Quick *et al*., MSH 1997)

The Defined daily dose (DDD) is the unit of measurement in DUS. It allows comparisons between drugs in the same therapeutic class and between different health care settings or geographical areas. DDD is usually the adult dose and is the typical dose of a drug used to treat the most common medical problem for which the drug is presented.

Drug utilization study at institutional or regional levels is termed drug utilization review (DUR) or drug use evaluation (DUE) (WHO 2003). Drug utilization review, sometimes referred to as drug use evaluation, is a system of continuous, systematic, criteria-based drug evaluation that ensures the appropriate use of drugs. It is a method of obtaining information to identify problems related to drug use and if properly developed, it also provides a means of correcting the problem and thereby contributes to rational drug therapy (Quick *et al.,* 1997; WHO 2003).

Reasons for carrying out drug use studies

There are 3 main reasons for carrying out drug use studies:

1. To describe current patterns of drug use:

   Measure consumption of particular drugs or therapeutic groups of drugs;

   Compare use by individual health facilities or prescribers, regions/countries;

   Decide whether drug us is clinically justified or cost effective;

   Learn about the influence of prescribing on pharmaceutical costs.

2. To Correct specific drug use problems:

   Find out about the factors that cause specific problem practices;

   Identify and correct problems in prescribing, dispensing or patient use.

3. To monitor drug use over time:

   Monitor the quality of care within a health facility or geographical area;

   Monitor the efficiency and cost effectiveness of prescribing.

A health manager or policy maker or researcher who wishes to improve drug use proceeds through a cycle of activities that includes:

1. Assessing current patterns of drug use;
2. Defining standards of appropriate practice and identifying problems and causes;
3. Carrying out interventions to improve specific problems;
4. Evaluating improvements and monitoring subsequent practices.

There are 2 basic ways to gather data for investigating or improving drug use either quantitatively or qualitatively:

Quantitative methods which answer the question "**what is happening**"?

Qualitative methods which answer the question "**why is it happening**"?

Quantitative DUS have been used to:

1. Ascertain the quantities of drugs consumed in a specific period and in a specific geographical area.
2. Investigate the development of drug utilization over time: quantitative methods are those used to collect data on such things as number of drugs prescribed or the cost of antibiotic therapy. Quantitative data are used to create rates, averages, or other summary measures to describe the nature and extent of a drug use practice.
3. Compare drug consumption in different geographical areas
4. Identify possible over-or under-utilization of drugs.
5. Estimate the utilization according to variables such as age, sex, social class, etc.
6. Estimate the prevalence of particular illnesses based on the consumption of drugs utilized in their treatment (Bakasaas and Lunde, 1981; Bergman *et al.*, 1978).
7. Evaluate impact of interventions.

Sources of quantitative data on drug use include:

Indicators for health facilities;

Drug utilization reviews;

Case records reviews

Aggregate data which measures consumption of specific drugs or drug classes

Private sector drug use

The most important source is the drug use encounter (period of interaction between patient and health provider) and the most common data sources are patients' charts, dispensing records/prescriptions, medication administration records, laboratory reports, medical records, drug supply orders and stock cards.

Qualitative DUS on the other hand assess the appropriateness of drug utilization. Qualitative methods answer the questions 'why is it happening'? They require the establishment of quality criteria for drug use such as indications for use, daily dose, duration or treatment, the most suitable dosage and dosage form for each indication, utilization of fixed combinations of drugs when only one of its components is justified.

Qualitative methods are useful for examining underlying feelings, beliefs, attitudes and motivations in an observed problem (MSH/INRUD 1995). The most common qualitative techniques include

- Focus group discussion
- In-depth interview
- Structured observation of the process of care
- Structured questionnaire
- Simulated patient survey

Each method has strengths and weaknesses and is appropriate for different circumstances.

Quantitative methods are used to describe drug use patterns or to pinpoint specific problems that need attention but they are not good for understanding why these patterns or problems exist. Qualitative methods are better suited for understanding why these patterns or problems exist. Interventions implemented without gathering this information are likely to fail.

One use of quantitative and qualitative methods is to gain a better understanding of the causes of problems before intervening to correct them.

2.4.2 Studying Drug Use in Health Facilities Using WHO Indicators

To encourage consistency in drug use studies the World Health Organization (WHO) and the International Network for Rational Use of Drug (INRUD) produced a manual for investigating drug use in health facilities (WHO/DAP 1993; Hogerzeil *et al.*, 1993). The manual defines core drug use indicators and provides a methodology for measuring these indicators.

The WHO Manual defines twelve core and seven complementary drug use indicators that measure key aspects of drug prescribing; patient care and availability of drugs and drug information at Out-patient facilities.

With these indicators, result should point to specific drug use problems that need to be examined in more details. All the necessary data are collected from medical records or by direct observation at individual health facilities.

To measure drug use, data is collected from a sample of health facilities. The number of health facilities to be included in the survey depends on the purpose of the survey. A regional or national drug use survey includes at least twenty facilities selected at random; with 30 drug use encounters sampled per facility, for a total of at least 600 encounters for the entire study. When the objective is to study drug use by individual facilities or prescribers in a sample, at least 100 prescriptions should be obtained at each health facility or for each prescriber. When possible, the prescribing data are based on one year of retrospective encounters, although prospective data can be collected if no retrospective data are available. Data on patient care and facility indicators are always collected prospectively.

WHO Drug Use Indicators (Out-patient Facilities) (WHO/DAP 1993)

Core drug use Indicators

Prescribing Indicators

1. Average number of drugs per encounter;
2. Percentage of drugs prescribed by generic name;
3. Percentage of encounter with an antibiotic prescribed;
4. Percentage of encounters with an injection prescribed;
5. Percentage of drugs prescribed from essential drugs list or formulary

Patient Care Indicators

6. Average consultation time
7. Average dispensing time
8. Percentage of drugs actually dispensed
9. Percentage of drugs adequately labeled
10. Patients' knowledge of correct dosage

Health Facility Indicators

11. Availability of a copy of essential drugs list or formulary
12. Availability of key drugs

Complementary Drug Use Indicators

13. Percentage of patients treated without drugs
14. Average drug cost per encounter
15. Percentage of drug costs spent on antibiotics
16. Percentage of drug costs spent on injections
17. Prescription in accordance with treatment guidelines

18. Percentage of patients satisfied with the care they received

19. Percentage of health facilities with access to impartial drug information.

2.4.3 Surveying Private Sector Drug Use

Private sector practices can be examined by surveying private practitioners and investigating practices at retail drug sales outlets. Retail studies use methods such as interviews, stock or prescription surveys and observation of interactions with customers or exit interviews. One method of studying retail drug use that deserves special mention is the simulated patient survey; such consist of visits to retail outlets by investigators posing as customers with specific health problems. It is a particularly useful technique for studying retail practices.

2.4.4 Examining Drug Use in the Community

To learn about community drug use, it is necessary to use techniques different from those discussed so far. A simplified methodology combines a household interview survey, surveys of drug distribution channels such as heath centers or pharmacies, and qualitative investigations using focus groups or in-depth interviews (WHO/DAP 1992).

A minimum of 100 - 400 households should be surveyed depending on the desired precision of the results and available resources. Different types of information that can be collected from household surveys include:

- Knowledge about drugs and illness, including sources of community information about drugs;

- Reported care-seeking and drug use behaviour in general or during specific episodes of illness;
- Drug inventories, to identify the type and source of all drugs present in the household;
- Health care and pharmaceutical expenditures;
- Adherence (compliance), including purchase of prescribed drugs and actual patterns of drug consumption.

2.5 INTERVENTIONS

Improving Prescribing

Inappropriate prescribing is a manifestation of irrational drug use behaviour when drugs are not prescribed in accordance with guidelines based on scientific evidence to ensure safe, effective and economic use.

Most of the strategies for improving prescribing practices are mutually supportive. A comprehensive policy should aim at influencing prescribing behaviour at all levels of the system, focusing on the priority problems and targeting prescribers involved.

The first step is to identify the nature and scope of the problem. This may be done through a prescription survey, review of drug management data or observation of a particular practice or event. If further investigation confirms that the observed behaviour is a significant problem in the health system, effort should be made to define the underlying causes clearly. A package of interventions is then planned,

focused on specific problems and targeting specific actor, prescriber, patient or community.

Different sets of interventions may be applied to address inappropriate prescribing practices and prevent them from re-occurring. Each intervention must be monitored and evaluated to assess its impact. Evaluation of impact needs to be directed at the specific prescribing pattern or prescribing behaviour that the intervention is designed to affect. Clearly, ineffective interventions can be dropped, and those that are partially effective can be revised to improve their efficacy. Effective interventions can then be incorporated and, if required, replicated on a wider scale in the health care system.

A wide range of intervention strategies is available to address irrational prescribing. These can be categorized as preventive or curative. Preventive approaches ensure that the prescriber starts off prescribing in an appropriate manner. Curative interventions attempt to reverse a pattern of irrational prescribing. As is often true in medicine, it is far easier/better to prevent than to cure prescribing problems.

Interventions can be characterized as educational, managerial and regulatory.

The best understanding of the origins of problems can often be obtained by using quantitative and qualitative methods together.

The first step in improving drug use is to measure existing practices and identify specific problems (quantitative). After narrowing attention to specific problems, it is necessary to understand why they occur (qualitative) and then to suggest possible actions to correct them (Intervention). Interventions implemented without gathering this information are likely to fail.

Basic Principles of Research Design

Step 1: Select the correct study unit:

The correct study unit is often a health facility.

Step 2: If Possible, Randomly assign study units to Intervention and Comparison Groups

This is not always possible but one can choose a comparison group that is as similar as possible. Using a comparison group can guard against many possible incorrect conclusions about the effects of intervention. Time series models can be used if it is not possible to identify a good comparison group.

Step 3: Measure outcomes before and after Intervention in both the Intervention and Comparison Groups

Data must be collected in the same way in the comparison and intervention groups.

Step 4: Measure Impacts over time

Short–term impacts often disappear unless they are reinforced. To know whether an intervention really works, the impact at short-term (one month), medium (six months) and long term (one year or more) is measured.

Outcomes of intervention should be evaluated using indicators that are meaningful, reliable and measurable, e.g. changes in prescribing that follows changes in knowledge about specific drugs.

Changing or correcting Drug use problems

The ultimate goals of studying and intervening in drug use practices include:

Improvement of quality of health care through effective and safe use of pharmaceuticals and improvement of cost-effectiveness of health care through economic and efficient use of pharmaceuticals.

No matter which point in the drug use process becomes the focus of an intervention strategy, there are common characteristics of effective interventions. These are to

- Identify key influence factors;
- Target individuals or groups with worst practices;
- Use credible information sources;
- Use personal contact whenever possible;
- Limit the number of messages;
- Repeat key messages using different media;
- Provide better alternatives.

Intervention Strategies to Improve Drug Use

The three major strategies commonly used to change drug use are educational, managerial and regulatory interventions (Quick et al 1991)

1. Educational Strategies

The basic objective here is to educate and persuade prescribers, dispensers and patients to prescribe, dispense and use drugs rationally. These strategies include lectures, seminars workshops, continuing education, face to face contact, using printed materials, patient education, influencing opinion leaders, etc (Nabiswa *et al.,* 1993; Ross-Degnan *et al.,* 1996; Santoso *et al.,* 1996; Wahlstrom *et al.,* 2003).

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Training of Prescribers:

- ❖ Formal education (pre-service)
- ❖ Continuing education (in-service)
- ❖ Supervisory visits

Printed Materials

- ❖ Clinical literature and newsletters
- ❖ Treatments guidelines and drug formularies
- ❖ Illustrated materials (flyers, leaflets)

Approaches Based on Face-to-face Contact

- ❖ Educational outreach
- ❖ Patient education
- ❖ Influencing opinion leaders
- ❖ Group lectures, seminars, and workshops

2. Managerial Strategies

These include using limited procurement lists, drug utilization review and feedback, supervision and monitoring, drug committees, cost information (selection, procurement and distribution). Standard diagnostic and treatment guidelines, course-of-therapy packaging and price setting. (Nabiswa *et al.*, 1993; Ross-Degnan *et al.*, 1996; Hogerzeil, 1995))

Selection, Procurement and Distribution

- ❖ Limited procurement lists
- ❖ Drug utilization reviews and feedback

- ❖ Hospital and regional drug committees
- ❖ Cost information

Prescribing and Dispensing Approaches

- ❖ Structured drug order forms
- ❖ Standard diagnostic and treatment guidelines Course-of-therapy packaging

Financing

- ❖ Price setting
- ❖ Capitation-based budgeting

3. Regulatory Strategies(Bhutta and Balchin, 1996)

- ❖ Drug registration
- ❖ Limited drug lists
- ❖ Prescribing restrictions
- ❖ Dispensing restrictions

The strategies above may either be used singly or in combination. The selection of an appropriate intervention should consider its:

- Likely effectiveness
- Feasibility
- Cost
- Potential impact
- Unlimited effects

Educational intervention is defined as any attempt to persuade physicians to modify their practice performance by communicating clinical information or guidelines. Educational strategies or interventions include educational materials, formal Continued Medical Education activities, outreach visits such as academic detailing, opinion leaders, audit with feedback, reminders and combination of these activities

Research has shown that the most effective means of changing prescribing behaviour has been face-to-face contact (Avorn and Soumerai, 1983; Putnam and Curry, 1985; Steele *et al*., 1989; Raisch *et al*., 1990). A study in Indonesia showed that a small group on-site face-to-face education was more effective than large group seminars (Quick *et al*., 1997). When interventions of different types are combined the impact is likely to be synergistically increased (Chase, 1983; Cohen *et al*., 1985; Jennet *et al*., 1988; Turner *et al.*, 1990; McPhee *et al*., 1991; Dietrich, 1992)

2.6 PHARMACOECONOMICS

In most countries, the resources available for health care are increasingly stretched in the face of the competing demands for their use. Therefore, health care policy makers, planners and managers have begun to scrutinize all health care procedures and treatments more closely in order to ensure that they give good value for money. Medicines have not been exempted from this process and there is increased emphasis on demonstrating additional benefit or social value from drug therapy or pharmacy services that is commensurate with their costs. This now brought about pharmacoeconomics, which is a branch of Health economics.

Also cost of medicine can be a heavy burden for patients with limited economic resources and health care providers should be sensitive to this fact. Cost of medicine can be a heavy burden to the health care system especially where the cost of the medicine is borne by the health care system. The actual knowledge of physicians about prices is generally low (Reichert *et al,* 2000) even for products they commonly prescribe (Hoffman *et al,* 1995). Irrational prescribing of chloroquine (antimalarial) is independent of cost consideration yet cost is a major determinant in health care delivery. Based on this pharmacoeconomics should be given consideration in antimalarial therapy especially in a depressed economy such as we have in developing countries like Nigeria.

Pharmacoeconomics is defined as "the description and analysis of the costs of drug therapy to health care system and society". It can also be defined as "the economic evaluation of drug therapy, pharmaceutical services and programmes or pharmacy technology" (Townsend 1987). It compares the impact of specific therapeutic alternatives on clinical and economic outcomes. It investigates total costs but emphasizes identifying which therapeutic options provide the greatest benefit with respect to total costs and limited options (Froemming *et al.,* 1989).

In today's competitive limited resources health care environment, choices and trade offs in providing healthcare services are inevitable. The primary objective of economic evaluations is to measure and compare both informed outcomes and costs of various options to ensure informed choices between alternative uses of resources.

The term 'outcome' is increasingly being used to describe the results and value of health care intervention. However, the outcomes of health care are multidimensional.

The clinician is concerned with clinical outcomes of treatments. The health care payer and administrators are concerned with resource use or economic outcome of health care decisions. The patients are concerned with the humanistic outcomes of therapy. Outcomes measurement must take into account *e*conomic considerations while recognizing that acceptable *c*linical and *h*umanistic outcomes are also important objectives (ECHO). Economic evaluations go beyond the traditional issues in medical evaluations of *efficacy*, (can this therapeutic option work especially under the conditions of well-controlled clinical trials?) and *effectiveness* (does this therapeutic option work especially under the real world conditions in which the medicine is prescribed and consumed according to the desires of physicians and patients) by addressing *efficiency* (does this therapeutic option produce the best outcomes for the lowest costs) (Drummond *et al.*, 1988).

Pharmacoeconomic research identifies measures and compares costs or inputs (i.e. resources consumed) and consequences or outputs or outcomes (chemical, economic and humanistic) of pharmaceutical products and services.

Successful implementation of 'pharmaceutical care' will come about only with sufficient pharmacoeconomic research that adequately documents the degree to which the benefits of such care outweigh the costs associated with those services. Pharmacists must become the key players in assuring that drug therapy and related pharmacy services are not only safe and effective but also provide real value in both economic and humanistic terms.

Pharmacoeconomics may help address the following questions:

- What drug should be included on the hospital formulary?

- What is the best drug for a particular patient?
- What is the best drug for a pharmaceutical manufacturer to develop?
- Which drug delivery system is the best for the hospital?
- How do two clinical pharmacy services compare?
- What is the cost per quality year of life extended by a drug?
- Will patient quality of life be improved by a particular drug therapy decision?
- What is the best drug for this particular disease?
- What are the patient outcomes of various treatment modalities (Bootman *et al.*, 1999)

THE ECHO MODEL

The economic, clinical and humanistic outcomes (ECHO) model is a theoretical framework for planning and conducting a pharmacoeconomic evaluations (Kozma *et al.*, 1993). The ECHO model views the value of a drug as some combination of its clinical, economic, and humanistic attributes.

Economics is about trade-offs and choices between wants, needs and the scarcity of resources to fulfill these wants. In economics, most people think of the trade-offs between goods and services and money but in pharmacoeconomics trade-offs might also be expressed in humanistic terms.

Economic outcomes include direct medical cost (e.g. cost of pharmaceuticals; emergency room care, physician office visits and in-patient hospitalization), direct non-medical costs (e.g. cost incurred by the patient in seeking care in terms of transportation to the hospital), indirect costs (e.g. costs of changes in worker productivity in terms of lost wages or absenteeism) and intangible cost (cost which

can not be expressed in a monetary value e.g. pain and grief) and consequences which may be positive (e.g. decreased length of hospital stay) or negative (e.g. adverse reactions, decreased quality of life) (Kozma *et al.*, 1993; Eisenberg 1989).

Clinical outcomes are the most familiar consequences of pharmaceuticals. Mortality, morbidity and disability, as well as specific clinical end-points like blood pressure, parasite clearance and serum glucose concentrations, may be used as clinical outcomes measures in pharmaceutical outcomes evaluation and pharmacoeconomic studies.

Humanistic (psychosocial) outcomes analysis measures the effects of medical care on the physical, social and emotional well-being of the patient, The ability of an individual to perform routine daily functions and complete normal job duties are very important outcomes that should be measured when assessing the value of a medical or pharmaceutical intervention (MacKeigan and Pathak, 1992).

Sound drug therapy decisions should contain three components viz safety, efficacy and pharmacoeconomic value (McGhan 1993).

PHARMACOECONOMIC METHODS

Four types of pharmacoeconomic methods are typically used to evaluate the cost and consequences of pharmaceutical therapies (Table 2) (Drummond *et al.*, 1987):

i. Cost-cost Analysis (CCA) or Cost-minimization therapies Analysis (CMA)

ii. Cost-Benefit Analysis (CBA)

iii. Cost-Effectiveness Analysis (CEA)

iv. Cost-Utility Analysis (CUA)

Cost-Cost Analysis (CCA) or Cost-Minimization Analysis (CMA)

This type of economic evaluation is used when it has been proved or assumed that outcomes are identical or at least differences are not clinically significant. The outcomes are not valued (costed) since the outcomes of the alternatives are assumed to be identical, only the cost of each alternative has to be estimated. In practice, it may be very difficult to establish that all reasonable alternatives have identical clinical effectiveness. A simple example for which cost minimization analysis might apply is the comparison of several therapeutically equivalent generic drugs or perhaps different formulations of the same pharmaceutical. Formulary drug selection processes often employ cost-minimization analysis.

Cost-Benefit Analysis (CBA)

Cost-Benefit analysis compares cost and consequences in monetary terms. CBA helps to find the alternative with the most favourable cost-to-benefit ratio. It helps decision makers select among various outcome objectives so that limited resources can be put to best use. For example, cost-benefit could be used in deciding whether to expand clinical in-patient services or build a new out-patient or clinic pharmacy. A limitation of CBA is that all costs and benefits are expressed in monetary terms and it is sometimes difficult to translate health care consequences (e.g. lives or years of life saved, into monetary terms.

Cost-Effectiveness Analysis (CEA)

Cost-effectiveness analysis attempts to address the limitations of cost-benefit analysis by expressing costs in monetary terms and consequences in natural or physical units (e.g. lives saved). CEA helps decision makers select among various options to

achieve a desired outcome. CEA assures that the objective of therapy has been specified and that the alternative that achieves the desired objectives at the least cost will be pursued.

Since a common objective (e.g. reducing mortality) is specified, cost-effectiveness analysis assumes that adequate resources (Naira) are available for pursuing the alternative with the most favourable cost-effectiveness ratio. For example, if the objective is to reduce mortality due to stroke, cost-effectiveness analysis could be used to compare various approaches to reducing serum triglyceride concentrations, assuming that such a reduction will save years of life. The approach with the lowest cost per year of life saved is preferred.

Cost-Utility Analysis (CUA)

Cost-utility analysis is similar to cost-effectiveness analysis except that outcomes are adjusted for patient preference or utility or in terms of value to patient or society (e.g. quality-adjusted life years, (QALYs), healthy days). In cost-effectiveness analysis, the decision maker assumes that each year of life saved is valued equally by everyone, but this is questionable. For example two people both broke their left arms, one is a typist, the other a singer. Both are equally disabled with respect to their injury but the typist is more likely to attach a greater significance to the broken arm due to being unable to continue to earn a living for a period of time. The value of life extension is very much a fraction of the patient's state of health during that period. Even though there is a difficulty in measuring quality of life, it is a very promising technique because of its potential to allow patient or societal preferences into the decision-making process.

Results in cost-utility analysis are usually expressed as the costs in currency (Naira) per QALYs).

METHODOLOGY	COST MEASUREMENT UNIT	OUTCOME UNIT
Cost-Benefit	Currency	Currency
Cost-Effectiveness	Currency	Natural units (life years gained, mmol/L blood glucose, mmHg blood pressure
Cost-Minimization	Currency	Assumed to be equivalent in groups
Cost-Utility	Currency	Quality-adjusted life Year or other utilities

Table 2: Pharmacoeconomic Methods (Drummond *et al.,* 1987)

Other Concepts Important to Pharmacoeconomic Evaluation

There are four other concepts important to pharmacoeconomics evaluation:

i. Decision analysis

ii. Sensitivity analysis

iii. Discounting

iv. Marginal cost and marginal benefits

Decision Analysis

This is a technique often used in pharmacoeconomic evaluation to structure the logical and chronological order of the analysis. Decision analysis is defined as a systematic, quantitative method of describing clinical problems, identifying possible courses of action, assessing the probability and value of outcomes, and finally making a calculation to select the optimum course of action. Decision analysis approach often

provides a valuable way of structuring many pharmacoeconomic evaluations especially cost-effectiveness analysis. Decision analysis summarizes or presents a decision problem by constructing a decision table or decision tree (Cano and Fujita, 1988).

The *decision table* is the first analytic tool used in decision analysis. It displays the relationship between pairs of decision elements. For example, the decision making criteria for an antibiotic might include the drug characteristics of spectrum of activity, pharmacokinetics, adverse drug reactions, daily cost of the drug and stability. If spectrum or activity against *Pseudomonas aeruginosa* was one of the criteria and the third generation cephalosporin were being compared, ceftazidime would receive a high rating in activity against *Pseudomonas aeruginosa* while ceftriaxone would receive a low rating. All the criteria can be similarly scored and summed for each alternative antibiotic. The final scores can then be compared and a decision made. An example of decision table is presented in Table 3.

Decision analysis is a systematic approach to decision-making to:

1. identify the available options when faced with a decision;
2. predict the consequences or outcomes of each option;
3. assess the likelihood or probability of the identified possible outcomes;
4. determine the value of each outcome; and
5. select the decision option that will yield the best pay off.

	Value	Assigned Weight	Criterion Rating	Value	Assigned Weight	Criterion Rating
Criterion 1	67	.20	13.4	67	.20	13.4
Criterion 2	100	.50	50.0	67	.50	33.5
Criterion 3	33	.30	9.9	67	.30	20.1
Sum of Criteria Rating		1.00	73.3		1.00	67.0

Table 3: An example of a Decision Table (Cano and Fujita, 1988)

Steps in Conducting a Decision Analysis:

1. Criterion Value x Assigned Weight (%) = Criterion Rating
2. Sum Criterion Ratings for each alternative
3. Compare Alternatives Summed Criterion Ratings
4. Select Best Option

The *decision tree* is the second analytic tool used in decision analysis. It displays the logical sequence of a clinical decision problem, identifies all the variables in the alternative treatment regimens, and includes both chance and choice occurrences.

Using a decision analysis approach to structure a pharmacoeconomic evaluation also has additional benefits. First, it serves as a communication tool between decision makers whose viewpoints and value systems may be very divergent. Second, as an outgrowth of communication and dialogue, consensus can be built regarding how choices will be made. Thirdly, it diffuses emotional issues and keeps decision makers focused on weighing the advantages and disadvantages of various options from appropriate outcome/cost comparisons.

Sensitivity Analysis

This determines the consistency of study findings with respect to changes in assumptions and/or parameter estimates. It is a technique designed to allow for uncertainty by testing whether plausible changes in the values of the main variables would affect the conclusions of an analysis.

Patrick and Wooley (1981) included sensitivity analysis in their CBA of three approaches to pneumococcal pneumonia vaccine for a health maintenance organization population. Their overall conclusions about identifying and immunizing high-risk patients did not change when they varied the cost of vaccine, duration of the programme, likelihood of adverse effects, cost of illness, and several other factors.

If the results of the analysis change a little when changes are made in the variables, confidence in the results is increased. On the other hand, if the results change substantially, then the analyst should be more concerned about the uncertainty of the particular variable.

Discounting

Discounting is a technique by which differences in the value of costs or health outcomes are adjusted over time. It looks at the monetary value of some event that will occur in the future and discounts it back at a certain rate called discount rate, to its present monetary value. Discounting is particularly important in pharmacoeconomic evaluations when benefit or costs are spread over several years. If all benefits and costs occur within one year, discounting is generally not used.

The present value (PV) can be calculated by multiplying the future value (FV) or future cost (FC) by the discount factor (DF). The discount factor depends on two

variables, the number of years into the future that the expenses is incurred (t or n) and the discount rate (r).

$$PV = FC \times DF^{(n, r)} \quad \text{or} \quad FV \times DF^{(t, r)}$$

$$DF = \frac{1}{(1 + r)^n} \quad \text{or} \quad \frac{1}{(1 + r)^t}$$

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. $$PV = \frac{FC}{(1 + r)^n} \quad \text{or} \quad \frac{FV}{(1 + r)^t}$$

Marginal Cost and Marginal Benefit

Marginal cost is the incremental cost of one or more unit of health benefit (e.g.. the cost of one more life saved by a particular treatment strategy) (Glick 1989). Marginal cost is used to decide if an expensive intervention is worth the additional cost and is typically very different from average cost.

Marginal benefit is the incremental health benefit (e.g. the prevention of an adverse health outcome) achieved for a given marginal cost (Glick 1989). Marginal benefit is used to decide if a given unit of health benefit is worth the additional cost.

Pharmacoeconomic Evaluation Steps

Regardless of the type of pharmacoeconomic evaluation employed, fourteen main steps are involved.

Conducting a Pharmacoeconomic evaluation should be guided by the criteria for quality economic evaluations (Bootman *et al.,* 1999; Detsky 1993; Drummond *et al.,*

1986; Eisenberg *et al.*, 1989; McGhan and Lewis 1992; Sacristan and Soto 1993). A 10-step process identified by Jolicoeur and associates (Jolicoeur,= *et al.*, 1992), and a 4 additional steps identified by Sanchez (1999), can provide readers with guidance for conducting a local Pharmacoeconomic study (Sanchez, 1995). This process contains 14 fundamental steps for conducting a Pharmacoeconomic evaluation in a health care system and can be applied to virtually any therapeutic area or health care service. They will be discussed briefly in the context of conducting an evaluation.

Step 1: identify or define the pharmacoeconomic problem

A broad problem might be "which antiemetic regimen represents the best value for the prevention of chemotherapy-induced emesis (CIE)?" However, a more succinct and measurable problem would be "which regimen is the best value for preventing acute CIE in patients receiving highly emetogenic chemotherapy"?

Step 2: assemble a cross-functional study team:

The study team can provide early "buy-in" and additional resources for a Pharmacoeconomic evaluation. Team members vary depending on the analysis, but may include representatives from medicine, nursing, pharmacy, hospital administration, and information systems.

Step 3: define the appropriate study perspective*:*

Choose a study perspective(s) most relevant to the problem. For example, if the problem is as listed in step 1, then the perspective of the institution or health care system may be most appropriate.

Step 4: identify treatment alternatives and outcomes

Treatment alternatives can include pharmacologic and non-pharmacologic options, but should include all clinically relevant alternatives. The outcomes identified should include both positive and negative clinical outcomes.

Step 5: identify the appropriate pharmacoeconomic method to employ

Pharmacoeconomic methods to choose from include cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses. Employing the incorrect method can adversely affect medication decisions influencing both cost and quality of care.

Step 6: place a monetary value on treatment alternatives and outcomes

Placing a monetary value on treatment alternatives and outcomes includes not only drug administration and acquisition costs but also the cost of positive and negative clinical outcomes (for example, determining the cost of ADRs and treatment failures). This can be measured prospectively or retrospectively, or estimated using comprehensive databases or expert panels.

Step 7: identify resources to conduct study in an efficient manner.

Resources necessary will vary by study, but may include access to medical or computerized records, average medical personnel wages, and specialty medical staff.

Step 8: identify probabilities that outcomes may occur in study population

What are the probabilities of the outcomes identified in step 4 actually occurring in clinical practice? Using primary literature and expert opinion, these probabilities can be obtained and may be manifested as efficacy rates and incidence of ADRs.

Step 9: employ decision analysis

The use of decision analysis can assist in conducting various economic evaluations, including CEA. Although not necessary for all pharmacoeconomic evaluations, decision analysis and decision trees may provide a solid backbone or platform for the decision at hand. Using a decision tree, treatment alternatives, outcomes, and probabilities may be graphically presented and algebraically reduced to a single value for comparison (i.e. C/E ratio).

Step 10: discount costs or perform a sensitivity or incremental cost analysis

Costs and consequences that occur in the future must be discounted back to their present value. Sensitive variables must be tested over a clinically relevant range and results recalculated. If appropriate, an incremental analysis of the costs and consequences should be performed.

Step 11: present study results

Results should be presented to the cross-functional team and the appropriate committees. Presentation style and content may vary depending on the audience.

Step 12: develop policy or an intervention

Take the study results and develop a policy or an intervention that can improve or maintain quality of care, possibly at a cost savings.

Step 13: implement policy and educate professionals

Spend adequate time and resources strategically implementing the policy or intervention. Educate those health care professionals most likely to be affected by this policy, using various strategies including verbal, written, and online communication.

Step 14: follow-up documentation

Once the intervention or policy has been implemented for a reasonable period of time, collect follow-up data. These data will provide feedback on the success and quality of the policy or intervention.

Pharmacoeconomic evaluation is a tool.

The principles and methods of pharmacoeconomics provide the means to quantify the value of pharmacotherapy through balancing costs and outcomes. Providing quality care with minimal resources is the future, and the future is here. By understanding the principles, methods, and the application of pharmacoeconomics, pharmacists will be prepared to determine and quantify the value of pharmacotherapy to health care system and society. Pharmacoeconomic evaluations give decision makers the ability to structure models that present them with a clearer picture of how costs relate to health care outcome. Pharmacoeconomic evaluations do not make the decision for the decision maker but do make the trade-offs between costs and healthcare benefits clear so that objective, well-informed decisions can be made.

2.7 Quality of Medicines

The quality of medicinal drugs in some less developed countries is inadequate (Maponga and Ondari, 2003). Shakoor *et al.*, (1997) assessed the quality of antimalarial and antibacterial drugs obtained from retail outlets in Nigeria and Thailand and reported an appreciable proportion of substandard samples. Taylor *et al.*,

(2001) analysed the contents of drugs from pharmacies in Nigeria and found that about half of the preparations had concentration of the drug outside upper and lower pharmacopoeial limits. Newton *et al.,* (2001, 2003) reported that just over a third of the samples of tablets labelled "artesunate" bought from shops in Cambodia, Laos, Myanmar, Thailand and Vietnam, contained no drug. Rozendaal (2001) showed that counterfeit artesunate and mefloquine preparations were sold widely in Cambodia. Maponga and Ondari (2003) in their study of quality of antimalarials in selected African countries reported failures in ingredient content ranging from 20% to 67% for chloroquine tablet and 5% to 38% for sulphadoxine-pyrimethamine tablet. In some cases, the use of poor quality medicines has resulted in treatment failure (Petralanda, 1995; Maponga and Ondari, 2003) and also can potentially increase the risk of development of resistance and increased mortality (Maponga and Ondari, 2003). The poor quality of drugs has been linked to counterfeiting of medicines (ten Ham, 1992), chemical instability especially in the tropical climates (Hogerzeil *et al.,* 1991) and poor quality control during manufacture (Arya, 1995) or non compliance with good manufacturing practice (GMP) guidelines by manufacturers (Mapong and Ondari, 2003).

There are a number of procedures which apply specifically to tablets, and which are designed to ensure that the patient receives a product containing the required amount of drug substance in a form which enables the latter to exert its full pharmacological action (Aulton, 1994). Such standards in the British Pharmacopoeia (BP 2002) and United State Pharmacopoeia (USP 27, 2004) are: uniformity of diameter, uniformity of weight, content of active ingredient, uniformity of content, disintegration, and

dissolution. In addition there are a number of quality control procedures, which though widely applied, are not defined by the Pharmacopoeia. These are crushing strength, often referred to as tablet 'hardness' and resistance to abrasion or 'tablet friability'. These two tests involve the measurement of the tablet's ability to retain its physical integrity

Uniformity of Diameter

It is reasonable to expect that tablets of the same diameter will not differ markedly in weight and amount of drug substance. The purpose of this standard is to help to remove the doubt about weight and amount of drug substance.

Uniformity of thickness

Thickness can vary with no change in weight because of difference in density of granulation and pressure applied to tablets as well as speed of tablet compression. Tablet thickness is important in reproducing tablet identical in appearance and also in counting tablets using filling equipment. Tablet thickness is determined using a caliper or thickness gauge that measures thickness in millimeters. Plus or minus 5% may be allowed depending on the size of the tablet (Rudnic and Schwartz 2000).

Uniformity of Weight

Not more than two tablets are permitted to differ from the mean by greater than the stated percentage and no tablet by more than double that percentage. Other national pharmacopoeias have similar standards, perhaps differing in minor details.

Where the drug substance forms the greater part of the tablet mass, dosage is obviously linked to tablet weight, and compliance with this standard helps to ensure that uniformity of dosage is achieved.

Content of Active Ingredient

To carry out this test, 20 tablets are chosen at random from a batch, powdered together and an assay is carried out on an aliquot of the resultant mixture according to the method given in the relevant pharmacopoeial monograph. The assay measures by chemical or physicochemical means, the amount of drug substance present. BP 2002 states that content of Chloroquine should be 95.0 to 105.0 % for injection; 92.5 to 107.5% for tablet but no specification for syrup.

Tablet Disintegration and Dissolution

Establishing the accuracy of the dose of a drug in a tablet is meaningless unless the drug can carry out its therapeutic function. In the majority of cases, this can only occur when the drug substance has dissolved in the fluids of the gastrointestinal tract.

Disintegration

Disintegration is defined as 'that state in which no residue of the tablet, except fragments of undissolved coating, remains on the screen of the test apparatus or, if any other residue remains, it consists of a soft mass having no palpably firm, unmoistened, core', and to comply with the standard, all tablets must normally disintegrate within 15 minutes.

Dissolution

Unless otherwise specified, not less than 70% of the stated content of the tablet should have dissolved in 45 minutes (BP 2002). The dissolution fluid is chosen bearing in mind the nature of the drug substance and also the sensitivity of the assay procedure. Thus, for example, 0.1N hydrochloric acid is specified for bases such as chloroquine phosphate and quinine sulphate.

Crushing strength

This is often referred to as tablet 'hardness'. 'Hardness' implies that the tablet is resistant to penetration. This test normally consists of breaking or crushing the tablet by application of a compressive load.

Resistance to abrasion

Tablet may be subjected to a tumbling motion e.g. during coating, packaging or transport which may abrade small particles from its surface. Method to examine this resistance to abrasion or 'tablet friability' has been devised.

Growth and Multiplication of Microorganisms in Pharmaceutical Products

The majority of medicines present a ready source of nutrients and moisture and there are many reports of the effects of microbial proliferation within them with attendant odours and visible spoilage (Aulton, 1994). Troublesome and expensive as this obvious deterioration may be, a more serious problem is the development of micro-organisms without obvious signs or involving delayed effects. For this reason it is important to have a knowledge of the microbial content of all drugs and medicines rather than restrict attention to those required to be sterile and those shown to be particularly spoilage prone. There has been reported microbial contamination of medicines (Akinmoji and Ogunlana, 1972; Onawunmi, 1987; Okore, 1992; Osazuwa, 1996), water (Ofogba *et al*., 1998; Mendie, 2002) and food (Bakare *et al*., 1998)

Consequences of Contamination

It is now realized that the presence of microorganisms in a pharmaceutical preparation may have a variety of consequences ranging from the negligible to the very serious. For example, spores of the mould *Mucor* may be present in a dormant form and never

produce spoilage or harm the patient who takes the medicine. In complete contrast to this would be the presence of *Salmonella* in a medicine which although causing little or no visible spoilage, would represent a serious health hazard.

Apart from possible infection of patients, the other important effect of contamination of medicines is that of general spoilage. This may result in obvious changes such as discoloration, break-down of emulsions and the production of gas and various odours. Such comparatively dramatic effects of deterioration do have the virtue of directing the consumer's attention to the problem and, hopefully, discouraging their use of the medicine.

Microbial Standards for Pharmaceutical Preparations

The design of microbial standards for pharmaceutical preparations must be realistic in that they relate to the intended use of the preparation and can be applied without ambiguity. The types of standard used to monitor microbial content, are two-fold, namely, an absolute exclusion of all microorganisms or named organisms, and a numerical limit upon all organisms or named organisms. Solutions for injection are required to be sterile.

Although such an absolute standard is not required for medicines for oral or topical use, nevertheless, certain bacteria can represent a hazard and be indicative of poor manufacturing practice and should be excluded. The United States Pharmacopoeia (USP 27, 2004) suggests an exclusion standard for *E. coli* to all solutions for oral use and for *S. aureus* and *Ps. aeruginosa* to topical preparations. For oral and rectal preparations the British Pharmacopoeia (BP 2002) states that there should not be more

than 10^3 aerobic bacteria and not more than 10^2 fungi per gram or per milliliter but there should be absence of *Escherichia coli*.

2.8 STATISTICS

A hypothesis is a conjectural statement of the relationship between two or more variables.

Hypotheses are always in declarative sentence form and they relate either generally or specifically, variable to variable. They are suggested answers to a research problem.

H_o (Null hypothesis) is the statement of 'no difference', 'no association', 'no relationship', 'no change', 'no effect' or 'no improvement' between two or more variables or proportions or means. We often have to test whether a new procedure produces a significant difference or a significant improvement over a standard approach (Gordon and Gordon, 1994).

H_1 or H_A (Alternative hypothesis) is the statement that there is difference, association, relationship, change or effect between variables or proportions or means.

The Chi-square is represented by X^2. The Chi-square (X^2) is used to find if a statistical difference exists between frequencies or proportions rather than absolute values or means.

Student's t-test and ANOVA (F statistic) are used to find if a statistical difference exists between means and parametric numeric variables. Kruskal-Wallis chi-square equivalent test is used for non-parametric numeric variables.

The calculated X^2 or t (z) or F ratio is then compared with the tabulated or critical X^2 or t (z) or F for the probability limits or level of significance (p) chosen and degree of freedom (df).

If the calculated X^2 or t (z) or F ratio $\geq$ tabulated X^2 or t (z) or F ratio, H_o is rejected and H_A accepted.

If the calculated X^2 or t(z) or F ratio < tabulated X^2 or t(z) or F ratio then H_o is accepted and the H_A is rejected

Probability or significance is usually set at $p = 0.05$. Results are considered to be statistically significant if calculated $p < 0.05$.

In view of all these it is believed that carrying out a drug evaluation review of chloroquine, looking at the prescribing pattern and determining the quality of the chloroquine dosage forms in Lagos State General Hospitals solutions might be proffered to any identified problem(s)

CHAPTER 3

3.0 MATERIALS AND METHODOLOGY

3.1 Study area

The study was carried out in Lagos State which has twenty local governments. Only nine of these local governments have General Hospitals, Epe has 2. (Fig 2). Population of the state is projected to be about 10 million based on 1991 census using 6% incremental rate.

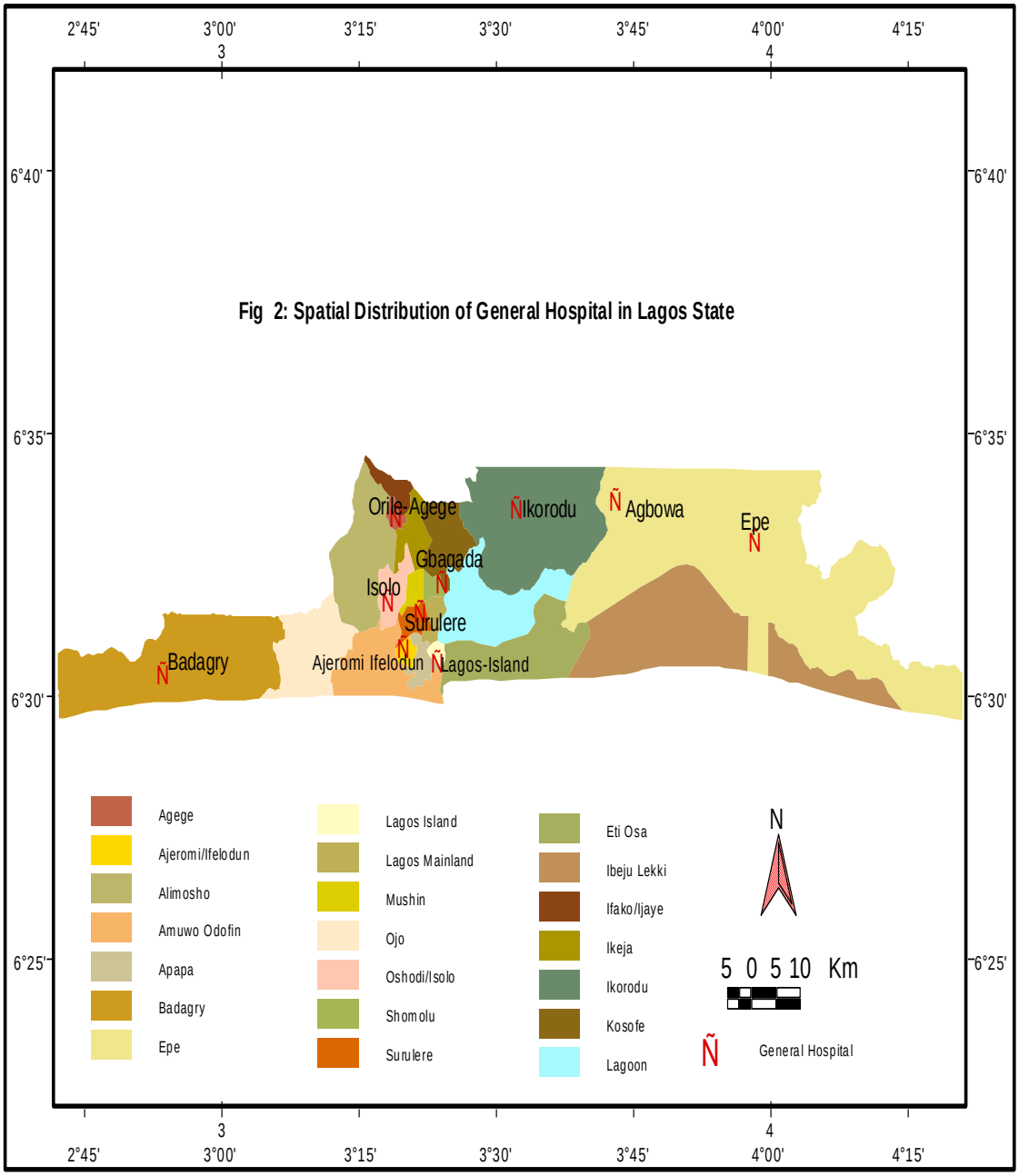

Fig 2: Spatial Distribution of General Hospitals in Lagos State
(From Geography Dept. of University of Lagos)

3.2 Study Population

All the ten General Hospitals in Lagos State were studied. These are Agbowa General Hospital (Epe local govt.), Ajeromi General Hospital (Ajeromi- Ifelodun local govt.), Badagry General Hospital (Badagry local govt.), Epe General Hospital (Epe local govt.), Gbagada General Hospital (Kosofe local govt.), Ikorodu General Hospital (Ikorodu local govt.), Isolo General Hospital (Oshodi-Isolo local govt.), Lagos Island General Hospital (Lagos Island local govt.), Orile Agege General Hospital (Agege local govt.) and Surulere General Hospital (Surulere local govt.).

3.3 Research Design

The research project is made up of 3 studies viz

1. Intervention study
2. Assessment of quality of chloroquine dosage forms
3. Cost effectiveness analysis of chloroquine tablet and injection

3.3.1 Study 1: Intervention study

A pre-test – post-test control group design was used for the intervention study. This study was conducted in three phases; the pre-intervention phase (phase1), intervention phase (phase 2) and post intervention phase (phase 3). The research methodology of this work is based on Quick *et al*., (1991) framework for formative and intervention studies.

3.3.2 Study 2: Quality Assessment study

This was a laboratory experimental study to determine the quality of chloroquine dosage forms available in the hospitals

3.3.3 Study 3: Cost effectiveness analysis

This study was to calculate the cost effectiveness analysis (CEA) of chloroquine tablet and injection using certain formula and information from literature and also making some assumptions (Tables 26 - 29)

3.4 Research Instruments/materials

3.4.1 Study 1

"Free Eko Malaria" prescriptions and questionnaires were used for phase 1 or formative studies. Seminar method was used for phase 2 or intervention phase. "Free Eko Malaria" prescriptions were used for phase 3 or post intervention phase.

3.4.2 Study 2

Materials

1. Chloroquine phosphate tablets (250mg chloroquine phosphate ≡ 150mg chloroquine base) samples collected from the hospitals
2. Chloroquine Phosphate Syrups (Each 5ml contains 80mg chloroquine phosphate ≡ 50mg chloroquine base) samples collected from the hospitals
3. Chloroquine injections (Each 1ml contains 64.5mg chloroquine phosphate≡ 40mg chloroquine base) samples collected from the hospitals
4. Chloroquine phosphate powder (May and Baker Ltd)
5. Chloroform (Fisher Scientific UK Ltd)
6. Hydrochloric Acid (BDH Chemicals Ltd)
7. Disintegration apparatus by Erweka Apparatebau GMBH
8. Dissolution Apparatus (paddle type) by Erweka Apparatebau GMBH

9. Tablet Friabilator by Erweka Apparatebau GMBH
10. Monsato Tablet Hardness tester
11. Micrometer screw gauge
12. Analytical balance
13. Hypodermic Syringe and Needles
14. Disposable Petri-dishes
15. 3% Tween 80 Solution
16. Tryptone Soya Agar
17. Mannitol Salt Agar
18. Eosin Methylene Blue Agar
19. 1ml Graduated Pipettes
20. Uv/visible spectrophotometer model 6305 by Jenway

3.5 Procedure for data collection

3.5.1 Study 1

3.5.1.1 Phase 1 (Pre-intervention phase) using "Free Eko Malaria" Prescriptions

A retrospective study period of one year (January – December, 2000) was selected. A total of 21,949 prescription forms of 'Free Eko Malaria' were sampled for children and adults from these General Hospitals. The prescription forms were sampled using systematic sampling method (WHO, 1993). Drugs in each prescription form were costed using the prices obtained from the hospitals except for drugs that were donated, whose prices were obtained from wholesalers. Cost of needle and syringe and cotton - swab were incorporated in prescriptions containing injections.

Core prescribing indicators and specific indicators of chloroquine were analyzed (WHO, 1993).

The core-prescribing indicators were:

- Average number of drugs per encounter (prescription form)
- Percentage of encounters with injections prescribed
- Average number of injection per encounter

Complementary Drug Use Indicator:

- Average drug cost per encounter
- Percentage of encounters with different antimalarials
- Percentage of encounters with other drugs prescribed with the antimalarials
- Percentage of encounters with dipyrone injection prescribed

Specific Chloroquine Indicators:

- Percentage of encounters with chloroquine
- Percentage of encounters with chloroquine tablets,
- Percentage of encounters with chloroquine syrup,
- Percentage of encounters with chloroquine injections,
- Percentage of encounters with chloroquine injection + tablets,
- Percentage of encounters with chloroquine injection + syrup
- Average chloroquine fraction per encounter

Dosage of chloroquine prescribed

- Percentage of encounters with correct dosage of chloroquine prescribed
- Percentage of encounters with overdosage of chloroquine prescribed
- Percentage of encounters with under-dosage of chloroquine prescribed

This was done for the different dosage forms prescribed, adults and children, each separate facility and all the facilities combined.

Dosage of chloroquine prescribed was calculated as:

$$F = \frac{T}{R}$$

F = Fraction of total dosage recommended in relation to age

T = Total dosage prescribed in relation to age

R = Total dosage recommended in relation to age

Correct Dosage is F = 1.0 $\pm$ 0.2 i.e. 0.8 to 1.20 (80 to 120 % of total recommended dose)

Age in years	Total Recommended Dosage of chloroquine base (FMH 2001)
<1 year	187.5mg
1 – 3	375mg
4 – 6	600mg
7 – 11	750mg
$\geq$12	1500mg

3.5.1.2 Phase1 using Questionnaire to determine the knowledge, attitude and practice (KAP) of the prescribers

A questionnaire was designed for the prescribers at the outpatients departments of these hospitals (Appendix I). The first part of the questionnaire was meant to generate the biodata of the prescribers. The second part was to find out about the choice of antimalarials drugs and reasons for the choice. The third part was to test their knowledge on the appropriate dosage for the different age groups. Most of the questions were multiple-choice.

Pretesting of questionnaire

The questionnaire was pre-tested among 20 physicians in Lagos University Teaching Hospital in September 2001 to identify difficulties that might have arisen if the questionnaire was administered directly to respondents of the main study. The pretest helped in reframing some questions and also to validate the questionnaire for the main study.

Administration of the questionnaire

The questionnaire was distributed to the prescribers at out patient departments of LSGH and retrieved between November and December 2001 in all the hospitals surveyed in order to corroborate and compliment the baseline data obtained from the prescriptions studied and also to address the knowledge, attitude and practice (KAP) of the prescribers in the hospitals which might have influenced the prescribing pattern

of chloroquine and use this information to design the intervention necessary to correct the prescribing pattern of chloroquine.

3.5.1.3 Phase 2 (Intervention phase)

Intervention was carried out between January and February 2002.

Educational intervention, a modification of Avon and Soumerai, 1983; Schaffner *et al*., 1983; Cohen *et al*., 1985; Marton *et al*., 1985 and Dietrich, 1992, was carried out by means of seminars which were held in each hospital on their clinical meeting days with doctors, pharmacists, nurses and medical laboratory scientists in attendance. The following findings and their consequences were highlighted and how to avoid/prevent the pitfalls were discussed:

- Prescribing pattern observed during the retrospective collection of baseline data, i.e. the pre-intervention phase
- Results obtained from the questionnaire
- Possible ways of improvement in the dosage of chloroquine prescribed such as prescribing tablets or syrups unless otherwise absolutely necessary e.g. vomiting
- Avoidance or decrease in the prescribing of injections only unless when absolutely necessary e.g. vomiting
- Prescribing of chloroquine injection followed by tablet or syrup to complete the recommended dose for the patient depending on the age or weight.
- Reducing the number of drugs per encounter.

The ten General Hospitals were randomly divided into three (3) groups. Groups 1 and 2 were the experimental groups while group 3 was the control group (Fig 3)

Experimental Group 1

This group comprised of Agbowa, Ajeromi, Badagry and Orile Agege General Hospitals which received seminar presentation plus plastic boxes (semi + bpad). The plastic box was to recall the different chloroquine dosage regimens appropriate to the various ages, especially children and was filled with loose sheets. This is similar to gift items that are used by corporate bodies for publicising either their products or their organizations. The dosing schedules of chloroquine corresponding to different age groups were printed on the boxes (Appendix II). They were placed on tables after the seminar and the prescribers were encouraged to refer to them while prescribing.

Experimental Group 2

This group comprised of Epe, Ikorodu, Isolo and Surulere General Hospitals which received seminar presentation plus poster (semi + post). The poster had pictures and appropriate doses for the corresponding age and weight (Appendix III). The poster was a modified one of Federal Ministry of Health.

Control Group 3

This comprised of Lagos Island and Gbagada General Hospitals which did not receive any intervention because they constitute the control group.

Fig 4: Map Showing Experimental Groups In Study Area

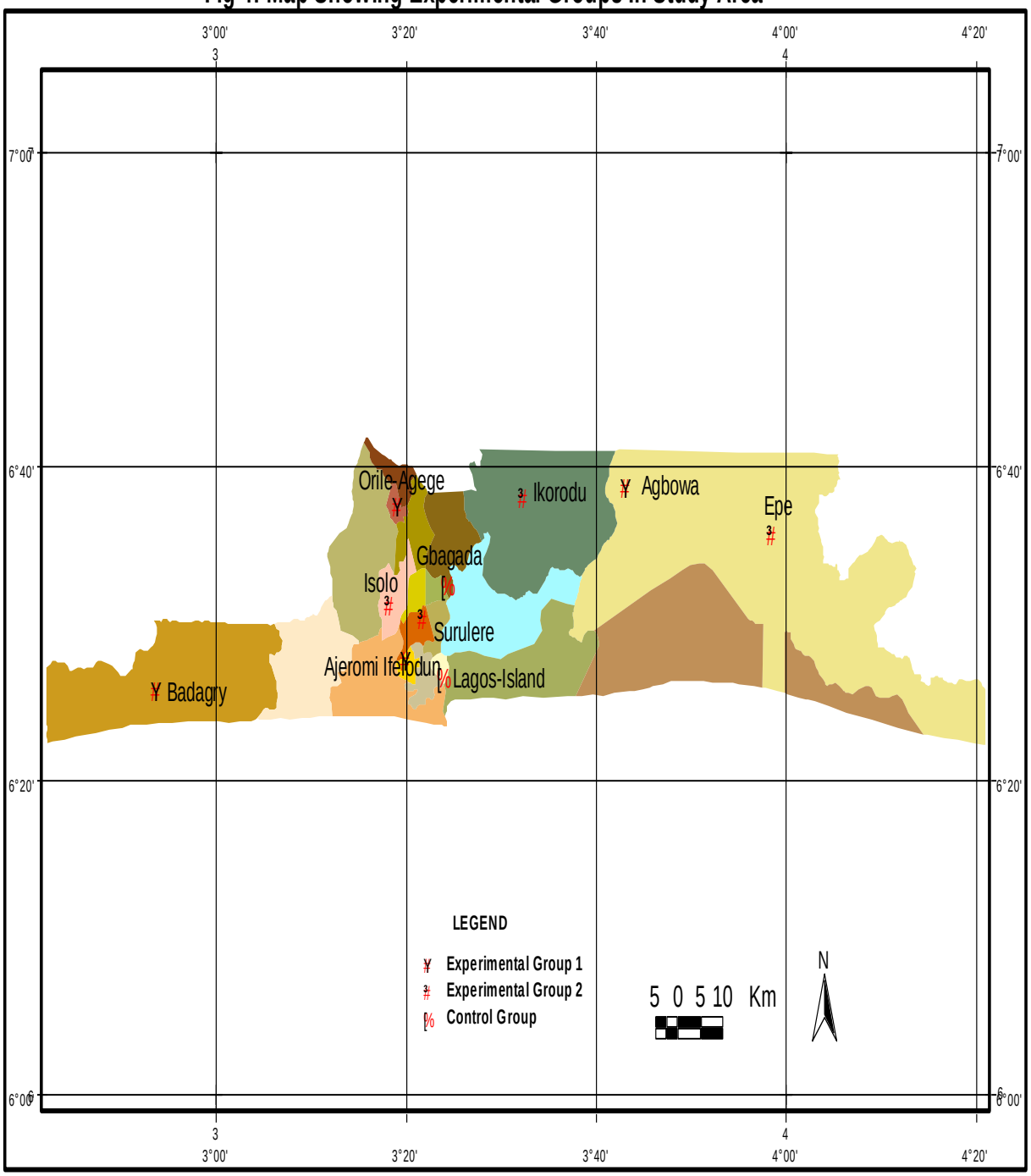

Fig 3: Map Showing Experimental Groups in Study Area
(From Geography Dept. of University of Lagos)

3.5.1.4 Phase 3 (Post -intervention phase)

Retrospective study of post-intervention prescribing patterns was carried out after 1, 3, 6 and 12 months to measure the impact of intervention. This was done to measure the short- (one and three months), medium- (six months) and long-term (one year) impacts. 2000 prescription forms were sampled each at 1,3 and 12 months post intervention while 1934 were sampled 6 months post intervention from the hospitals. Core prescribing indicators and specific indicators of chloroquine were analyzed (WHO, 1993) as was done during the pre-intervention study.

ASSESSMENT OF QUALITY OF CHLOROQUINE TABLETS, SYRUPS AND INJECTIONS FROM THE HOSPITALS

Chloroquine tablets, syrups and injections were collected in July 2003 and analysed in August 2003.

3.5.2.1 PHYSICAL ASSAY OF QUALITY

The following properties were assessed for tablets using British Pharmacopoeia (BP 2002) method:

Uniformity of diameter, uniformity of weight, content of active ingredient, disintegration, dissolution, crushing strength (tablet 'hardness') and resistance to abrasion ('tablet friability').

Uniformity of weight (mass)

Twenty tablets were taken and weighed individually, the average weight was determined (mg). Not more than two of the individual weights (masses) should

deviate from the average weight (Mass) by more than 5 percent and none deviates by more than twice that percentage.

Uniformity of diameter and thickness

The diameter and thickness of each of ten tablets was determined using a micrometer gauge, making sure that the tablet did not break or get chipped. This was done twice.

Disintegration

One tablet was introduced into each tube of six in an assembly and the assembly was suspended in the beaker containing the 0.1N hydrochloric acid and operated till all the six tablets disintegrated. The time for each tablet to disintegrate was determined. The assembly was removed from the liquid.

Dissolution

1000 ml of 0.1N hydrochloric acid was introduced into the vessel of the apparatus. The dissolution medium was warmed to $37.5^{o} \pm 1.0^{0}$. One tablet was placed into the vessel and allowed to sink to the bottom of the vessel prior to the rotation of the paddle. The apparatus was operated immediately at 100 rotations per minute. A 10 ml sample each was taken at every 10 minutes intervals for 60 minutes. A volume of dissolution medium equal to the volume of the samples withdrawn was returned into the vessel. The samples were filtered and diluted (1in 100). The amount of active ingredient present was determined by measuring the absorbance at 343nm

and intrapolating from the standard curve (Fig 9). The complete operation was repeated two times.

Friability of the tablets

Ten tablets were accurately weighed and placed in the drum. The drum was rotated 100 times and the tablets were removed. The tablets were reweighed to the nearest milligram.

Generally, the test was run once except for the results where the weight loss was greater than 1%, the test was repeated twice and the mean of the three tests was determined. A maximum weight loss of 1% of the weight of the tablets to be tested is considered to be acceptable for most products. The friability is expressed as the loss of weight and it is calculated as a percentage of the initial weight.

Resistance to crushing of tablets

The tablet was placed between the jaws of the hardness tester, one jaw was then moved towards the other. The measurement was carried out on 10 tablets.

The results are expressed as the mean, minimum and maximum values of the forces measured, all expressed in N.

3.5.2.2 CHEMICAL ASSAY OF QUALITY

Standard calibration curve

To prepare the standard calibration curve for Chloroquine phosphate, 100mg of Chloroquine phosphate was weighed and dissolved in 30ml of 0.1N hydrochloric acid

(HCL) and made up to 100ml. Then 0.5ml, 1.0ml, 1.5ml, 2.0ml and 2.5 ml were respectively diluted to 100ml to obtain concentrations of 0.0005%. 0.001%, 0.0015%, 0.002% and 0.0025% w/v. The absorbance of each solution was taken at 343nm. The concentration was plotted against absorbance to obtain the standard curve (Fig 9).

Assay of active ingredient of tablet

To carry out this test, 20 tablets were powdered together, and an equivalent of 100mg was taken and dissolved in 30ml of 0.1N hydrochloric acid (HCL) and made up to 100ml and filtered. 1ml of the filtrate was then made up to 100ml with 0.1N HCL to give a final concentration of 0.001% w/v. The absorbance of the resulting solution was taken at 343nm using uv spectrophotometer. The concentration was then intrapolated from the standard calibration curve of the pure sample of Chloroquine phosphate powder. This was done twice.

Assay of active ingredient of syrup

To carry out this test, 6.25 ml of each sample equivalent to 100mg of Chloroquine phosphate was measured and made up to 100ml with 0.1N hydrochloric acid (HCL). 1ml of this solution was then made up to 100ml with 0.1N HCL to give a final concentration of 0.001% w/v. The absorbance of the resulting solution was taken at 343nm using UV spectrophotometer. The concentration was then intrapolated from the standard calibration curve of the pure sample of Chloroquine phosphate powder. This was done twice.

Assay of active ingredient of injection

To carry out this test, 1.55 ml of each sample equivalent to 100mg of Chloroquine phosphate was measured, basified with sodium hydroxide and extracted with 4 x 20ml of chloroform. The chloroform extracts were combined and washed with 2 x 20ml of water. The chloroform layer was evaporated over a water bath and each sample reconstituted in 0.1N HCL and made up to 100ml with 0.1N hydrochloric acid (HCL) to get 1mg/ml (0.1% w/v) solution. 1ml of this solution was then made up to 100ml with 0.1N HCL to give a final concentration of 0.001% w/v. The absorbance of the resulting solution was taken at 343nm using UV spectrophotometer. The concentration was then intrapolated from the standard calibration curve. This was done twice.

3.5.2.3 MICROBIOLOGICAL ASSAY OF QUALITY

Syrups and Injections

Microbiological assay and determination of the content of active ingredient were carried out for syrups and injections using British Pharmacopoeia (BP 2002) method:

Sterilization:

All microbiological media used for the assay were sterilized using a simple non-jacketed laboratory autoclave. The 3% Tween 80 was also sterilized with the same autoclave. Pipettes were sterilized in the hot-air oven.

Sampling:

1ml sample of each batch of the Chloroquine phosphate syrup and injection was aseptically withdrawn using sterile hypodermic syringes and transferred into 9ml volume of 3% Tween 80 - to get a 1 in 10 dilution.

1ml of the 1 in 10 dilution was carefully and aseptically transferred into a pre-labeled sterile Petri-dish (1×10^{-1}), another 1ml was pipetted into another 9ml volume of 3% Tween 80 to give 1 in 100 dilution. 1ml volume of the 1 in 100 dilution was also pipetted into another pre-labeled (1×10^{-2}) petri-dish. A further 1ml was also aseptically pipetted into a 9ml volume of 3% Tween 80 to obtain 1×10^{-3} dilution; this was also aseptically pipetted into a pre-labeled (1×10^{-3}) petri-dish, all in duplicates.

19ml volume of each type of Agar (Tryptone Soya Agar, Mannitol Salt Agar and Eosin Methylene Blue Agar) were asceptically measured into each pre-labeled petri dish for each set (1×10^{-1}, 1×10^{-2}, 1×10^{-3}). The petri dishes were then gently swirled to obtain a homogenous mix, left on the bench to set and incubated in the laboratory incubator.

The plates were observed for any possible growth after 24 hours, 4 days, and 7 days.

Identification

The colonies obtained were gram-stained to ascertain their morphological appearances. Spore staining was carried out to confirm the presence of *Bacillus subtilis*.

3.5.3 Cost effectiveness analysis of chloroquine tablet and injection

Cost effectiveness analysis of chloroquine tablet and injection was calculated using bioavailability data from literature (Tracy and Webster, 2001), frequency of administration (White, 1996) and making some assumptions to calculate the criterion rating and effective rating. Unit cost of drug and other items required to administer the drug used in this study were employed to calculate medical cost. Annual salaries of pharmacist I, senior pharmacist, staff nurse and senior nursing officers in Lagos state were used to calculate personnel cost (Tables 26-29.)

3.5.4 Data Analysis

The data collected were analyzed using EPI Info Version 6 (EPI-6 Info) statistical software (Dean *et al.*, 1995), Statistical Package for Social Sciences (SPSS) and Excel.

3.5.5 Statistical Analysis

Continuous data are expressed as mean $\pm$ SEM (Standard Error of Mean) while discontinuous or categorical data are expressed as percentages.

Research questions or hypotheses were tested with Chi-square distribution to determine whether or not there is an association between intervention time, intervention type, dosage form and dosage of chloroquine prescribed.

Paired t tests and ANOVA were used to determine the significance of differences of arcsine-transformed percentages (Dietrich *et al.,* 1992). Tukey's honestly significant difference (HSD) was used for multiple comparisons to determine which means differ. Results were considered to be statistically significant if $p < 0.05$.

4.0 RESULTS

4.1a RESULTS OF STUDY 1: PRESCRIBING PATTERN AT PRE, 1, 3, 6 AND 12 MONTHS POST INTERVENTIONS

The average number of drugs per prescription for each health facility are in Table 8. Average number of injections per prescription are indicated in Table 4.

Average drug cost per prescription are presented in Table 4.

Percentage of prescriptions with at least one injection for each health facility are shown in Table 5. Percentage of prescriptions with dipyrone for each health facility are indicated in Table 5. Percentage of prescriptions with chloroquine are presented in Table 5.

Percentage of other 3 antimalarials that are frequently prescribed apart from chloroquine are indicated in Table 6.

The dosages of chloroquine prescribed for each health facility at pre, 1, 3, 6 and 12 months post intervention are as indicated in Table 7.

Total percentage of prescriptions with correct dosage of chloroquine increased from 45.3% at pre-intervention to 72.4% at 1 month post intervention but reduced to 70.4%, 65.3% and 68.6% at 3, 6 and 12 months post intervention respectively (Figure 4).

In adults, percentage of prescriptions containing correct dosage of chloroquine increased from 56.5% at pre-intervention to 84.5% at 1 and 3 months post intervention but dropped to 77.5% and 81.5% at 6 and 12 months post intervention respectively (Figure 5). In children, the percentage of prescriptions containing correct dosage of chloroquine increased from 34.4% at pre-intervention to 61.2% at 1 month post-intervention but dropped to 56.7%, 54.3% and 56.6% at 3, 6 and 12 months post-

intervention respectively (Figure 5). Percentage of correct dosage of chloroquine prescribed for each health facility at pre, 1, 3, 6 and 12 months post-intervention is as shown in Figure 6.

Percentage of prescriptions containing injection chloroquine only, reduced from 31.2% at pre-intervention to 12.6% and 11.9% 1 and 3 months post-intervention respectively but later increased to 16% and 14.3% at 6 and 12 months post-intervention respectively (Figure 7). Percentage of prescriptions containing chloroquine tablets only, increased from 28.5% at pre-intervention to 47.7% and 50.1% at 1 and 3 months post-intervention respectively but this reduced to 45.5% and 40.9% 6 and 12 months post-intervention respectively.

The percentage of prescriptions with correct dosage of chloroquine for the control group increased from 60% at pre-intervention to 72.8%, 78.5%, 75.7% and 71.1 % at 1, 3, 6 and 12 months post-intervention respectively. The percentage of prescriptions with correct dosage of chloroquine for the 'seminar + poster' group (semi+post) increased from 42.5% at pre-intervention to 71.5% at 1 month post-intervention but reduced to 69.9%, 62.2% and 67.3% at 3, 6 and 12 months post-intervention respectively. The percentage of prescriptions with correct dosage of chloroquine for the 'seminar + plastic box' group (semi+bpad) increased from 40.75% at pre-intervention to 72.9% at 1 month post-intervention but reduced to 66.9%, 63% and 68.6% at 3,6 and 12 months post-intervention respectively (Table 8, Figure 8).

The result of comparison of dosage of chloroquine in the different dosage forms prescribed at pre, 1, 3, 6 and 12 months post-intervention is as shown in Table 9. Chloroquine (CQ) underdosage occurred most frequently when injection chloroquine

only was prescribed than in other dosage forms. The result of comparison of dosage of chloroquine in the different dosage forms prescribed for the different intervention groups is as shown in Table 10 while in adults and children is as shown in Table 11. Chloroquine (CQ) underdosage occurred most frequently when injection chloroquine only was prescribed than in other dosage forms.

TABLE 4: AVERAGE NUMBER OF DRUGS AND INJECTIONS AND AVERAGE COST PER PRESCRIPTION IN THE DIFFERENT HEALTH FACILITIES AT PRE, 1 MONTH, 3 MONTHS, 6 MONTHS AND 12 MONTHS POST INTERVENTION

HEALTH FACILITIES	**PRE**			**1 MONTH POST**			**3 MONTHS POST**			**6 MONTH POST**			**12**
	Av. No. of drugs ± SE	Av. No. of injec. ± SE	Av. cost of drugs ± SE ₦	Av. No. of drugs ± SE	Av. No. of injec. ± SE	Av. cost of drugs ± SE ₦	Av. No. of drugs ± SE	Av. No. of injec. ± SE	Av. cost of drugs ± SE ₦	Av. No. of drugs ± SE	Av. No. of injec. ± SE	Av. cost of drugs ± SE ₦	Av. No. dru ± S
AGBOWA	4.360 ± 0.029	1.502 ± 0.027	135.389 ± 1.279	4.235 ± 0.107	0.940 ± 0.095	102.825 ± 5.026	4.025 ± 0.104	0.835 ± 0.090	86.725 ± 3.687	3.985 ± 0.122	0.746 ± 0.101	100.299 ± 5.132	4.5 ± 0.1
AJEROMI	4.075 ± 0.024	1.869 ± 0.030	183.935 ± 3.022	4.345 ± 0.094	1.255 ± 0.095	158.375 ± 7.180	4.140 ± 0.098	0.975 ± 0.082	154.275 ± 11.637	4.955 ± 0.102	1.175 ± 0.094	141.875 ± 7.940	4.6 ± 0.0
BADAGRY	4.186 ± 0.024	1.244 ± 0.028	139.547 ± 1.602	4.055 ± 0.059	0.990 ± 0.094	123.700 ± 5.621	4.340 ± 0.051	1.230 ± 0.101	136.825 ± 6.273	4.730 ± 0.069	1.620 ± 0.101	150.40 ± 6.128	4.0 ± 0.0
EPE	4.464 ± 0.028	1.808 ± 0.029	164.027 ± 2.685	4.310 ± 0.088	0.905 ± 0.095	120.890 ± 5.930	4.580 ± 0.107	1.120 ± 0.101	128.719 ± 7.487	4.915 ± 0.113	1.510 ± 0.108	141.90 ± 6.071	5.2 ± 0.1
GBAGADA	3.216 ± 0.022	0.495 ± 0.020	96.992 ± 1.529	3.520 ± 0.057	0.165 ± 0.039	76.725 ± 4.039	3.740 ± 0.054	0.200 ± 0.101	84.125± 5.973	3.590 ± 0.057	0.315 ± 0.060	85.150 ± 2.835	3.7 ± 0.0
IKORODU	4.076 ± 0.026	1.054 ± 0.026	119.292 ± 1.535	4.065 ± 0.089	0.890 ± 0.088	102.800 ± 3.866	4.710 ± 0.098	1.295 ± 0.085	117.1 ± 5.460	4.525 ± 0.084	1.150 ± 0.082	110.25 ± 5.080	4.2 ± 0.0
ISOLO	5.250 ± 0.037	2.124 ± 0.029	147.710 ± 2.251	5.205 ± 0.125	1.910 ± 0.103	216.200 ± 25.825	5.080 ± 0.082	1.670 ± 0.078	224.400 ± 24.496	4.645 ± 0.092	1.350 ± 0.087	299.40 ± 35.423	5.0 ± 0.1
LAGOS	3 .487 ± 0.024	0.775 ± 0.024	117.222 ± 2.425	3.870 ± 0.096	0.935 ± 0.082	134.675 ± 13.321	4.195 ± 0.107	1.095 ± 0.088	136.200 ± 8.602	4.140 ± 0.099	0.820 ± 0.078	128.685 ± 7.751	4.3 ± 0.0
ORILEAGEGE	3.650 ± 0.025	0.533 ± 0.022	109.793 ± 1.394	3.935 ± 0.074	0.465 ± 0.073	92.400 ± 3.755	3.875 ± 0.069	0.605 ± 0.083	95.705 ± 4.48	4.525 ± 0.089	1.040 ± 0.096	121.325 ± 6.408	4.5 ± 0.0
SURULERE	4.970 ± 0.028	2.333 ± 0.028	207.747 ± 2.096	3.260 ± 0.089	0.275 ± 0.055	76.870 ± 3.567	3.445 ± 0.071	0.105 ± 0.033	64.275 ± 2.005	3.690 ± 0.082	0.220 ± 0.050	81.875 ± 3.564	4.2 ± 0.0
AVERAGE	4.163 ± 0.009	1.352 ± 0.009	140.459 ± 0.678	4.080 ± 0.030	0.873 ± 0.029	118.546 ± 3.340	4.213 ± 0.029	0.913 ± 0.028	122.769 ± 3.313	4.383 ± 0.031	1.003 ± 0.029	137.338 ± 4.284	4.1 ± 0.0

TABLE 5: PERCENTAGE OF PRESCRIPTIONS WITH AT LEAST ONE INJECTION, DIPYRONE AND CHLOROQUINE IN THE DIFFERENT HEALTH FACILITIES AT PRE, 1 MONTH, 3 MONTHS, 6 MONTHS AND 12 MONTHS POST INTERVENTION

HEALTH FACILITIES	**PRE**			**1 MONTH POST**			**3 MONTHS POST**			**6 MONTH POST**			**12**
	% with inj.	% with dipyrone	% with CQ	% with inj.	% with dipyrone	% with CQ	% with inj.	% with dipyrone	% with CQ	% with inj.	% with dipyrone	% with CQ	% wit inj.
AGBOWA	63.6	51.4	87.8	34.5	33.5	98	33.0	29.0	96.5	32.8	26.1	96.3	37.0
AJEROMI	67.4	63.3	84.2	50	43	91	48.0	38.0	84.0	48.5	45.7	90.5	42.5
BADAGRY	47.2	39.1	90	39	34.5	94.5	45.5	45.0	96.0	59.5	57.0	96	47.0
EPE	66.3	58.9	90.8	64	29.5	92.5	39.0	38.0	92.5	51.0	48.5	91.5	63.5
GBAGADA	25.1	21.2	83.7	10	6.5	97.5	10.0	9.5	94.5	13.5	10.0	90	14.5
IKORODU	45.7	23.6	87.5	39	32.5	90.5	61.0	44.5	90.0	61	53.5	84	50.5
ISOLO	74.9	69.7	92.9	76.5	69	85	84.0	72.0	82.0	62	54.5	79	69.5
LAGOS	42.5	22.3	82.3	49	32.5	88.5	52.5	35.0	82.0	43	24	89	46.5
ORILEAGEGE	22.0	19.4	81.6	18	13.5	94.5	23.0	21.5	95.5	38.5	29.5	96	38.5
SURULERE	88.2	80.7	90.4	13.5	12.5	93.5	6.5	6.5	96.5	11.0	10	93.5	25.5
AVERAGE	53.4	44.1	87.1	36.2	30.7	92.5	40.3	33.9	91.0	42.4	36.2	90.5	41.9

Av. No. of drugs : Average number of drugs; Av. No. of injec. : Average number of injections; Av. cost of drugs: Average cost of drug

SE: Standard Error of mean; Inj.: injection; CQ : chloroquine

TABLE 6: PERCENTAGE OF PRESCRIPTIONS WITH HALOFANTRINE, SULPHADOXINE-PYRIMETHAMINE (S-P) AND QUININE IN THE DIFFERENT HEALTH FACILITIES AT PRE, 1 MONTH, 3 MONTHS, 6 MONTHS AND 12 MONTHS POST INTERVENTION

HEALTH FACILITIES	**PRE**			**1 MONTH POST**			**3 MONTHS POST**			**6 MONTH POST**			**12**
	% with Halfan	% with S-P	% with Quinine	% with Halfan	% with S-P	% with Quinine	% with Halfan	% with S-P	% with Quinine	% with Halfan	% with S-P	% with Quinine	% wit Hal
AGBOWA	0.3	13.2	1.6	0	2	0	0	3.5	0	0	4.5	0	0
AJEROMI	1.7	11.9	0.3	0	6	0	1.0	8.5	3.5	2.0	4.0	2.5	2.5
BADAGRY	1.2	9.5	0.2	1.5	5	0	1.0	2.0	0	0	4.0	0.5	1.0
EPE	1.3	6.9	0.6	1.0	6.5	0	0	4.5	3.0	1.0	7.5	0	0
GBAGADA	0.9	14.6	0.2	1.0	1.5	0	3.0	2.5	0	0	7.0	0	2.0
IKORODU	0.5	13.9	0	0	10	0	0	10	0	1.0	13.0	1.5	1.0
ISOLO	1.0	4.7	0.6	1.0	9.0	6.0	0	6.0	10	4.0	6.0	11.5	1.0
LAGOS	0.4	15.1	1.6	1.0	4.5	3.0	5.0	10.5	0	10.5	8.0	3.0	1.0
ORILEAGEGE	0.6	20.5	0.2	0.5	5.0	0	0.5	3.5	0.5	1.5	1.5	1.0	1.5
SURULERE	0.9	8.4	1.0	0	6.5	0	0	3.5	0	0.5	4.5	0	6.0
AVERAGE	0.9	11.9	0.6	0.6	5.6	0.9	1.1	5.5	1.7	1.1	6.0	2.1	1.6

TABLE 7: DOSAGE OF CHLOROQUINE PRESCRIBED IN THE DIFFERENT HEALTH FACILITIES AT PRE, 1 MONTH, 3 MONTHS, 6 MONTHS AND 12 MONTHS POST INTERVENTION

HEALTH FACILITIES	**PRE**			**1 MONTH POST**			**3 MONTHS POST**			**6 MONTH POST**			**12**
	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% cor dos
AGBOWA	38.6	25.4	36	80.6	6.6	12.8	71.0	14.0	15.0	81.4	7.0	11.6	77.
AJEROMI	21.7	7.4	71	65.4	8.2	26.4	64.3	7.7	28.0	63.5	5.5	30.9	70.
BADAGRY	38.7	19.6	41.7	63	5.8	31.2	52.6	8.3	39.1	48.4	6.3	45.3	52.
EPE	38.6	14.9	46.5	67	17.3	15.7	69.0	17.4	13.6	50.8	36.1	13.1	64.
GBAGADA	59.7	17.8	22.5	83.6	11.8	4.6	87.3	7.9	4.8	78.9	13.9	7.2	82.
IKORODU	57.9	14.3	27.8	72.4	16.6	11.0	57.8	21.1	21.1	75.0	17.3	7.7	66.
ISOLO	44.7	34.1	21.2	67.6	19.5	12.9	69.5	12.2	18.3	41.1	29.1	29.7	68.
LAGOS	60.5	8.4	31.1	61	9.1	29.9	68.3	6.7	25.0	72.5	7.3	20.2	59.
ORILEAGEGE	63.6	26.5	9.9	82	5.8	12.2	79.6	4.7	15.7	64.6	25.0	10.4	73.
SURULERE	28.7	11.3	60	78.6	5.9	15.5	82.4	15.5	2.1	79.7	15.0	5.3	70.
AVERAGE	45.3	18.5	36.2	72.4	10.5	17.1	70.4	11.6	18.0	65.3	16.4	18.4	68.

TABLE 8: DOSAGE OF CHLOROQUINE PRESCRIBED IN THE DIFFERENT INTERVENTION GROUPS AT PRE, 1 MONTH, 3 MONTHS, 6 MONTHS AND 12 MONTHS POST INTERVENTION

INTERVENTION GROUP	**PRE**			**1 MONTH POST**			**3 MONTHS POST**			**6 MONTH POST**			**1**
	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% co do
CONTROL	60.10	13.10	26.80	72.30	10.45	17.25	77.80	7.30	14.90	75.70	10.06	13.70	70
SEMINAR+ POSTER	42.48	18.65	38.87	71.4	14.83	13.77	69.68	16.55	13.77	61.65	24.38	13.95	67
SEMINAR+ PLASTIC BOX	40.65	19.70	39.65	72.75	6.6	20.65	66.88	8.67	24.45	64.48	10.95	24.55	68

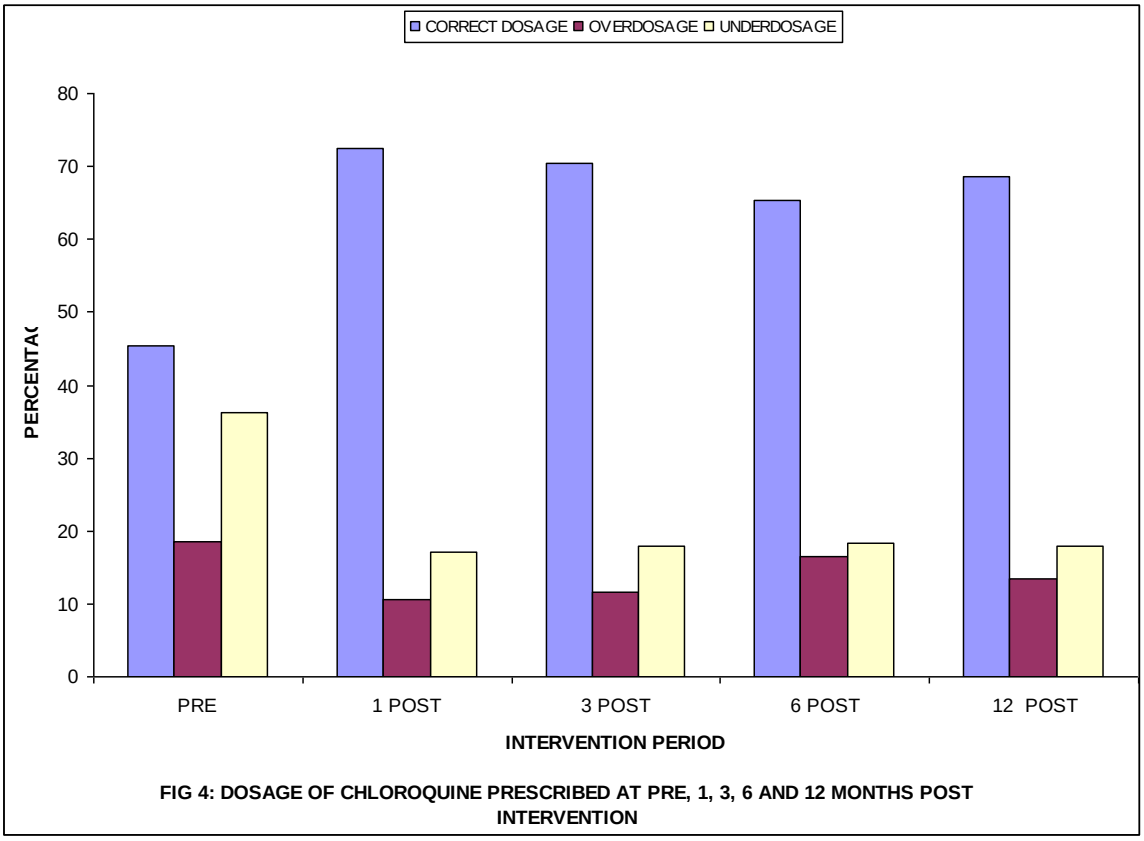

FIG 4: DOSAGE OF CHLOROQUINE PRESCRIBED AT PRE, 1, 3, 6 AND 12 MONTHS POST INTERVENTION

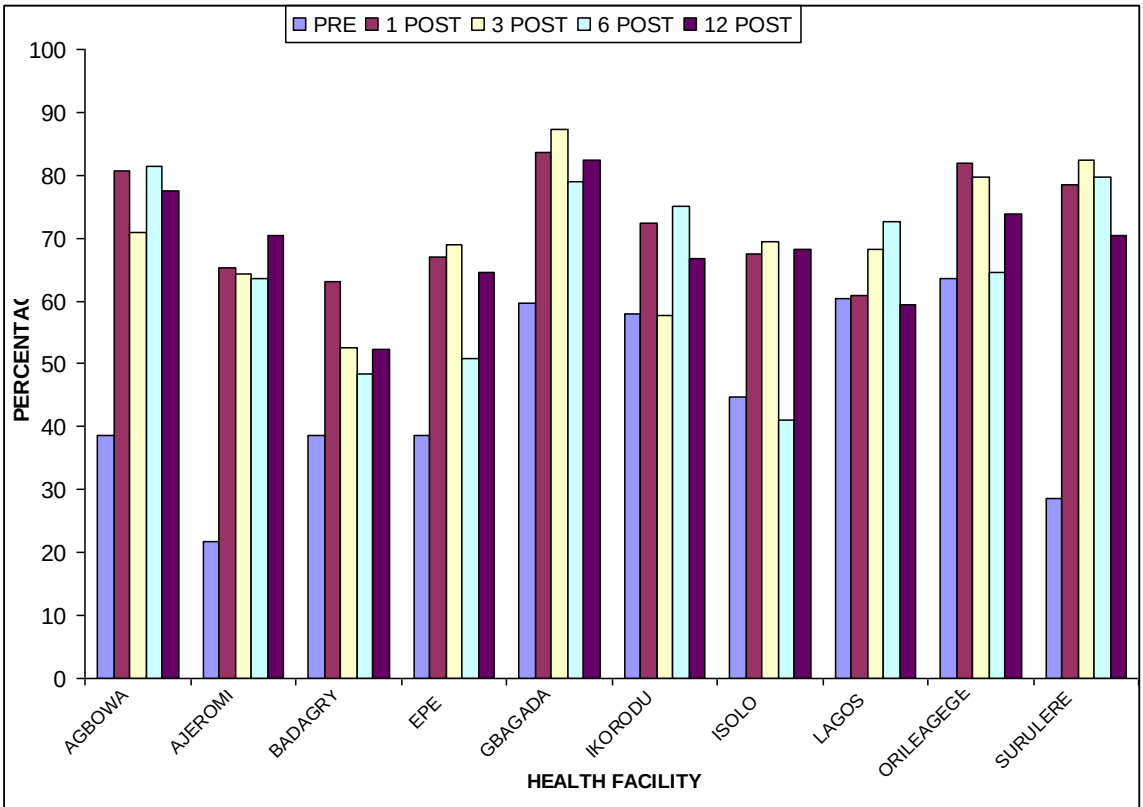

FIG 6: CORRECT DOSAGE OF CHLOROQUINE PRESCRIBED IN EACH HEALTH FACILITY AT PRE, 1, 3, 6 AND 12 MONTHS POST INTERVENTION

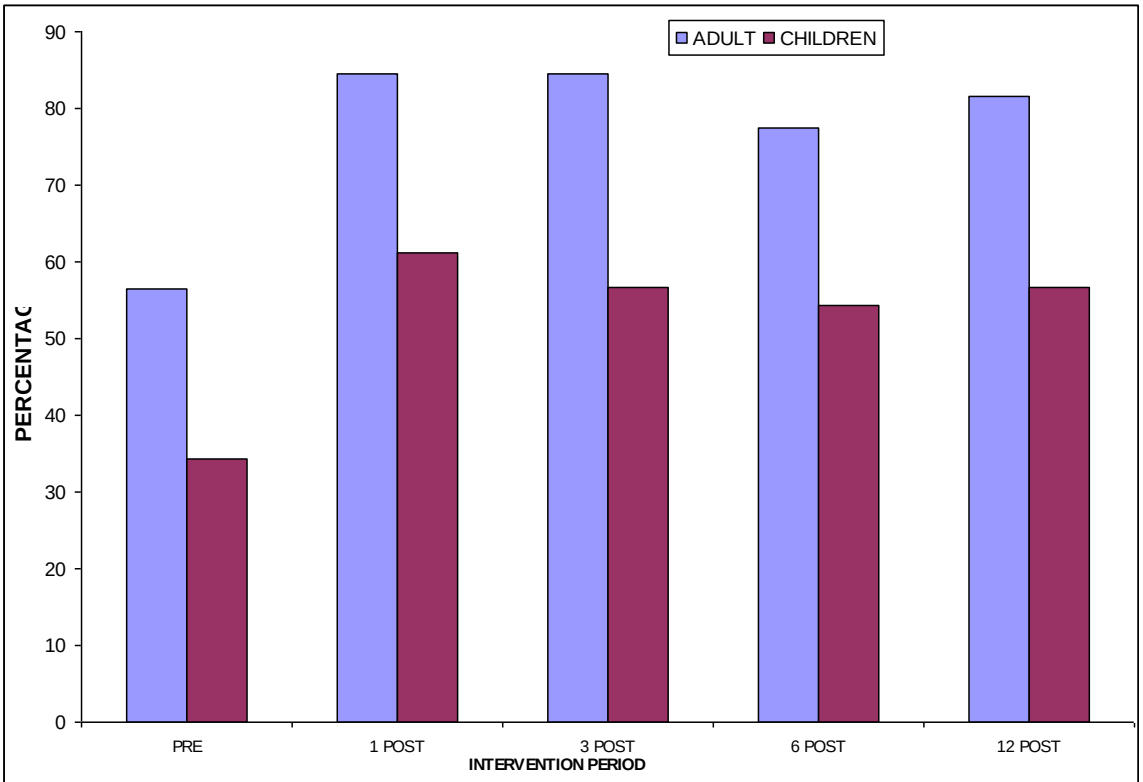

FIG 5: CORRECT DOSAGE OF CHLOROQUINE PRESCRIBED IN ADULT AND CHILDREN AT PRE, 1, 3, 6 AND 12 MONTHS POST INTERVENTION

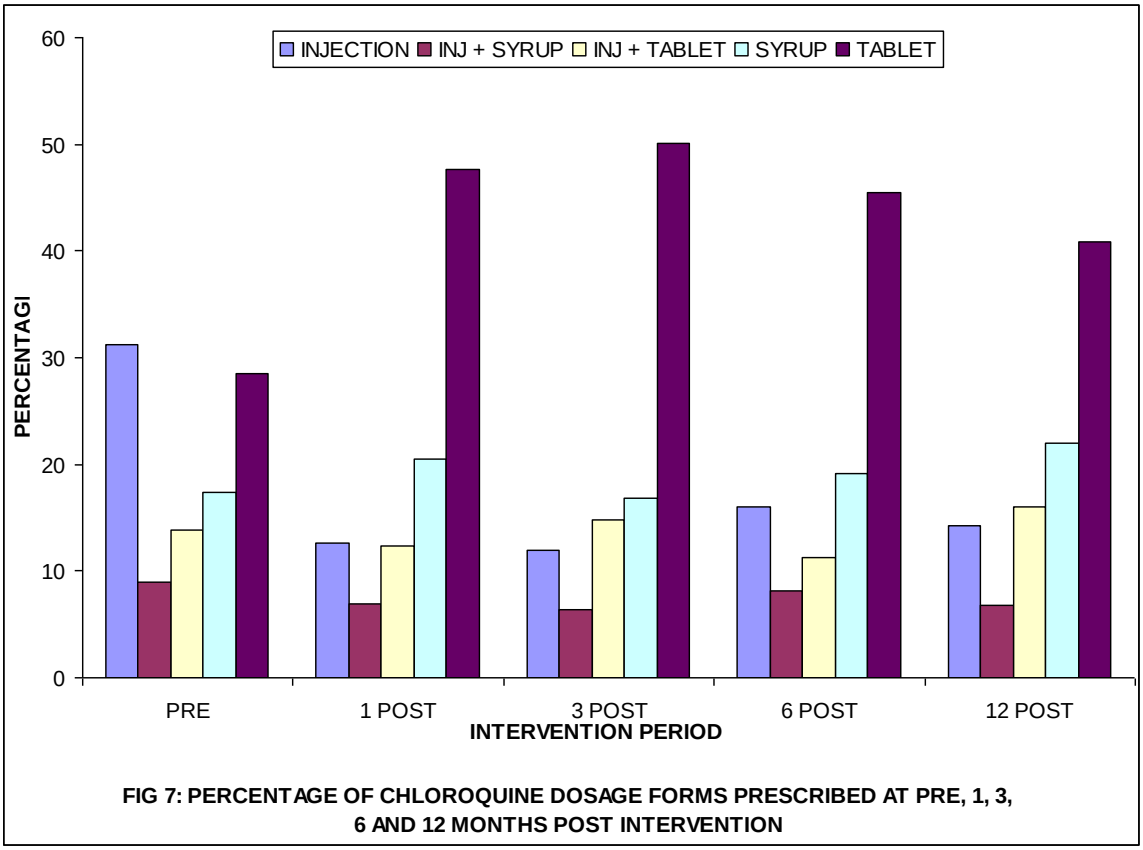

FIG 7: PERCENTAGE OF CHLOROQUINE DOSAGE FORMS PRESCRIBED AT PRE, 1, 3, 6 AND 12 MONTHS POST INTERVENTION

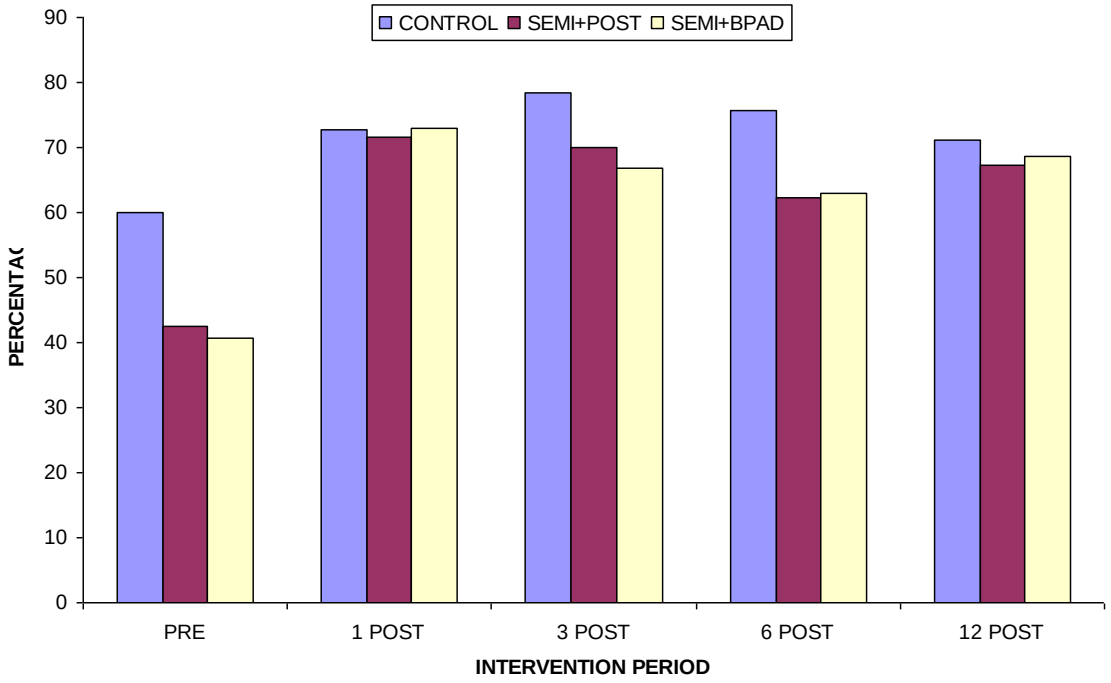

FIG 8: CORRECT DOSAGE OF CHLOROQUINE FOR THE DIFFERENT MODE OF INTERVENTION AT PRE, 1, 3, 6 AND 12 MONTHS POST INTERVENTION

TABLE 9: DOSAGE OF CHLOROQUINE IN THE DIFFERENT DOSAGE FORMS PRESCRIBED AT PRE,1 MONTH, 3 MONTHS, 6 MONTHS AND 12 MONTHS POST INTERVENTION

DOSAGE FORM	**PRE**			**1 MONTH POST**			**3 MONTHS POST**			**6 MONTH POST**			**12**
	% correct Dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% cor dos
INJECTION	6.6	1.2	92.2	14.6	2.6	82.8	8.4	0.9	90.7	10.8	2.2	87.0	17.
INJECTION + SYRUP	34.3	41.2	24.5	54.7	28.9	16.4	44.4	31.6	23.9	44.4	43.0	12.6	63.
INJECTION + TABLET	58.0	29.1	12.9	72.7	18.5	8.8	75.1	15.6	9.3	54.1	38.8	7.1	62.
SYRUP	40.5	45.1	14.3	71.3	10.0	18.7	62.3	18.7	19.0	65.4	23.0	11.6	64.
TABLET	88.0	8.7	3.3	90.5	8.2	1.4	89.6	8.0	2.4	90.8	8.3	0.9	92.

TABLE 10: DOSAGE OF CHLOROQUINE IN THE DIFFERENT DOSAGE FORMS PRESCRIBED FOR THE INTERVENTION GROUPS

DOSAGE FORM	**CONTROL**			**SEMI + POST**			**SEMI + BPAD**		
	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage
INJECTION	1.8	0	98.2	21.3	3.6	75.1	11.3	1.1	87.5
INJECTION + SYRUP	60.6	13.8	25.7	46.7	44.3	9.0	51.8	32.1	16.1
INJECTION + TABLET	79.6	11.6	8.8	60.9	30.8	8.3	72.6	20.7	6.8
SYRUP	70.2	5.9	23.9	57.1	24.2	18.8	71.7	17.2	11.1
TABLET	87.0	9.7	3.4	88.3	10.1	1.6	95.5	3.8	0.7

TABLE 11: DOSAGE OF CHLOROQUINE IN THE DIFFERENT DOSAGE FORMS PRESCRIBED FOR ADULTAND CHILDREN

DOSAGE FORM	**ADULT**			**CHILDREN**		
	% correct dosage	% over dosage	% under dosage	% correct dosage	% over dosage	% under dosage
INJECTION	3.0	0.4	96.6	12.9	2.5	84.7
INJECTION + SYRUP	47.4	47.3	5.3	38.2	39.3	22.5
INJECTION + TABLET	67.5	21.8	10.7	48.4	38.6	14.9
SYRUP	0	0	0	48.3	36.8	14.9
TABLET	96.4	1.9	1.7	64.2	29.8	6.0

4.1b RESULTS FROM THE QUESTIONNAIRE

The results are shown in Tables 12 to 21.

The response rate was about 90%. 75 questionnaires were distributed, 67 questionnaires were returned and used for the analysis.

There were 78% males among the respondents (prescribers) while 22% were females.

Over 50% of the prescribers were within the age range of 30-39. 34% of the respondents were within 1-5 years post qualification while 28% had 6-10 years post qualification.

Majority of the prescribers (74.2%) had the opinion that chloroquine resistant malaria occurs in 0 – 3 out of 10 patients (Table 12).

Underdosage was the reason given for chloroquine resistance by 66% of the respondents (Table 13).

Chloroquine was the first drug of choice by 94% of the respondents (Table 14). Sulphadoxine-pyrimethamine was the second drug of choice by 68.7% of the respondents.

Majority of the respondents (73.1%) selected effectiveness as the first reason for prescribing chloroquine as the first drug of choice while 16.4% of the respondents selected cost as their first reason for prescribing chloroquine as the first drug of choice (Table 15).

64.9% of the respondents selected cost as their second reason for prescribing chloroquine as first drug of choice while 24.6% prescribed chloroquine because it is the drug that is available in the hospital as their second reason (Table 15).

57.6% of the respondents chose oral dosage as their first dosage form to use in their patients while 22.7% chose injection only. 58.2% selected injection+ oral as their 2nd choice of dosage form while 29.1% chose injection only as their 2nd choice of dosage form. 56.3% chose injection only as their 3rd dosage form (Table 16).

70.0% of the respondents filled the correct dose for adults (64.0% filled the actual dose while 6.0% filled 25mg/kg). About 57.0% of the respondents filled the correct dose for children (26.0% filled the actual amount while 31.0% filled 25mg/kg) (Table 17).

47.6% of the respondents considered 5 doses of injection chloroquine only were adequate to treat malaria while 9.5% considered between 7 and 8 doses were adequate (Table 18).

22.7% of the respondents would prescribe 2 antimalarials at the same time (Table 19) and 60% would combine chloroquine and sulphadoxine-pyrimethamine while 20% each would prescribe chloroquine and halofantrine or chloroquine and quinine (Table 20).

More than half of the respondents (51.5%) claimed that therapeutic guidelines was their source of information for chloroquine dosage (Table 21)

TABLE 12: THE NUMBER OF PATIENTS WITH CHLOROQUINE RESISTANT MALARIA OUT OF 10 PATIENTS

NUMBER OF PATIENTS	FREQUENCY OF PRESCRIBERS (%)
0	3.2
1	19.4
2	25.8
3	25.8
4	9.7
5	11.3
6	1.6
ABOVE 6	3.2

TABLE 13: REASONS FOR CHLOROQUINE RESISTANT MALARIA

REASONS	FREQUENCY OF PRESCRIBERS (%)
CHLOROQUINE ABUSE	10.4
NON COMPLIANCE	3.0
CHLOROQUINE OVERDOSAGE	1.5
SUBSTANDARD CHLOROQUINE	13.4
CHLOROQUINE UNDERDOSAGE	65.7
OTHERS	6.0

TABLE 14: PERCENTAGE RESPONSE OF PRESCRIBERS' 1ST AND 2ND CHOICE OF ANTIMALARIAL

DRUG	1ST CHOICE FREQUENCY OF PRESCRIBERS (%)	2ND CHOICE FREQUENCY OF PRESCRIBERS (%)
AMODIAQUINE	3	0
CHLOROQUINE	94	1.5
SULHADOXINE-PYRIMETHAMINE	3	68.7
ARTEMISININ	0	1.5
FANSIMEF	0	4.5
HALOFANTRINE	0	16.4
QUININE	0	7.5

TABLE 15: PERCENTAGE RESPONSE OF PRESCRIBERS' 1ST AND 2ND REASON FOR CHOICE OF CHLOROQUINE

REASONS	FREQUENCY OF PRESCRIBERS (%) 1ST REASON	FREQUENCY OF PRESCRIBERS(%) 2ND REASON
COST	16.4	64.9
DRUG AVAILABILITY	3.0	24.6
TREATMENT GUIDELINE	3.0	1.8
EFFECTIVENESS	73.1	7.0
PATIENT DEMAND	1.5	0
OTHER REASONS	3.0	1.8

TABLE 16: PERCENTAGE RESPONSE OF PRESCRIBERS' CHOICE OF CHLOROQUINE DOSAGE FORMS

DOSAGE FORMS	FREQUENCY OF PRESCRIBERS(%) 1ST CHOICE	FREQUENCY OF PRESCRIBERS(%) 2ND CHOICE	FREQUENCY OF PRESCRIBERS(%) 3RD CHOICE
INJECTION ONLY	22.7	29.18	56.3
ORAL ONLY	57.6	12.7	34.4
INJECTION + ORAL	19.7	58.2	9.4

TABLE 17: PERCENTAGE RESPONSE OF PRESCRIBERS' CORRECT DOSAGE OF CHLOROQUINE IN ADULT AND CHILDREN

FREQUENCY OF PRESCRIBERS (%)	ADULT	CHILDREN
CORRECT DOSAGE	70 (64 + 6)	57 (26 + 31)
OVERDOSAGE	13.0	14
UNDERDOSAGE	17.0	29

TABLE 18: PERCENTAGE RESPONSE OF PRESCRIBERS' NUMBER OF DOSES OF INJECTION CHLOROQUINE ONLY, ADEQUATE TO TREAT MALARIA

NUMBER OF DOSES	FREQUENCY OF PRESCRIBERS (%)
2	1.6
3	22.2
4	11.1
5	47.6
6	7.9
7	3.2
8	6.3

TABLE 19: PERCENTAGE OF PRESCRIBERS WHO WOULD PRESCRIBE 2 ANTIMALARIALS TOGETHER

	FREQUENCY OF PRESCRIBERS (%)
YES	22.7
NO	77.3

TABLE 20: PERCENTAGE RESPONSE OF THE PRESCRIBERS TO THE COMBINATION OF THE 2 ANTIMALARIALS PRESCRIBED TOGETHER

COMBINATION	FREQUENCY OF PRESCRIBERS (%)
CHLOROQUINE+SULPHADOXINE-PYRIMETHAMINE	60
CHLOROQUINE+ HALOFANTRINE	20
CHLOROQUINE + QUININE	20

TABLE 21: SOURCE OF INFORMATION FOR CHLOROQUINE DOSAGE

SOURCE	FREQUENCY OF PRESCRIBERS (%)
THERAPEUTIC GUIDELINE	51.5
PHARMACIST	4.5
DRUG FORMULARY	18.2
MEDICAL REPS.	3
DRUG LEAFLET	1.5
PEERS	3
SENIOR COLLEAGUE	9.1
HOSP. DRUG BULLETIN	1.5
OTHERS	7.6

4.2 RESULTS OF QUALITY ASSESMENT OF CHLOROQUINE FORMULATIONS

All the tablet samples passed the dissolution and disintegration tests according to British Pharmacopoeia (BP) standard (Table 22). 85.7% of the tablet samples complied with BP standard for the content of active ingredient (Table 22) which was calculated from the concentration obtained from the standard curve (fig 9). 21% of the tablet samples failed the friability test (Table 23). All the tablet samples passed the BP requirements of weight variation from mean weight, none deviated by 5% from mean weight (Table 23).

92.3 % of the syrup samples failed the BP standard for active ingredient. They had higher amounts than the BP standard (Table 24).

23% of the syrup samples failed the BP standard for microbial growth (Table 24). These had more than 10^3 cfu/ml (*B. substilis*) but there was no growth of *Escherichia.coli*, *Staphylococcus aureus* and *Klebsiella spp.* All colonies stained showed a predominantly Gram Positive Large Bacilli indicative of the *Bacilus* spp.

There was no association between sample discolouration and microbial growth which implied that discolouration may be due to other processes like chemical degradation and not necessarily microbial spoilage

There was no growth in all the injection samples but all of them failed BP standard for active ingredient (Table 25).

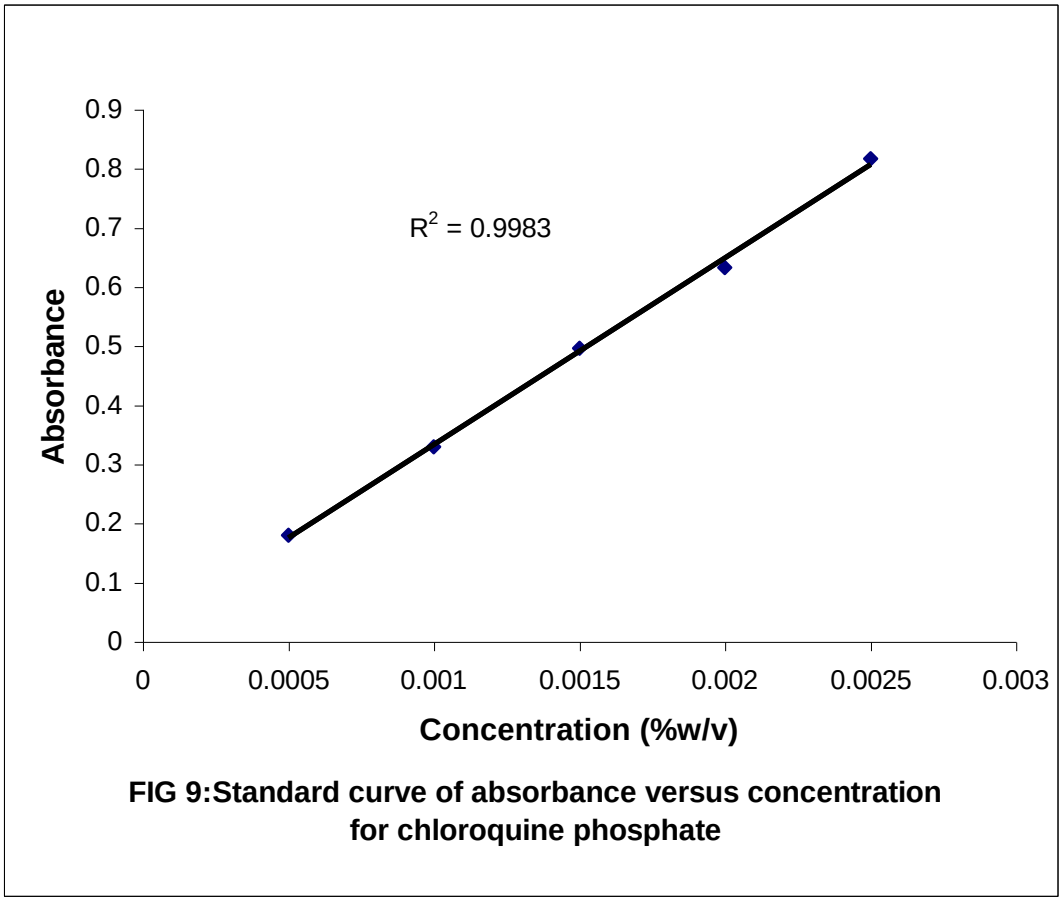

FIG 9:Standard curve of absorbance versus concentration for chloroquine phosphate

Concentration of chloroquine samples were intrapolated for the absorbance from the standard curve

TABLE 22: RESULTS OF QUALITY ASSESMENT OF CHLOROQUINE TABLETS

TABLET	% CONTENT ± SEM n = 2	% DISSOLUTION ± SEM n = 2	HARDNESS IN Newton MIN	AV	MAX	DISINTE GRATION TIME	BN/ED
AI	92.8± 0.800	86.0± 2.000	3.5	3.6	3.8	3 min 2 sec	4640E, AUG 2005
A2	106.0± 2.000	96.0± 1.000	4.5	4.9	5.2	2 min 50 sec	011203, DEC 2004
A3	93.0± 0.000	88.0± 2.000	2.8	3.2	3.5	1 min 31 sec	4640E, AUG 2005
A4	93.0± 1.000	100.0± 0.000	4.0	4.3	5.0	2 min 45 sec	011202, DEC 2004
A5	100.0± 1.000	90.0± 2.000	3.5	3.8	4.0	1 min 5 sec	011205, DEC 2004
A6	103.0± 2.000	100.0± 1.000	3.5	3.6	3.8	11 min 15 sec	2BW2313, FEB 2005
A7	97.0± 2.000	77.0± 0.000	2.5	2.8	3.0	5 min 50 sec	220010302, MAR 2006
A8	105.0± 1.000	86.0± 2.000	6.0	7.4	9.5	10 min 47 sec	A037G, SEPT 2004
A9	90.0± 2.000	92.8± 0.300	3.0	3.6	4.2	45 sec	W004, JUN 2006
A10	96.0± 2.000	100.0± 1.000	5.0	5.6	6.5	10 min	1J122029, SEPT 2004
A11	74.5± 0.500	72.0± 2.000	3.8	4.66	6.0	15 sec	5040 NOV 2005
A12	96.0± 2.000	70.4± 0.400	5.5	5.9	6.5	2 min 8 sec	011204 DEC 2004
A13	93.0± 1.000	74.0± 0.000	2.5	2.7	3.0	1 min 5 sec	5189E SEPT 2005
A14	98.0± 2.000	76.0± 1.000	3.5	3.86	4.5	59 sec	011204 DEC 2004

BN: Batch number
ED: Expiry date
SEM : Standard Error of Mean

BP 1998 Standards

Dissolution: 70% should dissolve in 45 minutes
Content: 92.5 – 107.5 % of the stated amount for tablet
95 – 105 % of the stated amount for injection
No stated amount for syrups but 92.5 – 107.5 % is chosen
Friability: Not more than 1%
Disintegration: All tablets must normally disintegrate within 15 minutes.

TABLE 23: RESULTS OF QUALITY ASSESMENT OF CHLOROQUINE TABLETS

TABLET	AVERAGE WEIGHT In (mg) ± SEM n = 10	AVERAGE DIAMETER In (mm) ± SEM n = 5	AVERAGE THICKNESS In (mm) ± SEM n = 5	FRIABILITY In %
A1	327.90 ± 1.79	9.71± 0.010	4.41± 0.037	1.00
A2	349.83 ± 1.10	10.19± 0.009	4.65± 0.030	0.38
A3	330.90 ± 3.05	9.72± 0.022	4.50± 0.032	1.00
A4	342.70 ± 1.66	10.24± 0.011	4.65± 0.019	0.39
A5	346.90 ± 3.49	10.23± 0.014	4.71± 0.019	0.78
A6	319.02 ± 0.60	9.74± 0.015	3.39± 0.022	0.28
A7	312.61 ± 1.56	10.16± 0.013	4.14± 0.041	1.99
A8	336.23 ± 0.52	9.68± 0.010	3.79± 0.024	0.50
A9	284.24 ± 4.19	9.14± 0.011	4.37± 0.016	2.81
A10	311.00 ± 2.41	9.68± 0.010	3.42± 0.043	0.36
A11	327.16 ± 2.09	9.84± 0.010	4.57± 0.017	0.38
A12	347.61 ± 0.32	10.18± 0.014	4.64± 0.017	0.39
A13	332.55 ± 2.14	9.74± 0.012	4.59± 0.019	1.15
A14	351.00 ± 0.48	10.22± 0.017	4.68± 0.027	0.28

TABLE 24: RESULTS OF QUALITY ASSESMENT OF CHLOROQUINE SYRUPS

SYRUP	GROWTH ON 4^{TH} DAY	CFU	%CONTENT± SEM n = 2	COLOUR	BN/ ED
TSA	NO	0	-	-	-
MSA	NO	0	-	-	-
EMBA	NO	0	-	-	-
B1	YES	40	122.0± 2.000	PINK	102, JUL 2004
B2	NO	0	118.0± 2.000	PINK	251144, APR 2006
B3	YES	$>10^3$	125.0± 2.000	PINK	A08, SEPT 2004
B4	YES	$>10^3$	117.0± 0.000	PINK	106, JUL 2004
B5	YES	40	117.0± 3.000	DARK	102, JUL 2004
B6	YES	$>10^3$	117.0± 1.000	DARK	103, JUL 2004
B7	NO	0	126.0± 1.000	PINK	104, JUL 2004
B8	YES	30	114.0± 0.000	PINK	251144, APR 2006
B9	YES	$>10^2$	140.0± 0.000	PINK	100, JUL 2004
B10	YES	40	106.0± 1.000	PINK	251144, APR 2006
B11	YES	40	126.0± 0.000	PINK	251142, JAN 2006
B12	NO	0	117.0± 2.000	DARK	102, JUL 2004
B13	YES	50	115.0± 2.000	PINK	251144, APR 2006

CFU: Colony Forming Unit
MSA: Mannitol Salt Agar
TSA: Tryptone Soya Agar
EMBA: Eosin Methylene Blue Agar
BN: Batch number
ED: Expiry date

Growth for oral solutions: should not be more than 10^3 aerobic bacteria and not more than 10^2 fungi per gram or per milliliter but there should be absence of *Escherichia coli* .

TABLE 25: RESULTS OF QUALITY ASSESMENT OF CHLOROQUINE INJECTIONS

INJECTION	GROWTH	%CONTENT± SEM n = 2	BN/ ED
C1	NO	116.0± 2.000	020202, FEB 2005
C2	NO	112.0± 3.000	CQ-01, MAR 2004
C3	NO	124.0± 2.000	20011147, NOV 2004
C4	NO	120.0± 0.000	1CE204, NOV 2004
C5	NO	121.0± 2.000	020702, JUL 2005

Growth for injection: Solutions for injection are required to be sterile.

4.3 COST-EFFECTIVENESS ANALYSIS (CEA) RESULTS

COST-EFFECTIVENESS ANALYSIS OF TABLET CHLOROQUINE AND INJECTION CHLOROQUINE

Table 26: DECISION TABLE

Criterion	Tablet Chloroquine	Value (%)	Injection Chloroquine	Value (%)
1. Spectrum of Activity Assumption	Desired therapeutic outcome (Parasite Clearance)	100	Parasite Clearance	100
2. Pharmacokinetics*	Bioavailability,	90	Bioavailability	90
3. Frequency of Administration**	Frequency of once daily	100	Frequency of administration (8 hourly)	33
4. Safety on administrati on	Risk of infection 0} Risk of abscess 0} 0% Pain at site of injection 0} Tolerability of administration 100 - 0	100	Risk of infection 50} Risk of abscess 50}60% Pain at site of injection 80} Tolerability of administration 100 – 60	40
5. Adverse Drug Reaction	Nausea and vomiting 10} Pruritus 10} 10% Tolerability = 100 –10	90	Pruritus 10} Hypotension 60} 50% Cardiac depression 80} Tolerability 100 - 50	50

NOTE

Once Daily = 100%
Twice Daily = 50%
Thrice Daily (8 hourly) = 33%
Four Times Daily = 25%
***** Tracy and Webster 2001
** White 1996

Table 27: EFFECTIVENESS RATING

	Criterion	Tablet Chloroquine			Injection Chloroquine		
		Value (%)	Assigned Weight	Criterion Rating	Value (%)	Assigned Weight	Criterion Rating
1	Spectrum of Activity	100	0.3	30	100	0.3	30
2	Bioavailability	90	0.2	18	90	0.2	18
3	Frequency of Administration	100	0.1	10	33	0.1	3.3
4	Safety on drug administration	100	0.2	20	40	0.2	8
5	Adverse Drug Reaction (Tolerability)	90	0.2	18	50	0.2	10
6	Sum of Criteria Rating		1.0	96		1.0	69.3

Criterion Rating = Criterion Value x Assigned Weight (%).

Sum of Criteria Ratings = Measure of Effectiveness

Table 28: CALCULATION OF COSTS

	Direct Medical Cost	Tablet Chloroquine	Injection Chloroquine
1	Acquisition Cost	10 Tablets x ₦2 = ₦20	8 Amps of 200mg x ₦15 = ₦120 8 Needles and Syringe x ₦10 = ₦80 8 Cotton wool and Spirit x ₦5 = ₦40 ₦240
2	Costs Associated with preparation and administration of drug	Pharmacist ₦0.0256 x 52 sec = ₦1.33	Nurse ₦0.0238 x 85 sec per injection ₦2.023 x 8 doses = ₦16.184
3	Travel Cost (to patient) assuming ₦20/trip	₦20 x 1 (1 visit)	₦20 x 8 (8 hourly injection) = ₦160
	TOTAL	₦41.33	₦416.184

NB

Time for dispensing tablet by the pharmacist = 52 sec

Time for administering the injection by the nurse = 85 sec

The cost here is based on the patient and health care system perspective. If only the health care system perspective is considered then the total cost for chloroquine tablet is ₦21.33 and for injection is ₦256.184

Table 29: HEALTH CARE PERSONNEL COST

Personnel	Salary Per Annum	Hours/Week	Number of Weeks/Annum	Mean Salary(₦)/Sec
Pharmacist I	₦176850	40	52	.0236
Senior Pharmacist	₦206772	40	52	+.0276 **.0512** **2** = **.0256**
Staff Nurse	₦149922	40	52	.0200
Senior Nursing Officer	₦206772	40	52	+ .0276 **.0476** **2** = **.0238**

Mean Salary/Second = Annual Salary

Hours/Week x Weeks/Annum x 3600s

COST-EFFECTIVENESS ANALYSIS (CEA)

Patient and health system perspective

CEA = Cost

Effectiveness

Tablet Chloroquine = ₦ 41.33 = ₦0.430/Unit of effectiveness

96

Injection Chloroquine = ₦ 416.184 = ₦6.006/Unit of effectiveness

69.3

Tablet Chloroquine was found to be 14 times more cost-effective than Injection Chloroquine.

Health care system perspective

$$CEA = \frac{Cost}{Effectiveness}$$

Tablet Chloroquine = $\frac{₦ 21.33}{96}$ = ₦0.222/Unit of effectiveness

Injection Chloroquine = $\frac{₦ 256.184}{69.3}$ = ₦3.697/Unit of effectiveness

Tablet Chloroquine was found to be 17 times more cost-effective than Injection Chloroquine.

SENSITIVITY ANALYSIS

1. Increasing the cost of Chloroquine tablet by 100%

   CEA = $\frac{₦ 82.66}{96}$ = ₦ 0.861/Unit of effectiveness

2. Increasing the cost of Chloroquine tablet by 500%

   CEA = $\frac{₦ 206.65}{96}$ = ₦2.153/Unit of effectiveness

3. Decreasing the effectiveness of chloroquine tablet to 69.3

   CEA = $\frac{₦ 41.33}{69.3}$ = ₦ 0.5964/Unit of effectiveness

4. Increasing the effectiveness of Injection Chloroquine to 96

CEA = ₦ 416.184 = ₦4.335/Unit of effectiveness

96

5. Decreasing the cost of Injection Chloroquine by 50%

CEA = ₦ 208.092 = ₦3.003/Unit of effectiveness

69.3

6. Decreasing nursing preparation and administration time to 40 secs. per Injection

CEA = 407.616 = ₦5.882/Unit of effectiveness

69.3

The decision remained valid justifying that Tablet Chloroquine was more cost effective than Injection Chloroquine

4.4 STATISTICAL ANALYSIS RESULTS

Hypothesis One

The percentage of prescriptions with correct dosage of chloroquine after the educational intervention was statistically different from before intervention ($p < 0.01$).

Hypothesis Two

The quality of some of the chloroquine formulations available in these hospitals especially the injections and the syrups did not meet the officially recommended standard

Hypothesis Three

Chloroquine tablet was found to be more cost effective than chloroquine injection

Hypothesis Four

Using one way ANOVA the percentage of prescriptions with correct dosage of chloroquine in the plastic box intervention group was not statistically different from that in the poster intervention group ($F = 0.000386$, $p > 0.05$).

Hypothesis Five

There was relationship between the dosage of chloroquine and the different dosage forms of chloroquine prescribed ($X^2 = 19811.04$, $p < 0.001$)

There was association between intervention and dosage of chloroquine prescribed ($p< 0.001$).

There was association between the mode of intervention and dosage of chloroquine prescribed ($X^2 = 1276.02$, $p< 0.001$)

Using Tukey HSD there was no statistically significant difference in percentage of correct prescriptions between 1 month, 3 months, 6 months and 12 months post intervention hence it is implied that the intervention was sustained (Table 30).

Table 30: Multiple Comparisons between Intervention Times using Tukey's HSD

Intervention Time (1)	Intervention Time (2)	MeanDifference (1) – (2)	Significance P
Pre-intervention	1 month post-intervention	-16.2233	.000*
Pre-intervention	3 months post-intervention	-15.1055	.001*
Pre-intervention	6 months post-intervention	-12.2939	.007*
Pre-intervention	12 months post-intervention	-13.9565	.002*
1 month post-intervention	3 months post-intervention	1.1178	.997^{ns}
1 month post-intervention	6 months post-intervention	3.9294	.765^{ns}
1 month post-intervention	12 months post-intervention	2.2668	.960^{ns}
3 months post-intervention	6 months post-intervention	2.8116	.916^{ns}
3 months post-intervention	12 months post-intervention	1.1489	.997^{ns}
6 months post-intervention	12 months post-intervention	-1.6626	.987^{ns}

* Significant ns = not significant

CHAPTER FIVE

5.1 DISCUSSION

From the prescriptions surveyed pre and post-intervention, some recurring results were observed. For example it was discovered that the highest percentage of underdose was observed where injection chloroquine only was prescribed while the highest percentage of correct dose of chloroquine was observed when tablet chloroquine only was prescribed whether considered per health facility, adult, children or overall in the total prescriptions studied.

Underdosage was a major problem when injection chloroquine only is prescribed. From literature (Bjorkman and Phillips-Howard, 1990; Hellgreen *et al*., 1994; Gomes *et al* 1998) underdosage is implicated in chloroquine resistant malaria. Oral dosage form should be encouraged to be prescribed with injection in order to complete the dosage. The number of doses required to attain complete dosage for injection chloroquine only, in an adult is about 7 – 8 which have to be given every 6 or 8 hours; this is not convenient for ambulatory patients. Also the cost of injection and its administration was found to be higher than that of oral dosage form. In addition, side effects or adverse effects to chloroquine injection are life threatening and these include hypotension, cardiac arrest, cardiac depression and cardiac arrhythmia (White, 1996). The scourge of HIV/AIDS, hepatitis, poliomyelitis etc. in the country militates against use of injection because of cross infection and there is the possibility of injection abscess which results in additional costs to the patient (Simonsen *et al.,* 1999; Frank *et al.,* 2000; Khan *et al.,* 2000). From the cost effectiveness analysis and sensitivity analysis chloroquine tablet was found to be more cost effective than the injection. The

quality analysis of chloroquine samples obtained from the hospitals showed that the tablets are better than the injections. The tablet chloroquine had the highest percentage of correct dosage of chloroquine prescribed whether in adults or children or overall in the health facilities. The cost of giving tablets was low and adverse effects are minimal with tablet while possibility of completing the dose is high.

For these reasons, injection should be discouraged and tablet chloroquine encouraged. The percentage of correct dosage was consistently higher in adults than in children (Fig 5). This may be attributed to the fact that tablets are mainly prescribed for adults. Also there are different age groups and different doses for the children. These doses may be cumbersome to remember by the prescribers hence the need to give them reminders, especially for the children doses. This was substantiated in the questionnaires where most of the prescribers filled 25mg/kg but could not fill the individual doses for the age groups. 64% of the prescribers filled the actual correct dose for adults while 6% just filled 25mg/kg whereas only 26 % of the prescribers filled the actual correct dose for children while 31% just filled 25mg/kg.

It was observed that injection dipyrone was prescribed frequently as antipyretic even when chloroquine tablet was prescribed. Although it has been recommended that oral dipyrone could only be used when other analgesics have failed (Arellano and Sacristan, 1990) but

this is unacceptable especially when this drug has been banned in many countries because it has been associated with irreversible agranulocytosis (Roberts and Morrow, 2001).

The average number of drugs per encounter was fairly high; this may be due to the fact that patients come to the hospital with multiple disease conditions and malnourished hence the inclusion of one vitamin preparation or the other in the prescriptions. Prescription of a large number of drugs is unacceptable because of the possibility of adverse drug reaction, the incidence of which increases with the number of drugs (Nies, 2001).

In this study, it was discovered that vitamin B complex was frequently prescribed as one tablet three times daily either for five days, one week or two weeks. Part of the reasons given for this was that patients were malnourished. The emphasis should be on eating adequate and balanced diet rather than taking drugs.

Generally, it was observed that there was improvement in the indicators under consideration at 1 month post-intervention but the degree of the improvement was reduced at 3, 6 and 12 months post-intervention though the reduction was not statistically significant. This implies that the intervention was sustained but there may be need for a constant reminder and not just leaving educative materials like posters or plastic box with the prescribers. There was the tendency for people to revert to old behaviour after some time (Quick *et al*. 1997). The pharmacist may serve as a reminder but there may be need to find out if pharmacists are ready for this or whether this will go well with the physicians. During the intervention seminars this issue was discussed and it was agreed that the pharmacist should call the attention of the physician to any unusual dose before correction.

The marked increase in the percentage of prescriptions with correct dose of chloroquine 1 month post-intervention either overall or for the different mode of

intervention shows that the intervention had impact on the prescribing habit. There was no visible pattern of prescribing peculiar to whether the hospital was in the rural or urban area. In this study it was not possible to determine whether the reason for irrational prescribing was culturally based but it was not economically based because the treatment was free as the state government bore the cost

From the questionnaires that chloroquine was the first choice of most of the respondents (prescribers) (94.0%) and sulphadoxine-pyrimethamine the second choice (68.7%) agreed with National Antimalarial Treatment Policy (FMOH, 2001). It is expected that chloroquine being the first line drug in the policy will make it to be readily available in the hospitals and be the first choice for this reason. However only 24.6% of the prescribers picked chloroquine as first choice because it was the drug that was available in the hospital. The first reason given by majority of the prescribers (73.1%) for picking chloroquine as first choice was effectiveness. This supports the findings that chloroquine is effective in this part of the country (Ekanem *et al* 1990; FMOH 2001; Salako, 2002).

Majority of the prescribers (74.2%) had the opinion that chloroquine-resistant malaria occurs in 0 – 3 out of 10 patients.

Under-dosage is a major problem with injection chloroquine only and since this under-dosage was even a major reason given by the prescribers as being responsible for chloroquine-resistance, then, there was need to address this during the intervention.

Some other reasons given for chloroquine resistance included hypersensitivity reaction to chloroquine. This will lead to non-compliance and eventually under-dosage since the patient will not complete the prescribed course of treatment.

It is welcoming to know that a little more than half of the respondents (57.6%) would prescribe oral chloroquine as first choice though this percentage could be higher because it was found that the tendency for the dose to be correct was highest for oral and lowest for injection only . Some of the reasons given by respondents for prescribing injection-only as first choice included when a patient is vomiting, acutely ill or demands it. None of the prescribers believed that injection was more effective than tablets. This is contrary to the reports of Taylor *et al.,* (1998) where 43.3% of physicians surveyed believed chloroquine injection was more effective. Proper counseling and patient education on the part of the prescriber should discourage the demand for injection by patients. This demand is usually due to erroneous belief that injections are more effective than tablets.

Only a few of the respondents (9.5%) got the right number of doses of injection chloroquine only, that are adequate. This made it mandatory to remind them about the right number of doses for the complete dosage for injection chloroquine only, during intervention.

Only few respondents (4.5%) would use the pharmacist on duty as the source of information for chloroquine dosage. One of the reasons given for this was that there was no intercom to communicate with the pharmacist on duty and it was not convenient to leave the consulting room to go to the pharmacy considering patient pressure. There is need to encourage the authority to provide intercom service in every hospital in order to encourage the prescribers to use the pharmacist on duty as a source of information and this is for the benefit of the patient.

Some of the respondents (22.7%) would prescribe two antimalarials together and a few of the prescriptions studied (0.014%) had 2 antimalarials prescribed together, majority of which were chloroquine plus sulphadoxine-pyrimethamine. Though combination drugs is being advocated to reduce the likelihood of resistance, there is need to carry out further studies on the safety and pharmacokinetics of any drug combination to be used (White *et al.*, 1999; FMOH 2001). Wongrichanalai *et al.*, (2000) suggested the need to determine and validate the most suitable antimalarial combination regimens for each epidemiologically distinct area and each operationally different circumstance. There must be measures to ensure compliance and maintain the fixed dose of each partner compound so that the expected benefit will not be lost.

All the tablet samples passed the dissolution and disintegration tests according to British Pharmacopoeia (BP) standard. 21% of the tablet samples failed the friability test. 85.7% of the tablet samples complied with BP standard for active ingredient.

92.3 % of the syrup samples failed the BP standard for active ingredient. They had higher amounts than the BP standard. This tallies with the report of (Taylor *et al.*, 2001) where all the Chloroquine phosphate syrups analysed had higher amount than the BP limits.

23% of the syrup samples failed the BP standard for microbial growth. These had more than 10^3 cfu/ml of *Bacillus substilis* but there was no growth of *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella species.*

There was no association between sample discolouration and microbial growth which implies that discolouration may be due to other processes like chemical degradation and not necessarily microbial spoilage

There was no growth in all the injection samples but all of them failed BP standard for active ingredient. This is similar to the results obtained by Taylor *et al.,* 2001 where 93% of injection Chloroquine phosphate were outside the BP standard for active ingredient.

The use of poor quality drugs is of concern. Where the amount of active drug is well below stated amount, use of these preparations could lead to therapeutic failure and select for drug- resistant organisms. An excess of active content could also have serious consequences such as toxicity and side effects, especially in pediatric formulations. High chloroquine plasma concentrations are toxic and lead to resistant cardiac arrhythmia with an 80% death rate in some circumstances (Kelly *et al.,* 1990). It is realized that the presence of microorganisms in a pharmaceutical preparations may have a variety of consequences ranging from the negligible to the very serious. Microbial contamination of medicines can lead to possible infection of patients and spoilage of the product. This is wastage of human and financial resources.

At the tail end of writing this thesis, a debate arose on the use of chloroquine as first-line drug for malaria in West African sub-region. From the directive, Artemisinin based combination therapy (ACT) was favoured. Indeed in some West African countries, e.g. The Gambia and Ghana, by 2006, use of chloroquine will be banned. Among the reasons adduced for this action is that *Plasmodium* specie has shown a 'high' degree of resistance to chloroquine. Some observers question this decision for many reasons viz:

- Access to Artemisinin derivatives would constitute a problem because they are derived from plant sources and predominantly produced in China (Hien and White, 1993);
- Cost of Artemisinin-based therapy is over 50 times that of chloroquine and this is unrealistic in a region where the annual earning of people is nothing to write home about and abject poverty abounds;
- We know very little about Artemisinin derivatives compared to chloroquine in terms of their toxicity profile in humans. Although there is no reported neurotoxicity in humans, there are reports in literature of neuropathological/neurotoxic effects in vitro and in a variety of experimental animals (Brewer *et al*., 1994a and 1994b; Wesche *et al*., 1994; Kamchonwongpaisan *et al.*, 1995; Nontprasert *et al*., 2000)
- When Artemisinins were first introduced, the manufacturers specifically warned against the use in infants, pregnant women and nursing mothers - 3 most vulnerable groups. Reduced fetal survival and increased abortion rate was observed in some animal studies so these drugs should be used during pregnancy only as a last resort (Wesche *et al*., 1994)
- Presently, those who are on Artemisinin based combination have to swallow over ten tablets e.g. 24 tablets of Riamet^{R} or Coartem^{R} over 60 hours; 12 tablets of Malarone^{R} over 48 hours (BNF 2004). This will not encourage compliance and will lead to underdosage. Therefore, the resistance we are supposed to circumvent may eventually resuscitate.

- These Artemisinin derivatives will be available as over the counter drugs once they become first line drugs. This makes them to be easily obtained and used any time and as often as deemed necessary. This problem coupled with problem of self medication, presumptive treatment and repeated treatment of uncomplicated malaria brings about the question of drug toxicity and resistance
- Despite the efficacy of the Artemisinin derivatives to reduce parasite count there is high rate of recrudescence. To address this they are often used in combination with other antimalarial agents. The second agent must be chosen carefully; there is in vitro evidence of drug-drug antagonism with chloroquine (Stahel *et al*., 1988). There is in vivo evidence of antagonism with antifolates and in vivo synergy between Artemisinin and tetracycline and mefloquine (Chawira *et al*., 1987) The selection of a particular regimen is likely to depend on local parasite sensitivities and target population (e.g. tetracyclines are contraindicated in pregnant women and children) and fiscal realities.

5.2 CONCLUSION

From the results of this study it can be concluded that the intervention had significant effect on the correct dosage of chloroquine prescribed. The effect was more at 1 month post- intervention. Correct dosage was obtained more when tablet chloroquine only, was prescribed than any other dosage form. Under-dosage was obtained more when injection chloroquine only, was prescribed than any other dosage form. The other dosage forms or combination of dosage forms were in between. From the results of the pharmacoeconomics (cost-effectiveness) analysis the tablet chloroquine was more cost effective than the injection chloroquine. Also from the results of the quality determination of the chloroquine dosage forms obtained from the health facilities the tablets complied more with the BP standard in terms of active content than the other dosage forms.

It is suggested that tablet chloroquine should be used to treat uncomplicated malaria in our hospitals and where injection cannot be avoided, in case of vomiting patients, the injection should be followed by tablet as soon as the vomiting stops. Also there should be a reminder of the appropriate dosage of chloroquine especially for the different age groups among the children. Quality of drugs being supplied to our hospitals should be verified and monitored.

There was no statistically significant difference in percentage of correct prescriptions between 1 month, 3 months, 6 months and 12 months post intervention hence it is hereby implied that the intervention was sustained.

5.3 Recommendations

To maintain improvement, it is being recommended that

1. Flyers be sent out monthly or quarterly to prescribers and pharmacists
2. Regular monthly or bimonthly seminars be held in Government hospitals
3. Compensating or rewarding prescribers for correct prescribing
4. Functional communication system should be in place e.g. intercom
5. Managerial intervention such as structured drug order forms and/or course-of-therapy packaging
6. Patient education on correct dose should be initiated

Before making a blanket statement of banning chloroquine and making Artemisinin base combination therapy (ACT) first line in West Africa sub-region in general and Nigeria in particular there is need to

1. Make these drugs to be readily available and affordable to the masses through government subsidy.
2. Educate the populace about completing drug regimen
3. Make laboratory facility available in our health facilities so that the parasitaemia level of the patient is determined before prescribing or using these ACTs, that is, presumptive treatment should be avoided as much as possible
4. The best combination appropriate for our local setting should be determined through appropriate clinical studies

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II

APPENDIX I

QUESTIONAIRE TO DETERMINE KNOWLEDGE, ATTITUDE AND PRACTICE OF PRESCRIBERS IN TREATMENT OF MALARIA IN LAGOS STATE GENERAL HOSPITALS (BY B.A.AINA(MRS.), SCHOOL OF PHARMACY, CMUL, IDI-ARABA)

HOSPITAL _____

Please tick as appropriate

1. **SEX** MALE ☐ FEMALE ☐

2. **AGE**
   20 – 29 ☐
   30 – 39 ☐
   40 – 49 ☐
   50 – 59 ☐
   Above 60 ☐

3. **QUALIFICATION**: _____

4. **YEARS OF POST-QUALIFICATION**: _____

5. **AREA OF SPECIALTY**: _____

6. **Indicate the order of your choice of antimalaria drug** : Chloroquine ☐ Halfan (Halofantrine) ☐ Fansidar (Sulphadoxine-Pyrimethamine) ☐ Fansimef(Sulphadoxine-Pyrimethamine- Mefloquine) ☐ Lariam (Mefloquine) ☐ Quinine ☐ Cotecxin (Artemether-Lumefantrine) ☐ Coartem (Artemether-Lumefantrine) ☐ Artesunate (Artemisinin) ☐ Artemether (Artemisinin) ☐ Artemether-Lumefantrine ☐ Artesunate-Amodiaquine ☐ Dihydroartemisin ☐ Any Other _____(**NB: 1** Being the first choice;**2**Being the second choice etc.)

7. **What is your first drug of choice in treating malaria: _____**

8. **Reason(s) for your answer to Questions 6 & 7(**In order of preference**1** Being the first reason)
   (a) Cost ☐
   (b) The drug that is available in the hospital ☐
   (c) According to hospital treatment guideline ☐
   (d) Effectiveness ☐
   (e) Patient demands/prefers it ☐
   (f) Any other reason(s) (please state)_____

9. Chloroquine Resistant malaria occurs in ___out of 10 patients
   (a) above 6 ☐ (b) 6 ☐ (c) 5 ☐ (d) 4 ☐ (e)3 ☐ ☐
   (f) 2 ☐ (g) 1 ☐ (h) None

10. **What do you think could be responsible for Chloroquine resistance** ☐
Underdosage
Overdosage ☐ Chloroquine abuse ☐ Substandard Chloroquine ☐
Lack of
compliance with previous Chloroquine exposure ☐ Any other reason(s)
_____
____

11. **What dosage form of Chloroquine would you use in your patients in order of preference** Oral ☐ Injection ☐ Oral + Injection ☐ (**NB 1** means 1st preference, **2** means 2nd preference)

12. **Why would you prefer Injection first?**
(a) It works faster than Tablet/Syrup ☐
(b) It ensures compliance ☐
(c) Patient demands/prefers it ☐
(d) It doesn't itch ☐
(e) It is cheaper than Tablet/Syrup ☐
(f) It is the only dosage form available in the hospital ☐
(g) It is first choice in the hospital treatment guideline ☐
(h) When a patient is vomiting ☐
(i) When a patient is unconscious ☐
(j) It has always worked better than oral dosage form from clinical experience
(k) Any other reason(s) (please state)
_____

13. **Why would you prefer Tablet/Syrup first?**
(a) It works faster than Injection ☐
(b) It ensures compliance ☐
(c) Patient demands/prefers it ☐
(d) It doesn't itch ☐
(e) It is cheaper than Injection ☐
(f) It is the only dosage form available in the hospital ☐
(g) It is the first choice in the hospital treatment guideline ☐
(h) It has always worked better than Injection dosage form from clinical experience ☐
(i) Any other reason(s) (please state)_____

14. **Would you prefer to carry out malaria parasite test in febrile patients before treatment**
Yes ☐ No ☐

15. **Do you carry out malaria parasite test in febrile patients before treatment** ☐ ☐
Yes No

If No, Why?

(a) No facility ☐
(b) Too busy ☐
(c) Not necessary ☐
(d) Too expensive for patients ☐
(e) Too many patients ☐
(f) Time wasting ☐
(g) Other reason(s) (please state)

_____

16. **Please indicate what you considered the appropriate total dose of chloroquine for the following age group:**

Adult	_____mg
Under 1 year	_____mg
1 – 3 years	_____mg
4 – 6 years	_____mg
7 – 11 years	_____mg
Above 12 years	_____mg

17. **How many doses of chloroquine injection do you consider adequate when used alone in an adult**

(a) 1 (b) 2 (c) 3 (d) 4 (e) 5 (f)6 (g) 7

(h) 8 (i) 9 (j) 10 (k) Others _____

18. **How are the doses above administered**

(a) 6 hourly (b) 8 hourly (c) 12 hourly (d) 24 hourly

19. **Source of information for chloroquine dosage**

(a) Therapeutic guidelines ☐
(b) Pharmacist on duty ☐
(c) Drug formulary ☐
(d) Medical representative ☐
(e) Drug leaflet ☐
(f) Peers ☐
(g) Senior colleagues ☐
(h) Hospital drug bulletin ☐
(i) Others (please state)

_____

20. **What other drugs do you usually prescribe with an antimalarial drug. Give reasons for these other drugs using any of the following options**

(A) Need for symptomatic treatment
(B) To satisfy the patient
(C) For more rapid elimination of malaria parasites
(D) To improve patient compliance
(E) They are part of the treatment guidelines
(F) To minimise side effects
(G) Other reasons (please state)

_____

DRUG PRESCRIBED	REASON(S) (e.g. A, B & C)
(a) Paracetamol	_____
(b) Dipyrone	_____
(c) Multivitamin	_____
(d) Antihistamine	_____
(e) B complex	_____
(f) Vitamin C	_____
(g) Iron	_____
(h) Iron + Multivitamin	_____

(i) Other drugs (please state)

_____

21. **Would you prescribe 2 or more antimalarial drugs for your patient at the same time**

Yes ☐ No ☐

22. **If Yes to (21), what is/are your combination, in order of preference**

(a) Chloroquine followed by Fansidar ☐
(b) Chloroquine followed by Halfan ☐
(c) Chloroquine followed by Quinine ☐
(d) Chloroquine followed by Artemisinin ☐
(e) Others (please state)

_____

23. **If Yes to (21), why?**

(a) More effective than single drug ☐
(b) Patient prefers combination ☐
(c) Side effect minimised ☐
(d) According to treatment guideline ☐
(e) Others (please state)

_____

24. **How many drugs do you consider appropriate to be prescribed to a patient at once**

(a) 1 (b) 2 (c) 3 (d) 4 (e) 5 (f)6 (g) 7

(h) 8 (i) 9 (j) 10 (k) Others _____

25. **Give reasons for your answer in (24)**

(a) Patients come in with multiple disease conditions ☐
(b) To satisfy the patients demand ☐
(c) No adequate laboratory facility to determine the exact disease condition ☐
(d) To improve patient compliance ☐
(e) For fast relieve of symptoms ☐
(f) Others (please state) _____

26. **Any other information that may be relevant to this study**

_____
_____
_____
_____

APPENDIX II

CQ TREATMENT OF NON – SEVERE MALARIA 1 Tablet = 150mg CQ base Syrup 1 tsp (5ml) = 50mg CQ base Injection: 3.5mg/kg 6 or 8 hourly until a total dose of 25mg/ kg (1 amp (5ml) = 200mg CQ base; 1ml = 40mg CQ base)				
AGE (YRS)	WEGHT (KG)	1ST DAY	2ND DAY	3RD DAY
<1	<9.9	½ Tab ◗	½ Tab ◗	¼ Tab ◔
		7.5ml(1½tsp)	7.5ml(1½tsp)	3.75 ml(¾ tsp)
1 - 3	10 – 14.4	1 Tab ●	1 Tab ●	½ Tab ◗
		15ml(3tsp)	15ml(3tsp)	7.5 ml(1½tsp)
4 - 6	14.5 – 18.4	●◗	●◗	●
		1 ½ TABS	1 ½ TABS	1 TAB
7 - 11	18.5 – 34.9	●●	●●	●
		2 TABS	2 TABS	1 TAB
> 12	>35	●●●●	●●●●	●●
		4 TABS	4 TABS	2 TABS

CQ TREATMENT OF NON-SEVERE MALARIA

1 TABLET = 150MG CQ BASE
SYRUP 1 TEASPOONFUL (5ML) = 50 MG CQ BASE
INJECTION: 3.5MG/KG 6 OR 8 HOURLY UNTIL A TOTAL DOSE OF 25MG/KG
(1 AMP (5ML) = 200MG CQ BASE; 1 ML = 40 MG CQ BASE)

AGE	WEIGHT	1ST DAY	2ND DAY	3RD DAY
LESS THAN ONE YEAR 	UNDER 9.9 KG	75 MG ½ TABLET OR 1 ½ TEASPOONFULS 7.5 ML SYRUP	75 MG ½ TABLET OR 1 ½ TEASPOONFULS 7.5 ML SYRUP	37.5 MG ¼ TABLET OR 3/4 TEASPOONFUL 3.75 ML SYRUP
1-3 YEARS 	10 KG TO 14.4 KG	150 MG 1 TABLET OR 3 TEASPOONFULS 15 ML SYRUP	150 MG 1 TABLET OR 3 TEASPOONFULS 15 ML SYRUP	75 MG ½ TABLET OR 1 ½ TEASPOONFULS 7.5 ML SYRUP
 4-6 YEARS (SCHOOL AGE)	14.5 KG TO 18.4 KG	225 MG 1 ½ TABLETS	225 MG 1 ½ TABLETS	150 MG 1 TABLET
 7-11 YEARS	18.5 KG TO 34.9 KG	300 MG 2 TABLETS	300 MG 2 TABLETS	150 MG 1 TABLET
 12 YEARS AND ABOVE	OVER 35 KG	600 MG 4 TABLETS	600 MG 4 TABLETS	300 MG 2 TABLETS