PREVALENCE OF PAIN, ITS CHARACTERISTICS AND CORRELATES AMONG OUTPATIENTS PRESENTING WITH MALARIA TO OUTPATIENT CLINICS IN IBADAN, NIGERIA

By:

ABRAHAM BRAIMAH, IDOKOKO

MB;BS (Lagos), PgD. Mgt. (Ife)

MATRICULATION NUMBER: 160629

A dissertation submitted to the Department of Epidemiology and Medical Statistics, Faculty of Public Health, University of Ibadan, Nigeria in partial fulfillment of the requirements for the award of Master of Sciences (MSc.) degree in Epidemiology and Medical Statistics of the University of Ibadan.

AUGUST, 2012

CERTIFICATION

This is to certify that this thesis is the original and independent research work of **Abraham Braimah, IDOKOKO,** under my supervision. All materials listed from other works have been duly acknowledged and referenced accordingly.

.....Date.....30/9/2012

Dr. Ikeoluwapo O. Ajayi

MB;BS (Ibadan), M. Cl. Sc. (Canada), MPH (Ibadan), PhD (Ibadan), FMCGP (Nig.), FWACP (GP)

SUPERVISOR

ABSTRACT

Background: Malaria still exert tremendous burden on the inhabitants of sub-Sahara Africa in spite of numerous control measures. The burden is attributable to its high morbidity (resulting from the acute onset of fever, pains including headache, rapid progression and debilitation) and mortality. Although, pain is one of the commonest reasons why patients suffering from malaria seek medical attention yet, the pain due to malaria is largely ignored, poorly evaluated and virtually un-studied. This pilot study explored pain due to malaria among outpatients in Ibadan, south-west Nigeria to determine its prevalence, characteristics and correlates.

Methods: This was a hospital-based, two-centre, cross-sectional survey conducted in Ibadan. Out-patients, aged six years or more, clinically diagnosed of acute uncomplicated malaria were enrolled consecutively over a three-month period. Seven hundred consenting enrollees were evaluated for the presence, quality, intensity and perceived effects of malaria pains using structured, interviewer-administered questionnaires. Pain intensity was measured with category pain rating scales for adults (≥12years) and the Wong-Baker faces scale for children (<12years) where, pain was rated as mild, moderate, severe and worst imaginable. Descriptive statistics such as means ± standard deviations and proportions were used to summarize quantitative and qualitative variables, respectively. The χ^2 test was used to investigate bivariate association between two qualitative variables at 5% level of significance while, logistic regression model of covariates and factors was used to determine the risk of occurrence of malaria pain.

Results: Six hundred and sixty-eight questionnaires were returned suitably completed and were analysed. The mean age of respondents was 33.0years (SD 16.1), range (6-81 years), 12.7% were children under 12 years, 66.6% were females and 72.3% had malaria pain. The head (66.0% vs. 72.8%), general muscular sites (17.0% vs. 39.5%), abdomen (37.7% vs. 11.4%) and joints (5.7% vs. 17.0%) were the most common location of malaria pain among children versus adults, respectively. The character of malaria pain was aching in 90.6% vs. 91.9% and intermittent in 64.7% vs. 71.2% among adults versus children, respectively. The pain at worst was reported as mild, moderate and severe by 28.6%, 47.2% and 23.4%, respectively; while 0.8% had worst pain imaginable. The pain

was severe enough to completely interrupt work or school activities in 4.3% of respondents. Respondents' sex (p=0.003), age (p=0.028), PCV level (p=0.005), use of any antimalarial (p=0.009) or use of a potent ACTs (p=0.002) were significantly associated with having malaria pain.

Conclusions: This study highlighted pain as a significant contributor to the burden of malaria and did show that being a child or male or having PCV<30% or not using ACTs early increased the risk of developing malaria pain. More attention needs to be paid to the understanding of the pathophysiology of pain, its course and treatment in malaria patients. Malaria control efforts should consider incorporating accurate pain evaluation and treatment into management protocols in order to minimize the impact of this disease that takes its heaviest toll on the most impoverished corners of our planet.

Keywords: Malaria, Pain, Prevalence, Pain intensity

Word Count: 482

DEDICATION

I dedicate this work to THE MEMORY OF MY SWEET MOTHER (**Mrs. Victoria Alimoh Irene Idokoko, nee Oyasor**) who transited to glory while i was in the middle of this work. Her unflinching love, steadfast care, contagious courage and inspiring sacrifices were pivotal to my academic pursuit up to this level. Her contributions shall remain green in my efforts.

And to my LORD, GOD ALMIGHTY, who is my ageless source, strength and inspiration; to Him alone be all THE GLORY AND HONOUR. **Great is His faithfulness!!**

And to the progress of efforts aimed at winning the war against malaria in the world's tropics!

IDOKOKO, A. B.
2012.

ACKNOWLEDGEMENT

I am most grateful to Dr. (Mrs.) I. O. Ajayi who stimulated my interest and meticulously supervised this work. Her unflinching motherly support and understanding coupled with her erudite scholarly supervision made working on this project most rewarding. And to her always available staff (Mr. Taiwo), I say thank you, very much.

Prof. (Mrs.) O. A. Soyannwo initiated this research concept more than a decade earlier and she was readily available to see through to its execution. I am so grateful that she gave me this shoulder top to fly from. God bless you richly ma!

What more can I say than to thank Dr. (Mrs.) C. O. Falade and her staff (Mrs. Bola, Miss Grace, etc.) who made the laboratory aspect of this work feasible within the time frame. And to Dr. F. A. Fehintola who intervened at critical junctions during data collection, thank you sir.

The research assistants (Tope & Co.), the Staff at UCH GOPD laboratory (particularly, Mr. Adegoke, Mr. Lateef, Mr. Banjoko and their IT-Students), Dr. Okedare and the staff at O.L.A. Catholic Hospital Laboratory were invaluable to the data collection process and I say thanks a million. May you all find help when you are just in need of some!

Every other person, too many to list here, that contributed in diverse measures, technically and otherwise, to the success of this research work are hereby appreciated especially, the various admin staff I had to go through and the patients who consented to this study despite their ill health. You were all wonderful. Thank you!

Friends, colleagues and classmates that I met here will not be forgotten in a hurry. They made this adult education a worthwhile experience. Franklin, Lydia, Ore, Dami and Drs. Olabisi, Aniwada, Dayo and many others were very helpful in their own ways. God bless you all!

Finally, going back to school meant some competing alternative were relatively forgone. In that wise, I remain indebted and loyal to my parents for their ageless support and prayers and my siblings for having been there from the very beginning. I love you all!

However, the ultimate glory and thanks goes to God Almighty. He is my trusted help in time past, my solace for today and my certain hope for the future. Amen!

IDOKOKO, A. B.
2012

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF ACRONYMS

ACT	Artemisinin-based Combination Therapy
AFR	WHO African Region
AFRO	WHO Regional Office for Africa
ALMA	African Leaders Malaria Alliance
AMA	American Medical Association
AMFm	Affordable Medicine Facility for malaria
AMR	WHO Region of the Americas
AMRO	WHO Regional Office for the Americas
CQ	Chloroquine
DDT	Dichloro-Diphenyl-Trichloroethane
EMR	WHO Eastern Mediterranean Region
EMRO	WHO Regional Office for the Eastern Mediterranean
EUR	WHO European Region
EURO	WHO Regional Office for Europe
GHO	WHO Global Health Observatory
Global Fund	The Global Fund to fight AIDS Tuberculosis and Malaria
GMP	WHO Global Malaria Programme
GOPD	General Outpatient Department
IPTi	Intermittent Preventive Treatment in infants
IPTp	Intermittent Preventive Treatment in pregnancy
IRS	Indoor residual spraying
ITN	Insecticide-treated mosquito net
LLIN	Long-lasting insecticidal net
MDG	Millennium Development Goal
MIS	Malaria indicator survey
MPAC	Malaria Policy Advisory Committee, WHO
MPQ	McGill's Pain Questionnaire
MVI	Malaria Vaccine Initiative
NDHS	Nigeria Demographic and Health Survey
NMCP	National Malaria Control Programme, Nigeria
NMIS	Nigeria Malaria Indicator Survey
NPC	National Population Commission, Nigeria
NRS	Numerical Rating Scale for pain
NSAID	Non-Steroidal Anti-Inflammatory Drugs

PATH	Program for Appropriate Technology in Health
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
SEAR	WHO South-East Asia Region
SEARO	WHO Regional Office for South-East Asia
SP	Sulfadoxine-pyrimethamine
TDR	WHO Special Programme for Research and Training in Tropical Diseases
T_3	Test, Treat, Track
UCH	University College Hospital, Ibadan
VAS	Visual Analogue Scale for pain
VRS	Verbal Rating Scale for pain
WER	WHO Weekly Epidemiological Report
WHA	World Health Assembly, WHO
WHO	World Health Organization
WPR	WHO Western Pacific Region
WPRO	WHO Regional Office for the Western Pacific

Chapter One

INTRODUCTION

1.1. Background to the Study

Malaria is an ancient disease that has come to be accepted by experts as one of the greatest scourge of the developing world (Kakkilaya, 2006). Acute malaria illness is known to afflict victims with fever and pains aside other symptoms and complications including death (Kumar & Clark, 2006).

According to the WHO World Malaria Report 2011, malaria remains an enormous public health challenge in over 106 endemic countries with an estimated 3.3 billion people at risk. Over 216 million cases were recorded in 2010 and 81% of these occurred in the WHO African Region, where 91% of the estimated 655,000 malaria deaths also occurred. Six countries (Nigeria, the Democratic Republic of Congo, Burkina Faso, Mozambique, Cote d'Ivoire and Mali) accounted for 60% of these deaths. In Nigeria, a high transmission zone, malaria is the most common (60%) reason for outpatient visits to health institutions and the highly virulent *Plasmodium falciparum* species account for nearly 100% of reported cases. (WHO GMP, 2011; NPC & ICF Macro., 2009)

Clinical malaria is an infectious disease observed in those exposed to the Plasmodium parasite either through an infectious female anopheline mosquito bite or by direct transfusion of infected blood; and in very rare situations, vertical transmission from an infected mother to her child in utero do occur. After an incubation period of 10-21 days, the disease present clinically as fever, general malaise, headache, muscle aches, joint pains, vomiting, diarrhoea and clinical anaemia among others. (Kumar & Clark, 2006; Martin-Rabadá & Bouza, 2004; Krause, 2008; Song, O, Kim, Moon, & Kim, 2003)

In most endemic settings, malaria is wrongly construed as essentially fever at the expense of many other equally devastating symptoms including pain. These other symptoms, particularly the pain, incapacitate the sufferers so much so that economic production is reduced due to resultant absenteeism from schools and place of works. (Gallup & Sachs, 2000)

Pain is a subjective symptom. Generally, it is one of the most common reasons for patients to seek medical attention and one of the most prevalent medical complaints (Watkins, Wollan, Melton, & Yawn, 2008; American Medical Association, 2010). The International Association for the Study of Pain (IASP) define pain as any unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Turk & Okifuji, 2001). Pain as a symptom seen in malaria is a common experience that aggravates the morbidity from the illness and probably contributes most to the incapacitation experienced by sufferers. This study was designed to explore malaria pain and its prevalence.

1.2. Justification for this Study

Malaria pain is often overlooked and not always documented by doctors and other healthcare personnel providing clinical care to these patients. Analgesics are prescribed routinely as part of malaria treatment, principally for their antipyretic effects, without fully evaluating the pain.

The adequacy of such treatment provided for pain in Malaria and the effectiveness of analgesics commonly prescribed is not known. No study was found to have evaluated the pain seen in malaria in extensive literature search.

Elucidating the prevalence and characteristics of malaria pain, as well as, evaluating its severity is essential to determining the need for effective treatment in endemic populations. In addition, such knowledge will aid objective clinical monitoring of the effectiveness of treatment provided for malaria and that may go a long way in ameliorating the health and economic burden of the disease.

Hence, this study was designed to determine the prevalence of pain in patients clinically diagnosed of malaria and explore the pattern, character, site, severity and effect of this pain; as well as, the relationship of this pain with some selected variables such as fever, level of parasitaemia, temperature and socio-demographic variables.

1.3. Statement of Problem

Malaria morbidity and mortality pose an enormous health, economic and development challenge in Nigeria, Sub-Sahara Africa and in over 106 countries worldwide. Patients who suffer from malaria experience pain very commonly and this pain usually aggravate the morbidity and probably contribute most to the incapacitation experienced by sufferers.

The direct economic and development consequence of malaria is much linked with the pain and fever suffered by the patients as this prevents them from engaging in any meaningful socio-economic activity during the period of the illness. There has been no empirical research done to study the pain seen in malaria in the extensive literature reviewed

1.4. Research Questions

1. What proportions of malaria patients suffer pain in Ibadan?
2. What are the characteristics of the pain due to malaria and in what body parts does it occur?
3. How severe is the pain due to malaria?
4. How much does malaria pain affect the routine life activities of malaria patients with pain?
5. How does the characteristic of malaria differ for children compared to adult? Is there any sex variation?
6. What factors in the patients show statistical association with occurrence of pain? And by how much can these factors predict the likelihood of pain in a patient with malaria?

1.5. Objectives of this Study

1.5.1. General Objective:

- To determine the prevalence, characteristics, associations, effects and possible predictors of pain due to malaria among out-patients suffering from acute uncomplicated malaria in Ibadan, south-western, Nigeria.

1.5.2. Specific Objectives: this survey was designed to:

1) Determine the prevalence of pain among out-patients suffering from acute uncomplicated malaria in Ibadan, Nigeria.
2) Determine the characteristics of malaria pain among respondents.
3) Determine socio-demographic and other factors associated with the presence of malaria pain in these patients.
4) Determine possible predictors of the occurrence of pain in malaria patients

1.6. Relevance/Significance of this Study

Findings from this study will be of value to clinicians and other health care practitioners who provide secondary level prevention services to malaria patients in knowing the dynamics of the pain suffered by their patients.

It will also allow policy makers to further appreciate the implications of persisting malaria burden such that more effective policies that directly or indirectly support the global effort to roll back malaria will be enunciated, promulgated and enabled.

Also, the results of this study will contribute new knowledge to the large pool of what we already know about malaria and may to a large extent revolutionalize current approaches to clinical management of malaria especially, as it relates to pain.

1.7. Scope and Limitations of this Study

This study assessed only out-patients clinically diagnosed of acute uncomplicated malaria according to the WHO standard in resource restricted areas as obtainable during the time of data collection. It was a facility-based survey that excluded cases of complicated malaria, children below six (6) years of age, pregnant women, sickle cell disease patients, persons with history of chronic pain and anyone who did not present to hospital.

Application of findings may be limited to patients in urban settings in the forest regions of Nigeria and may not be generalized to the entire country or other settings.

1.8. Operational Definitions

A number of regular terms were used technically in this study. Here are their operational definitions for interpreting the results.

- **Fever:** an axillary temperature $\geq 37.5^{o}C$.
- **Malaria:** an illness resulting from infection with plasmodium parasite
- **Clinical Malaria:** illness in a person who has an axillary temperature of $37.5^{o}C$ or more, a 24-hour history of fever and/or a thick blood film report of more than 5000 *P. falciparum* parasites per mm^3 of whole blood (WHO, 2006).
- **Pain:** the International Association for the Study of Pain (IASP) definition, as any unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
- **Children:** persons of chronological age below 12 years
- **Adult:** persons with chronological age of 12 years and above.
- **Recurrence:** It is repeatedly re-occurring acute malaria disease in an individual over a relatively short period of time that could be due to relapse, recrudescence or drug resistance.
- **Relapse** is defined as the reappearance of malaria originating from dormant liver schizonts and this can be expected in 50% of patients who have *P. vivax* or *P. ovale* infection who did not receive primaquine.
- **Recrudescence** is the reappearance of disease after a partially effective treatment.

Chapter Two

REVIEW OF LITERATURE

2.0. Etymology and Conception of Malaria

The term "malaria" originated in Medieval Europe from the Italian words {*malo* (feminine, *mala*), bad, + *aria*, air} coined in the mid-18th century to literally mean "bad air"; referring to an era when the old miasmatic theory of disease held sway and the then mysterious and pervasive "Roman Fever" was thought to be caused by inhaling bad air in the swamps and marshlands. (Stedman, 2001; Microsoft® Encarta, 2008; Kakkilaya, 2006; Martín-Rabadá & Bouza, 2004)

This highly fatal infectious disease of humans was found to also affect birds, reptiles, monkeys, chimpanzees and rodents long before its causative agent was identified to be a single-celled protozoan parasite of the genus *Plasmodium*, transmitted by the bite of several genera of female mosquitoes (including *culex, aedes, mansonia, culiseta, theobaldia* and *anopheline*) that uniquely differ for each animal and geographic location. (Adams, 2008; Wikipedia, 2011)

Human malaria is a debilitating disease characterized by chills, shaking (rigors), vomiting, pains and periodic bouts of intense fever that has plagued global communities from antiquity and continues to pose a major public health threat in about 109 countries in the 21st century. (WHO GMP, 2011; Adams, 2008; Park, 2009)

2.1.Malaria through the Ages: Historical Perspectives

Malaria is an ancient disease that has afflicted humans throughout history. Some experts claim it has infected humans for over 50,000years. References to the unique periodic fever and pains of malaria abound throughout recorded history, beginning 2700BC in China to the early civilizations in Rome, the Middle East and Egypt. The Greek physician, Hippocrates, described malaria in his writings in the 400's BC and till date, outbreaks of malaria have often been associated with warfare, migrations, and other societal disruptions. More soldiers are said to have been lost to malaria than to bullets in the wars of the 20th century. (Adams, 2008; Kakkilaya, 2006)

Malaria's association with bodies of stagnant water has long been recognized, and civilizations as early as the Etruscans (1st 1000BC) drained marshes and swamps in an effort to combat the disease. The first effective malaria treatment emerged in 1638, when Spanish Jesuit missionaries brought cinchona bark (the source of quinine) back to Europe from South America (the Andes in Peru). Tonic water, which contains quinine, was developed in an attempt to make the drug more palatable. But, the active ingredient, quinine, was not known until it was isolated in 1820 by French chemists Pierre Joseph Pelletier and Joseph Bienaimé Caventou. In 1921-22, a fish called *Gambusia affinis* or mosquitofish was released into water collections for its larvivorous habits and was found useful in the control of mosquitoes in California. The less toxic chloroquine replaced quinine in the 20th century until resistance emerged and artemisinin, discovered by the Chinese in the 1970s, is now the recommended treatment for falciparum malaria. (Kakkilaya, 2006; Wikipedia, 2011)

However, the exact cause of malaria was not understood until the closing years of the 19th century. In 1880 (November 6th), a French army surgeon, Charles Alphonse Laveran, working in a military hospital in Constantine, Algeria identified the malaria parasite for the first time in the blood of a patient and he was awarded the 1907 Nobel prize for physiology and medicine. (Wikipedia, 2011)

The malaria parasite was named *plasmodium* by Italian scientist Ettore Marchiafava and Angelo Celli in 1885. Another Italian, Dr. Giovanni Battista Grassi in 1898 isolated and showed *plasmodium* could only be transmitted by female anopheline mosquito to man. Same year (1898), Sir Ronald Ross, a Scottish physician, working in the Presidency General Hospital in Calcutta, India identified & isolated *plasmodium* from the midgut and salivary gland of Culex mosquitoes feeding on infected birds, described the complete life cycle of the parasite in mosquitoes and demonstrated that the parasite is transmitted from human to human by a vector, the female Anopheles mosquito. Ross was awarded the 1902 Nobel Prize in physiology or medicine. (Adams, 2008; Kakkilaya, 2006)

In 2002, the genome of *Plasmodium falciparum* and other malaria parasites was deciphered by an international team of scientist that hope to use the information gained in designing more effective

antimalarial drugs and vaccines. Scientists have also decoded the genome sequence of *Anopheles, gambiae*, one of the most common malaria mosquitoes. Insecticides that target specific proteins produced by one or more genes in this mosquito's genome may one day be used to control and possibly eliminate mosquitoes from many areas. (Adams, 2008)

In 2011, Agnandji et al published the First Results of a Phase 3 Trial of RTS,S /AS01 Malaria Vaccine in African Children. No malaria vaccine development effort has ever gone that far and if the early findings are sustained by the end of the trial in 2014, WHO promised to ensure its deployment by 2015.

Today, malaria is seen, not just as an infectious disease associated with poverty but, as a cause and consequence of poverty. It has been a major hindrance to socio-economic development of affected regions such that the slow economic and demographic transition in sub-Sahara Africa has been largely attributed to malaria. Moreso, that the pains due to malaria under study play a key role in the disease burden. (Gallup & Sachs, 2000; Jimoh, Sofola, Petu, & Okorosobo, 2007; WHO GMP, 2011)

2.2.Epidemiology of Human Malaria

Malaria occurs worldwide but, it is endemic to a broad band of tropical and sub-tropical countries around the equator, spanning all continents with the greatest burden afflicting the poorest of people in the poorer nations thereby, defining under-development and poverty. Precise statistics remain a challenge as many cases occur in rural areas where people do not have access to hospitals or the means to afford healthcare and the health system is weakest. Hence, majority of cases are undocumented making it difficult to estimate the exact impact of a disease that some expert consider as one of the greatest scourge of the developing world. (Shiff, 2006; WHO, 2007)

2.2.1. Actiology of Malaria

Malaria in man is usually caused by four distinct species of the malaria parasite: *Plasmodium vivax, P. ovale, P. malariae and P. falciparum. P. Vivax* has the widest global geographic distribution and

antimalarial drugs and vaccines. Scientists have also decoded the genome sequence of *Anopheles gambiae*, one of the most common malaria mosquitoes. Insecticides that target specific proteins produced by one or more genes in this mosquito's genome may one day be used to control and possibly eliminate mosquitoes from many areas. (Adams, 2008)

In 2011, Agnandji et al published the First Results of a Phase 3 Trial of RTS,S /AS01 Malaria Vaccine in African Children. No malaria vaccine development effort has ever gone that far and if the early findings are sustained by the end of the trial in 2014, WHO promised to ensure its deployment by 2015.

Today, malaria is seen, not just as an infectious disease associated with poverty but, as a cause and consequence of poverty. It has been a major hindrance to socio-economic development of affected regions such that the slow economic and demographic transition in sub-Sahara Africa has been largely attributed to malaria. Moreso, that the pains due to malaria under study play a key role in the disease burden. (Gallup & Sachs, 2000; Jimoh, Sofola, Petu, & Okorosobo, 2007; WHO GMP, 2011)

2.2.Epidemiology of Human Malaria

Malaria occurs worldwide but, it is endemic to a broad band of tropical and sub-tropical countries around the equator, spanning all continents with the greatest burden afflicting the poorest of people in the poorer nations thereby, defining under-development and poverty. Precise statistics remain a challenge as many cases occur in rural areas where people do not have access to hospitals or the means to afford healthcare and the health system is weakest. Hence, majority of cases are undocumented making it difficult to estimate the exact impact of a disease that some expert consider as one of the greatest scourge of the developing world. (Shiff, 2006; WHO, 2007)

2.2.1. Aetiology of Malaria

Malaria in man is usually caused by four distinct species of the malaria parasite: *Plasmodium vivax, P. ovale, P. malariae and P. falciparum*. *P. Vivax* has the widest global geographic distribution and

antimalarial drugs and vaccines. Scientists have also decoded the genome sequence of *Anopheles gambiae*, one of the most common malaria mosquitoes. Insecticides that target specific proteins produced by one or more genes in this mosquito's genome may one day be used to control and possibly eliminate mosquitoes from many areas. (Adams, 2008)

In 2011, Agnandji et al published the First Results of a Phase 3 Trial of RTS,S /AS01 Malaria Vaccine in African Children. No malaria vaccine development effort has ever gone that far and if the early findings are sustained by the end of the trial in 2014, WHO promised to ensure its deployment by 2015.

Today, malaria is seen, not just as an infectious disease associated with poverty but, as a cause and consequence of poverty. It has been a major hindrance to socio-economic development of affected regions such that the slow economic and demographic transition in sub-Sahara Africa has been largely attributed to malaria. Moreso, that the pains due to malaria under study play a key role in the disease burden. (Gallup & Sachs, 2000; Jimoh, Sofola, Petu, & Okorosobo, 2007; WHO GMP, 2011)

2.2.Epidemiology of Human Malaria

Malaria occurs worldwide but, it is endemic to a broad band of tropical and sub-tropical countries around the equator, spanning all continents with the greatest burden afflicting the poorest of people in the poorer nations thereby, defining under-development and poverty. Precise statistics remain a challenge as many cases occur in rural areas where people do not have access to hospitals or the means to afford healthcare and the health system is weakest. Hence, majority of cases are undocumented making it difficult to estimate the exact impact of a disease that some expert consider as one of the greatest scourge of the developing world. (Shiff, 2006; WHO, 2007)

2.2.1. Aetiology of Malaria

Malaria in man is usually caused by four distinct species of the malaria parasite: *Plasmodium vivax, P. ovale, P. malariae and P. falciparum*. *P. Vivax* has the widest global geographic distribution and

P. falciparum account for the most severe disease and almost all of the fatality resulting from malaria. (Krause, 2008; WHO, 2006; Kumar & Clark, 2006)

Current evidence shows that about 11 species of *plasmodium* can infect man but, only 6 cause significant disease and are of public health importance viz: *P. falciparum, P. malariae, P. ovale, P. semiovale, P. vivax* and *P. knowlesi. P. knowlesi* and *P. semiovale* primarily infect primates but, have been documented to cause human disease mostly in south-east Asia. (Wikipedia, 2011)

In Nigeria, particularly Ibadan, this study location, *P. falciparum* was the cause of over 99.9% of tested malaria cases in 2010. (WHO GMP, 2011; NPC, NMCP & ICF Macro., 2010)

2.2.2. Transmission of Malaria

Except for the possibility of Chimpanzees in tropical Africa that may carry the infection with *P. malariae,* man is the only known reservoir of human plasmodia (Park, 2009) and children are epidemiologically more important reservoir than adult in that the parasite is more likely to achieve differentiation into the sexual forms (gametocytes needed to infect mosquitoes) in children than in adult. Besides, one person can harbour several species of the parasite at the same time. An on-going illness does not prevent another infection. (Park, 2009; Wikipedia, 2011) The parasites are transmitted in the affected population via the following modes:

2.2.2.1. Vector Borne

An infective bite of certain species of the female anopheline mosquitoes is the major means by which malaria parasite is transmitted in human populations. As long as mature, viable gametocytes exist in infected circulating blood in sufficient density ($\geq 12/mm^3$), malaria is communicable to mosquitoes and back to humans. This insect thrives in the warm-humid climate of the tropics requiring an optimum temperature of 20-30°C (68-86°F) and a relative humidity ≥ 60% to survive. Anopheline mosquitoes require adequate rainfall to breed, exhibit a nocturnal feeding habit (dusk to dawn, peaks at about 1:00am) and are not found at altitudes above 2000-2500 metres. (Park, 2009)

2.2.2.2. Direct Transmission

Some evidence exists of accidental transmission of malaria parasite directly from person-to-person by blood transfusion and in intravenous drug users, such that, people from endemic areas should not be accepted as blood donors until 3years afterwards. The parasites can keep their infective activity up to 14 days in blood bottles stored at -4°C. (Park, 2009)

2.2.2.3. Congenital Transmission

Rarely, malaria has been proven to be congenitally transmitted from an infected mother to her newborn and in-utero. Hence, malaria remains a significant cause of spontaneous abortion, intra-uterine growth retardation (IUGR), still-birth and premature labour in endemic nations. (Park, 2009)

2.2.3. Malaria Distribution

Malaria affects persons of all ages but, children under 5 years and pregnant women (especially, primigravida) are most susceptible, resulting in their vulnerability to the most severe form of the disease and accounting for the highest mortality. (Park, 2009)

Males are more frequently exposed than females by occupation, lifestyle and cultural roles. Malaria is predominantly a rural disease closely related to agricultural practices, sleeping out of doors, nomadism and refusal to accept personal protection measures (Park, 2009).

In endemic communities, malaria transmission is stable but, there usually exist varying levels of herd immunity depending on the level of stability and intensity (high or low) of transmission or the degree of endemicity (Holo-, Hyper-, Meso-, Hypo- endemic). Newborns have considerable resistance to *P falciparum* in the first 3-5 months of life due to the high concentration of foetal haemoglobin and persisting maternal IgG that suppresses *P. falciparum* development (Wikipedia, 2011; Park, 2009) Persons with genotype AS or Glucose-6-Phosphate Dehydrogenase (G6PD) enzyme deficiency or thalassemia have milder falciparum disease. Also, people without the Duffy^{-} antigen on their red cell surfaces (mostly Africans) are resistant to *P. vivax* infection. (Park, 2009)

Housing play a critical role in malaria transmission as the disease is known to be acquired often times from mosquito bites within houses. Poorly ventilated and ill-lighted rooms provide ideal resting places for mosquitoes. (Park, 2009)

Suitable environmental conditions for the survival and breeding of mosquitoes are essential for the prevalence of malaria in any community. The warm temperature (20-30 ^{o}C), high humidity (≥60%), adequate rainfall, abundance of vegetation and breeding sites in the tropics and sub-tropics including Ibadan, Nigeria account for the endemicity of malaria in these regions. (Park, 2009)

2.2.3.1.1. The Global Picture

The WHO World Malaria Report 2011 says there were 106 countries malaria endemic nations and 99 had on-going transmission that put about 3.3 billion people at risk in all continents.

There were 216 million cases of malaria in 2010 (range 149-274 million) resulting in 655, 000 deaths (range 537,000 – 907,000), 86% of those killed were children under five (5) years and 91% of all malaria deaths occurred in WHO African Region. (WHO GMP, 2011)

Globally, estimated malaria incidence dropped by 17% and mortality fell by 25% in 2010 as compared to 2000. About 43 countries recorded decreases of more than 50% in the number of malaria cases between 2000 and 2010. Another 8 countries recorded decreases of more than 25%. Also, Europe (99%), America (55%), Western Pacific (42%) and African Region (33%) made the largest percentage reductions in mortality in that order. (WHO GMP, 2011)

More so, the malaria map is shrinking progressively. United Arab Emirate was out in 2007, Morocco & Turkmenistan in 2010 and Armenia was certified malaria free in 2011; making it four (4) countries in 5 years. (WHO GMP, 2011)

Despite, Artemisinin monotherapy resistance persists in the Mekong Region while insecticide resistance is expanding rapidly. Forty-five (45) countries around the world have identified resistance to at least one of the four classes of insecticides used for malaria vector control and 27 of these are in sub-Saharan Africa.

Still, funding pose the greatest challenge as an estimated $32billion is needed to achieve zero malaria death by 2015 according to African Leaders Malaria Alliance (ALMA) & the UN (2012).

2.2.3.2. The Sub-Sahara Africa Outlook

The WHO African Region accounted for 81% of global malaria cases and 91% of malaria deaths in 2010. Six countries in this region (Nigeria, the Democratic Republic of Congo, Burkina Faso, Mozambique, Cote d'Ivoire and Mali) accounted for 60% (390,000) of all malaria deaths in 2010. In addition, Sub-Saharan Africa account for 27 of all 45 countries globally with resistance to insecticides used for malaria vector control. (WHO GMP, 2011)

However, this region achieved about 33% reduction in malaria mortality between 2000 and 2010. The number of long-lasting insecticidal nets (LLINs) delivered to malaria-endemic countries in sub-Saharan Africa increased from 88.5 million in 2009 to 145 million in 2010 (63.8%) such that, from 2008-2010, 290 million insecticide treated bednets (ITNs) were delivered to the region. An estimated 50% of households in sub-Saharan Africa now have at least one bed net and 96% of persons with access used it. Diagnostic testing rate in the public sector in the WHO African Region rose from 20% in 2005 to 45% in 2010 and no Artemisin resistance is reported yet in this region. (WHO GMP, 2011)

Malaria is said to contribute much to the cycle of poverty and limit economic development in Africa where, an estimated $12 million is directly lost per annum and considerably more is lost in economic growth. (Gallup & Sachs, 2000)

2.2.3.3. The Nigeria Situation

Almost all of Nigeria's over 158 million people live in malaria high transmission areas (i.e. ≥1 case of malaria / 1000 population) and transmission intensity is distributed un-evenly from the coastal mangrove swamps through the Rain forest belt to the savannahs (Guinea, Sudan, Sahel) and along the Niger and Benue river courses and tributaries. (WHO GMP, 2011)

Still, funding pose the greatest challenge as an estimated $32billion is needed to achieve zero malaria death by 2015 according to African Leaders Malaria Alliance (ALMA) & the UN (2012).

2.2.3.2. The Sub-Sahara Africa Outlook

The WHO African Region accounted for 81% of global malaria cases and 91% of malaria deaths in 2010. Six countries in this region (Nigeria, the Democratic Republic of Congo, Burkina Faso, Mozambique, Cote d'Ivoire and Mali) accounted for 60% (390,000) of all malaria deaths in 2010. In addition, Sub-Saharan Africa account for 27 of all 45 countries globally with resistance to insecticides used for malaria vector control. (WHO GMP, 2011)

However, this region achieved about 33% reduction in malaria mortality between 2000 and 2010. The number of long-lasting insecticidal nets (LLINs) delivered to malaria-endemic countries in sub-Saharan Africa increased from 88.5 million in 2009 to 145 million in 2010 (63.8%) such that, from 2008-2010, 290 million insecticide treated bednets (ITNs) were delivered to the region. An estimated 50% of households in sub-Saharan Africa now have at least one bed net and 96% of persons with access used it. Diagnostic testing rate in the public sector in the WHO African Region rose from 20% in 2005 to 45% in 2010 and no Artemisin resistance is reported yet in this region. (WHO GMP, 2011)

Malaria is said to contribute much to the cycle of poverty and limit economic development in Africa where, an estimated $12 million is directly lost per annum and considerably more is lost in economic growth. (Gallup & Sachs, 2000)

2.2.3.3. The Nigeria Situation

Almost all of Nigeria's over 158 million people live in malaria high transmission areas (i.e. ≥1 case of malaria / 1000 population) and transmission intensity is distributed un-evenly from the coastal mangrove swamps through the Rain forest belt to the savannahs (Guinea, Sudan, Sahel) and along the Niger and Benue river courses and tributaries. (WHO GMP, 2011)

The vectors of malaria seen in Nigeria include several species of the anopheline mosquitoes such as *Anopheles gambiae, A. arabiensis, A. funestus, A. Moucheti, A. melas, and A. nili.* The causative agent is *P. falciparum* in over 99.9% of cases but, *P. vivax* and other infection do occur, very rarely. (WHO GMP, 2011)

Nigeria shares about a quarter of the sub-Sahara Africa malaria burden. 44% (290,000) of all global malaria deaths in 2010 occurred in Nigeria and Congo DR. The 2010 Nigeria Malaria Indicator Survey (NMIS) reported that 42% of children aged 6-59months had malaria by microscopy test; and that the prevalence increases with age (about 28% in the 6-8 months old to 49% in the 48-59 months olds). (NPC, NMCP & ICF Macro., 2010; WHO GMP, 2011)

Overall, malaria prevalence in children ranges from 28% in South East zone to 56% in North West zone such that it accounts for over 60% outpatient visits to health facilities, 30% childhood death, 25% infant death and 11% maternal death; making it the number one killer of children under 5years (2009) and consistently ranking among the three most common cause of death for all ages. (NMCP, Nigeria, 2012; NPC, NMCP & ICF Macro., 2010; NPC & ICF Macro., 2009; WHO GMP, 2011)

Current national control strategy focuses on integrated vector control and prompt case management with Artemisin-based Combination therapy. Over 46.8million LLINs have been delivered to Nigeria and distributed in 30 states (this is the largest to any country in the world). Almost 30% of Under-5 year children slept under an ITN the night before the 2010 NMIS survey (A five-fold increase since 2008). Ownership of ITNs is higher than the proportion of children using them and only 13% of pregnant women received two or more doses of the very-important Intermittent Preventive Treatment (IPT) with Sulphadoxine-Pyrimethamine (Fansidar) during pregnancy. (WHO GMP, 2011; NMCP, Nigeria, 2012)

In Nigeria, the economic losses due to malaria annually is estimated to be about by 132 billion Naira in form of treatment costs, prevention, loss of man-hours, etc that can be attributed to the pain and fever due to the disease. (NMCP, Nigeria, 2012)

2.3. Malaria Pathogenesis and Pathology (The Malaria Life Cycle):

The production of disease by Plasmodium spp. is complex and not fully understood. The pathogenesis of malaria is tightly knitted with the life cycle of the plasmodium parasite in man; and current knowledge of the pathologic processes involved is very far from being complete especially, as it pertains to the exact mechanism of the pain seen (McAdam & Sharpe, 2005; Gilles, 2002; Martín-Rabadá & Bouza, 2004).

Typically, human infection begins with the inoculation of sporozoites into the inter-vascular skin matrix by infected female anopheles mosquitoes. The sporozoites (now referred to as the skin stage of the parasite) transverses several epithelial cells and undergo inmunologic changes in the skin for about 5-8 minutes to evade recognition and engulfment as well as suppress immune response before entry into the circulation such that an on-going infection does not prevent a new infection (Guilbride, Guilbride, & Gawlinski, 2012).

Within 30-minutes, most of the inoculated sporozoites will have reached the liver where they invade hepatocytes and undergo multiplication for about a week (8-30 days) to release several thousands of merozoites into the circulation. Each sporozoite transverses several hepatic cells before replicating in one and ruptures it to release merozoites. In about one hour after an infective mosquito bite, no sporozoites will be found in the peripheral circulation. (Guilbride, Guilbride, & Gawlinski, 2012; Wikipedia, 2011; Gilles, 2002)

Merozoites released from the exo-erythrocytic (hepatic) stage escape from the liver undetected after being wrapped in the cell membrane of the hepatocytes. They invade erythrocytes, where they grow (trophozoites) and divide (schizonts) to release more merozoites, in the erythrocytic cycle. *P. vivax* selectively infects reticulocytes but, *P. falciparum* infect all stages of red cells. (McAdam & Sharpe, 2005; Miller, Good, & Milon, 1994; Park, 2009)

Some *P.vivax* and *P.ovale* sporozoites do not immediately develop into the erythrocytic stage merozoites but, instead produce hypnozoites that remain dormant in the liver cells for several months, up to 3years. These hypnozoites later reactivate, produce merozoites and cause a relapse. They also account for the long incubation periods of these species. (Wikipedia, 2011)

The liver stages are not responsible for any disease. The pathological changes in malaria are related to the development of asexual parasites in the blood. The pathogenic processes occur during repeated cycles of developmental stages of the parasites in erythrocytes. During this stage, cytokines are released by immunocompetent cells in a highly regulated fashion and periodic amplification of parasite population occurs that may enhance the probability of differentiation into gametocytes (the stage infectious to mosquitoes) in the peripheral vascular beds. All these factors synchronize to yield impaired microcirculation that may explain the generalized muscular aches from hypoxia and the haemolytic anaemia from red cell use-up and lysis. (Miller, Good, & Milon, 1994; Gilles, 2002; McAdam & Sharpe, 2005)

In *P. falciparum* infections, the multifaceted nature of the interaction between the erythrocyte, the host immune system and the parasite is central to the pathogenesis of severe malaria and results in mechanical and rheological changes to the infected erythrocyte. *P. falciparum* has a special ability to cause cytoadherence to venous endothelium of parasitized erythrocytes with maturing parasites until they are released to invade other erythrocytes. These modifications lead to knob protrusions, cytoadherence and rosette formation of infected red cells that account for their sequestration and other haemorrhagic complications seen. The release of malaria antigens, pigment and toxins (being implicated as haemozoin, a brownish-green pigment and bye-product of haemoglobin used up by the parasites) give rise to a cascade of pathological events. Cytokines (especially, TNF-α, IL-6 and IL-1) released during the erythrocytic stage account for the fever, chills and possibly some of the pains and other symptomatology seen in the disease by regulating immune-competent cells to secrete other chemical mediators like Interferon-γ (IFN-γ). (Gilles, 2002; Guilbride, Guilbride, & Gawlinski, 2012; Miller, Good, & Milon, 1994)

2.4.Clinical Features of Malaria: Symptomatology

Malaria must be suspected in any febrile patient who has been in an endemic area in the previous three years. Before the onset of fever, non-specific symptoms such as malaise, headache, myalgia, fatigue, abdominal discomfort, dry cough, nausea, vomiting and diarrhea can occur, misleading the diagnosis. (Kumar & Clark, 2006; Adams, 2008)

Fever, the hallmark of malaria, usually develops 2 weeks after the infective bite, and in 95% of cases within the first 6 weeks and occasionally may follow the classic paroxysmal patterns: quartan pattern (peaks on days 1, 4, 7, etc.) — characteristic of *P. malariae*; or the tertian pattern of fever (peaks on day 1, 3, 5, etc.) — characteristic of all other species. The absence of a typical fever pattern does not exclude a diagnosis of malaria. (Adams, 2008; Gilles, 2002)

Physical examination of a malaria patient may reveal signs like tachycardia, splenomegaly, liver enlargement and jaundice. Malaria does not cause lymph node enlargement. In uncomplicated malaria, discrete hemolytic anemia, leukopenia and thrombocytopenia and other minor abnormalities of routine laboratory tests are usual. (Kumar & Clark, 2006; Krause, 2008; Wikipedia, 2011)

However, complications do occur as a result of malaria infection. Usually, persons infected with Plasmodium spp. other than *P. falciparum* rarely die of the infection in the developed world. The fatalities caused by 'benign' malaria are usually related to severe chronic anemia or rupture of an enlarged spleen. Patients infected with *P. malariae* may develop nephrotic syndrome. On the other hand, *P. falciparum* infection must always be considered a life-threatening condition. This makes the definition of severe or complicated malaria controversial. On practical grounds, in developed countries where malaria is not endemic, the practice is to treat every patient who has *P. falciparum* malaria as an inpatient. Intravenous treatment is prescribed if the patient is seriously ill, regardless of strict fulfillment of the WHO definition of severe malaria. (World Health Organization, 2006; Kumar & Clark, 2006)

An important complication of acute falciparum malaria is central nervous system (CNS) involvement (cerebral malaria). Cerebral malaria is defined strictly as unrousable coma in a diagnosed malaria patient. Less severe neurologic manifestations are common, and high fever alone can cause confusion and delirium and, in children, seizures. In cerebral malaria, focal signs are uncommon and physical examination shows symmetric encephalopathy. Cerebrospinal fluid (CSF) is usually unrevealing. Untreated cerebral malaria is uniformly fatal. If adequately treated, the mortality ranges from 15 to 25%. There are persistent neurologic sequelae in 10% of children and 3% of adults. (Kumar & Clark, 2006; Krause, 2008)

A rare complication called postmalaria neurologic syndrome has been defined in patients recently recovered from *P. falciparum* malaria who have negative blood films at the time of onset of neurological or neuropsychiatric symptoms. Clinical manifestations emerge a few days or weeks after recovery from malaria and can be confused with mefloquine neurotoxicity. Non-neurologic complications of malaria include renal failure, heart failure, acute pulmonary edema, adult respiratory distress syndrome, shock, coagulation disorders, severe anemia, hypoglycemia, metabolic acidosis, drug-related toxicity, malaria relapses and malarial hyper-reactive syndrome. Tropical splenomegaly or hyper-reactive malarial syndrome is occasionally seen in countries where malaria is endemic. It is defined as the presence of an enlarged spleen (often massive), raised IgM levels and high levels of antiplasmodium antibodies in patients who have negative smears for Plasmodium spp. and for whom no other cause of splenomegaly can be elicited. (McAdam & Sharpe, 2005; Wikipedia, 2011; Gilles, 2002)

Frequent **recurrence** is one complication of malaria that is escalating the burden of the disease and it could due to relapse, recrudescence or drug resistance. **Relapse** is defined as the reappearance of malaria originating from dormant liver schizonts, whereas **recrudescence** is the reappearance of disease after a partially effective treatment. Relapses can be expected in 50% of patients who have *P. vivax* or *P. ovale* infection who do not receive primaquine. (Wikipedia, 2011)

2.4.1. Pain: what it is?

Pain is an unpleasant sensation that can be defined only in the terms of what the person experiencing it says it is. Dickinson (1988) states "Pain is a subjective sensation and therefore pain is what the individual says it is and not what others think it should be". (Dickinson, 1998)

The most popular definition is that given by the International Association for the Study of Pain (IASP). IASP defined pain as "an unpleasant sensory and emotional experience that is primarily associated with actual or potential tissue damage or described in terms of such damage, or both." (American Medical Association, 2010; Chapman & Syrjala, 2001)

Those definitions recognize pain as a perception and not necessarily a sensation. In that light, pain may or may not correlate with an identifiable source of injury. Another important implication of this is that: It is almost always best to believe that the patient is experiencing what is being reported. Because there is no objective indicator for pain, experts agree that the best clinical approach in most circumstances is to assume that the patient is reporting a true experience, even in the absence of a clear explanation. The risk that rare cases of malingering or factitious disorder may lead the credulous physician to initial error is more than balanced by the benefits associated with a stance of compassionate acceptance and concern. (Chapman, 2001; American Medical Association, 2010)

One influential model described pain in terms of three hierarchical levels: a sensory-discriminative component (e.g., location, intensity, quality), a motivational–affective component (e.g., depression, anxiety), and a cognitive-evaluative component (e.g., thoughts concerning the cause and significance of the pain). In all cases, the reality that pain is a perception indicates the potential for profound influence of psychological and emotional factors, cognitions, and varied external events. (American Medical Association, 2010)

2.4.1.1. Pathophysiology of Pain

The activity in the body's "nociceptive" system, which senses noxious stimuli and generates a physiological and behavioral response, can be initiated by injury and sustained by neuroplastic

changes even after healing. It's important to note that activity in this system can occur in the absence of any discrete injury but in association with a recognizable disease (as may be ascribed to pain seen in infectious diseases such as malaria). (American Medical Association, 2010; Coda & Bonica, 2001)

Significant strides have been made in understanding the neurophysiology and neurochemistry of the systems that transmit and modulate information about noxious events. Also, much is known about acute inflammation, which commonly drives these neural processes. In contrast, relatively little is known about the exact pathophysiology underlying most pain syndromes especially, that seen in infectious diseases like malaria. Nonetheless, experts agree that clinical characteristics can be used to broadly divide pain syndromes into **nociceptive, neuropathic, psychogenic, mixed, or idiopathic pain**. (American Medical Association, 2010; Wikipedia, 2011; Turk & Okifuji, 2001)

2.4.1.1.1 Nociceptive Pain Mechanisms: Clinically, pain can be labelled "nociceptive" if the pain is due to ongoing activation of the nociceptive system by tissue injury. Tissue injury activates primary afferent neurons called nociceptors, which are small diameter afferent neurons (with A-delta and C-fibers) that respond to noxious stimuli and are found in skin, muscle, joints, and some visceral tissues. These fibers have specific receptors that may be responsible for noxious mechanical, chemical or thermal stimuli. Presumably, nociceptive processes linked to noxious events involving somatic or visceral structures begin with activation of these specific receptors, which leads to transduction, the process by which exposure to a sufficient stimulus produces depolarization of the peripheral nerve. (American Medical Association, 2010; Wikipedia, 2011)

Depolarization of the primary afferent involves a complex neurochemistry, in which substances produced by tissues, inflammatory cells and the neuron itself influence transduction. The role of prostaglandins, bradykinin, protons, nerve growth factor, and other compounds provide opportunities for the development of new analgesic drugs. Once depolarization occurs, transmission of information proceeds proximally along the axon to the spinal cord and then on to higher centers. Complex systems that modulate this input occur at all levels of the neuraxis and are best

changes even after healing. It's important to note that activity in this system can occur in the absence of any discrete injury but in association with a recognizable disease (as may be ascribed to pain seen in infectious diseases such as malaria). (American Medical Association, 2010; Coda & Bonica, 2001)

Significant strides have been made in understanding the neurophysiology and neurochemistry of the systems that transmit and modulate information about noxious events. Also, much is known about acute inflammation, which commonly drives these neural processes. In contrast, relatively little is known about the exact pathophysiology underlying most pain syndromes especially, that seen in infectious diseases like malaria. Nonetheless, experts agree that clinical characteristics can be used to broadly divide pain syndromes into **nociceptive, neuropathic, psychogenic, mixed, or idiopathic pain**. (American Medical Association, 2010; Wikipedia, 2011; Turk & Okifuji, 2001)

2.4.1.1.1 Nociceptive Pain Mechanisms: Clinically, pain can be labelled "nociceptive" if the pain is due to ongoing activation of the nociceptive system by tissue injury. Tissue injury activates primary afferent neurons called nociceptors, which are small diameter afferent neurons (with A-delta and C-fibers) that respond to noxious stimuli and are found in skin, muscle, joints, and some visceral tissues. These fibers have specific receptors that may be responsible for noxious mechanical, chemical or thermal stimuli. Presumably, nociceptive processes linked to noxious events involving somatic or visceral structures begin with activation of these specific receptors, which leads to transduction, the process by which exposure to a sufficient stimulus produces depolarization of the peripheral nerve. (American Medical Association, 2010; Wikipedia, 2011)

Depolarization of the primary afferent involves a complex neurochemistry, in which substances produced by tissues, inflammatory cells and the neuron itself influence transduction. The role of prostaglandins, bradykinin, protons, nerve growth factor, and other compounds provide opportunities for the development of new analgesic drugs. Once depolarization occurs, transmission of information proceeds proximally along the axon to the spinal cord and then on to higher centers. Complex systems that modulate this input occur at all levels of the neuraxis and are best

characterized in the spinal cord. The neuroanatomy, neurophysiology and neurochemistry of these processes are very complex (Chapman, 2001; American Medical Association, 2010; Wikipedia, 2011). Figure 2.1 gives a pictorial view of how pain signals flows through the neural system.

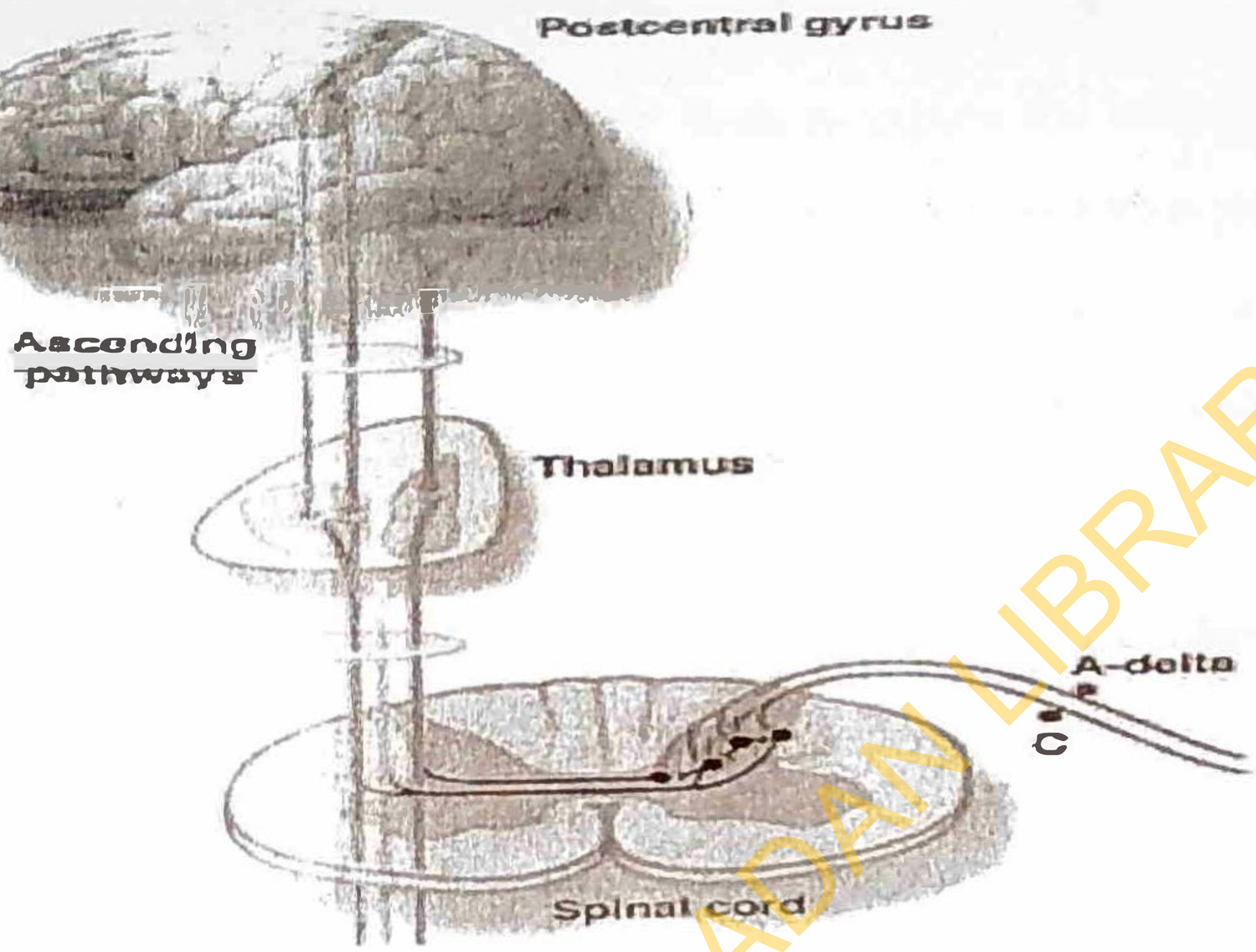


Figure 2.1. Neural Pathway for Nociceptive Pain © (American Medical Association, 2010)

2.4.1.1.2. Neuropathic Pain Mechanisms: Neuropathic pain refers to pain syndromes inferred to result from direct injury or dysfunction of the peripheral or central nervous system. These changes may be caused by injury to either neural or non-neural tissues. Although neuropathic pain may be strongly influenced by ongoing tissue injury, or other stimuli that activate the sensory system, there is an assumption that the fundamental mechanisms sustaining the pain have become independent of any ongoing tissue injury. (Chapman, 2001; American Medical Association, 2010; Turk & Okifuji, 2001)

Injury to a peripheral nerve axon can result in abnormal nerve morphology. The damaged axon may grow multiple nerve sprouts, some of which form neuromas. These nerve sprouts, including those forming neuromas, can generate spontaneous activity, which peaks in intensity several weeks after injury. These areas of increased sensitivity are associated with a change in sodium receptor concentration, and other molecular processes, and also can occur at sites of demyelination or nerve

fibre injury not associated with the severing of axons. After a period of time, atypical connections may develop between nerve sprouts or demyelinated axons in the region of the nerve damage, permitting "cross-talk" between somatic or sympathetic efferent nerves and nociceptors. (American Medical Association, 2010)

Neuropathic pain syndromes mechanisms are least likely to explain the acute pain due to an infectious disease like malaria but, may be associated with referred pain, allodynia (pain induced by non-noxious stimuli, *e.g.* light touch), hyperalgesia (increased response to a noxious stimuli), or hyperpathia (exaggerated pain responses following a stimulus, often with after sensation and intense emotional reaction). (American Medical Association, 2010)

2.4.1.1.3. Psychological and "Idiopathic" Pain Mechanisms: Pain is a complex aversive experience normally associated with tissue trauma, inflammation, or a disease process. Because it is subjective and personal, pain is inherently psychological in nature. Increasing evidence supports the existence of an exceedingly complex relationship between the psyche and pain perception. To this end, not much has been elucidated by empirical science. However, clinical evidence shows that in some patients, the experience of persistent pain appears to induce disturbances in mood (reactive depression or anxiety), impaired coping (often with catastrophization), and other processes, which in turn, appear to worsen pain and pain-related distress. Other patients have premorbid or comorbid psychosocial concerns or psychiatric disorders that are best understood as evolving in parallel to the pain. These disturbances also can contribute to the pain experience and driver pain-related distress. (Chapman & Turner, Psychological Aspects of Pain, 2001; American Medical Association, 2010; Wikipedia, 2011)

Classical lines of thinking in neurophysiology, particularly the energy metaphor and Cartesian dualism, are conceptually incompatible with much of the work in current psychology with regards to pain. This complexity highlights the importance of psychosocial and psychiatric evaluation as a fundamental aspect of pain assessment. (Chapman & Turner, Psychological Aspects of Pain, 2001)

2.4.1.2. Pain Measurement

Pain is a multidimensional experience. Healthcare professionals have high tendency to underestimate its severity in an attempt to quantify it using unidimensional tools whereas, pain is whatever the experiencing person says it is, existing whenever he says it does. (Chapman & Syrjala, 2001; American Medical Association, 2010)

Pain is inherently subjective and a person's self-report is the most reliable measure and gold standard of assessment. Ideally, the description of the pain should characterize its temporal relations, intensity, location, quality and factors that exacerbate or relieve it. Factors that either exacerbate or relieve pain can suggest an underlying cause that can contribute to diagnosis. Clinically, history and physical examination are the cornerstones of diagnosis for the patient with acute or chronic pain. In eliciting the history of the pain and in examining the painful part, it is essential to obtain a detailed description of the onset, location and distribution of the pain, quality of the pain, severity or intensity of the pain, and periodicity and duration of the pain and the affective concomitants of pain. The distinction between acute and persistent (Chronic) pain is particularly relevant. Acute pain characteristically is of recent onset and is anticipated to have a relatively short duration of no more than days or weeks. Pain is usually considered persistent if it continues more than 3 to 6 months or if it meets one of the following criteria: 1) persisting for at least one month beyond the usual course of an acute illness or the time required for an injury to heal, 2) associated with a chronic pathologic process, or 3) recurring at relatively short intervals (days, weeks, or several months). By these definitions, malaria pain is acute as it resolves with treatment. (Loeser, 2001; American Medical Association, 2010)

In measuring pain, the most intriguing aspect is how to assess the intensity of pain in quantifiable terms, as a way of estimating its severity. Efforts towards making this process as objective as possible resulted in the development of several pain measurement guidelines and instruments by as many experts, disciplines and institutions as are involved in the study of pain over the years. Though, the instruments are structurally different yet, they are all similar in concept and

application. Broadly, self-reported pain measuring tools can be divided into two: **the singe dimensional tools** based on individual categorical or pictorial scales and **the multi-dimensional instruments** that comprehensively incorporate one or more unidimensional scales with other validated questions that assess other characteristics of the pain in one evaluation tool. (Chapman & Syrjala, 2001; Loeser, 2001)

The Commonly used unidimensional scales include the **Verbal Rating Scale (VRS)**, the **Numeric Rating Scale (NRS)**, a **Visual Analogue Scale (VAS)**, and the **Pictorial Scale (e.g. the Wong Baker Faces Scale)**. These category scales consist of numbers, verbal or visual descriptors that offer patients a simple method for reporting the private intensity of pain. These scales require only the choice of the best word or picture or the most appropriate number from the patient. The choice of pain scale depends on the patient's age, ability to communicate, or other specific circumstances. While the VRS is the simplest measure, other scales can provide additional information. In clinical setting, the NRS is simple to use and is one of the most common approaches for quantifying pain. Patients indicate their pain intensity on a scale of 0 to 10, with 0 indicating no pain and 10 the worst pain imaginable. In research setting, this scale is more sensitive to treatment-induced changes than the VRS. The VAS is conceptually similar to an NRS. It consists of a 10-cm line drawn to scale, with one end labelled "no pain" and the other end labelled "worst pain imaginable." The patient marks the line at the point that best describes the pain intensity. The length of the line to the patient's mark is measured and recorded in millimetres. The main theoretical advantage of the VAS is that it does not limit pain to 10 discrete levels of intensity, permitting a more detailed rating of pain. The Faces pain scale presents pictures of 6 to 8 different facial expressions depicting a range of emotions. This scale is useful in young children, in patients who have mild to moderate cognitive impairment, or patients with other language barriers. (Wikipedia, 2011; American Medical Association, 2010; Chapman & Syrjala, 2001)

On the other hand, multidimensional pain assessment tools have been developed to quantitate the characteristics of pain and its effect on mood and function. They take longer to administer unlike

the unidimensional scales and some patients who are cognitively impaired or poorly educated may find them difficult to complete. They are generally used in pain research, but can be adapted for clinical use, if appropriate and valuable. The most popular of these instruments is the **McGill Pain Questionnaire (MPQ)**, a validated clinical tool that assesses pain in 3 dimensions (sensory, affective, and evaluative) based on 20 sets of words that patients select to describe their pain. It is one of the more extensively tested multidimensional scales available. The **Brief Pain Inventory (BPI)** is another well validated pain measurement tool with demonstrated reliability and validity in patients with cancer, AIDS, and arthritis. It includes 4 pain intensity scales ("right now", "on average", "at its worst", and "at its least"), as well as 7 scales assessing the impact of pain on general activity, mood, ability to walk, work, relationships, sleep, and enjoyment of life. The BPI is widely used in pain research. (Chapman & Syrjala, 2001; Cleeland, 1991; Dickinson, 1998; American Medical Association, 2010)

Other instruments have been created in recent years to assess persistent pain and provide a means to track potentially large numbers of patients in terms of key functional domains. Examples include the **Memory Pain Assessment Card** that scales pain, pain relief, and mood on VASs and adds a set of adjectives reflecting pain intensity, the **Neuropathic Pain Scale** (a neuropathic pain specific scale used in research setting), the **Treatment Outcomes of Pain Survey (TOPS)**, which is a pain-enhanced version of the health-related quality of life (HRQoL) instrument, known as the Medical Outcomes Study Short Form 36 (MOS SF-36 or SF-36). The SF-36 is a useful research tool to determine group change, but lacks the sensitivity to determine individual patient changes. (Chapman & Syrjala, 2001)

More examples include the **Pain Perception Profile** that uses cross-modality matching. It (a) measures sensation threshold; (b) uses magnitude estimation procedures to judge induced pain; (c) measures pain on intensity, reaction, and sensation dimensions via psychophysical scaling of verbal pain descriptors; and (d) allows the user to administer the three dimensions of psychophysically scaled verbal descriptors in a diary format for repeated assessment over time. Compared with the

the unidimensional scales and some patients who are cognitively impaired or poorly educated may find them difficult to complete. They are generally used in pain research, but can be adapted for clinical use, if appropriate and valuable. The most popular of these instruments is the **McGill Pain Questionnaire (MPQ)**, a validated clinical tool that assesses pain in 3 dimensions (sensory, affective, and evaluative) based on 20 sets of words that patients select to describe their pain. It is one of the more extensively tested multidimensional scales available. The **Brief Pain Inventory (BPI)** is another well validated pain measurement tool with demonstrated reliability and validity in patients with cancer, AIDS, and arthritis. It includes 4 pain intensity scales ("right now", "on average", "at its worst", and "at its least"), as well as 7 scales assessing the impact of pain on general activity, mood, ability to walk, work, relationships, sleep, and enjoyment of life. The BPI is widely used in pain research. (Chapman & Syrjala, 2001; Cleeland, 1991; Dickinson, 1998; American Medical Association, 2010)

Other instruments have been created in recent years to assess persistent pain and provide a means to track potentially large numbers of patients in terms of key functional domains. Examples include the **Memory Pain Assessment Card** that scales pain, pain relief, and mood on VASs and adds a set of adjectives reflecting pain intensity, the **Neuropathic Pain Scale** (a neuropathic pain specific scale used in research setting), the **Treatment Outcomes of Pain Survey (TOPS)**, which is a pain-enhanced version of the health-related quality of life (HRQoL) instrument, known as the Medical Outcomes Study Short Form 36 (MOS SF-36 or SF-36). The SF-36 is a useful research tool to determine group change, but lacks the sensitivity to determine individual patient changes. (Chapman & Syrjala, 2001)

More examples include the **Pain Perception Profile** that uses cross-modality matching. It (a) measures sensation threshold; (b) uses magnitude estimation procedures to judge induced pain; (c) measures pain on intensity, reaction, and sensation dimensions via psychophysical scaling of verbal pain descriptors; and (d) allows the user to administer the three dimensions of psychophysically scaled verbal descriptors in a diary format for repeated assessment over time. Compared with the

MPQ, cross-modality matching is shorter and less demanding once the psychophysical scaling is complete. The **West Haven–Yale Multidimensional Pain Inventory** provides an alternative to the MPQ. By design, it is shorter and more classical in its psychometric approach to multidimensional scaling than the MPQ. The 56-item inventory comprises three parts: (a) five general dimensions of the experience of pain and suffering, interference with normal family and work functioning, and social support; (b) patients' perceptions of the responses of others to displays of pain and suffering; and (c) frequency of engagement in common daily activities. The instrument is linked to cognitive-behavioral theory and assesses constructs beyond subjective distress, including effect of the pain problem on general functioning. As such, it represents a broader approach to scaling than the MPQ. The Multidimensional Pain Inventory has found wide use with diverse pain syndromes, and various studies have replicated the scale structures. (American Medical Association, 2010; Chapman & Syrjala, 2001)

However, the measurement of pain remains a knotty problem that is receiving considerable attention. There has been substantial progress in the development of theory and technology that can be deployed in the study of the mechanism of pain in infectious diseases like malaria. (Chapman & Syrjala, 2001)

2.4.2. Pain as seen in Malaria

The only study that specifically looked at malaria pain from the literature reviewed was that reported by Zaki (2010). It was a retrospective study of 227 cases of children (aged one month to 12years) who had malaria in India and were on admission in the paediatrics general wards and intensive care unit between January to December 2009. In his report, abdominal pain was a frequent complaint in about 33.5% (76) of the children, 38 (50%) of whom had *P. falciparum*, 36(46.2%) had *P. vivax* and 2 had mixed infection. 52(66.7%) of the children with abdominal pain were over 5years and none was less than 2years of age. The abdominal pain was mild, continous and dull in 52 (66.7%) patients, of whom 46 had pain in the periumbilical region whereas in the remaining it was poorly localised. On examination, the abdomen was nontender without guarding or rigidity. Bowel

sounds were normal. All investigations in the 52 patients were normal and the pain disappeared within 48 hours of starting antimalarial treatment. Abdominal pain in these patients could be due to ischaemic changes in the intestine secondary to microvascular changes due to sequestered red blood cells (Zaki, 2010; Song, O, Kim, Moon, Kim, & Yoom, 2003; Dass, Barman, Duwarah, & Deka, 2010; Krause, 2008)

Obviously, malaria pain is sparingly studied or reported despite its being a very common feature of the disease affecting millions globally, every year.

2.5. Diagnosis of Malaria

Clinically, malaria is a differential diagnosis of anyone who presents with a febrile illness in, or having recently left, a malarious area. Falciparum malaria is unlikely to present more than 3 months after exposure, even if the patient has not been taking prophylaxis, but vivax malaria may cause symptoms for the first time up to a year after leaving a malarious area. (Kumar & Clark, 2006; Park, 2009; WHO, 2006)

Definitive diagnosis of malaria is based on laboratory findings. The gold standard is diagnosis made by identifying parasites on a Giemsa-stained thick or thin blood film showing the signet-ring merozoites or trophozoites or halter-shaped gametocytes or round-oval schizonts or haemozoin crystals (thick films are more difficult to interpret, and it may be difficult to speciate the parasite, but they have a higher yield). At least three films should be examined before malaria is declared unlikely. (Kumar & Clark, 2006; WHO, 2006)

An alternative microscopic method is quantitative buffy coat analysis (QBC), in which the centrifuged buffy coat is stained with a fluorochrome which 'lights up' malarial parasites. A number of antigen-detection methods for identifying malarial proteins and enzymes have been developed. Some of these are available in card or dipstick form, and are potentially suitable for use in resource-poor settings. The *P. Falciparum* specific Rapid diagnostic test (RDT) based on ELISA, with

sounds were normal. All investigations in the 52 patients were normal and the pain disappeared within 48 hours of starting antimalarial treatment. Abdominal pain in these patients could be due to ischaemic changes in the intestine secondary to microvascular changes due to sequestered red blood cells. (Zaki, 2010; Song, O, Kim, Moon, Kim, & Yoom, 2003; Dass, Barman, Duwarah, & Deka, 2010; Krause, 2008)

Obviously, malaria pain is sparingly studied or reported despite its being a very common feature of the disease affecting millions globally, every year.

2.5. Diagnosis of Malaria

Clinically, malaria is a differential diagnosis of anyone who presents with a febrile illness in, or having recently left, a malarious area. Falciparum malaria is unlikely to present more than 3 months after exposure, even if the patient has not been taking prophylaxis, but vivax malaria may cause symptoms for the first time up to a year after leaving a malarious area. (Kumar & Clark, 2006; Park, 2009; WHO, 2006)

Definitive diagnosis of malaria is based on laboratory findings. The gold standard is diagnosis made by identifying parasites on a Giemsa-stained thick or thin blood film showing the signet-ring merozoites or trophozoites or halter-shaped gametocytes or round-oval schizonts or haemozoin crystals (thick films are more difficult to interpret, and it may be difficult to speciate the parasite, but they have a higher yield). At least three films should be examined before malaria is declared unlikely. (Kumar & Clark, 2006; WHO, 2006)

An alternative microscopic method is quantitative buffy coat analysis (QBC), in which the centrifuged buffy coat is stained with a fluorochrome which 'lights up' malarial parasites. A number of antigen-detection methods for identifying malarial proteins and enzymes have been developed. Some of these are available in card or dipstick form, and are potentially suitable for use in resource-poor settings. The *P. Falciparum* specific Rapid diagnostic test (RDT) based on ELISA, with

sensitivity as high as 76%, is being popularized, disseminated and encouraged in resource-restricted zones. Serological tests are of no diagnostic value (Kumar & Clark, 2006; WHO, 2006).

However, parasitaemia is common in endemic areas, and the presence of parasites does not necessarily mean that malaria is the cause of the patient's symptoms. Further investigations, including a lumbar puncture, may be needed to exclude bacterial infection. (Park, 2009; WHO, 2006; Kumar & Clark, 2006)

2.6.Malaria Control Efforts in Brief

The age-long effort to roll back malaria is now more than ever being scaled-up amidst alleged funding shortages. The most current strategy is **T_3 (Test, Treat, Track)**, launched by the World Health Organization during the commemoration of the World Malaria Day 2012 on April 25th to scale up the three fundamental pillars of existing global strategy to fight malaria. This is in tandem with the case management component of the more comprehensive on-going policies of the National Malaria Control Programme (NMCP) of Nigeria. (WHO GMP, 2012)

2.6.1. Test: Every suspected malaria case should be confirmed by microscopy or RDT prior to treatment. Treatment based on clinical suspicion alone is no longer recommended. (WHO GMP, 2012)

2.6.2. Treat: After diagnostic confirmation, every uncomplicated case of *P. falciparum* malaria should be treated with a quality-assured Artemisinin-based Combination Therapy (ACT). Every severe case of *P. falciparum* malaria should be treated with intravenous or intramuscular artesunate, followed by a full course of an ACT. Chloroquine (CQ) is first line for *P. Vivax* infection (use ACT if resistance to CQ) and IM / IV Artesunate followed by full course ACTs for severe Malaria. (WHO GMP, 2012). Findings from this study may initiate policy influence such that analgesics are included as compulsory critical component of treatment regimen.

2.6.3. Track: To ensure the disease is tracked through timely and accurate surveillance systems to guide policy and operational decisions. Individual cases should be registered at health facility level.

This allows for the recording of suspected cases, diagnostic test results, and treatments administered. In the malaria control phase, countries should report suspected, presumed and confirmed cases separately, and summarize aggregate data on cases and deaths on a monthly basis. Countries in elimination phase should undertake a full investigation of each malaria case. (WHO GMP, 2012)

Other key components of the NMCP strategies include Integrated Vector Management (which include use of ITNs & LLINs, IRS –indoor residual spraying, Larviciding with temephos, Outdoor Spraying, Wearing protective clothing, Environmental management, drainage and application of bye-laws and Improved housing and screening), Chemoprophylaxis (IPT during pregnancy with SP & Proguanil in SCDx), Advocacy, Communication and Social Mobilization. (NMCP, Nigeria, 2012)

The Target remains the WHO's World Health Assembly 2012 & MDG goal of achieving zero death and reducing the malaria burden by at least 75% by 2015. Global malaria eradication is a dream that now look possible with the initial results of the on-going trial of a malaria vaccine (RTS, S /AS01) in seven African Countries. According to the World Health organization, the mid study results are promising and the vaccine may be deployed by the first quarter of 2015 if the mid-study findings are sustained when the trials end by 2014. However, it is vital that malaria remains high on the political agenda in both malaria-endemic and donor countries, and that investment are scaled up further to support research, control and elimination efforts including prompt and accurate pain evaluation with effective treatment (Waters, 2006; Good & Doolan, 2010; WHO GMP, 2011; Agnandji, Lell, Soulanoudjingar, Fernandes, Abossolo, & Conzelmann, 2011).

Chapter Three

METHODOLOGY

3.1. The Study Area:

This study was conducted in Ibadan, the largest metropolitan geographical area in Nigeria and the third largest city by population, after Lagos and Kano, with a population of 1,338,659 (NPC, 2006).

Ibadan is the capital city of Oyo State and has 11 Local Governments Areas (five urban and six semi-urban). It is situated close to the boundary between the rain forest zone and the savanna, in the south-eastern part of the state in south-western Nigeria. This is a prominent transit point between the coastal region and the areas to the north of Nigeria. (Wikipedia, 2012)

The city's total area is 1,190 square mile (3,080 km^2) and ranges in elevation from 150m in the valley area, to 275m above sea level on the major north-south ridge which crosses the central part of the city. (Wikipedia, 2012)

Ibadan has a tropical wet and dry climate, with a lengthy wet season (March to October) that sees somewhat of a lull in precipitation in August which nearly divides the wet season into two different wet seasons. Rainfall peaks in June and September and the mean total rainfall is 1420.06mm, falling in approximately 109days. November to February is the city's dry season, during which the typical West African harmattan is experienced. Temperature throughout the course of the year is relatively constant and the mean maximum temperature is 26.46 °C, minimum 21.42 °C while the average relative humidity is 74.55%. The foregoing factors synergize to make Ibadan a plasmodium high transmission zone (≥1 case/1000person) that is holoendemic to malaria. (Wikipedia, 2012; WHO GMP, 2011)

Two popular first call centres for outpatient consultations among Ibadan people with relatively high turnover of patients having febrile illnesses were purposively selected as study centres for this research. These are: The General Outpatient Department (GOPD) of the University College Hospital (UCH) and Our Lady of Apostles (OLA) Catholic Hospital.

3.1.1. The Study Sites:

The University College Hospital (UCH), Ibadan is Nigeria's premier federal teaching hospital located along Queen Elizabeth drive, Yemetu-Mokola area in central Ibadan city. It is primarily a multi-specialty tertiary care centre that provides teaching facility for the College of Medicine of the University of Ibadan. Aside her many specialist departments, the hospital run a massive general outpatient department (GOPD) that offer primary and secondary level care which attract patients from all over Ibadan and environs. This GOPD served as one of the centre for this study. As expected, qualified medical personnel manned every unit in the department. (UCH, 2011)

On the other hand, Our Lady Apostles Catholic Hospital, Oluyoro, Oke-Ofa, Ibadan is a not-for-profit Catholic missionary hospital located in the heart of Ibadan. "Oluyoro" as the facility is popularly called is renowned for providing a broad spectrum of essential primary and secondary level care that attracts patients from across socio-economic divides within Ibadan and environs. Fees are charged, but the proceeds are said to be reinvested in the staff, patients and facilities. Her outpatient section and adjoining laboratories were found to be uniquely suitable for this study. (Wikimapia, 2007)

3.2. The Study Design:

This was a hospital-based, two-centre, cross sectional survey.

3.3. The Study Population:

The study population was made up of persons clinically diagnosed of acute uncomplicated malaria by the attending physician in Ibadan who satisfied the inclusion criteria for this study.

3.3.1. Inclusion Criteria:

All consenting, consecutive patients aged six years or more, presenting to the study centre outpatient clinic with a 24-hour history of fever, and/or an axillary temperature $\geq 37.5^{0}C$, or other symptoms of malaria and were clinically diagnosed of acute uncomplicated malaria (WHO, 2006) by the attending physician were enrolled as subjects for this study and were evaluated.

3.3.2. Exclusion Criteria:

The following persons diagnosed of malaria were excluded from the study:

1. Patients with any sign of severe /complicated malaria
2. Pregnant women
3. Known patients with Haemoglobin SS or SC (HbSS or HbSC)
4. Patient with a recent history of trauma
5. Patients with history or evidence of chronic pain including arthritis
6. Patients considered to be very ill by themselves or the interviewer

And of course, patients who met the inclusion criteria but did not give consent for study as well as those who withdrew their consent at any time during the interview were excluded.

3.4. Sample Size Estimation:

The minimum sample size for this survey was estimated using the following formula:

$$n = (Z_{\alpha} + Z_{\beta})^2 P (1-P) / d^2$$

Where n = minimum sample size required

Z_{α} = 1.96 (standard normal deviate corresponding to 5% level of significance)

Z_{β} = 0.84 {standard normal deviate corresponding to chosen power (1-β) of 80%, β =20%}

P = 50% {hypothetical prevalence of pain due to malaria that will maximize the sample size as no study on pain due to malaria was found in the literature reviewed}

d = 5.42% (level of precision or acceptable margin of error allowed of sample estimates)

$$\text{i.e. } n = (1.96 + 0.84)^2 (0.50)(0.50) / (0.0542)^2$$

$$= 667.20$$

Therefore, the minimum sample size of subjects with malaria that should be selected for this study is approximately 667. However, to account for 5% expected incomplete responses and still achieve a statistically valid sample size for analysis, a sample of 700 patients was taken for this study.

3.5. Sampling (Subjects Selection):

This study employed a serial consecutive enrollment of all out-patients that were clinically diagnosed of acute uncomplicated malaria (WHO, 2006) at the study centres over a three (3) month period (October to December, 2011) as long as they met the inclusion criteria.

3.6. Data Collection Procedures:

A team of interviewers and laboratory scientist with in-depth knowledge of the local Yoruba language were employed and trained to correctly identify and recruit satisfactory subjects, administer the instruments as well as collect needed capillary blood samples and thick films. The interview for selecting subjects was done in 2 phases:

3.6.1. Interview Phase 1:

An initial brief interview of all patients presenting in the sorting hall of the General Outpatient Department (GOPD) of the University College Hospital (UCH), Ibadan and the reception hall of the other study centre was carried out. This helped prepare the patients and gave an idea of their presenting complaints for appropriate directive on which physician they should see.

All those with malaria-related complaints were attended to by physicians as done routinely in the clinics including good history, physical examination and laboratory investigations. A thick blood film was made and examined for malaria parasite in the laboratories following an aseptic finger-prick procedure. One to two (1-2) ml. of whole blood was collected for capillary Packed Cell Volume (PCV) from the same finger prick.

3.6.2. Interview Phase 2:

All consenting, consecutive patients clinically diagnosed of malaria by the attending physicians were interviewed using a validated structured questionnaire.

3.7. The Data Collection Instrument

Data collection was done with the aid of a structured questionnaire adapted from validated pain measuring instruments including the McGill Pain Questionnaire (MPQ) and the Brief Pain

Inventory (BPI). (Melzack, 2005; Cleeland, 1991). The questionnaire was pretested among similar patients in the Staff Clinic section of the University College Hospital, Ibadan before a final draft was made.

Each questionnaire had four sections and a unique serial number, matched with the patient's serial slide number and the capillary tube code. Date of data collection was obtained but, names and other personal identifying information were not obtained.

3.7.1. Section A (questions 1-8) was designed to collect respondent's socio-demographic data such as age, sex, religion, nationality, ethnicity, occupation, level of education and marital status.

3.7.2. Section B (questions 9-13) obtained a brief medical history from respondents including their presenting complaint(s), number of days of onset of illness, clinical diagnosis by the physician, axillary temperature as measured, Height, Weight, history of other medical conditions like sickle cell disease, pregnancy, trauma, chronic pain and the presence or absence of pain.

3.7.3. Section C (question 14 – 28) made a detailed exploration of the pain (if present) as experienced by the subject in the current illness. This critical section asked about the character/quality of the pain, the pattern of the pain, associated symptoms before or after the pains, the site or location of the pain, whether the pain radiate or not, site of radiation, the severity/intensity of this pain and of course, the assessment of the effect of this pain on occupational/school activity, mood, walking, house chores, relations with other people and general sense of enjoyment of life. Also, information on previous drugs used (including analgesics, anti-Malarias and herbal) prior to presentation were assessed in this section.

The intensity of pain was evaluated using categorical scales including the subjective VERBAL RATING SCALE (VRS) developed by Melzack and Torgerson (Chapman & Syrjala, 2001), where respondents described their perceived pain intensity as mild, discomforting, distressing, horrible or excruciating. Concurrently, the following more objective, validated, unidimensional pain intensity assessment tools were used.

Inventory (BPI). (Melzack, 2005; Cleeland, 1991). The questionnaire was pretested among similar patients in the Staff Clinic section of the University College Hospital, Ibadan before a final draft was made.

Each questionnaire had four sections and a unique serial number, matched with the patient's serial slide number and the capillary tube code. Date of data collection was obtained but, names and other personal identifying information were not obtained.

3.7.1. Section A (questions 1-8) was designed to collect respondent's socio-demographic data such as age, sex, religion, nationality, ethnicity, occupation, level of education and marital status.

3.7.2. Section B (questions 9-13) obtained a brief medical history from respondents including their presenting complaint(s), number of days of onset of illness, clinical diagnosis by the physician, axillary temperature as measured, Height, Weight, history of other medical conditions like sickle cell disease, pregnancy, trauma, chronic pain and the presence or absence of pain.

3.7.3. Section C (question 14 – 28) made a detailed exploration of the pain (if present) as experienced by the subject in the current illness. This critical section asked about the character/quality of the pain, the pattern of the pain, associated symptoms before or after the pains, the site or location of the pain, whether the pain radiate or not, site of radiation, the severity/intensity of this pain and of course, the assessment of the effect of this pain on occupational/school activity, mood, walking, house chores, relations with other people and general sense of enjoyment of life. Also, information on previous drugs used (including analgesics, anti-Malarias and herbal) prior to presentation were assessed in this section.

The intensity of pain was evaluated using categorical scales including the subjective VERBAL RATING SCALE (VRS) developed by Melzack and Torgerson (Chapman & Syrjala, 2001), where respondents described their perceived pain intensity as mild, discomforting, distressing, horrible or excruciating. Concurrently, the following more objective, validated, unidimensional pain intensity assessment tools were used.

3.7.3.1. The 0-10 Numeric Pain Intensity Rating Scale (NRS) shown in figure 3.1 below was used to assess the severity of the malaria pain experienced by subjects older than 10 years and literate. Subjects verbally stated the intensity of their pain as a value between zero (0) and ten (10) where, No pain = 0, Mild pain (1-3), Moderate pain (4-6), Severe pain (7-9) and Worst pain imaginable (10).

3.7.3.2. For illiterate subjects over 12years, a similar 10cm Visual Analogue Scale (VAS) was made available for their assessment (figure 3.2). The subjects rated their pain by making a mark along the 10cm line. A ruler was then used to measure the length and this was recorded after approximation to the nearest whole number digit. The values carried exactly the same meaning as described for the Numeric Rating Scale above.

Figure 3.1: The Numeric Pain Rating Scale (VAS) © (American Medical Association, 2010)

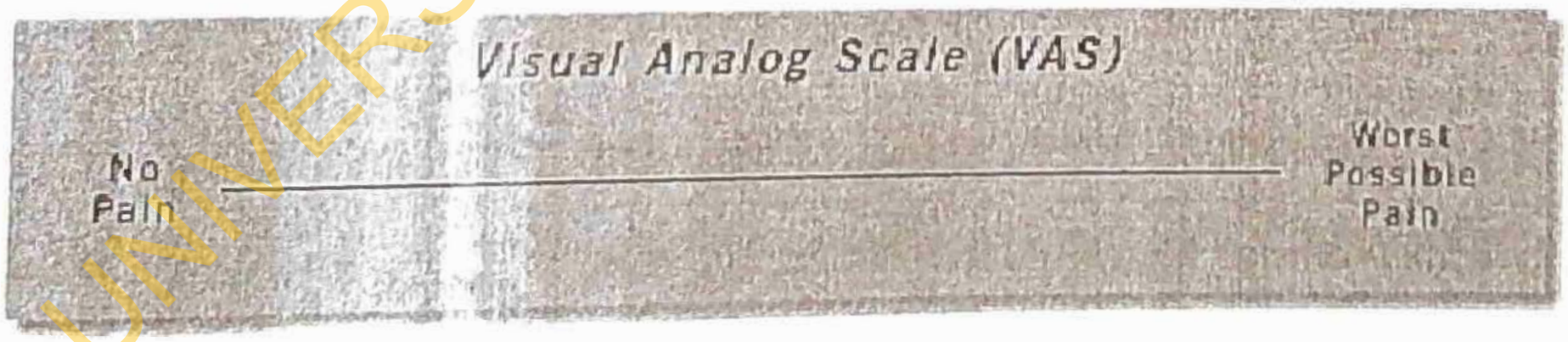


Figure 3.2: The Visual Analogue Scale (VAS)© (American Medical Association, 2010)

3.7.3.3. The **Wong-Baker FACES Pain Rating Scale** shown in figure 3.3 was validated for use in persons aged 6 years or older. This study used this for subjects less than 12 years in age. Each graphic on this scale has a number value attached which was recorded for subject depending on the picture they chose as an expression of their pain intensity.

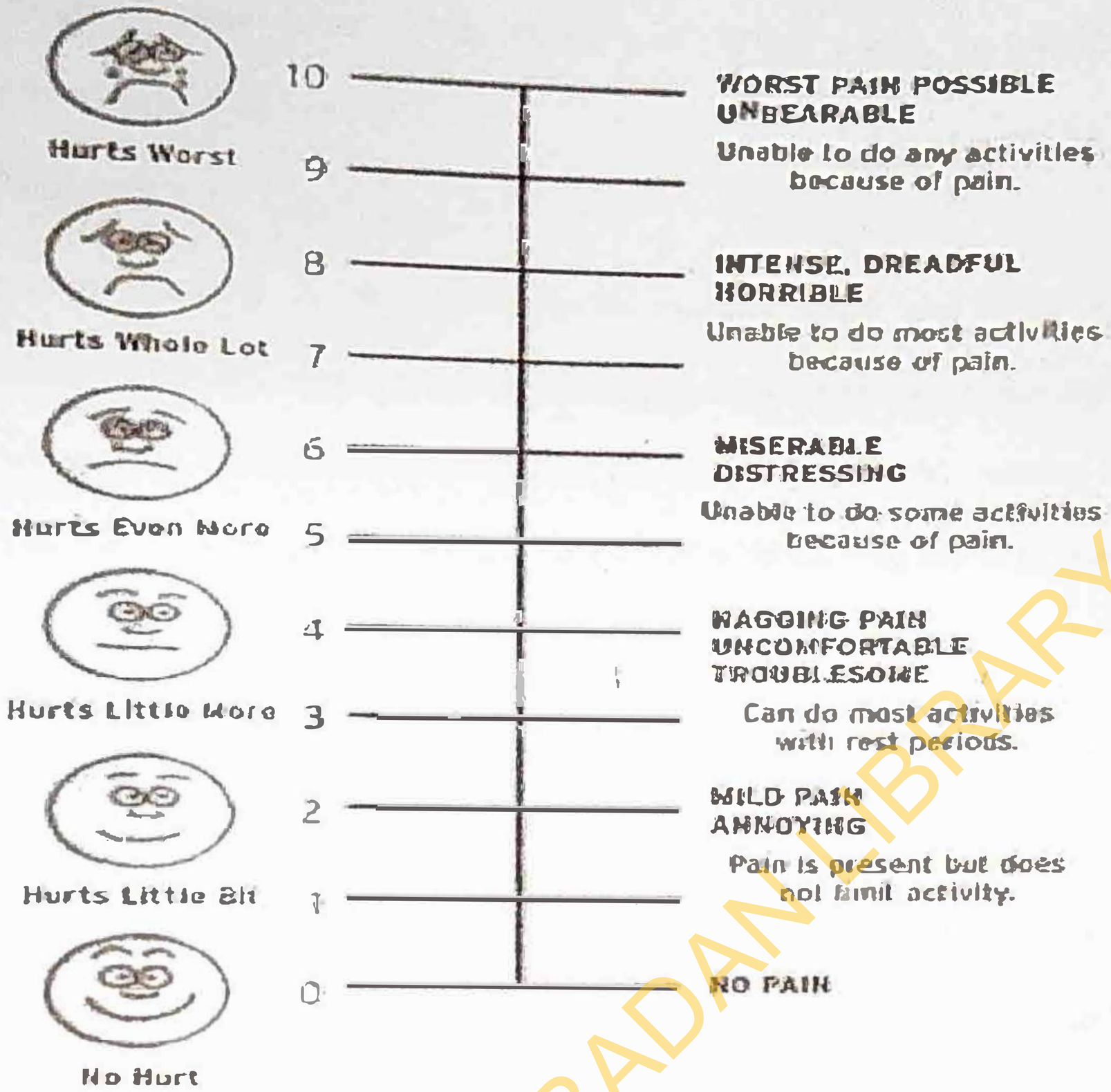


Figure 3.3: The Wong-Baker FACES Pain Rating Scale © (American Medical Association, 2010)

3.7.3.4. The subject's perceived gross effect of their malaria pain on occupational activities, school activities, mood, walking, sleep, relation with people, house chores and enjoyment of life was measured using an adapted numeric (0-10) scale (figure 3.4), rated in the same pattern as the pain intensity scale above. On this scale, 0 = No interference, 1-3 = mild interference, 4-6 =moderate interference, 7-9 = severe interference, and 10 = complete interference.

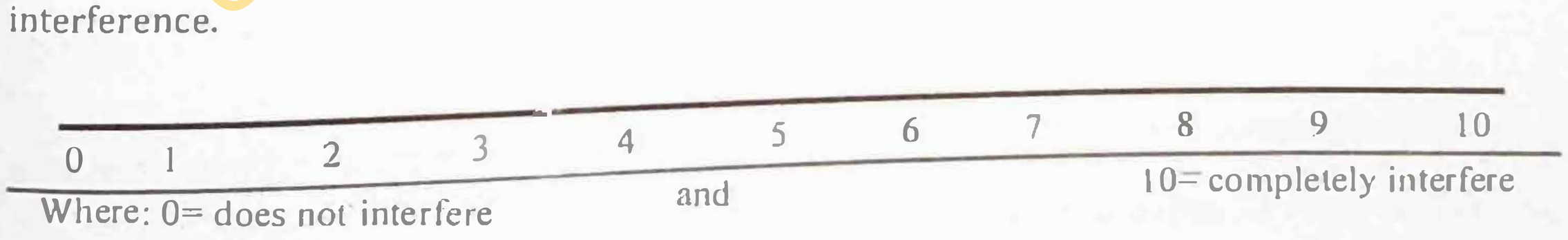


Figure 3.4: A Numerical Scale assessing effect of pain on essential activities

3.7.4. Section D (questions 29-30) of the questionnaire took a record of the laboratory findings and results from the blood samples taken from the subject's including: presence or absence of

parasitaemia, absolute parasite count, White Blood Cell (WBC) count, the calculated Parasite density (P_d) and the Packed Cell Volume (PCV).

3.8. Data Analysis:

The study variables assessed include demographic variable (age, sex, level of education, occupation, religion, nationality, ethnic origin and marital status), presenting symptoms, duration of onset, axillary temperature, presence of pain (its location, character, intensity, pattern, and effect on patient), as well as, the level of parasitaemia and packed cell volume. The key dependent (outcome) variables were having pain and having severe pain.

Data entry, cleaning, exploring and analysis were done with the aid of SPSS (Statistical Package for Social Sciences) version 17.0.

Descriptive statistics such as means ± standard deviations were used to summarize quantitative variables while qualitative variables were summarized with proportions. The χ^2 test was used to. investigate association between qualitative variables at 5% level of significance in bivariate analysis while, logistic regression models of covariates and factors was used to determine the risk of occurrence of pain and severe pain in the respondents. The Hosmer and Lemeshow test was used to determine goodness-of-fit of models of explanatory variables such that models with $p \geqslant 0.05$ were assumed to be good and fit well to the data.

3.11. Ethical Considerations.

This study was carried out according to the WMA (World Medical Association) declaration of Helsinki (1964) as modified in Seoul (2008).

Ethical approval was obtained from the University of Ibadan/University College Hospital Joint Ethical Review Board and also from The Research Ethic Review Committee at O. L. A. Catholic Mission Hospital. Copies of this letters are in the Appendix section of this work.

In addition to getting approval from the ethical boards, permission from the management of the various health facilities were obtained as well as individual informed verbal consent from each of

the patients. Inform consent information leaflet were made available to potential participants. Participants were fully informed of the study objectives, the purpose and procedure of data collection. Respondents were fully allowed to exercise their right to make a choice to participate in the study and their right to withdraw from the study at any time was upheld.

All data obtained were treated in absolute confidence and exclusively for this research purpose ONLY. No unique identifying information was obtained from the participants.

The laboratory investigations were done free of charge for the study subjects.

3.12. Conflict of Interest/Sponsorship.

The author hereby declares that there is no conflict of interest with respect to any aspect of this work and that this was essentially an academic research with no external funding. The investigator and his supervisors bore the direct and indirect cost of this work. Adhoc staffs used were properly remunerated according to pre-agreed terms. Contributions and support by other parties have been adequately documented in the acknowledgement section of this dissertation.

3.13. Limitations of the Study.

Language difference made translation to the local Yoruba language imperative but, that could not have been perfect especially, that pain is a highly subjective symptom.

The study participants were ill and this made getting their consent and data collection somewhat difficult.

The diagnosis of malaria in this study was clinical or presumptive and patients who had non-malaria febrile illnesses might have been included.

Some of the respondents may have used some medications (analgesics, antimalarial, antibiotics, etc.) prior to presentation. This could have affected their perception of pain, the course of the illness and the prevalence estimated.

Chapter Four

RESULTS

Seven hundred persons clinically diagnosed of acute uncomplicated malaria by independent physicians at the two study centres gave informed consent and were enrolled consecutively over a three month period for this study. However, 4.6% of their responses were unsuitable, resulting in six hundred and sixty-eight questionnaires that were analysed. Table 4.0 shows the return analysis.

The table below reflects the volume of malaria patient that visited the hospitals used as study centres. 499 (74.7%) respondents were enrolled at UCH alone. More cases of malaria sought medical care at the study centres in December (54.5%) compared to only 11.1% and 34.4% seen in October and November, respectively.

Table 4.0: Questionnaire Return Distribution by Completeness of Responses, Study Centre and Period of Data Collection

	FREQUENCY	PERCENTAGE (%)
(a.) COMPLETENESS OF RESPONSES (n=700)		
Returned fully completed	668	95.43
Returned partly completed	32	4.57
(b.) STUDY CENTRE (n=668)		
University College Hospital (UCH)	499	74.7
O. L. A. Catholic Hospital(Oluyoro)	169	25.3
(c.) PERIOD (Month) (n=668)		
October 2011	74	11.1
November 2011	230	34.4
December 2011	364	54.5

Table 4.1 below shows that the respondents were predominantly from the Yoruba ethnic group (81.6%), 583 (88.7%) were adults (12years or older), 66.6% were females, 58.2% were married, 35.9% were unemployed and 94.6% has had at least some primary education. The age of respondents followed the normal distribution and mean was 32.54 years (SD =16.13), range 6–81years (Median was 32 years).

Table 4.1: Socio-Demographic Distribution of Respondents

SOCIO-DEMOGRAPHIC CHARACTERISTIC	CATEGORY	FREQUENCY (N=668)	PERCENTAGE (%)
Age (years)	Children(<12years)	85	12.7
	Adult (≥12years)	583	87.3
Age Group (Years)	Less than 10	58	8.7
	10-19	83	12.4
	20-29	148	22.2
	30-39	175	26.2
	40-49	98	14.7
	50-59	60	9.0
	60 or more	46	6.9
Sex	Male	223	33.4
	Female	445	66.6
Nationality	Nigerians	665	99.6
	Non-Nigerians	3	0.4
Ethnic Origin of Nigerians	Yoruba	545	81.6
	Igbo	69	10.6
	Edo	18	2.7
	Hausa	10	1.5
	Delta-Urhobo	10	1.5
	Others	16	2.4
Highest education level	No Formal Education	36	5.4
	Primary	114	17.1
	Secondary	148	22.2
	Tertiary	370	55.4
Employment Status	Unemployed	240	35.9
	Self-employed	175	26.2
	Employee	253	37.9
Marital status	Single	268	40.1
	Married	389	58.2
	Others	11	1.6
Religion	Christians	501	75.0
	Muslims	167	25.0

Table 4.1 below shows that the respondents were predominantly from the Yoruba ethnic group (81.6%), 583 (88.7%) were adults (12years or older), 66.6% were females, 58.2% were married, 35.9% were unemployed and 94.6% has had at least some primary education. The age of respondents followed the normal distribution and mean was 32.54 years (SD =16.13), range 6–81years (Median was 32 years).

Table 4.1: Socio-Demographic Distribution of Respondents

SOCIO-DEMOGRAPHIC CHARACTERISTIC	CATEGORY	FREQUENCY (N=668)	PERCENTAGE (%)
Age (years)	Children(<12years)	85	12.7
	Adult (≥12years)	583	87.3
Age Group (Years)	Less than 10	58	8.7
	10-19	83	12.4
	20-29	148	22.2
	30-39	175	26.2
	40-49	98	14.7
	50-59	60	9.0
	60 or more	46	6.9
Sex	Male	223	33.4
	Female	445	66.6
Nationality	Nigerians	665	99.6
	Non-Nigerians	3	0.4
Ethnic Origin of Nigerians	Yoruba	545	81.6
	Igbo	69	10.6
	Edo	18	2.7
	Hausa	10	1.5
	Delta-Urhobo	10	1.5
	Others	16	2.4
Highest education level	No Formal Education	36	5.4
	Primary	114	17.1
	Secondary	148	22.2
	Tertiary	370	55.4
Employment Status	Unemployed	240	35.9
	Self-employed	175	26.2
	Employee	253	37.9
Marital status	Single	268	40.1
	Married	389	58.2
	Others	11	1.6
Religion	Christians	501	75.0
	Muslims	167	25.0

Table 4.2 shows that all the respondents presented with a history of fever and malaise to their physician. 348 (52.1%) of them were concerned about headache while, only 10.3% complained of abdominal pains.

Table 4.2: Distribution of Respondents by Presenting Complaints

COMPLAINT	CATEGORY	FREQUENCY (n=668)	PERCENTAGE (%)
History of Fever	Yes	668	100.0
Had Headache	Yes	348	52.1
Had General Body aches	Yes	179	26.8
Had Joint aches	Yes	76	11.4
Had Abdominal pains	Yes	69	10.3
Had Chest pains	Yes	18	2.7
Had Malaise	Yes	668	100.0
Had Chills	Yes	43	6.4
Had Rigors	Yes	2	0.3
Had Bitter taste	Yes	9	1.3
Had Poor appetite	Yes	15	2.2
Vomited	Yes	22	3.3
Feeling weak/fatigued	Yes	73	10.9
Had poor sleep	Yes	12	1.8

Table 4.3 shows that only 31 (10.9%) respondents were febrile at presentation, mean axillary temperature was 36.6°C (SD = 0.7°C) and only 51 (7.9%) had parasitaemia on thick film microscopy while, the proportion with PCV< 30% was 7.8%.

Table 4.3 Distribution of Respondents by Clinical Vital Signs and Laboratory Findings

VARIABLE	CATEGORY	FREQUENCY	%
Axillary temperature (°C) (n = 668)	**Afebrile (<37.5)**	595	89.1
	Low grade fever (37.5 – 37.9)	31	4.6
	High grade fever (≥38.0)	42	6.3
Parasitaemia seen in thick film (n = 652)	**Yes**	51	7.8
	No	601	90.0
Capillary PCV (%) n = 422	**Anaemic (<30)**	31	7.3
	Normal (≥30)	391	92.7

Table 4.4 shows that 304 (70.9%) respondents had used some antipyretics/analgesics before reporting to hospital and paracetamol was the drug used by 95.4% of those who used analgesics. Also, 150 (22.5%) respondents had started self-medication on antimalarials prior to presentation and 70% (105) of these used one of the Artemisinin-based combination Therapies (ACTs).

Table 4.4: Distribution of Respondents by Medications used before presentation

VARIABLE	CATEGORY	FREQUENCY	PERC. (%)
Used Analgesics /Antipyretics before presentation (n=429)	**Yes**	304	70.9
	No	125	29.1
Used Antimalarials before presentation (n = 668)	**Yes**	150	22.5
	No	518	77.5
Used ACTs as antimalarial (n = 668)	**Yes**	105	15.7
	No	563	84.3

Figure 4.1.(a) below shows the overall prevalence of malaria pain among the respondents. Further elaboration as seen in Figure 4.1.(b) and 4.1.(c) overleaf show that the prevalence of malaria pain varies with age (children and adults) and sex (males and females), respectively. More adults (73.8%) felt pain when compared to children (62.4%) in figure 4.1.(b) while more females felt pain when compared to males in figure 4.1.(c).

Figure 4.1.(a): Distribution of Respondents by Experience of Pain due to Malaria

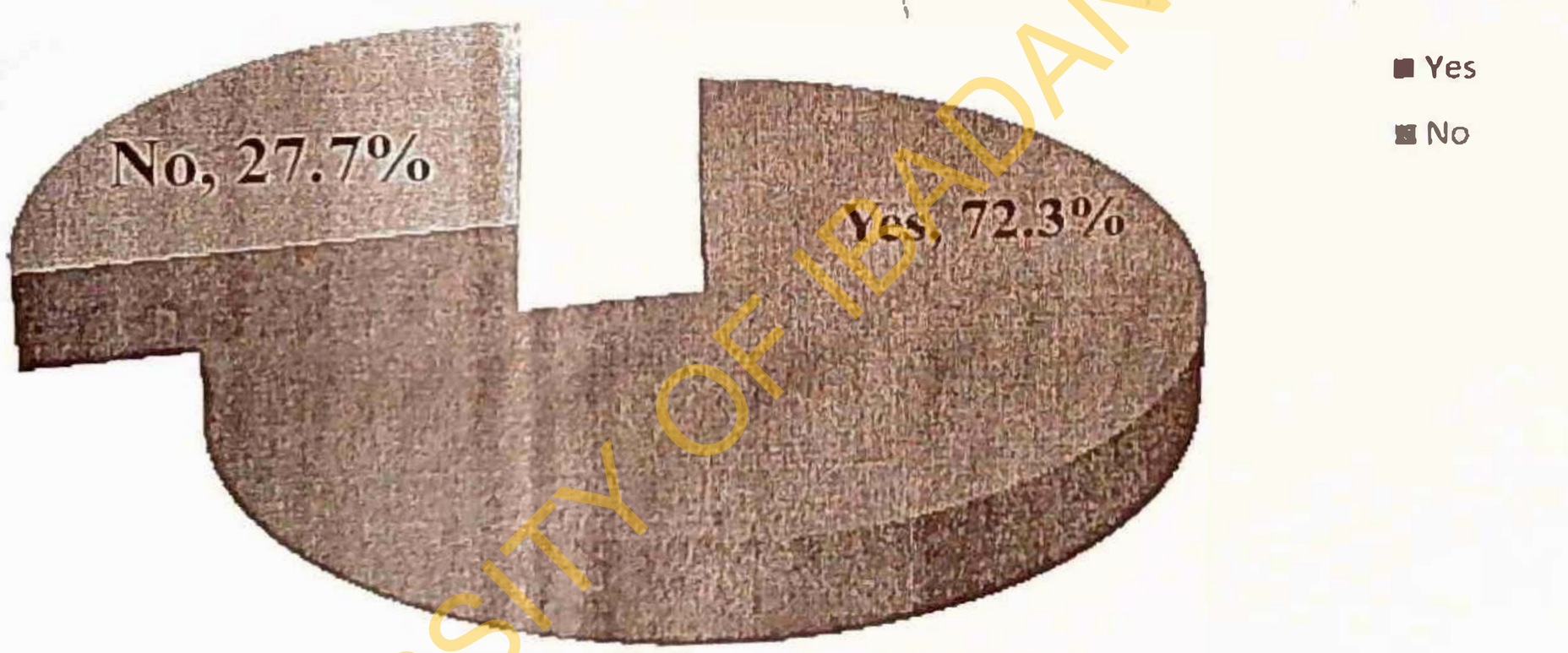
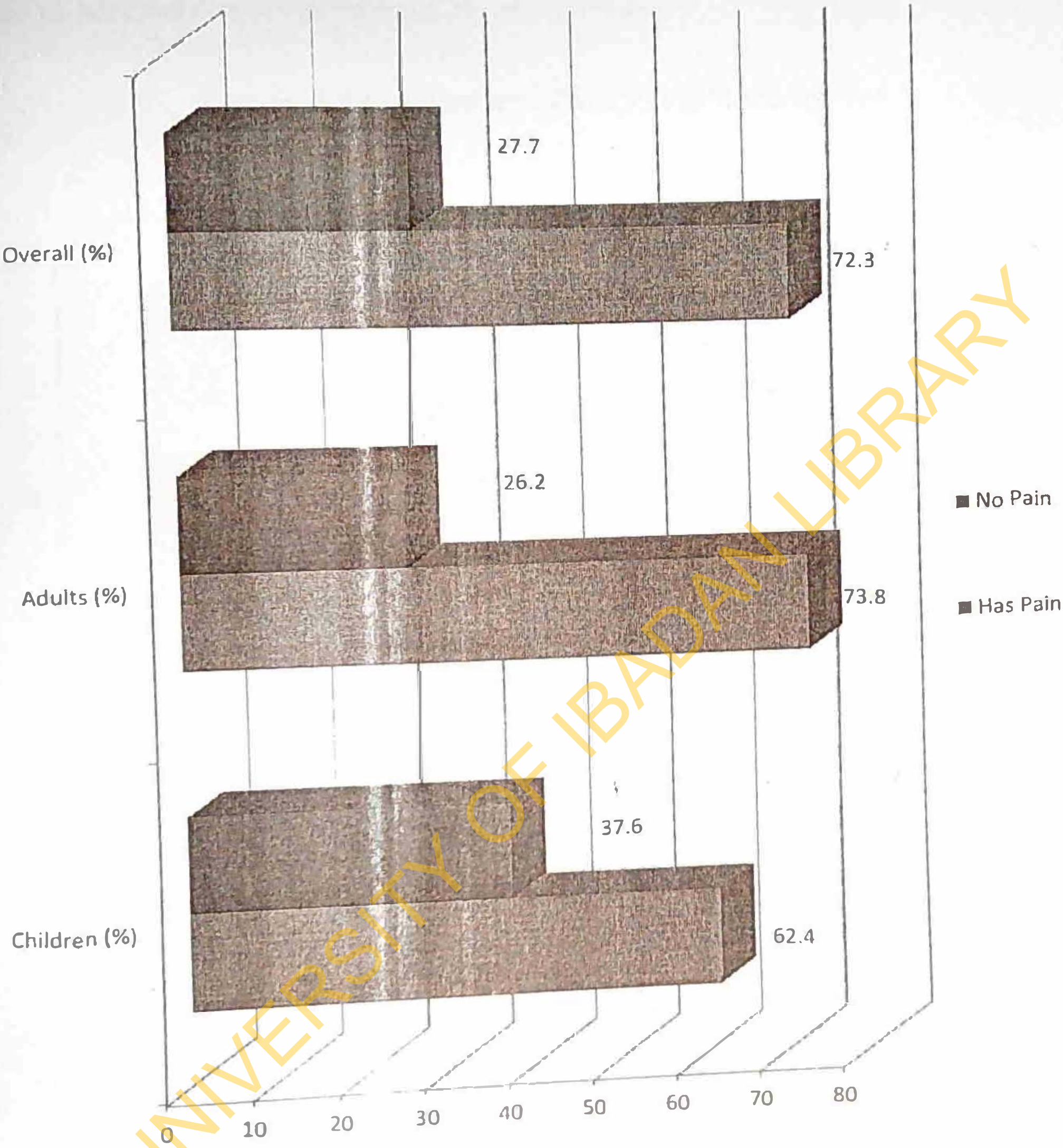


Figure 4.1.(b): Malaria Pain Prevalence by Age



When the data shown in figure 4.1.(c) below was further stratified by age, the sex variation remains such that: 65.1% of female children had pain compared to 59.5% of male children. Similarly, 77.1% of adult females had pain compared to 66.3% of adult males.

Figure 4.1.(c): Malaria Pain Prevalence by Sex

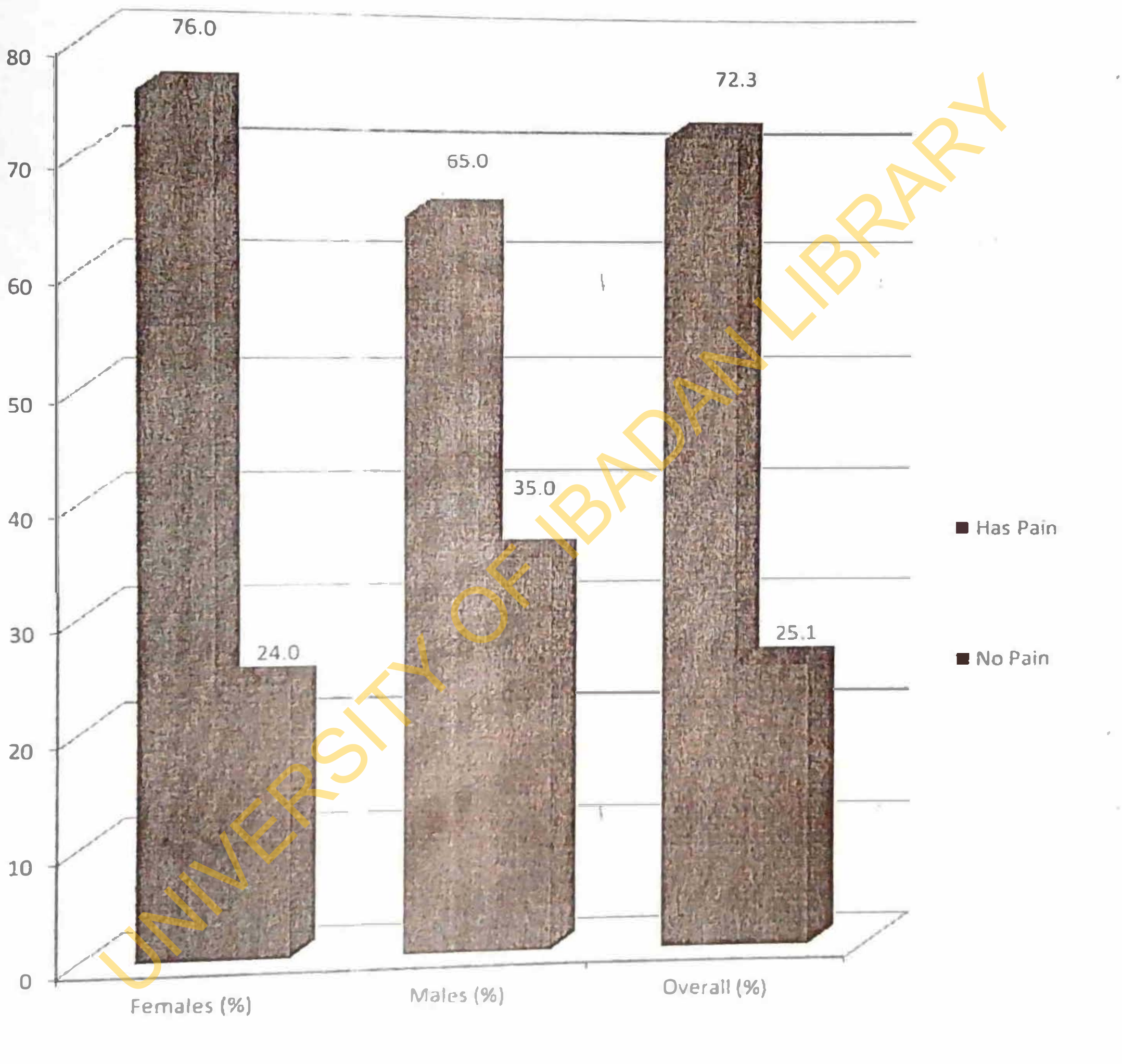


Table 4.5 shows that malaria pain as experienced by respondents is most commonly aching (91.7%) in character. The pattern of occurrence of malaria pain was assessed and 315 (70.5%) respondents said their pain occur intermittently (70.5%) while 132 (29.5%) said it was a continuous pain (n=447 for this variable).

Table 4.5: Character of Malaria Pain in Respondents

PAIN CHARACTER	FREQUENCY	PERCENTAGE (%)
Aching	443	91.7
Biting	12	2.5
Burning	5	1.0
Throbbing/Pounding	11	2.3
Sharp	2	0.4
Colicky	10	2.1
TOTAL	483	100.0

Table 4.5 shows that malaria pain as experienced by respondents is most commonly aching (91.7%) in character. The pattern of occurrence of malaria pain was assessed and 315 (70.5%) respondents said their pain occur intermittently (70.5%) while 132 (29.5%) said it was a continuous pain (n=447 for this variable).

Table 4.5: Character of Malaria Pain in Respondents

PAIN CHARACTER	FREQUENCY	PERCENTAGE (%)
Aching	443	91.7
Biting	12	2.5
Burning	5	1.0
Throbbing/Pounding	11	2.3
Sharp	2	0.4
Colicky	10	2.1
TOTAL	483	100.0

Table 4.6 shows that the head (72%), general muscular sites (37.1), joints (15.7) and abdomen (14.3%) are the most common sites of malaria pain in these respondents.

Table 4.6: Distribution of Respondents by Pain Location

BODY REGION	FREQUENCY(N=483)	PERCENTAGE (%)
Head	348	72.0
General Muscular	179	37.1
Joints	76	15.7
Abdomen	69	14.3
Lower Limb	39	8.1
Back	29	6.0
Upper Limb	20	4.1
Chest	18	3.7
Neck	12	2.5
Other Body Areas (genitals, etc.)	5	1.0

Figure 4.2 shows that malaria pain does not radiate to other body location in most respondents (87.2%).

Figure 4.2: Distribution of Respondents by whether Pain Radiate to other body parts (n=329)

As at when the respondents' pain was worst, most of the respondents described their malaria pain as discomforting, 311 (64.4%) and 113 (23.4%) said their malaria pain was mild while a few said it was horrible 4 (0.8%) or excruciating 1 (0.2%). Table 4.7 shows below this.

Table 4.7: Distribution of Respondents by Perceived Pain Intensity at Peak using the Verbal Rating Scale (VRS)

PAIN INTENSITY	FREQUENCY	PERCENTAGE (%)
Mild	113	23.4
Discomforting	311	64.4
Distressing	54	11.2
Horrible	4	0.8
Excruciating	1	0.2
TOTAL	483	100.0

Using the more objective NRS, table 4.8 overleaf shows that at presentation, most respondents (230) had moderate pain (47.6%), 189 (39.1%) had mild pain and 55 (11.4%) had severe pain.

At peak or when the malaria pain was worst, most respondents pain intensity (228) was moderate (47.2%), 138 (28.6%) had mild pain, 113 (23.4%) had severe pain and 4 (0.8%) had worst pain imaginable.

The table also show the levels of pain intensity that the respondents' would accept normally (a relative estimate of pain threshold). Most respondents would accept No pain, 237 (49.1%) while, moderate pain was acceptable to some, 26 (5.4%).

Table 4.8: Distribution of Respondents by Acceptable Level of Pain and Perceived Pain Intensity at Presentation and at Peak Using the Numeric Rating Scale (NRS)

	PAIN INTENSITY					
	NO PAIN	MILD PAIN	MODERATE PAIN	SEVERE PAIN	WORST PAIN IMAGINABLE	TOTAL
	Freq. (%)	Freq. (%)	Freq. (%)	Freq. (%)	Freq. (%)	Freq. (%)
AT PRESENTATION	**5 (1.0)**	**189 (39.1)**	**230 (47.6)**	**55 (11.4)**	**4 (0.8)**	**483 (100)**
AT PEAK	**0 (0.0)**	**138 (28.6)**	**228 (47.2)**	**113 (23.4)**	**4 (0.8)**	**483 (100)**
ACCEPTABLE LEVEL OF PAIN	**237 (49.1)**	**220 (45.5)**	**26 (5.4)**	**0 (0.0)**	**0 (0.0)**	**483 (100)**

Table 4.9 below shows that malaria pain was perceived by respondents to have affected their basic life activities in varying degree. 175 (36.2%) respondents with pain said it does interfere with their work or school while 21 (4.3%) said it completely interfered (meaning they were unable to do the activity at all). Malaria pain did not interfere with the mood of 173 (35.8%) respondents. However, malaria pain influenced the mood of respondents mildly 141 (29.2%), moderately 115 (23.8%), severely 47 (9.7%) and completely 7 (1.4%).

The pain interfered with 301 (60.2%) respondents' ability to ambulate in varying degree as shown but, 192 (39.8%) said their pain did not interfere with walking.

Also, 185 (38.3%) respondents had no interruption in the performance of routine house chores as against 283 (60.7%) that had interruption of house chores as a result of their malaria pain and this occurred in varying degree as shown on the table.

Likewise, the pain affected respondents' relation with people by varying degree but, 202 (41.8%) said it did not. On the same table, it is shown that most of the respondents 219 (45.3%) had their normal sleep despite the malaria pain experienced.

The table shows how malaria pain experienced by respondents affected their usual feeling of enjoyment of life as 273 (56.7%) respondents had interruption in their enjoyment of life; some mildly 135 (28.0%), others moderately 93 (19.3%), severely 38 (7.9%) and completely 7 (1.4%).

Table 4.9: Distribution of Respondents by Perceived Effect of Pain on selected Life Activities

LIFE ACTIVITIES	DOES NOT INTERFERE Freq. (%)	MILDLY INTERFERE Freq. (%)	MODERATELY INTERFERE Freq. (%)	SEVERELY INTERFERE Freq. (%)	COMPLETELY INTERFERE Freq. (%)	TOTAL Freq. (%)
School or work	175 (36.2)	122 (25.3)	103 (21.3)	62 (12.8)	21 (4.3)	483 (100)
Mood	173 (35.8)	141 (29.2)	115 (23.8)	47 (9.7)	7 (1.4)	483 (100)
Walking	192 (39.8)	149 (30.8)	97 (20.1)	41 (8.5)	4 (0.8)	483 (100)
House chores	185 (38.3)	143 (29.6)	113 (23.4)	36 (7.5)	6 (1.2)	483 (100)
Relation with people	202 (41.8)	160 (33.1)	93 (19.3)	23 (4.8)	5 (1.0)	483 (100)
Sleep	219 (45.3)	120 (24.8)	91 (18.8)	41 (8.5)	12 (2.5)	483 (100)
Enjoyment of life	210 (43.5)	135 (28.0)	93 (19.3)	38 (7.9)	7 (1.4)	483 (100)

Table 4.10 shows that only age (in two groups) and sex of respondents had statistically significant association with having pain during malaria illness. The differences seen with the bivariate analysis of other socio-demographic variables were not statistically significant at 95% confidence level.

Table 4.10: Association between having Malaria Pain and Socio-Demographic Characteristics of Respondents

SOCIO-DEMOGRA-PHIC CHARACT-ERISTIC	CATEGORY	HAD PAIN YES (n=483) Freq. (%)	HAD PAIN NO (n=185) Freq. (%)	χ^2	df	p-VALUE
Age (years)	Children	53 (11.0)	32 (17.3)	4.8	1	0.028
	Adult	430 (89.0)	153 (82.7)			
Sex	Male	145 (30.0)	78 (42.2)	8.9	1	0.003
	Female	338 (70.0)	107 (57.8)			
Ethnic Origin	Yoruba	397 (82.2)	148 (80.0)	0.43	1	0.513
	Others	86 (17.8)	37 (20.0)			
Highest education level	No Formal Edu.	29 (6.0)	7 (3.8)	3.1	3	0.383
	Primary	83 (17.2)	31 (16.8)			
	Secondary	100 (20.7)	48 925.9)			
	Tertiary	271 (56.1)	99 (53.5)			
Employment Status	Unemployed	168 (34.8)	72 (38.9)	3.2	2	0.199
	Self-employed	122 (25.3)	53 (28.6)			
	Employee	193 (40.0)	60 (32.4)			
Marital status	Single	186 (38.5)	82 (44.3)	2.5	2	0.284
	Married	290 (60.0)	99 (53.5)			
	Others	7 (1.5)	4 (2.2)			
Religion	Christians	367 (76.0)	134 (72.4)	0.9	1	0.343
	Muslims	116 (24.0)	51 (27.6)			

Table 4.11 shows that respondents' use of antimalarial or use of ACTs before presentation and their PCV status had statistically significant association with experiencing pain during malaria illness.

Table 4.11: Association between having Malaria Pain and Selected Variables

		HAD PAIN				
		YES	NO			p-
VARIABLE	CATEGORY	Freq. (%)	Freq. (%)	χ^2	df	VALUE
Axillary Temperature (n=483 had pain)	Afebrile	427 (88.4)	168 (90.8)	0.8	1	0.373
	Febrile	56 (11.6)	17 (9.2)			
Used Analgesics (n=351 had pain)	**Yes**	250 (71.2)	54 (69.2)	0.1	1	0.726
	No	101 (28.8)	24 (30.8)			
Used Antimalarial (n=483 had pain)	**Yes**	121 (25.1)	29 (15.7)	6.8	1	0.009
	No	362 (74.9)	156 (84.3)			
Used ACTs (n=483 had pain)	**Yes**	89 (18.4)	16 (8.6)	9.7	1	0.002
	No	394 (81.6)	169 (91.4)			
Had parasitaemia (n=472 had pain)	**Yes**	36 (7.6)	15 (8.3)	0.1	1	0.764
	No	436 (92.4)	165 (91.7)			
PCV <30% (n=320 had pain)	**Yes**	17 (5.3)	14 (13.7)	8.0	1	0.005
	No	303 (94.7)	88 (86.3)			

Table 4.11 shows that respondents' use of antimalarial or use of ACTs before presentation and their PCV status had statistically significant association with experiencing pain during malaria illness.

Table 4.11: Association between having Malaria Pain and Selected Variables

		HAD PAIN				
		YES	NO			p-
VARIABLE	CATEGORY	Freq. (%)	Freq. (%)	χ^2	df	VALUE
Axillary Temperature (n=483 had pain)	Afebrile	427 (88.4)	168 (90.8)	0.8	1	0.373
	Febrile	56 (11.6)	17 (9.2)			
Used Analgesics (n=351 had pain)	**Yes**	250 (71.2)	54 (69.2)	0.1	1	0.726
	No	101 (28.8)	24 (30.8)			
Used Antimalarial (n=483 had pain)	**Yes**	121 (25.1)	29 (15.7)	6.8	1	0.009
	No	362 (74.9)	156 (84.3)			
Used ACTs (n=483 had pain)	**Yes**	89 (18.4)	16 (8.6)	9.7	1	0.002
	No	394 (81.6)	169 (91.4)			
Had parasitaemia (n=472 had pain)	**Yes**	36 (7.6)	15 (8.3)	0.1	1	0.764
	No	436 (92.4)	165 (91.7)			
PCV <30% (n=320 had pain)	**Yes**	17 (5.3)	14 (13.7)	8.0	1	0.005
	No	303 (94.7)	88 (86.3)			

Variables that were found statistically associated with experiencing pain during malaria illness were pulled stepwise into a logistic regression model to determine the risk of experiencing pain due to malaria in the respondents. The outputs were as shown in table 4.12 and 4.13 below.

The Hosmer and Lemeshow goodness of fit test was significant (p=0.918) for model 1 and table 4.12 shows that children were 1.7 times more likely than adults; and males were 1.4 times more likely than females to experience malaria pain but, both findings were not statistically significant.

Table 4.12: Logistic Regression Model (1) of Demographic Factors that predict having Pain during Malaria Illness

EXPLANATORY VARIABLE	CATEGORY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL		
			LOWER	UPPER	p-VALUE
Age (years)	**Children**	1.65	0.91	3.01	0.10
	Adult (ref.)	1.00			
Sex	**Male**	1.43	0.90	2.29	0.13
	Female (ref.)	1.00			

When respondent's clinical characteristics were pulled into model 1, model 2 was formed as shown in table 4.13 below. Hosmer and Lemeshow model fit test was still significant (p=0.461) and the p-value of age and sex improved. From the table, respondents who did not use ACT prior to presentation were 5.4 times more likely than those who did to have malaria pain. Also, respondents with PCV <30% were 2.8 times more likely than those with PCV ≥30% to suffer pain during a bout of malaria. Both findings were statistically significant as shown.

In other words, model 1 and 2 shows that there is statistically significant evidence that being male or a child or having PCV < 30% or not using Artemisinin-based Combination Therapy (ACT) early increased respondent's risk of having malaria pain in the presence of all other associated factors.

Table 4.13: Logistic Regression Model (2) of Demographic and Clinical Factors that predict having Pain during Malaria Illness

EXPLANATORY VARIABLE	CATEGORY	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL		p-VALUE
			LOWER	UPPER	
Age (years)	**Children**	1.72	0.93	3.20	0.086
	Adult (ref.)	1.00			
Sex	**Male**	1.53	0.94	2.58	0.087
	Female (ref.)	1.00			
Used Antimalarial	**Yes**	1.71	0.77	3.82	0.190
	No (ref.)	1.00			
Used ACTs	**No**	5.40	1.71	16.88	0.004
	Yes (ref.)	1.00			
Anaemic?	**No**	0.36	0.17	0.78	0.009
	Yes (ref.)	1.00			

Table 4.14 below shows that no socio-demographic characteristic of respondent is significantly associated with their experience of severe malaria pain at the 5% level of significance.

Table 4.14: Association between having Severe Malaria Pain and Socio-Demographic Characteristics of Respondents

SOCIO-DEMOGRAPHIC CHARACTERISTIC	CATEGORY	HAD SEVERE PAIN YES (n=117) Freq. (%)	HAD SEVERE PAIN NO (n=366) Freq. (%)	χ^2	df	p-VALUE
Age (years)	Children	13 (11.1)	40 (10.9)	0.0		0.956
	Adult	104 (88.9)	326 (89.1)		1	
Sex	Male	38 (32.5)	107 (29.2)	0.4		0.505
	Female	79 (67.5)	259 (70.8)		1	
Ethnic Origin	Yoruba	97 (82.9)	300 (82.0)	0.43		0.817
	Others	20 (17.1)	66 (18.0)		1	
Highest education level	No Formal Edu.	8 (6.8)	21 (5.7)	4.3		0.232
	Primary	24 (20.5)	59 (16.1)			
	Secondary	29 (24.8)	71 (19.4)			
	Tertiary	56 (47.9)	215 (58.7)		3	
Employment Status	Unemployed	43 (36.8)	125 (34.2)	1.6		0.441
	Self-employed	33 (28.2)	89 (24.3)			
	Employee	41 (35.0)	152 (41.5)		2	
Marital status	Single	48 (41.0)	138 (37.7)	0.7		0.696
	Married	68 (58.1)	222 (60.7)			
	Others	1 (0.9)	6 (1.6)		2	
Religion	Christians	85 (76.2)	282 (77.0)	0.9		0.332
	Muslims	32 (27.4)	84 (23.0)		1	

Table 4.15 shows that no statistically significant association exist between any of the selected clinical parameters and respondents experience of severe pain at 5% level of significance.

Table 4.15: Association between having Severe Malaria Pain and Selected Clinical Parameters

VARIABLE	CATEGORY	HAD SEVRE PAIN				
		YES Freq. (%)	NO Freq. (%)	χ^2	df	p-VALUE
Axillary Temperature (n=117 had severe pain, 366 didn't)	Afebrile	100 (85.5)	327 (89.3)	1.3	1	0.255
	Febrile	17 (14.5)	39 (10.7)			
Used Analgesics (n=93 had severe pain, 258 didn't)	**Yes**	65 (69.9)	185 (71.7)	0.1	1	0.741
	No	28 (30.1)	73 (28.3)			
Used Antimalarial (n=117 had severe pain, 366 didn't)	**Yes**	32 (27.4)	89 (24.3)	0.4	1	0.510
	No	85 (72.6)	277 (75.7)			
Used ACTs (n=117 had severe pain)	**Yes**	21 (17.9)	68 (18.6)	0.0	1	0.878
	No	96 (82.1)	298 (81.4)			
Had parasitaemia (n=116 had severe pain, 366 didn't)	**Yes**	5 (4.3)	31 (8.7)	2.4	1	0.121
	No	111 (95.7)	325 (91.3)			
PCV <30% (n=78 had severe pain, 242 didn't)	**Yes**	3 (3.8)	14 (5.8)	0.4	1	0.507
	No	75 (96.2)	288 (94.2)			

Chapter Five

DISCUSSIONS

Questionnaires from all enrolled subjects were returned and that was likely due to the interviewer administration technique that was employed. Translation of key components of the questions into the local Yoruba language and the use of interviewers that could speak and interpret expressions in Yoruba improved the accuracy of responses. The few unsuitable responses observed could be explained by the subjective nature of pain under study, the easily irritable respondents involved because they were all acutely ill and the multi-ethnic distribution of the study population which influenced their interpretation of concepts.

The higher enrolment of respondent at the University College Hospital centre was proportionate to the higher volume of patients that visited the hospital relative to the other centre. Transmission of malaria was expected to decline in the study population with the onset of dry season but, it was observed in this study that more cases of malaria sought medical care at the study centres in December compared to October and November. This may be explained by workers' strike actions observed during the first two months of data collection among other factors.

Most of the respondents in this study were Nigerians of Yoruba extraction because they constitute the predominant and indigenous ethnic group in Ibadan city. Majority of the respondents (48.4%) were aged between 20 and 39 years and this group holds high economic and social value in any community; thereby, accentuating the impact of malaria on this endemic city. The fact that majority of the respondents were females can be explained by a socio-cultural trend that makes women more likely to seek medical care compared to males. Again, most of the respondents had at least primary education which may have informed their choice of hospital care as against traditional herbal alternatives that is more common with the un-educated population in this region.

One of the highlight of the result of this study is that while all the respondents had a history of fever, more than half of them had headache as one of their presenting complaints which goes a long

Chapter Five

DISCUSSIONS

Questionnaires from all enrolled subjects were returned and that was likely due to the interviewer administration technique that was employed. Translation of key components of the questions into the local Yoruba language and the use of interviewers that could speak and interpret expressions in Yoruba improved the accuracy of responses. The few unsuitable responses observed could be explained by the subjective nature of pain under study, the easily irritable respondents involved because they were all acutely ill and the multi-ethnic distribution of the study population which influenced their interpretation of concepts.

The higher enrolment of respondent at the University College Hospital centre was proportionate to the higher volume of patients that visited the hospital relative to the other centre. Transmission of malaria was expected to decline in the study population with the onset of dry season but, it was observed in this study that more cases of malaria sought medical care at the study centres in December compared to October and November. This may be explained by workers' strike actions observed during the first two months of data collection among other factors.

Most of the respondents in this study were Nigerians of Yoruba extraction because they constitute the predominant and indigenous ethnic group in Ibadan city. Majority of the respondents (48.4%) were aged between 20 and 39 years and this group holds high economic and social value in any community; thereby, accentuating the impact of malaria on this endemic city. The fact that majority of the respondents were females can be explained by a socio-cultural trend that makes women more likely to seek medical care compared to males. Again, most of the respondents had at least primary education which may have informed their choice of hospital care as against traditional herbal alternatives that is more common with the un-educated population in this region.

One of the highlight of the result of this study is that while all the respondents had a history of fever, more than half of them had headache as one of their presenting complaints which goes a long

way to underscore how the experience of pain was of concern to these respondents with malaria. This can explain why majority of the respondents had used some analgesics prior to presenting in hospital as self-medication. Paracetamol was the most commonly used drug by those who used analgesics because of the relatively fewer side-effect profile of this drug, its lower cost and easy availability over the counter compared to Ibuprofen and other NSAIDS that are known to have better antipyretic effect. This widespread self-medication with paracetamol can account for why most of the respondents had axillary temperature < 37.5 °C at presentation. Also, the finding that some of the respondents had started antimalarial medication prior to reporting in hospital and that most of these used one of the ACTs regimen can explain why very few showed parasitaemia on thick film microscopy.

The overall prevalence of pain due to acute uncomplicated malaria among the respondents was 72.3% despite analgesics abuse and home use of antimalarial medication before presentation implying that the actual prevalence of pain among un-treated malaria cases in the community could be much higher. The reasons why more adults had pain when compared with children requires further research. Though, we may postulate that adults have more socio-psychological factors that could potentiate their feeling of pains aside the fact that children were less likely to understand what pain really is as compared to adults. More females were found with malaria pain compared to males which may be explained by some differences in the pain tolerance threshold between the sexes. However, no statistically significant association existed between the presence of pain in the respondents and their being febrile at presentation or their having had some education or their occupation, religion, marital status or ethnic group at 5% level of significance.

When the prevalence of pain by sex was further stratified by age, the sex variation remains such that: more female children had pain compared to male children and more adult females had pain compared to adult males. These were statistically significant differences (p=0.003).

The character of malaria pain experienced by the respondents was most commonly aching and the pattern of occurrence of the pain was intermittent in most respondents. The head, non-specific

way to underscore how the experience of pain was of concern to these respondents with malaria. This can explain why majority of the respondents had used some analgesics prior to presenting in hospital as self-medication. Paracetamol was the most commonly used drug by those who used analgesics because of the relatively fewer side-effect profile of this drug, its lower cost and easy availability over the counter compared to Ibuprofen and other NSAIDS that are known to have better antipyretic effect. This widespread self-medication with paracetamol can account for why most of the respondents had axillary temperature < 37.5 ^{o}C at presentation. Also, the finding that some of the respondents had started antimalarial medication prior to reporting in hospital and that most of these used one of the ACTs regimen can explain why very few showed parasitaemia on thick film microscopy.

The overall prevalence of pain due to acute uncomplicated malaria among the respondents was 72.3% despite analgesics abuse and home use of antimalarial medication before presentation implying that the actual prevalence of pain among un-treated malaria cases in the community could be much higher. The reasons why more adults had pain when compared with children requires further research. Though, we may postulate that adults have more socio-psychological factors that could potentiate their feeling of pains aside the fact that children were less likely to understand what pain really is as compared to adults. More females were found with malaria pain compared to males which may be explained by some differences in the pain tolerance threshold between the sexes. However, no statistically significant association existed between the presence of pain in the respondents and their being febrile at presentation or their having had some education or their occupation, religion, marital status or ethnic group at 5% level of significance.

When the prevalence of pain by sex was further stratified by age, the sex variation remains such that: more female children had pain compared to male children and more adult females had pain compared to adult males. These were statistically significant differences (p=0.003).

The character of malaria pain experienced by the respondents was most commonly aching and the pattern of occurrence of the pain was intermittent in most respondents. The head, non-specific

general muscular sites, joints and abdomen were the most common sites of malaria pain in the respondents. When pain location was stratified for age, variations were observed for children and adults, respectively: more adults had head, joint and general muscular pains while, more children had abdominal pains. This is consistent with the prevalence of abdominal pain among hospitalised children in Pakistan as found in a study by Zaki (2010). The pathophysiological mechanisms of these findings require more research attention. Besides, malaria pain did not radiate to other body location in most respondents in this study. There was some difficulty with determining the specific site of pain radiation during data collection because most of the respondents had more than one site of pain at the same time. Hence, defining which pain radiate to another site was difficult.

When evaluated at peak and at presentation, most respondents found their malaria pain moderate in intensity irrespective of the pain rating scale used. On the verbal rating scale, this moderate pain was more commonly described as discomforting as against mild, moderate, horrible or excruciating. These findings may have been influenced by the fact that most of the respondents routinely use analgesics and had used some prior to presentation. Though, a few of them considered their malaria as severe, horrible, excruciating or worst pain imaginable. The level of pain intensity that respondents' would accept normally (a relative estimate of pain threshold) was assessed using the NRS and the result showed that most respondents would accept "No pain" but surprisingly, moderate pain was found acceptable to some.

The result of the assessment of the perceived effect of malaria pain experience on respondents' routine essential life activities support the knowledge that malaria inhibit individual productivity with enormous economic consequences resulting in slowed development of endemic societies. Malaria pain was perceived by respondents to mildly, moderately, severely and in some instances, to completely interfere with respondents' work or schpol activities, walking, mood, sleep, relation with people as well as general enjoyment of life by varying degree.

Bivariate analysis revealed that respondents' age, sex, use of ACTs as antimalarial medication and PCV level had statistically significant association with experiencing malaria pain at 5% level of

significance. When these variables associated with malaria pain were pulled block-wisely into a logistic regression analysis, it was evident that children were 1.7 times more likely than adults and males were 1.4 times more likely than females to experience malaria pain but, both findings were not statistically significant. As other clinical factors were pulled into the logistic analysis, respondents who did not use ACT prior to presentation were found to be 5.4 times more likely than those who did to have malaria pain. Also, respondents with PCV less than 30% were found to be 2.8 times more likely than those with PCV ≥30% to suffer pain during a bout of malaria. Both findings were statistically significant. These findings implied statistically significant evidence that being a child or male or having PCV<30% or not using Artemisinin-based Combination Therapy (ACT) early increased respondent's risk of developing malaria pain in the presence of other associated factors.

Finally, this study showed that a considerable number of respondents experienced severe pain as a result of their malaria illness but, none of the socio-demographic characteristic of respondents or their clinical parameters were found to be significantly associated with their experience of severe malaria pain at the 5% level of significance. Hence, no factors could be pulled into a logistic regression model that could determine the risk of developing severe pain during malaria illness in the respondents studied.

CONCLUSIONS

This study found a high prevalence of pain among outpatients who suffer from acute uncomplicated malaria and the characteristics of the pain varied significantly with age, sex and the packed cell volume of the patients as well as their early use of potent antimalarial medications.

Also, malaria pain was found to be severe enough to interfere with the essential life activities of respondents such that it may be exacerbating the impact of the disease on families and endemic communities since individual productivity will have been impaired.

These findings underscore the need to improve accurate evaluation and ensure adequate treatment of pain in the on-going efforts to control and eradicate the disease as a way to minimize the impact of the disease in endemic communities.

RECOMMENDATIONS

Achieving success with malaria control remain a priority target and critical challenge to African governments and global institutions. From the results of this study, the burden of the disease is strongly influenced by the pain experienced by the sufferers. I hereby make the following synoptic recommendations to the various stakeholders as thus:

Clinicians and health researchers

1. Should recognise, accurately evaluate and adequately treat the pain experienced by malaria patients.
2. Should begin to document and report the characteristics of the pain experienced by patients suffering from malaria and design studies to elucidate the many grey areas.

Individuals, families and communities

1. Individuals should recognize pain as a common symptom of malaria that must be reported to their health care provider promptly for effective care
2. Families and communities should improve their attention to malaria control measures in their environment and homes, knowing that the disease does not only cause fever, it does inflict pain that reduce gross family and community productivity.

Government, policy makers and donor agencies

1. Now more than ever, government at every level should improve funding for research in malaria pain that will spur more scientific approach to care
2. The malaria treatment policies of the National Malaria Control Programme should be reviewed to reflect pain as a critical component of malaria illness which must be adequately evaluated/measured to ascertain its intensity before treatment and should be given the same attention as the fever due to the disease.

REFERENCES

Adams, JH. (2008). Malaria. *Microsoft® Student 2008 [DVD]*. Redmond, WA: Microsoft Corporation, 1993-2007.

Adefioye, O., Adeyeba, OA., Hassan, W., & Oyeniran, O. (2007). Prevalence of Malaria Parasite Infection among Pregnant Women in Osogbo, Southwest, Nigeria. *American-Eurasian Journal of Scientific Research, 2*(1), 43-45.

Agnandji, ST., Lell, B., Soulanoudjingar, SS., Fernandes, JF., Abossolo, BP., & Conzelmann, C. (2011). First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children. *The New England Journal of Medicine, 365*(20), 1863-1875.

American Medical Association. (2010). Pathophysiology of Pain and Pain Assessment. *AMA CME Module 1: Pain Management*. Chicago.

Chapman, CR. (2001). The Psychophysiology of Pain. In J. D. Loeser, S. H. Butler, C. R. Chapman, & D. C. Turk, *Bonica's Management of Pain* (3 ed.). Washington: Lippincott Williams & Wilkins Publishers.

Chapman, CR., & Syrjala, KL. (2001). Measurement of Pain. In J. D. Loeser, S. H. Butler, C. R. Chapman, & D. C. Turk, *Bonica's Management of Pain* (3 ed.). Washington: Lippincott Williams & Wilkins Publishers.

Chapman, CR., & Turner, JA. (2001). Psychological Aspects of Pain. In J. D. Loeser, S. H. Butler, C. R. Chapman, & D. C. Turk, *Bonica's Management of Pain* (3 ed.). Washington: Lippincott Williams & Wilkins Publishers.

Cleeland, CS. (1991). Brief Pain Inventory (Short Form).

Coda, BA., & Bonica, JJ. (2001). General Considerations of Acute Pain. In J. D. Loeser, S. H. Butler, C. R. Chapman, & D. C. Turk, *Bonica's Management of Pain* (3 ed.). Washington: Lippincott Williams & Wilkins Publishers.

Dass, R., Barman, H., Duwarah, SG., & Deka, NM. (2010). Unusual presentations of malaria in children: an experience from a tertiary care centre in North East India. *Indian Journal of Pediatrics, 77*, 655-660.

Dickinson, JA. (1998). Symptom control in palliative care. *Australian Prescriber, 11*(4), 78-82.

Fehintola, F., & Balogun, S. (2010). Malaria: passive case detection and healthcare providers' choices of chemotherapy. *African Journal Medical Sciences, 39*(1), 49-54.

Gallup, JL., & Sachs, JD. (2000). The Economic Burden of Malaria. *CID Working Papers, Harvard University, 52*, pp. 1-24.

Gilles, HM. (2002). Pathology of Malaria. In D. A. Warrell, H. M. Gilles, D. A. Warrell, & H. M. Gilles (Eds.), *Essential Malariology* (4 ed.). London: Holder Arnold.

Goldschneider, KR., Mancuso, TJ., & Berde, CB. (2001). Pain and Its Management in Children. In J. D. Loeser, S. H. Butler, C. R. Chapman, & D. C. Turk, *Bonica's Management of Pain, 3rd edition (January 15, 2001)* (3 ed.). Washington: Lippincott Williams & Wilkins Publishers.

Good, MF., & Doolan, DL. (2010). Malaria Vaccine Design: Immunological Considerations. *Immunity, 33*, 555-566.

Gregson, AL., & Mackowiak, PA. (2004). Pathogenesis of Fever. In J. Cohen, W. G. Powderly, S. M. Opal, S. F. Berkley, T. Calandra, N. Clumeck, et al., *Infectious Disease* (2 ed., pp. 851-858). Edinburgh: Elsevier.

Guilbride, DL., Guilbride, PD., & Gawlinski, P. (2012). Malaria's deadly secret: a skin stage. *Trends in Parasitology, 28*(4), 142-150.

Gyapong, M., & Garshong, B. (2007). *Lessons learned in Home Management of Malaria: Implementation research in four African countries.* Geneva: WHO Special Programme for Research & Training in Tropical Diseases (TDR).

Jimoh, A., Sofola, O., Petu, A., & Okorosobo, T. (2007). Quantifyingthe economic burden of malaria in Nigeria using the willingness to pay approach. *BioMed Central online*.

Kakkilaya, BS. (2006). *History of Malaria Control.* Retrieved 06 07, 2012, from Malaria Site: all about malaria: http://www.malariasite.com/malaria/history_control.htm

Kleinschmidt, I., et al. (2001). Malaria Prevalence Model. *Tropical Medicine and International Health, 6*, 779-786.

Krause, PJ. (2008). Malaria (Plasmodium). In R. E. Behrman, R. M. Kliegman, H. B. Jenson, & F. B. Stanton, *Nelson Textbook of Paediatrics* (18 ed., pp. 1477-1485). Philadelphia: WB Saunders.

Kumar, P., & Clark, M. (2006). Infectious diseases;tropical medicine and sexually transmitted diseases: Protozoal Infections. In P. Kumar, & M. Clark, *Kumar and Clark Clinical Medicine* (6 ed., pp. 95-106). London: Elsevier.

Loeser, JD. (2001). Medical Evaluation of the Patient with Pain. In J. D. Loeser, S. H. Butler, C. R. Chapman, & D. C. Turk, *Bonica's Management of Pain* (3 ed.). Washington: Lippincott Williams & Wilkins Publishers.

Martín-Rabadá, P., & Bouza, E. (2004). Blood and Tissue Protozoa. In J. Cohen, W. G. Powderly, S. M. Opal, S. F. Berkley, T. Calandra, N. Clumeck, et al., *Infectious Disease* (2 ed., pp. 2443-2447). Edinburgh: Elsevier.

McAdam, AJ., & Sharpe, AH. (2005). Infectious Diseases. In V. Kumar, A. K. Abbas, & N. Fausto, *Robbins and Cotran Pathologic Basis of Diseases* (7 ed., pp. 403, 414, 439, 440). Philadelphia: Elsevier.

Melzack, R. (1975). The McGill Pain Questionnaire: Major properties and scoring methods. *Pain, 1*, 277-299.

Melzack, R. (2005). The McGill Pain Questionnaire: From Description to Measurement. (S. N. Raja, Ed.) *Anesthesiology, 103*(1), 199-202.

Microsoft® Encarta. (2008). *Encarta Dictionaries.* Redmond, WA: Microsoft Corporation, 1993-2007.

Miller, LH., Good, MF., & Milon, G. (1994). Malaria Pathogenesis. *Science, 264*, 1878-1883.

Newman, R. (2012). *WHO Malaria Policy Advisory Committee: Reports and Recommendations (Draft Version for the new Malaria Journal thematic series).* WHO Global Malaria Programme, Malaria Policy Advisory Committee. Geneva: WHO.

Newman, RD. (2011). Learning to outwit malaria. *Bulletin of the World Health Organization, 89*, 10-11. Geneva: WHO Press.

NMCP, Nigeria. (2012). *National Malaria Control Programme.* Retrieved June 07, 2012, from National Malaria Control Programme (NMCP): http://www.nmcpnigeria.org

NPC & ICF Macro. (2009). *Nigeria Demographic and Health Survey 2008.* Abuja: National Population Commission (NPC) and ICF Macro.

NPC, NMCP & ICF Macro. (2010). *Nigeria Malaria Indicator Survey.* Abuja: National Population Commission (NPC), National Malaria Control Programme (NMCP) and ICF Macro.

Okonko, IO., Donbraye-Emmanuel, OO., Donbraye, E., Abubakar, MJ., Fowotade, A., Fadeyi, A. (2010). Malaria parasitaemia among patients in Ibadan, Southwestern Nigeria. *Journal of Applied Biosciences, 29*, 1774-1780.

Park, K. (2009). Epidemiology of Communicable Diseases: Malaria. In K. Park, *Park's Textbook of Peventive and Social Medicine* (20 ed., pp. 222-232). Jabalpur: M/s Banarsidas Bhanot.

Pinault, LL., & Hunter, FF. (2012). Malaria in Highlands of Ecuador since 1900. *Emerging Infectious Diseases, 18*(4), 615-622.

Ringwald, P. (2012). *The status of drug-resistant malaria along the Thailand-Myanmar border.* Geneva: WHO Global Malaria Programme.

Shiff, C. (2006). Malaria Epidemiology. *Johns Hopkins University Bloomberg School of Public Health Lecture*. Maryland.

Smith, B. H., & Torrance, N. (2008). Epidemiology of Chronic pain. In H. J. McQuay, E. Kalso, & R. A. Moore, *Systematic Reviews in Pain Research: Methodology Refined* (pp. 247-273). Seattle: IASP Press.

Song, HH., O, S. O., Kim, SH., Moon, SH., Kim, JB., & Yoom, JW. (2003). Clinical features of Plasmodium vivax malaria. *Korean Journal of Internal Medicine, 18*, 220-224.

Stedman. (2001). *Stedman's Concise Medical Dictionary for the Health Professional* (4 ed.). Philadelphia: Lippincott, Williams & Wilkins.

Turk, DC., & Okifuji, A. (2001). Pain Terms and Taxonomies of Pain. In J. D. Loeser, S. H. Butler, C. R. Chapman, & D. C. Turk, *Bonica's Management of Pain* (3 ed.). Washington: Lippincott Williams & Wilkins Publishers.

University College Hospital. (2011). *General Out Patient*. Retrieved 12 24, 2011, from University College Hospital (UCH), Ibadan: http://www.uch-ibadan.org.ng/General_Out_Patients

Waters, A. (2006). Malaria: New Vaccines for Old? *Cell, 124*, 689-693.

Watkins, EA., Wollan, PC., Melton, LJ., & Yawn, BP. (2008). A population in pain: report from the Olmsted County health study. *Pain Medicine. 2008;9(2), 9*(2), 166-174.

WHO. (2000). *Management of Severe Malaria : A practical handbook*. Geneva: WHO Press.

WHO. (2006). Diagnosis of Malaria. In WHO, *Guidelines for the treatment of Malaria* (pp. 8-12). Geneva: WHO Press.

WHO. (2006). *Guidelines for the treatment of malaria.* Geneva: WHO Press.

Ringwald, P. (2012). *The status of drug-resistant malaria along the Thailand-Myanmar border.* Geneva: WHO Global Malaria Programme.

Shiff, C. (2006). Malaria Epidemiology. *Johns Hopkins University Bloomberg School of Public Health Lecture*. Maryland.

Smith, B. H., & Torrance, N. (2008). Epidemiology of Chronic pain. In H. J. McQuay, E. Kalso, & R. A. Moore, *Systematic Reviews in Pain Research: Methodology Refined* (pp. 247-273). Seattle: IASP Press.

Song, HH., O, S. O., Kim, SH., Moon, SH., Kim, JB., & Yoom, JW. (2003). Clinical features of Plasmodium vivax malaria. *Korean Journal of Internal Medicine, 18*, 220-224.

Stedman. (2001). *Stedman's Concise Medical Dictionary for the Health Professional* (4 ed.). Philadelphia: Lippincott, Williams & Wilkins.

Turk, DC., & Okifuji, A. (2001). Pain Terms and Taxonomies of Pain. In J. D. Loeser, S. H. Butler, C. R. Chapman, & D. C. Turk, *Bonica's Management of Pain* (3 ed.). Washington: Lippincott Williams & Wilkins Publishers.

University College Hospital. (2011). *General Out Patient*. Retrieved 12 24, 2011, from University College Hospital (UCH), Ibadan: http://www.uch-ibadan.org.ng/General_Out_Patients

Waters, A. (2006). Malaria: New Vaccines for Old? *Cell, 124*, 689-693.

Watkins, EA., Wollan, PC., Melton, LJ., & Yawn, BP. (2008). A population in pain: report from the Olmsted County health study. *Pain Medicine. 2008; 9(2), 9*(2), 166-174.

WHO. (2000). *Management of Severe Malaria : A practical handbook.* Geneva: WHO Press.

WHO. (2006). Diagnosis of Malaria. In WHO, *Guidelines for the treatment of Malaria* (pp. 8-12). Geneva: WHO Press.

WHO. (2006). *Guidelines for the treatment of malaria.* Geneva: WHO Press.

WHO. (2007). Malaria. *Fact Sheet No. 94*, 1-4. Geneva: WHO Media Centre.

WHO. (2011). *Nigeria: Health Profile*. Retrieved October 30, 2011, from http://www.who.int/gho

WHO. (2011). Health System Financing -The path to universal coverage. *World Health Report 2011*.

WHO AFRO & EMRO. (2004). *Malaria Control in Africa: Progress Report on Implementation of Plan of Action of the Abuja Declaration*. Division of Prevention and Control of Communicable Diseases. Harare: WHO AFRO.

WHO AFRO Malaria Programme. (2001). Combination Therapy for Uncomplicated Malaria in Africa? *Malaria, 4*(1), pp. 1-4.

WHO GHO. (2011). *Nigeria: Health Profile*. Retrieved October 30, 2011, from Global Health Observatory: http://www.who.int/gho

WHO GMP. (2010). *World Malaria Report 2010*. Geneva: WHO Press.

WHO GMP. (2011). *World Malaria Report 2011*. Geneva: WHO Press.

WHO GMP. (2012). *T3 -Scaling up diagnostic Testing, Treatment and Surveillance for Malaria*. Geneva: WHO Press.

WHO RBM. (2002). *Scaling-up insecticide-treated netting programmes in Africa: A Strategic Framework for Coordinated National Action*. Retrieved October 30, 2011, from Roll Back Malaria (RBM): www.rbm.who.int/

WHO TDR. (2004). *Scaling up Home-Based Management of Malaria: From Research to Implementation*. Geneva: WHO Press.

WHO TDR. (2011). *World Malaria Report Show Malaria Decreasing*. Retrieved April 15, 2012, from TDR: http://www.who.int/tdr/news/2011/world-malaria-report-2011/en/

Wikimapia. (2007). *Catholic Hospital, Oluyoro, Oke-Ofa, Ibadan, Oyo*. Retrieved 10 20, 2011, from Wikimapia: http://wikimapia.org/4295337/Catholic_Hospital_Oluyoro_Oke-Ofa

Wikipedia. (2011). *Antimalarial Drug*. Retrieved 10 20, 2011, from Wikipedia, the free encyclopedia: http://en.wikipedia.org/wiki/Antimalarial

Wikipedia. (2011). *Malaria*. Retrieved 08 26, 2011, from Wikipedia, the free encyclopedia: http://en.wikipedia.org/wiki/Malaria

Wikipedia. (2011). *Pain*. Retrieved December 22, 2011, from Wikipedia, the free encyclopedia: http://en.wikipedia.org/wiki/pain

Wikipedia. (2012). *Ibadan*. Retrieved June 25, 2012, from Wikipedia, the free encyclopedia: http://en.wikipedia.org/wiki/Ibadan

Zaki, SA. (2010). Abdominal Pain as a Presenting Feature in Malaria. *Sri Lanka Journal of Child Health, 39*, 158-159.

Appendixes

QUESTIONNAIRES

DEPARTMENT OF EPIDEMIOLOGY, MEDICAL STATISTICS AND ENVIRONMENTAL HEALTH, COLLEGE OF MEDICINE, UNIVERSITY OF IBADAN, NIGERIA

Pain in Malaria Questionnaire

Date: ...../...../..... ***S/C:*** .....

SECTION A (Socio-Demographic Data)

1. Age in years: _____ (as at the last birthday).
2. Sex: [ ] Male (1) [ ] Female (2)
3. Religion: [ ](1)Christianity [ ] (2)Islam; Others (3) _____
4. Nationality: [ ]Nigerian(1) [ ] Non-Nigerian(2)
5. Ethnic group(if Nigerian): Yoruba(1) Igbo(2) Hausa(3); Others(4):_____
6. Occupation? **(if a child {<12years}, Occupation of Father/Guardian)**

   [ ]Unemployed (0)

   [ ] Subsistence farmer/Petty trader (1)

   [ ] Junior Worker in civil service/other institution (2)

   [ ] Senior Worker in civil service/other institution (3)

   [ ] Business -Self-employed (4)

   [ ] Self-Employed –Artisans/barbers/carpenters/Technicians (5)

   [ ] Student (6) [ ] Retired Employee (7)
7. Highest level of education completed? **(if a child, then mother's/Guardian's)**

   [ ]No formal education (0)[ ] Primary School (1) [ ] Secondary (2)

   [ ] Diploma/NCE/Polytechnic/University or Higher (3)
8. Marital status: [ ] Single (0)[ ] Married (1)[ ] Separated/Divorced (2)

   [ ] Widowed (3) Others (Pls Specify-4) _____

SECTION B (Brief Medical History)

9. (a.) Presenting Complaints? (1)_____ (2)_____

   (3)_____ (4) _____

   (b.) Clinical Diagnosis/Impression: _____
10. Onset of Illness? (in days) _____
11. (a.) Temperature (in ^{0}C): _____

    (b.) Weight (in Kg.): _____

    (c.) Height (in metres): _____

12. Other Medical Conditions present: [ ] Sickle cell Disease (1)
    Others (2) Pls state: _____

13. Do you have pain? [ ] YES (1) [ ] NO (2)

NB: If NO pain, go to 26 & STOP THE INTERVIEW! Otherwise continue serially⇨

SECTION C (Assessment of Pain in Malaria)

14. If yes, what is the character/quality of this pain? (E.g. aching, biting, burning, colicky, etc.): _____

15. When did the pain start? (state in days): _____

16. Duration of pain from onset (estimate from question 15 above): _____

17. What is the pattern of the pain?
    (1) Continuous [ ] (2) Intermittent [ ]

18. Is onset of pain related to other symptoms? **(Pls, note respondent's presenting complain above)**

Before		After
[ ]	(a) Fever	[ ]
[ ]	(b) Headache	[ ]
[ ]	(c) Bitter taste	[ ]
[ ]	(d) Loss of appetite	[ ]
[ ]	(e) Fatigue	[ ]
[ ]	(f) Nausea	[ ]
[ ]	(g) Vomiting	[ ]

(h) Others (Specify): .....

19. Where is the pain now?(State location in the body): _____

20. Does the pain radiate to other part of the body? [ ] Yes (1) [ ] NO (2)

21. If yes to 20, site of radiation(state body location): _____

22. Rate the severity of your pain **AT PRESENT** by indicating along this line

0 1 2 3 4 5 6 7 8 9 10

Where: 0 end= No Pain and 10 end= Worst Pain Imaginable

23. Also indicate if your pain is:
    (0) Mild (1) Discomforting (2) Distressing (3) Horrible (4) Excruciating

24. Now, think about **WHEN THE PAIN IS MOST SEVERE** and indicate its severity on this line

0 1 2 3 4 5 6 7 8 9 10

Where: 0 end= No Pain and 10 end= Worst Pain Imaginable

25. What level of pain do find acceptable? Indicate the severity when pain is acceptable to you

0 1 2 3 4 5 6 7 8 9 10

Where: 0 end= No Pain and 10 end= Worst Pain Imaginable

26. What drugs/medications are you receiving now?

	DRUG THERAPY	PERCEIVED EFFECTIVENESS			
		Very effective(1)	Moderate(2)	Low(3)	Not at all(4)
a.	None (no drugs of any type)				
b.	Analgesics (list) 1. 2.				
c.	Herbs				
d.	Non Drug therapy (list) 1. 2.				
e.	Others (please, specify) 1. 2.				

27. How does your pain interfere with the following activities? **(use this scale 1–10)**

0 1 2 3 4 5 6 7 8 9 10

Where: 0= does not interfere and 10= completely interfere

ACTIVITY	Interference Score
a.) Occupational/School activity	
b.) Mood	
c.) Walking	
d.) Normal work within the house	
e.) Relations with other people	
f.) Sleep	
g.) Enjoyment of life	

28. What types of thought come to your mind as result of your pain? Please list:

_____

_____

SECTION D (Laboratory Results)

29. (a.) Malaria Parasite present?: [ ] YES (1) [ ] NO (2)

(b.) Malaria Parasite (MP Density on thick blood film): _____

30. Packed Cell Volume (Capillary PCV): _____

DEPARTMENT OF EPIDEMIOLOGY, MEDICAL STATISTICS AND ENVIRONMENTAL HEALTH, COLLEGE OF MEDICINE, UNIVERSITY OF IBADAN, NIGERIA

Pain in Malaria Questionnaire (YORUBA TRANSLATION)

Date: ...../...../..... *S/C:* .....

SECTION A (Socio-Demographic Data)

1. Kini ojo ori yin? :_____(as at the last birthday).
2. Sex: [ ] okunrin (1) [ ] Obirin(2)
3. Religion: [ ] (1)Christianity [ ] Islam (2); Others (3) _____
4. Nationality: [ ] Nigerian(1) [ ] Non-Nigerian(2) [ ]
5. Ethnic group(if Nigerian): Yoruba(1) Igbo(2), Hausa(3); Others(4):_____
6. **Ise wo ni e nse? (if a child, Occupation of Father/Guardian)**

   [ ] Unemployed (0) [ ] Agbe (1)

   [ ] Osise kekere ni ibise ijoba i (3) [ ] osise agba ni ibise ijoba

   [ ] Osise aladani (3) [ ] Oni sowo ni yin (4)

   [ ] Oni ise ada ni yi (5) [ ] Omo ile iwe (6)
7. Highest level of education completed? **(if a child, level of education of mother/Guardian)**

   [ ]No formal education (0) [ ] Primary School (1) [ ] Secondary (2)

   [ ] Diploma/NCE/Polytechnic/University or Higher (3)
8. Marital status: [ ] Apon (0) [ ] wa ni ile oko (1) [ ] eyin ati oko ko gbe po mo (2) [ ]lopo (3) Others (Pls Specify-4) _____

SECTION B (Brief Medical History)

9. Kini awon apere ti eri ki e to wa ri dokita loni? (1)_____ (2)_____ (3)_____ (4) _____ (5) _____
10. Igbawo ni aisan yi bere? (in days) _____
11. Ara gbigbo na (in OC): _____
12. kini awon aisan miran ti e tun ma gba itoju fun tabi ti o ma nse yin ?: ☐ Sickle cell Disease (1) Others (2) Pls state: _____
13. Nje e ni arariro lati igba ti aisan yi ti bere? ☐ Beeni (1) ☐ Beeko (2)

NB: If NO pain, STOP THE INTERVIEW HERE! If YES, go to section C ⇨.

SECTION C (Assessment of Pain in Malaria)

14. Ti e bani arariro, iru arariro wo? (fun apere: riro (aching), jijanije (biting), tita (peppery), luelue (dull) etc) _____

15. Ni igbawo ni arariro yi obere? (ojo) _____

16. Duration of pain from onset (estimate from question 16 above): _____

17. What is the pattern of the pain?

(2) O nwa ni igbagbogbo ☐ (2) Ekan kan ni o ma nwa ☐

18. Bawo ni igbati arariro yi bere se je si igba ti awon apere miran bere?

	Ki oto ebere	leyin ti obere
(a) Iba	☐	☐
(b) Ori fi fo	☐	☐
(c) Enu kikoro	☐	☐
(d) ai le jeun	☐	☐
(e) rire n	☐	☐
(f) gbigbe eyin lebi	☐	☐
(g) ebi	☐	☐

(h) Awon nkan mi (Specify): .....

19. Nibo ni ara yin ni oun ro yin? (fun apere: apa otun, ese osi ibo?): _____

20. Se arariro yi lo kakiri si ibomiran ni ara yin? ☐ beni (1) ☐ Beko (2)

21. Ti o baje be, nibo ni ara yin ni o lo? (state body location): _____

22. So bi arariro yi se po to ni lowo lowo bayi; fi ami si ori nomba ti o fi han bi arariro naa se po to?

0 1 2 3 4 5 6 7 8 9 10

Where: 0 end= No Pain and 10 end= Worst Pain Imaginable

23. Bawo ni iroro na seri: (0) o po die (1) O fun yin ni inira (2) O fun yin ni inira to po (3) inira ti ko da rara (4) inira ti o buru jai

24. Nibayi, ronu igbati irora yi buru julo, fi ami si ori nomba ti o fi han bi o se po to.

0 1 2 3 4 5 6 7 8 9 10

Where: 0 end= No Pain and 10 end= Worst Pain Imaginable

25. Fi nomba se apejuwe bi irora ti e le farada se po to. (Indicate the severity when pain is acceptable to you)

0 1 2 3 4 5 6 7 8 9 10

Where: 0 end= No Pain and 10 end= Worst Pain Imaginable

26. Iru ogun wo ni e ti lo?

	DRUG THERAPY	EFFECTIVENESS			
		Very effective	Moderate	Low	Not at all
0	None (no drugs of any type)				
1	(Ogun ararıro) (so oruko re) 1. 2.				
2	Agbo (herbs)				
3	Non Drug therapy (list) 1. 2.				
4	Omiran (please, specify) 1. 2.				

27. Bawo ni idiwo ti ararıro yi se fun yin lati se awon nkan wonyi se po to? **(Score with this scale of 1 – 10)**

0 1 2 3 4 5 6 7 8 9 10

Where: 0= does not interfere and 10= completely interfere

ACTIVITY	Interference Score
h.) Ise sise	
i.) Mood	_____
j.) Ati rin	_____
k.) Ise sise larin ile	_____
l.) Biba awon eyan se ere tabi se nkan po	_____
m.) Sisu Orun	_____
n.) Sise igbadun	_____

28. Iru ero wo lo ma wa si okan yin bi ararıro ba ti wa? Please list: _____

SECTION D (Laboratory Results)

29. Malaria Parasite (MP Density): (0) thick or thin blood film: _____

30. Packed Cell Volume (Capillary PCV): _____

INFORMED CONSENT FORM

DEPARTMENT OF EPIDEMIOLOGY, MEDICAL STATISTICS AND ENVIRONMENTAL HEALTH, COLLEGE OF MEDICINE, UNIVERSITY OF IBADAN, NIGERIA

Informed Consent Form

UI/UCH Ethics Committee Approval number: .....

Date of Approval Expiry: ...../...../.....

Title: AN ASSESSMENT OF THE PREVALENCE AND NATURE OF PAIN IN MALARIA

Investigators & Affiliations: This study is being conducted by Dr. IKEOLUWAPO O. AJAYI and Dr. ABRAHAM B. IDOKOKO of the *Department of Epidemiology, Medical Statistics and Environmental Health, The College of Medicine, University of Ibadan.*

Sponsors: This study is sponsored entirely by the researchers listed above

Purpose of Research: Malaria is a serious health problem in Nigeria as it causes a lot of illness and even death especially among children. Pain is a symptom of Malaria that is commonly experienced by most patients. It aggravates the illness and probably contributes most to the incapacitation experience by sufferers. However, this pain is often overlooked and not always documented by doctors/medical personnel. Analgesics are prescribed routinely as part of Malaria treatment without fully evaluating the pain. The adequacy of treatment provided for pain in Malaria and effectiveness of analgesics commonly prescribed is not known. Evaluation of the severity of pain is essential to monitor the effectiveness of treatment provided. No study has been reported in the literature on evaluation of pain in Malaria. This study is being conducted to determine the prevalence, pattern, character, site and severity of the pain in patients who have Malaria as well as the treatment modalities used, their effectiveness.

Procedure of Research: we enroll all persons six (6) years and above who present to this clinic with fever into this study. We are hereby asking you permission to allow enroll you or your child into this study.

You or your child will be asked basic demographic information at start. A finger prick to obtain about 1-2ml of blood for Malaria test and to find out about your packed cell volume and genotype will be done at no cost to you. If Malaria parasite is found in your blood we will then ask more information about your pain experience in this illness. Medications to treat Malaria will be given to you for free and you will be required to come tomorrow and the day after for us to evaluate how well the medications given to you are working and also to test the change in the level of Malaria parasite in your blood. All results of test done will be given to you.

This study to the best of our knowledge will not expose you or your child unnecessarily to any danger. However, you or your child may experience a slight pain from the needle prick which will go away in few minutes or at most in a few days.

All information obtained will be treated in all confidence and for this research purpose only. Your name and other personal identifier information will never be made public. Analyzed data without your identity variables will be used in scientific publications to improve the care and management of pain in people who have Malaria.

Taking part in this study is absolutely voluntary. You are free to withdraw your consent or that of your child at any time without any repercussion on you or the care of your child in this hospital. It is possible when this study is over, we may want to look again at the laboratory and medical record data collected during this study to help us answer other questions. If this happen, neither you nor your child's name or identity will be made public.

This research has been approved by the **University College Hospital Ethics Committee. The Chairman can be contacted at Biode Building, Room T10, 2nd floor, IMRAT, UCH, Ibadan. Tel: 08032397993; email: uiuchirc@yahoo.com. In case of emergency or more questions, please contact Dr. I. O. Ajayi at her office in the Department of Epidemiology and Medical Statistics, College of Medicine, University of Ibadan; Tel: 08023268431; Email: ikeajayi2003@yahoo.com.**

Statement of the person obtaining informed consent: I have fully explained this research to _____ and I have given sufficient information, including about risk and benefit to enable an informed decision.

Name: _____ Signature: _____ Date: _____

Statement of the person giving informed consent: I have read the above information or it has been read to me and I understand the content. I have asked all the necessary questions and satisfactory answers have been given to me.

I, _____of _____ hereby consent or give consent to have my child (name)_____ Study ID. No. _____to participate in this study. I understand I have the right to withdraw myself/child from the study at any time without it in any way affecting my medical care in this hospital.

Your Name: _____ Signature: _____ Date: _____

Witness Name: _____ Signature: _____ Date: _____

ETHICAL APPROVAL LETTER

INSTITUTE FOR ADVANCED MEDICAL RESEARCH AND TRAINING (IAMRAT)
COLLEGE OF MEDICINE, UNIVERSITY OF IBADAN. IBADAN, NIGERIA.
Director: Prof. A. Ogunniyi, B.Sc(Hons), MBChB, FMCP, FWACP, FRCP (Edin), FRCP (Lond)
Tel: 08023038583, 08038094173
E-mail: aogunniyi@comui.edu.ng

UI/UCH EC Registration Number: **NHREC/05/01/2008a**

NOTICE OF EXPEDITED REVIEW AND APPROVAL

Re: Pain in Malaria: An Assessment of the Prevalence and Character.

UI/UCH Ethics Committee assigned number: **UI/EC/11/0280**

Name of Principal Investigator:	**Prof. Olaitan A. Soyannwo**
Address of Principal Investigator:	Department of Anaesthesia, College of Medicine, University of Ibadan, Ibadan
Date of receipt of valid application:	23/11/2011

Date of meeting when final determination on ethical approval was made: N/A

This is to inform you that the research described in the submitted protocol, the consent forms, and other participant information materials have been reviewed and given *expedited approval by the UI/UCH Ethics Committee*

This approval dates from 29/11/2011 to 28/11/2012. If there is delay in starting the research, please inform the UI/UCH Ethics Committee so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. *All informed consent forms used in this study must carry the* UI/UCH EC *assigned number and duration of* UI/UCH EC *approval of the study.* It is expected that you submit your annual report as well as an annual request for the project renewal to the UI/UCH EC early in order to obtain renewal of your approval to avoid disruption of your research.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the UI/UCH EC. *No changes are permitted in the research without prior approval by the* UI/UCH EC *except in circumstances outlined in the Code. The* UI/UCH EC *reserves the right to conduct compliance visit to your research site without previous notification.*

UI/UCH EC
29 NOV 2011
APPROVED
COLLEGE OF MEDICINE

Prof. A. Ogunniyi
Director, IAMRAT
Chairman, UI/UCH Ethics Committee
E-mail: uiuchirc@yahoo.com

OLA CATHOLIC HOSPITAL

Oluyoro Oke-Ofa

P. O. Box 7044 Secretariat, Ibadan, Nigeria
Tel: 0803-7031735, 028729026
E-mail: oluyorocatholic@yahoo.com

Your Ref. No: _____ Our Ref. No: _____ Date: 7th December, 2011

Dear Dr. Ajayi,

ETHICAL APPROVAL

It is my pleasure to inform you that the hospital Ethics Committee has granted your request to interview patients and administer questionnaire for a study titled "PAIN IN MALARIA" as specified in your proposal.

The hospital however, considers seriously conducting researches within the standards of best practices and also requires you to submit to the committee a bound copy of the final study for hospital records.

Please feel free to contact the committee for any assistance you may require.

Wishing you the very best.

Yours sincerely,

J. Ayo Badejo
Secretary, Ethics Committee

OLA CATHOLIC HOSPITAL

Oluyoro Oke-Ofa

P. O. Box 7044 Secretariat, Ibadan, Nigeria

Tel: 0803-7031735, 028729028

E-mail: oluyorocatholic@yahoo.com

Your Ref. No. _____ Our Ref. No. _____ Date: 7th December, 2011

Dear Dr. Ajayi,

ETHICAL APPROVAL

It is my pleasure to inform you that the hospital Ethics Committee has granted your request to interview patients and administer questionnaire for a study titled "PAIN IN MALARIA" as specified in your proposal.

The hospital however, considers seriously conducting researches within the standards of best practices and also requires you to submit to the committee a bound copy of the final study for hospital records.

Please feel free to contact the committee for any assistance you may require.

Wishing you the very best.

Yours sincerely,

.....

J. Ayo Badejo
Secretary ,Ethics Committee