HOME MANAGEMENT OF UNCOMPLICATED CHILDHOOD MALARIA BY MOTHERS AND FATHERS IN LAGOS STATE, NIGERIA.

BY

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MATRICULATION NUMBER: 950703010

DEPARTMENT OF CLINICAL PHARMACY AND BIOPHARMACY,

UNIVERSITY OF LAGOS

NOVEMBER, 2014.

HOME MANAGEMENT OF UNCOMPLICATED CHILDHOOD MALARIA BY MOTHERS AND FATHERS IN LAGOS STATE, NIGERIA.

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IN

CLINICAL PHARMACY

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DECLARATION

This work titled "**Home Management of Uncomplicated Childhood Malaria by Mothers and Fathers in Lagos State"** submitted to the School of Postgraduate Studies, University of Lagos, Lagos, Nigeria for the award of the degree of Doctor of Philosophy is an original research carried out by **AILOJE, Kemi Oremeyi** in the Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, University of Lagos under the supervision of Prof. 'Fola Tayo, Dr (Mrs) Bolajoko A. Aina and Professor (Mrs) A.F. Fagbenro-Beyioku. This work has not been submitted previously, in part or whole, to qualify for any other academic award.

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DEDICATION

This work is dedicated to The Almighty God, my Help in ages past and my Hope for the future. The One Who makes all things beautiful in HIS time.

It is also dedicated to Under-5 children in Africa and other malaria endemic regions of the world and also to my wonderful parents especially my darling mother, an advocate of education, whose belief and confidence in her "little Professor" keeps me going with zeal and determination to succeed always against all odds.

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ABSTRACT

Malaria is a major public health disease. About 90% of all malaria deaths globally occur in Sub- Saharan Africa where Nigeria is located. Children are particularly susceptible resulting in high mortality. Mothers stay at home to care for children with malaria, thereby increasing absenteeism resulting in economic loss at the micro and macro levels.

World Health Organization (WHO) in an attempt to ensure prompt treatment of uncomplicated childhood malaria, introduced home management of malaria involving care givers.

The work was designed to study home management of uncomplicated childhood malaria by 485 mothers and 324 fathers in Lagos State, Nigeria using artemisinin combination therapy (ACT) drugs and to determine compliance with the National Treatment Guidelines for malaria.

Lagos State is situated in the south-west of Nigeria with 20 local government areas (LGAs). Four LGAs were randomly selected. A town was selected from each LGA. Each town was zoned into 4 (east, west, north and south). From each zone, 30 mothers and 30 fathers were randomly selected.

The instrument used for data collection was a structured questionnaire which was either self-administered or interviewer-administered (non-formal education respondents). Data were analysed statistically as means, standard deviation, standard error, Chi-Square test, Pearson analysis were done as appropriate and $P<0.05$ was accepted as the level of significance.

Majority of respondents (87%) were in the age range 18 – 40 years, and 93% had one or two children. Mothers and fathers had a good knowledge of home management of uncomplicated

childhood malaria (HMM). Irrespective of educational background, they commenced treatment between 0 and 7hrs after noticing the signs of malaria.

Majority of them used artemether-lumefantrine (an ACT) in compliance with the National Treatment Guidelines for malaria. Chloroquine, though withdrawn, was used by 22% of respondents, whilst artesunate-amodiaquine, the second official drug, was rarely used.

Educational background was a determinant of their knowledge of the cause and prevention of malaria. Fever ranked highest among the signs of malaria, followed by chills/rigors, vomiting, pallor, dehydration and body temperature in descending order. Majority (72%) of respondents always noticed improvement irrespective of gender and education. Unresolved cases (76%) were referred to a formal health facility. An average of 86% did not notice any of the signs of complicated malaria suggesting that they managed uncomplicated malaria. Fathers (83%) always practised HMM, while 12% did occasionally, 66% preferred paracetamol and/or antimalarial drugs, followed by tepid sponging and others. The rest were counselled as to the importance of referral. Drugs were mostly obtained from the pharmacy > doctors > primary health centre >> "chemist" > others. Factors determining access to drugs included cost, availability, brand, previous efficacy and packaging, were significantly influenced by the educational status.

In conclusion, mothers and fathers understood and practised HMM of uncomplicated childhood malaria in Lagos State, using ACTs in compliance with The National Treatment Guidelines for malaria, with referral in unresolved cases.

CHAPTER ONE

1.0 Introduction

1.1 Background of Study

Malaria is a major public health challenge in the tropics. It is estimated that about 400 to 900 million episodes of fever occur annually in African children. Over 50% is probably due to malaria, resulting in over one million deaths (Kidane and Morrow, 2000; FMoH, 2004). Prompt treatment with effective antimalarial therapy is essential. The Abuja Declaration of African Heads of States (2000) committed African leaders to ensure that 80% of malaria episodes are adequately treated within 24 hours of onset of symptoms by 2010 (WHO/TDR, 2003). It was soon realised that this laudable declaration of intent could be hindered by infrastructural inadequacy, limited resources, poor or lack of access to care as a result of travelling distance, inability to meet financial needs, human resource challenges, and inadequate or lack of essential medicines (Breman, 2001; Kager, 2002). The direct and especially indirect costs of seeking health care from formal facilities may be substantial, constituting a major barrier for many households (Breman, *et al*., 2004). For example, it is quite enormous in Nigeria where patients pay between 2 to 64 times the international reference prices for medicines in both the public and private sectors (FMoH, 2006; Tayo, 2013). Thus, febrile illnesses are commonly treated at home, frequently with drugs purchased from pharmacies, patent medicines vendors and quacks (Snow, *et al*., 2005).

The World Health Organization (WHO), in a bid to improve access to treatment, has introduced and promoted home-based management of malaria (HMM) as a major strategy for Africa. HMM strategy is based on treating febrile children presumptively with antimalarial drugs in their homes (Reyburn, *et al.,* 1999). Community distributors provide medications and educate primary caregivers about recognition of severe illness,

administration of drugs, and treatment. Emphasis on prompt treatment and distribution of pre-packaged antimalarial drugs are strengths of the HMM strategy (Moerman, *et al.*, 2003; WHO/RBM, 2005).

1.2 Statement of Problem

Infant and under five (U_{-5}) mortality rates (75 and 157 deaths per 1,000 live births respectively) in Nigeria are unacceptably high (Aigbe and Zannu, 2012). Malaria is responsible for up to 50% of these. Malaria attacks during the day and in the night. During the night healthcare facilities and/or givers are not available. Mothers are believed to be the first care givers in the home. Fathers are also parents and it is usually assumed that they do not take part in home management of their children's illness. This assumption is not evidence based. The potential role of home-based management of malaria dictates the need for an assessment of artemisinin combination therapy (ACT) and other antimalarial drugs. Preference by clients, source, access in HMM, and the issue of rational use of such drugs (to avoid development of resistance and toxicity), made it expedient to study the knowledge and practice of mothers and fathers as first line care givers in home management of uncomplicated childhood malaria. This study will contribute to the attainment of Millennium Development Goal (MDG) 4 in Lagos State. Most ethnic groups in Nigeria are represented in Lagos, giving the study a potential for a widespread view of home management of uncomplicated childhood malaria by mothers and fathers using ACTs as recommended by the National Treatment Guidelines for Malaria.

1.3 Aims and Objectives of the Study

The overall aim of this study was to determine the role of mothers and fathers in home management of uncomplicated childhood malaria using ACTs in compliance with the

National Treatment Guidelines for Malaria to prevent progression of uncomplicated to complicated malaria.

Specific Objectives were as follows:

1. To assess the baseline knowledge and practice of mothers and fathers in home management of uncomplicated childhood malaria in Lagos State.
2. To assess the use of antimalarial drugs and compliance with the National Treatment Guidelines for Malaria in HMM.
3. To identify the sources of antimalarial drugs used in HMM.
4. To determine factors influencing access to antimalarial drugs in HMM.
5. To identify the point of referral by mothers and fathers in unresolved cases.

1.4 Significance of Study

Malaria is a major public health challenge in Nigeria with a huge economic burden and inflicting a high childhood morbidity and mortality thereby decimating Nigeria's future labour force. Recognition of the signs of malaria, prompt treatment at home with effective antimalarial drugs and appropriate referral are the cornerstones of malaria control. HMM, with appropriate referral when necessary, is an effective intervention to prevent complicated malaria which leads to death. The use of ACTs in HMM has not been well documented in Nigeria. Choice, availability and access to antimalarial drugs are essential features of home management of malaria. In addition, involvement of fathers as care givers has not been documented before this time.

1.5 Operational Definition of Terms

Complicated malaria: **(Severe malaria is only caused by *P. falciparum*)**

Infection with *P. falciparum*, if not promptly treated, can quickly progress to severe malaria. The main symptoms of severe malaria include: coma, severe breathing

difficulties, low blood sugar, and low blood haemoglobin (severe anaemia). It is diagnosed on the basis of the presence *P. falciparum* parasites and one of the above symptoms with no other obvious cause. Children are particularly vulnerable since they have little or no immunity to the parasite. If untreated, severe malaria can lead to death.

Cerebral malaria (only caused by *P. falciparum*)

Malaria is classified as cerebral when it manifests with cerebral symptoms, such as coma.

The priority requirement is the early recognition of signs and symptoms of severe malaria that should lead to prompt emergency care of patient. The signs and symptoms that can be used are non-specific and may be due to any severe febrile disease, which may be severe malaria, other severe febrile disease or concomitant malaria.. The symptoms are a history of high fever, plus at least one of the following:-

- Prostration (inability to sit), altered consciousness, lethargy or coma
- Breathing difficulties
- Severe anaemia
- Generalized convulsions/fits
- Inability to drink/vomiting
- Dark and/or limited production of urine.

Uncomplicated malaria:

All symptoms and signs of uncomplicated malaria are non-specific, as shared with other febrile conditions, and can occur early or later in the course of the disease. In endemic areas, the presence of hepatosplenomegaly, thrombocytopenia and anaemia is clearly associated with malaria, particularly in children. Fever, cephalgias, fatigue, malaise, and musculoskeletal pain constitute the most frequent clinical features in malaria. Following single exposure to Plasmodium falciparum infection, the patient will either

die in the acute attack or survive with the development of some immunity. The non-fatal P. vivax and P. ovale cause similar initial illnesses, with bouts of fever relapsing periodically, but irregularly over a period of up to 5 years. Renal involvement of a moderate degree is more common in mild falciparum malaria than initially suspected. The liver is also afflicted in mild disease, but organ damage is limited and fully reversible after parasitological cure.

1.6 Abbreviations and Acronyms Used

A-A	Artesunate-Amodiaquine
ACT	Artemisinin Combination Therapy
A-L	Artemether-Lumefantrine
A-M	Artesunate-Mefloquine
A-P	Artesunate-Piperaquine
A-SP	Artesunate-Sulphadoxine-Pyrimethamine
CHW	Community Health Worker
CQ	Chloroquine
HMM	Home Management of (uncomplicated childhood) Malaria
IRS	Indoor Residual Spray
ITN	Insecticide Treated Net
LGA	Local Government Area
LSMoH	Lagos State Ministry of Health.

NTGM	National Treatment Guidelines for Malaria
PHC	Primary Health Care
PCM	Paracetamol
QUI	Quinine
RBM	Roll Back Malaria
UNICEF	United Nations Children's Fund
UNDP	United Nations Development Programme
W H O	World Health Organization

CHAPTER TWO

2.0 Literature Review

2.1 Malaria

The term malaria is used generically for diseases arising from the infection due to any of the following human parasites of the genus *Plasmodium* (*P. falciparum*, *P. vivax*, *P. malariae* and *P.ovale*). They are transmitted via a bite of a female mosquito of the genus *Anopheles.* Human malarias have no animal reservoir; only exceptionally, mainly as laboratory accidents, some plasmodia of monkeys have infected man, and only chimpanzees and a few South American monkeys can be infected with human parasites, to serve as laboratory animal models of the malaria infection (Najera and Hempel, 1996). Under natural conditions the infection is almost exclusively transmitted from man to man by the anophelese mosquito, in which the parasite has to undergo its sexual reproduction. Congenital transmission, although possible, is quite rare; antibodies traverse the placenta more readily than infected erythrocytes, so that congenital malaria disease is rarer than congenital infection and is more frequent when the mother has no immunity (Najera and Hempel, 1996). However.in endemic areas, infants inherit their mother's immunity, so that malaria seldom occurs during the first six months of life. Malaria parasites can also be transmitted from man to man by the inoculation of infected blood, either intentionally or accidentally through blood transfusion or sharing of injection needles; *e.g.* localized malaria outbreaks have been reported among drug addicts transmitted in this way (Simonsen *et al.*, 1999).

2.1.1. Life Cycle of Malaria Parasite

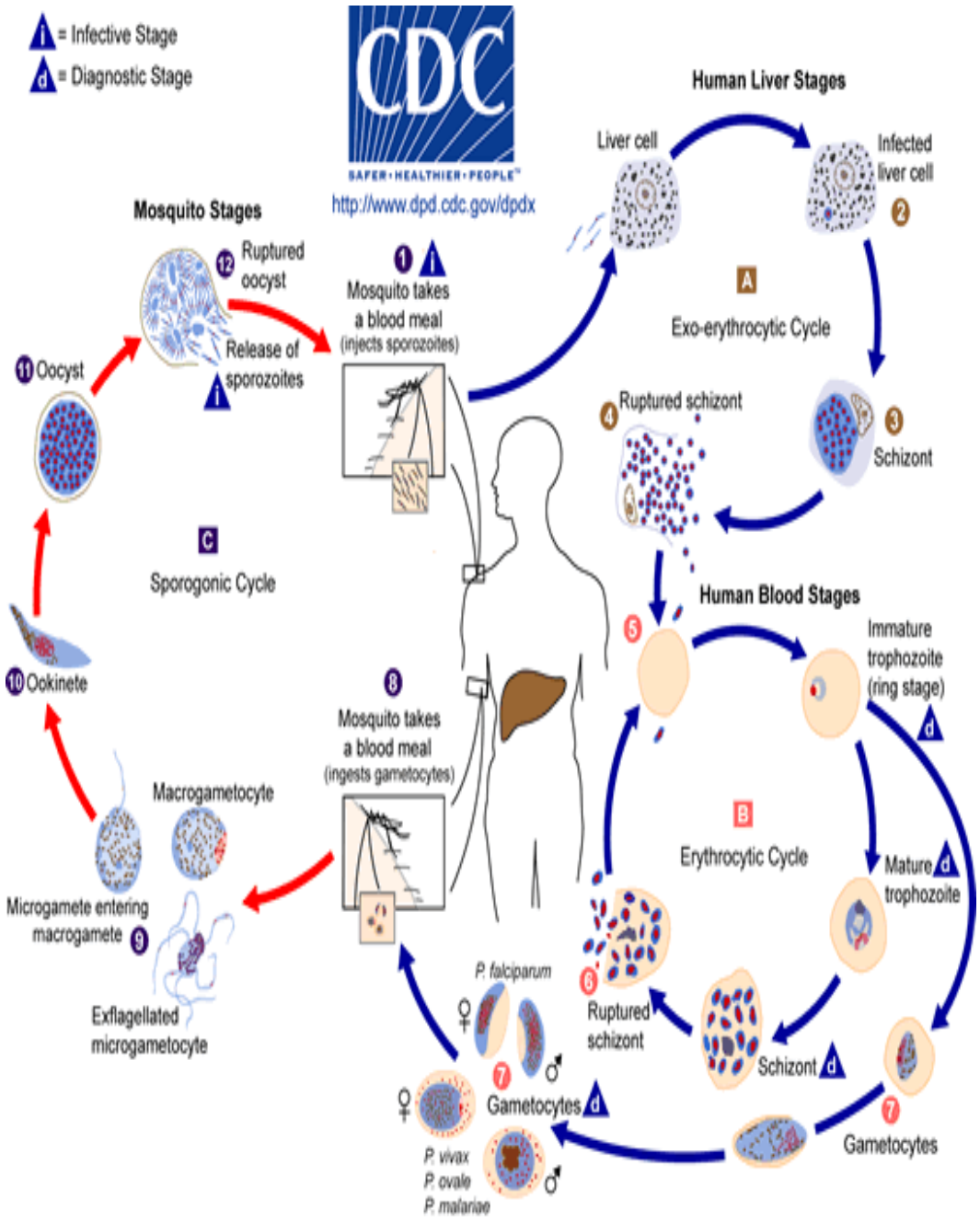

Fig. 2.1. Life cycle of malaria parasite showing the infective and diagnostic stages.

Source: Center for Disease Control (CDC).

The life cycle of malaria parasites passes through a sequence of three different types of reproduction (Fig. 2.1) : a) a single run of sexual reproduction, called the "sporogonic cycle", taking place in the *Anopheles* host; b) a single run of asexual reproduction, called the "exo-erythrocytic" or "pre-erythrocytic cycle", in a liver cell of the human host; and c) an indefinite number of runs of asexual reproduction, called the "erythrocytic cycle", in the red blood cells of the human host. During this erythrocytic cycle some parasites differentiate into male and female gametocytes which, if taken in with the blood meal of an *Anopheles*, will initiate the sporogonic cycle.

The sporogonic cycle takes between 9 and 30 days or longer depending on the parasite species. The duration of this cycle is even more dependent on the temperature. The gametocytes present in the blood meal mature in the stomach of the mosquito and, after fertilization, produce a motile egg that penetrates and encysts in the stomach wall, where it divides into about 1,000 motile sporozoites, which burst into the mosquito's body cavity and invade the salivary glands, where they are ready to infect a human host in each successive bite (Fig. 2.1).

Not all species of anophelines are vectors of malaria and, even among those that are vectors, there are great differences in their ability to transmit an infection. Mosquito refractoriness to malaria may be essential, due to the inability of the *Plasmodium* species to develop or to invade the salivary glands of a particular species or strain of *Anopheles*, or conditional to insufficient mosquito survival for the completion of the extrinsic cycle of the parasite, or to inadequate man/vector contact, *e. g*. low attraction of the anopheline to bite a human, so that, even if infected, the probability of biting again after completing parasite development becomes negligible. There are about 400 species of *Anopheles*, but only about 60 are vectors of malaria under natural conditions, some 30 of which being of major importance.

The habitat of the immature *Anopheles* is water. Eggs are laid on or on the edge of water and hatch in 2-3 days to produce larvae (wrigglers), which develop through four larval and one pupal aquatic stages to produce adult flying mosquitos. Only the female mosquito bites, as it requires blood for the maturation of the eggs; the male feeds on vegetable juices. Mating occurs soon after emergence of the adult female, it takes place only once, the female storing the spermatozoa in a deposit called spermatheca, from where they are released to fertilize successive egg batches. The aquatic stages commonly last between 7 and 20 days according to temperature, the adult female may live from a few days to well over a month, going through several cycles of blood feeds and egg laying (some 100-200 per batch), every 2-4 days; survival and egg development are mainly dependent on temperature and relative humidity; under extreme climatic conditions mosquitos may go into hibernation or estivation, which allows the survival of the species through the winter in temperate climates, or long dry seasons in tropical arid areas.

Seasonal variation in the availability of specific breeding places as well as the great influence of weather conditions on mosquito activity and survival are, to a large extent, responsible for the marked seasonality observed in mosquito densities and malaria transmission in most areas, outside of permanently humid tropical areas.

Mosquitos also show specific behavioural characteristics, which may affect their vectorial ability. Mosquitos preferences to feed on man or animals and their feeding frequency are very important determinants of the probability of their transmitting malaria. Human habitations or domestic animal shelters, particularly those with thatched roofs, abundant cracks in wall surfaces and dark corners, provide good and, for some species, preferred resting places for mosquitos to digest their blood meals and mature their eggs; as such, they favour mosquito survival. The use of indoor spraying of

residual insecticides for the eradication of malaria was based on the expectation that indoor resting was the most common behaviour of malaria vectors.

Sporozoites inoculated with the saliva of a biting mosquito into the blood of a susceptible human host reach within about half an hour a liver tissue cell, where each successful sporozoite will develop into a mature liver schizont, which will burst and liberate into the blood as many as 20,000 merozoites, small forms capable of invading red blood cells. The time needed to multiply in the liver varies with the parasite species: 6 to 12 days for *P. falciparum*, 14 to 30 days for *P. malariae*, 8 to 20 days for *P. vivax* and 12 to 20 for *P. ovale*, although some *P. vivax* and *P. ovale* parasites remain dormant in the liver for months, or even some years, in a form called hypnozoite, responsible for the true relapses, characteristic of the two latter species. *P. vivax* has adapted to areas of very short seasonal transmission (because of long winters or dry seasons) by developing patterns of long incubation or interrelapse periods, when hypnozoites assure the survival of the parasite.

Merozoites penetrate red blood cells initiating the erythrocytic cycle by maturing into blood schizonts which burst, producing between 8 to 24 (depending on the parasite species) new merozoites that rapidly invade red blood cells. This development is accomplished in 48 hours for the so-called tertian malarias (benign in the case of *P. vivax* and *P. ovale*; malignant in the case of *P. falciparum*) and 72 hours for the quartan malaria (*P. malariae*); *P. vivax* and *P. ovale* selectively invade young erythrocytes and *P. malariae* selects the old, while *P. falciparum* indiscriminately invades any. This is why the former three species are self-limiting while the latter may reach any density; parasitaemias over 5% should be considered as severe and exchange or partial exchange transfusion has been recommended, if it is possible to ensure pathogen free blood and to prevent transfusion related infections, in parasitaemias exceeding 10%. As the parasite

grows, the surface of *P. falciparum* infected erythrocytes becomes adhesive and they are sequestered in the capillaries of internal organs, such as the brain, producing the severe manifestations typical of this parasite; this is the reason why in the peripheral blood only very young forms and gametocytes of *P. falciparum* are found (presence of mature schizonts is a sign of severity), while all the developmental forms of the three other species are commonly found.

The disease manifestations are the result of the parasitization and destruction of the red blood cells, while the development of the parasite in the liver, or its persistence as hypnozoites, do not produce any symptoms. Initial symptoms of the disease are quite variable, particularly in children, and may include irregular fever, malaise, headaches, muscular pains, sweats, chills, nausea, vomiting, and diarrhoea. If untreated the fever acquires a tendency to periodic bouts alternating with days with less or no fever. The classical fever paroxysm, lasting 8-12 hours, goes through three typical stages: cold shivering rigor, hot with burning dry skin reaching high temperature (up to 40-42^{o}C) and sweating with drenching sweat and lowering temperature. It is more typical of *P. vivax* (tertian periodicity) and *P. malariae* (quartan) than *P. falciparum*, which shows prostrating fever, with brief and incomplete remissions of a tertian periodicity, but which can be quite irregular. The untreated acute attack of *P. falciparum* is shorter than that of *P. vivax*; in fatal cases death often happens in 2-3 weeks, although in some cases it may occur as early as 2-3 days after onset of symptoms. Repeated infections give rise to the immune response of the host, which eventually controls the disease and the infection. Common antimalarial drugs are effective against the parasites developing in the blood, but not against hypnozoites in the liver, so that while *P. falciparum* and *P. malariae* could be fully cured, *P. vivax* and *P. ovale* may produce true relapses by new invasion of the blood from latent

hypnozoites, even after complete clearance of parasites from the blood. The elimination of hypnozoites requires a long treatment (14 days or more) with primaquine or related drugs. In any case, untreated or incompletely treated infections will produce several recrudescence, after more or less long symptomless periods, from parasites surviving in the blood.

Acute severity and mortality, in the absence of other complicating factors, occurs almost exclusively in *P. falciparum* infections. Besides its rapid multiplication and therefore its capacity for massive destruction of erythrocytes, this parasite causes the surface of infected red blood cells to become adhesive and to be sequestered in the capillaries of internal organs, hampering blood flow and leading to local hypoxia and damage of the vascular endothelium. The main forms of severe malaria are: cerebral, hepatic, renal, pulmonary oedema, gastrointestinal, severe anaemia and haemoglobinuria or blackwater fever (Gilles, 1991).

P. falciparum malaria can proceed very rapidly to extreme severity and death. It is very important, therefore, that there is very early recognition of signs of severity which should require immediate referral for medical care; such signs include impairment of consciousness, anaemia, renal failure, respiratory distress, shock, spontaneous bleeding, convulsions, macroscopic haemoglobinuria, jaundice and hyperpyrexia. Health services and workers should treat suspected severe malaria as a medical emergency, instituting immediate treatment; whenever possible, patients should be immediately transferred to services capable of intensive care and laboratory monitoring of signs of severity, such as parasite density, hypoglycaemia, fluid and electrolyte imbalance (Warrell *et al.*, 1990; Gilles, 1991).

The risk of malaria severity and death is almost exclusively limited to non-immunes, being most serious for young children over six months of age, when they have lost the

immunity transferred from their mothers, in highly endemic areas in Africa and the Western Pacific; in rural areas, surviving children develop their own immunity between the age of 3-5 years. It has been reported by African health authorities that in the last few years, cerebral malaria is being seen with increasing frequency in older children and even in young adults; it has been suggested that this may be the result of increasing urbanization and use of antimalarial drugs and personal protection, which would reduce infection risk and delay development of immunity, compounded with increasingly ineffective treatment of disease, due to drug resistance and the proliferation of fake and counterfeit drugs (Elesha *et al.,* 1993). The decline in prevalence of parasitaemia in some urban areas of Africa has been illustrated at the University College Hospital of Ibadan (Nigeria) from 70% of outpatient children in 1960 to <30% in 1968 (Hendrickse, 1976).

Severity in adults is seen in areas of low endemicity, where people may reach adult age without immunity. During epidemics all age groups are affected; equally at risk are immigrants and travellers from non-endemic into endemic areas, particularly labourers, who are often concentrating in camps, where non-immunes and infected live in overcrowded conditions with high risk of transmission. Severe malaria in adult local populations has, therefore, had a rather focal distribution, mainly in South-East Asia, the Amazon and Orinoco basins in South America and some areas of East Africa (Elamin, 1981).

Also at risk are pregnant women, possibly due to the natural immune depression in pregnancy. During pregnancy, *P. falciparum* malaria in the non- immune may lead to death, abortion, prematurity or low birth weight; in the semi-immune inhabitants of highly endemic areas malaria represents a serious risk in the first and second pregnancy as they are more frequently infected, and are susceptible to anaemia, hypoglycaemia

and other complications. The placenta being a preferential site for parasite development, malaria is an important cause of low birth weight and high neonatal mortality in first and second born in endemic areas.

Cerebral malaria is the most common complication and cause of death in *P. falciparum* infections, and could represent as much as 50% of all cases of falciparum malaria admitted to hospital and 80% of fatal malaria cases. Case fatality of cerebral malaria is always high, even in hospital (10-40%), depending on a complex of factors not clearly understood, hypoglycaemia being a common complication of bad prognosis. Recovery from cerebral malaria is often complete, but some survivors retain a wide range of neurological sequelae, such as cortical blindness, hemipareses, extrapyramidal syndromes and severe mental impairment (Brewster *et al.*, 1990). While cerebral malaria is the most frequent serious manifestation, there are clinical differences in severe malaria between African children and South East Asian adults, which include the higher frequency of profound anaemia, hypoglycaemia and frequency of neurological sequelae (>10%) in the former, and the higher frequency of jaundice, pulmonary oedema and renal failure among the latter, who have lesser neurological sequelae (< 5%) (Warrell, 1992).

Severe anaemia is the second most important complication which, in some parts of Africa, may be even more common than cerebral malaria and it may also be a serious complication in pregnancy, particularly in primigravidae after the first trimester; it depends, to a large extent, on the severity and duration of parasitaemia and may predispose to secondary bacterial infection and puerperal sepsis. The relative importance of severe anaemia varies considerably from place to place, being highest in areas of year-round high transmission. A recent study in two large hospitals in Malawi, one serving an area with perennial high transmission and the other an area with marked

seasonal fluctuations, indicated that malaria associated severe anaemia was 8.5% of all paediatric admissions and accounted for 54% of malaria related deaths in the former, and 5.2% and 32% respectively in the latter, while the proportion of deaths due to malaria was rather similar in both places – 17.5% and 20.4% respectively – and in both places malaria associated severe anaemia peaked at the age group 6-11 months (Slutsker *et al.*, 1994).

In the highly endemic areas of tropical Africa, where the risk of death is practically limited to children between 6 months and 5 years of age, both sickness and death appear as highly seasonal, peaking at the end of the rainy season or seasons. There is a striking difference in the age at which the two main fatal syndromes occur; while severe malaria anaemia occurs at an early age, between 22 and 27 months, cerebral malaria occurs in children who are between 40 and 45 months old and may already be semi-immune (Marsh, 1992).

Severe disease and fatal outcome may also be the result of rupture of the spleen in *P. vivax* infections and of quartan malaria nephrosis in *P. malariae*, in which it is possible to detect depositions of antibody complexes on the basement membrane of the glomeruli; in highly malarious areas, new cases of nephrotic syndrome may represent about 2% of hospital admissions (Kibukamusoke, 1973).

Circulating malaria parasites can be eliminated from the blood with effective specific drugs, called schizontocides, which include quinine, chloroquine, amodiaquine, sulphadoxine-pyrimethamine, mefloquine, halofantrine, artemisinin, artemether and artesunate. At appropriate doses they completely cure a malaria disease episode with a short treatment (between a single dose of sulphadoxine-pyrimethamine to ten days of quinine), unless the *Plasmodium* is resistant to the given drug. None of these drugs will

destroy hypnozoites of *P. vivax* or *P. ovale* in the liver, for which other drugs like primaquine and longer treatments of 14 days or more are needed.

2.2. Antimalarial Drugs.

Also known as antimalarial, are designed to prevent or cure malaria. Such drugs may be used for some or all of the following:

- Treatment of malaria in individuals with suspected or confirmed infection
- Prevention of infection in individuals visiting a malaria-endemic region who have no immunity (malaria prophylaxis)
- Routine intermittent treatment of certain groups in endemic regions (intermittent preventive therapy).

Some antimalarial agents, particularly chloroquine and hydroxychloroquine, are also used in the treatment of rheumatoid arthritis and lupus-associated arthritis.

Current practice in treating cases of malaria is based on the concept of combination therapy, since this offers several advantages, including reduced risk of treatment failure, reduced risk of developing resistance, enhanced convenience, and reduced side-effects. Prompt parasitological confirmation by microscopy, or alternatively by rapid diagnostic tests, is recommended in all patients suspected of malaria before treatment is started (WHO, 2010).

Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible (WHO2010).It is practical to consider antimalarial by chemical structure since this is associated with important properties of each drug, such as mechanism of action.

2.2.1. Quinine And Related Agents

Quinine has a long history stretching from Peru, and the discovery of the cinchona tree, and the potential uses of its bark, to the current day and a collection of derivatives that are still frequently used in the prevention and treatment of malaria. Quinine is an alkaloid acting as a blood schizonticide and weak gametocide against *Plasmodium vivax* and *Plasmodium malariae*. As an alkaloid, it is accumulated in the food vacuoles of Plasmodium species, especially *Plasmodium falciparum*. It acts by inhibiting the hemozoin biocrystallization, thus facilitating an aggregation of cytotoxic heme. Quinine is less effective and more toxic as a blood schizonticidal agent than chloroquine; however, it is still very effective and widely used in the treatment of acute cases of severe *P. falciparum*. It is especially useful in areas where there is known to be a high level of resistance to chloroquine, mefloquine, and combinations with pyrimethamine. Quinine is also used in post-exposure treatment of individuals returning from an area where malaria is endemic.

The treatment regimen of quinine is complex and is determined largely by the parasite's level of resistance and the reason for drug therapy (i.e. acute treatment or prophylaxis). The World Health Organization recommendation for quinine is 20 mg/kg *stat* dose and 10 mg/kg 8 hours for 5 days where parasites are sensitive to quinine, combined with doxycycline, tetracycline or clindamycin. Doses can be given by oral, intravenous or intramuscular routes. The recommended method depends on the urgency of treatment and the available resources (i.e. sterilised needles for intravenous or intramuscular injections).

Use of quinine is characterised by a frequently experienced syndrome called cinchonism. Among the side effects of quinine are tinnitus (a hearing impairment), rashes, vertigo, nausea, vomiting and abdominal pain. Neurological

effects are experienced in some cases due to the drug's neurotoxic properties. These actions are mediated through the interactions of quinine causing a decrease in the excitability of the motor neuron end plates. This often results in functional impairment of the eighth cranial nerve, resulting in confusion, delirium and coma (Tracy & Webster, 2001). Quinine can cause hypoglycaemia through its action of stimulating insulin secretion; this occurs in therapeutic doses and therefore it is advised that glucose levels are monitored in all patients every 4–6 hours. This effect can be exaggerated in pregnancy and therefore additional care in administering and monitoring the dosage is essential. Repeated or over-dosage can result in renal failure and death through depression of the respiratory system.

Quinimax and quinidine are the two most commonly used alkaloids related to quinine in the treatment or prevention of malaria. Quinimax is a combination of four alkaloids (quinine, quinidine, cinchonine and cinchonidine). This combination has been shown in several studies to be more effective than quinine, supposedly due to a synergistic action between the four cinchona derivatives. Quinidine is a direct derivative of quinine. It is a diastereoisomer, thus having similar anti-malarial properties to the parent compound. Quinidine is recommended only for the treatment of severe cases of malaria.

2.2.2. Chloroquine

Chloroquine was, until recently, the most widely used anti-malarial. It was the original prototype from which most methods of treatment are derived. It is also the least expensive, best tested and safest of all available drugs. The emergence of drug-resistant parasitic strains is rapidly decreasing its effectiveness; however, it is still the first-line drug of choice in most sub-Saharan African countries. It is now suggested that it is used in combination with other antimalarial drugs to extend its effective usage. Chloroquine is a 4-aminoquinolone compound with a complicated and still unclear mechanism of

action. It is believed to reach high concentrations in the vacuoles of the parasite, which, due to its alkaline nature, raises the internal pH. It controls the conversion of toxic heme to hemozoin by inhibiting the biocrystallization of hemozoin, thus poisoning the parasite through excess levels of toxicity. Other potential mechanisms through which it may act include interfering with the biosynthesis of parasitic nucleic acids and the formation of a chloroquine-haem or chloroquine-DNA complex. The most significant level of activity found is against all forms of the schizonts (with the obvious exception of chloroquine-resistant *P. falciparum* and *P. vivax* strains) and the gametocytes of *P. vivax, P. malariae, P. ovale* as well as the immature gametocytes of *P. falciparum*. Chloroquine also has a significant anti-pyretic and anti-inflammatory effect when used to treat *P. vivax* infections, and

Children and adults should receive 25 mg of chloroquine per kg given over 3 days. A pharmacokinetically superior regime, recommended by the WHO, involves giving an initial dose of 10 mg/kg followed 6–8 hours later by 5 mg/kg, then 5 mg/kg on the following 2 days. For chemoprophylaxis: 5 mg/kg/week (single dose) or 10 mg/kg/week divided into 6 daily doses is advised. Chloroquine is only recommended as a prophylactic drug in regions only affected by *P. vivax* and sensitive *P. falciparum* strains. Chloroquine has been used in the treatment of malaria for many years and no abortifacient or teratogenic effects have been reported during this time; therefore, it is considered very safe to use during pregnancy. However, itching can occur at intolerable level and chloroquine can be a provocation factor of psoriasis.

2.2.3. Amodiaquine

Amodiaquine is a 4-aminoquinolone anti-malarial drug similar in structure and mechanism of action to chloroquine. Amodiaquine has tended to be administered in

areas of chloroquine resistance while some patients prefer its tendency to cause less itching than chloroquine. Amodiaquine is now available in a combined formulation with artesunate and is among the artemisinin-combination therapies recommended by the World Health Organisation. Combination with sulphadoxine-pyrimethamine is no longer recommended (WHO, 2010).

The drug should be given in doses between 25 mg/kg and 35 mg/kg over 3 days in a similar method to that used in chloroquine administration. Adverse reactions are generally similar in severity and type to that seen in chloroquine treatment. In addition, bradycardia, itching, nausea, vomiting and some abdominal pain have been recorded. Some blood and hepatic disorders have also been seen in a small number of patients.

2.2.4. Pyrimethamine

Pyrimethamine is used in the treatment of uncomplicated malaria. It is particularly useful in cases of chloroquine-resistant *P. falciparum* strains when combined with sulphadoxine. It acts by inhibiting dihydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, thereby halting the processes of DNA replication, cell division and reproduction. It acts primarily on the schizonts during the erythrocytic phase, and nowadays is only used in concert with a sulphonamide.

2.2.5. Proguanil (Chloroguanide)

Proguanil (chloroguanide) is a biguanide; a synthetic derivative of pyrimidine. It was developed in 1945 by a British Antimalarial research group. It has many mechanisms of action but primarily is mediated through conversion to the active metabolite cycloguanil. This inhibits the malarial dihydrofolate reductase

enzyme. Its most prominent effect is on the primary tissue stages of *P. falciparum*, *P. vivax* and *P. ovale*. It has no known effect against hypnozoites therefore is not used in the prevention of relapse. It has a weak blood schizonticidal activity and is not recommended for therapy of acute infection. However it is useful in prophylaxis when combined with atovaquone or chloroquine (in areas where there is no chloroquine resistance). 3 mg/kg is the advised dosage per day, (hence approximate adult dosage is 200 mg). The pharmacokinetic profile of the drugs indicates that a half dose, twice daily maintains the plasma levels with a greater level of consistency, thus giving a greater level of protection. The proguanil-chloroquine combination does not provide effective protection against resistant strains of *P. falciparum*. There are very few side effects to proguanil, with slight hair loss and mouth ulcers being occasionally reported following prophylactic use. Proguanil hydrochloride is marketed as Paludrine® by AstraZeneca.

2.2.6. Sulphonamides

Sulphadoxine and sulphamethoxypyridazine are specific inhibitors of the enzyme dihydropteroate synthetase in the tetrahydrofolate synthesis pathway of malaria parasites. They are structural analogs of *p*-aminobenzoic acid (PABA) and compete with PABA to block its conversion to dihydrofolic acid. Sulphonamides act on the schizont stages of the erythrocytic (asexual) cycle.

2.2.6.1. Sulphadoxine

When administered alone sulphonamides are not efficacious in treating malaria but co-administration with the antifolate pyrimethamine, most commonly as fixed-dose sulphadoxine-pyrimethamine (Fansidar®), produces synergistic effects sufficient to cure sensitive strains of malaria.

Sulphonamides are not recommended for chemoprophylaxis because of rare but severe skin reactions experienced. However it is used frequently for clinical episodes of the disease. (Henry 1943).

2.2.7. Mefloquine

Mefloquine was developed during the Vietnam War and is chemically related to quinine. It was developed to protect American troops against multi-drug resistant *P. falciparum*. It is a very potent blood schizonticide with a long half-life. It is thought to act by forming toxic heme complexes that damage parasitic food vacuoles. It is now used solely for the prevention of resistant strains of *P. falciparum* despite being effective against *P. vivax*, *P. ovale* and *P. malariae*. Mefloquine is effective in prophylaxis and for acute therapy. It is now strictly used for resistant strains (and is usually combined with Artesunate). Chloroquine/proguanil or sulphonamides, pyrimethamine combinations should be used in all other *Plasmodia* infections.

A dose of 15–25 mg/kg is recommended, depending on the prevalence of mefloquine resistance. The increased dosage is associated with a much greater level of intolerance, most noticeably in young children; with the drug inducing vomiting and oesophagitis. It was not recommended for use during the first trimester, although considered safe during the second and third trimesters. The Centre for Disease Control and Prevention (CDC 2011) updated its recommendation and approved use of mefloquine for both prophylaxis and treatment of malaria in all trimesters, after the Food and Drug Administration (FDA) changed its categorization from C to B. Mefloquine frequently produces side effects, including nausea, vomiting, diarrhoea, abdominal pain and dizziness. Several associations with neurological events have been made,

namely affective and anxiety disorders, hallucinations, sleep disturbances, psychosis, toxic encephalopathy, convulsions and delirium.

Cardiovascular effects have been recorded with bradycardia and sinus arrhythmia being consistently recorded in 68% of patients treated with mefloquine. Mefloquine can only be taken for a period up to 6 months due to side effects. After this, other drugs (such as those based on proguanil/chloroquine sulphate again need to be taken.

2.2.8. Primaquine

Primaquine is a highly active 8-aminoquinolone that is used in treating all types of malaria infection. It is most effective against gametocytes but also acts on hypnozoites, blood schizonticytes and the dormant plasmodia in *P. vivax* and *P. ovale*. It is the only known drug to cure both relapsing malaria infections and acute cases. The mechanism of action is not fully understood but it is thought to block oxidative metabolism in *Plasmodia*.

For the prevention of relapse in *P. vivax* and *P. ovale* 0.15 mg/kg should be given for 14 days. As a gametocidal drug in *P. falciparum* infections a single dose of 0.75 mg/kg repeated 7 days later is sufficient. This treatment method is only used in conjunction with another effective blood schizonticidal drug. There are few significant side effects although it has been shown that primaquine may cause anorexia, nausea, vomiting, cramps, chest weakness, anaemia, some suppression of myeloid activity and abdominal pains. In cases of over-dosage granulocytopenia may occur.

2.2.9. Artemisinin and Derivatives

2.2.9.1. Artemisinin is a Chinese herb (qinghaosu) that has been used in the treatment of fevers for over 1,000 years, thus predating the use of quinine in the

Western world. It is derived from the plant *Artemisia annua*, with the first documentation as a successful therapeutic agent in the treatment of malaria is in 340 AD by Ge Hong in his book *Zhou Hou Bei Ji Fang*(*A Handbook of Prescriptions for Emergencies*) (Ge Hong extracted the artemisinin using a simple macerate, and this method is still in use today (van Vugt, 1998). The active compound was isolated first in 1971 and named artemisinin. It is a sesquiterpene lactone with a chemically rare peroxide bridge linkage. It is this that is thought to be responsible for the majority of its anti-malarial action, although the target within the parasite remains controversial. At present it is strictly controlled under WHO guidelines as it has proven to be effective against all forms of multi-drug resistant *P. falciparum*, thus every care is taken to ensure compliance and adherence together with other behaviours associated with the development of resistance. It is also only given in combination with other anti-malarial drugs

Artemisinin has a very rapid action and the vast majority of acute patients treated show significant improvement within 1–3 days of receiving treatment. It has demonstrated the fastest clearance of all anti-malarials currently used and acts primarily on the trophozite phase, thus preventing progression of the disease. Semi-synthetic artemisinin derivatives (e.g. artesunate, artemether) are easier to use than the parent compound and are converted rapidly once in the body to the active compound dihydroartemisinin. On the first day of treatment 20 mg/kg should be given, this dose is then reduced to 10 mg/kg per day for the 6 following days. Few side effects are associated with artemisinin use. However, headaches, nausea, vomiting, abnormal bleeding, dark urine, itching and some drug fever have been reported by a small number of patients. Some cardiac changes were reported during a clinical trial, notably non-specific ST changes and a first degree atrioventricular block (these disappeared when the patients recovered from the malarial fever).

2.2.9.2. Artemether is a methyl ether derivative of dihydroartemisinin. It is similar to artemisinin in mode of action but demonstrates a reduced ability as a hypnozoiticidal compound, instead acting more significantly to decrease gametocyte carriage. Similar restrictions are in place, as with artemisinin, to prevent the development of resistance, therefore it is only used in combination therapy for severe acute cases of drug-resistant *P. falciparum*. It should be administered in a 7 day course with 4 mg/kg given per day for 3 days, followed by 1.6 mg/kg for 3 days. Side effects of the drug are few but include potential neurotoxicity developing if high doses are given (Gbotosho *et al*, 2011).

2.2.9.3. Artesunate is a hemi-succinate derivative of the active metabolite dihydroartemisin. Currently it is the most frequently used of all the artemisinin-type drugs. Its only effect is mediated through a reduction in the gametocyte transmission. It is used in combination therapy and is effective in cases of uncomplicated *P. falciparum*. The dosage recommended by the WHO is a 5 or 7 day course (depending on the predicted adherence level) of 4 mg/kg for 3 days (usually given in combination with mefloquine) followed by 2 mg/kg for the remaining 2 or 4 days. In large studies carried out on over 10,000 patients in Thailand no adverse effects have been shown (Price, Van Vugt, Nosten *et al,* 1998).

In an open-label randomised controlled trial in patients admitted to hospital with severe falciparum malaria in Bangladesh, India, Indonesia, and Myanmar, mortality in artesunate recipients was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34·7% (95% CI 18·5–47·6%; p=0·0002). Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia

(relative risk 3·2, 1·3–7·8; p=0·009) (South East Asian Quinine Artesunate Malaria Trial, 2005).

2.2.9.4. **Dihydroartemisinin** is the active metabolite to which artemisinin is reduced. It is the most effective artemisinin compound and the least stable.

It has a strong blood schizonticidal action and reduces gametocyte transmission. It is used for therapeutic treatment of cases of resistant and uncomplicated *P. falciparum*. 4 mg/kg doses are recommended on the first day of therapy followed by 2 mg/kg for 6 days. As with artesunate, no side effects to treatment have thus far been recorded.

2.2.9.5. Arteether

Arteether is an ethyl ether derivative of dihydroartemisinin. It is used in combination therapy for cases of uncomplicated resistant P. falciparum. The recommended dosage is 150 mg/kg per day for 3 days given by intramuscular injections. With the exception of a small number of cases demonstrating neurotoxicity following parenteral administration no side effects have been recorded.

It is noteworthy that the use of oral artemisinin based monotherapy has been by WHO (WHO, 2010).

2.2.10 Halofantrine

Halofantrine was developed by Walter Reed Army Institute of Research in the 1960s. It is a phenanthrene methanol, chemically related to quinine and acts acting as a blood schizonticide effective against all plasmodium parasites. Its mechanism of action is similar to other anti-malarials. Cytotoxic complexes are formed with ferritoporphyrin XI that cause plasmodial membrane damage. Despite being effective against drug

resistant parasites, halofantrine is not commonly used in the treatment (prophylactic or therapeutic) of malaria due to its high cost. It has very variable bioavailability and has been shown to have potentially high levels of cardiotoxicity. It is still a useful drug and can be used in patients that are known to be free of heart disease and are suffering from severe and resistant forms of acute malaria. The proprietary name of halofantrine is Halfan®. The level of governmental control and the prescription-only basis on which it can be used contributes to the cost, thus halofantrine is not frequently used (van Vugt *et al,* 1998).

Halofantrine 8 mg/kg is advised to be given in three doses at six hour intervals for the duration of the clinical episode. It is not recommended for children under 10 kg despite data supporting the use and demonstrating that it is well tolerated. The most frequently experienced side-effects include nausea, abdominal pain, diarrhoea, and itch. Severe ventricular dysrhythmias, occasionally causing death are seen when high doses are administered. This is due to prolongation of the QTc interval. Halofantrine is not recommended for use in pregnancy and lactation, in small children, or in patients that have taken mefloquine previously (Van Vugt *et al,* 1998).

2.2.11. Atovaquone is a chemical compound that belongs to the class of naphthoquinones. Atovaquone is a hydroxy-1, 4-naphthoquinone, an analogue of ubiquinone, with antipneumocystic activity. Atovaquone, as a combination preparation with proguanil, has been commercially available from GlaxoSmithKline since 2000 as Malarone{R} for the treatment and prevention of malaria. It is also used to treat or prevent:

a) Pneumocystis pneumonia (PCP), it is used in mild cases, although it is not approved for treatment of severe cases.
b) Toxoplasmosis, the medication has antiparasitic and therapeutic effects.

c) Babesia, it is often used in conjunction with oral azithromycin (White, 2004).

Trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim) is generally considered first-line therapy for PCP or toxoplasmosis. However, atovaquone may be used in patients who cannot tolerate, or are allergic to, TMP-SMX. In addition, atovaquone has the advantage of not causing myelosuppression, which is an important issue in patients who have undergone bone marrow transplantation.

2.2.12. Doxycycline

Probably one of the more prevalent antimalarial drugs prescribed, due to its relative effectiveness and cheapness, doxycycline is a tetracycline compound derived from oxytetracycline. The tetracyclines were one of the earliest groups of antibiotics to be developed and are still used widely in many types of infection. It is a bacteriostatic agent that acts to inhibit the process of protein synthesis by binding to the 30S ribosomal subunit thus preventing the 50s and 30s units from bonding. Doxycycline is used primarily for chemoprophylaxis in areas where chloroquine resistance exists. It can also be used in combination with quinine to treat resistant cases of *P. falciparum* but has a very slow action in acute malaria, and should not be used as monotherapy (van Vugt *et al*, 1998).

When treating acute cases and given in combination with quinine; 100 mg of doxycycline should be given per day for 7 days. In prophylactic therapy, 100 mg (adult dose) of doxycycline should be given every day during exposure to malaria.

The most commonly experienced side effects are permanent enamel hypoplasia, transient depression of bone growth, gastrointestinal disturbances and some increased levels of photosensitivity. Due to its effect of bone and tooth growth it is not used in

children under 8, pregnant or lactating women and those with a known hepatic dysfunction.

Tetracycline is only used in combination for the treatment of acute cases of *P. falciparum* infections. This is due to its slow onset. Unlike doxycycline it is not used in chemoprophylaxis. For tetracycline, 250 mg is the recommended adult dosage (it should not be used in children) for 5 or 7 days depending on the level of adherence and compliance expected. Oesophageal ulceration, gastrointestinal upset and interferences with the process of ossification and depression of bone growth are known to occur. The majority of side effects associated with doxycycline are also experienced.

2.2.13. Clindamycin

Clindamycin is a derivative of lincomycin, with a slow action against blood schizonticides. It is only used in combination with quinine in the treatment of acute cases of resistant *P. falciparum* infections and not as a prophylactic. Being more expensive and toxic than the other antibiotic alternatives, it is used only in cases where the tetracyclines are contraindicated (for example in children). Clindamycin should be given in conjunction with quinine as a 300 mg dose (in adults) four times a day for 5 days. The only side effects recorded in patients taking clindamycin are nausea, vomiting and abdominal pains and cramps. However, these can be alleviated by consuming large quantities of water and food when taking the drug. Pseudomembranous colitis (caused by *Clostridium difficile*) has also developed in some patients; this condition may be fatal in a small number of cases.

2.3. Resistance to Antimalarial Drugs

Anti-malarial drug resistance has been defined as: "the ability of a parasite to survive and/or multiply despite the administration and absorption of a drug given in doses equal

to or higher than those usually recommended but within tolerance of the subject. Resistance to drugs has become a very serious problem with *P. falciparum*; during the last decades there has been an increasingly rapid selection and dispersal of *P.falciparum* parasites resistant to antimalarial drugs, as more frequently these drugs are used as prophylactics and for self-medication, often in insufficient doses. Resistance to chloroquine was first discovered in South America and in South-East Asia in the late 1950's, spread through South America, Asia and the Pacific. Between the late 1970's and 1980s it has shown a particularly alarming evolution in Africa. In addition, resistance to amodiaquine, and sulfadoxine-pyrimethamine (SP) followed a similar pattern. Resistance to mefloquine has also developed in many areas. The continuous intensification of this problem is hampering the efforts to provide adequate treatment in peripheral areas. It is difficult to assess how much of this phenomenon is due to migration of resistant parasites and how much to local selection, as both mobility and drug consumption have increased considerably in the recent past. There are many places in Africa where people use chloroquine more often than aspirin for minor fevers and aches.

The drug in question must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action." In most instances this refers to parasites that are remaining following on from an observed treatment. Thus excluding all cases where anti-malarial prophylaxis has failed. In order for a case to be defined as resistant, the patient under question must have received a known and observed anti-malarial therapy whilst the blood drug and metabolite concentrations are monitored concurrently. The techniques used to demonstrate this are: *in vivo, in vitro,* animal model testing and the most recently developed molecular techniques.

Drug resistant parasites are often used to explain malaria treatment failure. However, they are two potentially very different clinical scenarios. The failure to clear parasitemia and recover from an acute clinical episode when a suitable treatment has been given and anti-malarial resistance in its true form. Drug resistance may lead to treatment failure, but treatment failure is not necessarily caused by drug resistance despite assisting with its development. A multitude of factors can be involved in the processes including problems with non-compliance and adherence, poor drug quality, interactions with other pharmaceuticals, poor absorption, misdiagnosis and incorrect doses being given. The majority of these factors also contribute to the development of drug resistance.

The generation of resistance can be complicated and varies between plasmodium species. It is generally accepted to be initiated primarily through a spontaneous mutation that provides some evolutionary benefit, thus giving an anti-malarial used a reduced level of sensitivity. This can be caused by a single point mutation or multiple mutations. In most instances a mutation will be fatal for the parasite or the drug pressure will remove parasites that remain susceptible, however some resistant parasites will survive. Resistance can become firmly established within a parasite population, existing for long periods of time.

The first type of resistance to be acknowledged was to chloroquine in Thailand in 1957. The biological mechanism behind this resistance was subsequently discovered to be related to the development of an efflux mechanism that expels chloroquine from the parasite before the level required to effectively inhibit the process of haem polymerization (that is necessary to prevent accumulation of toxic by-products formed by haemoglobin digestion). This theory has been supported by evidence showing that resistance can be effectively reversed on the addition of substances which halt the

efflux. The resistance of other quinolone anti-malarial drugs such as amiodiaquine, mefloquine, halofantrine and quinine are thought to have occurred by similar mechanisms.

Plasmodium have developed resistance against antifolate combination drugs, the most commonly used being sulfadoxine and pyrimethamine. Two gene mutations are thought to be responsible, allowing synergistic blockages of two enzymes involved in folate synthesis. Regional variations of specific mutations give differing levels of resistance.

Atovaquone is recommended to be used only in combination with another anti-malarial compound as the selection of resistant parasites occurs very quickly when used in mono-therapy. Resistance is thought to originate from a single-point mutation in the gene coding for cytochrome-b.

2.3.1. Spread of Resistance

There is no single factor that confers the greatest degree of influence on the spread of drug resistance, but a number of plausible causes associated with an increase have been acknowledged. These include aspects of economics, human behaviour, and the biology of vectors and parasites. The most influential causes are examined below:

a) The biological influences are based on the parasites ability to survive the presence of an anti-malarial thus enabling the persistence of resistance and the potential for further transmission despite treatment. In normal circumstances any parasites that persist after treatment are destroyed by the host's immune system, therefore any factors that act to reduce the elimination of parasites could facilitate the development of resistance. This attempts to explain the poorer

response associated with immuno-compromised individuals, pregnant women and young children.

b) There has been evidence to suggest that certain parasite-vector combinations can alternatively enhance or inhibit the transmission of resistant parasites, causing 'pocket-like' areas of resistance.

c) The use of anti-malarials developed from similar basic chemical compounds can increase the rate of resistance development, for example cross-resistance to chloroquine and amodiaquine, two 4-aminoquinolones and mefloquine conferring resistance to quinine and halofantrine. This phenomenon may reduce the usefulness of newly developed therapies prior to large-scale usage.

d) The resistance to anti-malarial drugs may be increased by a process found in some species of plasmodium, where a degree of phenotypic plasticity was exhibited, allowing the rapid development of resistance to a new drug, even if the drug has not been previously experienced.

e) The pharmacokinetics of the chosen anti-malarial are key; the decision of choosing a long half-life over a drug that is metabolised quickly is complex and still remains unclear. Drugs with shorter half-life require more frequent administration to maintain the correct plasma concentrations, therefore potentially presenting more problems if levels of adherence is unreliable, but longer-lasting drugs can increase the development of resistance due to prolonged periods of low drug concentration.

f) The pharmacokinetics of anti-malarial drugs is important when using combination therapy. Mismatched drug combinations, for example having an 'unprotected' period where one drug dominates can seriously increase the likelihood of selection for resistant parasites.

g) Ecologically there is a linkage between the level of transmission and the development of resistance, however at present this still remains unclear.

h) The treatment regime prescribed can have a substantial influence on the development of resistance. This can involve the drug intake, combination and interactions as well as the drug's pharmacokinetic and pharmacodynamic properties.

2.3.2. Prevention of Resistance

The prevention of anti-malarial drug resistance is of enormous public health importance. It can be assumed that no therapy currently under development or to be developed in the foreseeable future will be totally protective against malaria. In accordance with this, there is the possibility of resistance developing to any given therapy that is developed. This is a serious concern, as the rate at which new drugs are produced by no means matches the rate of the development of resistance. In addition, the most newly developed therapeutics tend to be the most expensive and are required in the largest quantities by some of the poorest areas of the world. Therefore it is apparent that the degree to which malaria can be controlled depends on the careful use of the current drugs to limit, insofar as it is possible, any further development of resistance.

Provisions essential to this process include the delivery of fast primary care where staff are well trained and supported with the necessary supplies for efficient treatment. This in itself is inadequate in large areas where malaria is endemic thus presenting an initial problem. One method proposed that aims to avoid the fundamental lack in certain countries health care infrastructure is the privatisation of some areas, thus enabling drugs to be purchased on the open market from sources that are not officially related to the health care industry. Although this is now gaining some support there are many

problems related to limited access and improper drug use, which could potentially increase the rate of resistance development to an even greater extent.

There are two general approaches to preventing the spread of resistance: preventing malaria infections and, preventing the transmission of resistant parasites.

Preventing malaria infections developing has a substantial effect on the potential rate of development of resistance, by directly reducing the number of cases of malaria thus decreasing the requirement for anti-malarial therapy. Preventing the transmission of resistant parasites limits the risk of resistant malarial infections becoming endemic and can be controlled by a variety of non-medical methods including insecticide-treated bed nets, indoor residual spraying, environmental controls (such as swamp draining) and personal protective methods such as using mosquito repellent. Chemoprophylaxis is also important in the transmission of malaria infection and resistance in defined populations, for example, travellers.

A hope for future of anti-malarial therapy is the development of an effective malaria vaccine. This could have enormous public health benefits, providing a cost-effective and easily applicable approach to preventing not only the onset of malaria but the transmission of gametocytes, thus reducing the risk of resistance developing. Anti-malarial therapy could be also be diversified by combining a potentially effective vaccine with current chemotherapy, thereby reducing the chance of vaccine resistance developing.

2.3.3. Combination Therapy

The problem of the development of malaria resistance must be weighed against the essential goal of anti-malarial care; that is to reduce morbidity and mortality. Thus, a balance must be reached that attempts to achieve both goals whilst not compromising

either too much by doing so. The most successful attempts so far have been in the administration of combination therapy. This can be defined as, 'the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite'. There is much evidence to support the use of combination therapies, some of which has been discussed previously, however several problems prevent the wide use in the areas where its use is most advisable (Whitty and Staedke, 2005). These include: problems identifying the most suitable drug for different epidemiological situations, the expense of combined therapy (it is over 10 times more expensive than traditional mono-therapy), how soon the programmes should be introduced and problems linked with policy implementation and issues of compliance.

The combinations of drugs currently prescribed can be divided into two categories: non-artemisinin-based combinations and artemisinin based combinations. It is also important to distinguish fixed-dose combination therapies (in which two or more drugs are co-formulated into a single tablet) from combinations achieved by taking two separate antimalarial drugs.

2.3.4. Non-artemisinin Based Combinations

Sulphadoxine-pyrimethamine (SP): This fixed-dose combination has been used for many years, causes few adverse effects, and is cheap and effective in a single dose, thus decreasing problems associated with adherence and compliance. In technical terms SP is not generally considered a true combination therapy since the components do not possess independent curative activity (WHO 2010). SP is no longer be used alone for treatment of falciparum malaria. The combination contains sulphadoxine 25 mg/kg and pyrimethamine 1.25 mg/kg. This combination is effective in few locations and it is no longer recommended (WHO 2010). It is given as chloroquine 25 mg/kg over 3 days with a single dose of sulphadoxine/pyrimethamine as described above.

Sulphadoxine/Pyrimethamine + Amodiaquine: This combination has been shown to produce a faster rate of clinical recovery than sulphadoxine/pyrimethamine and chloroquine, but is clearly inferior to ACTs for the treatment of malaria. The combination contains 10 mg/kg of amodiaquine per day for 3 days with a single standard dose of sulphadoxine/pyrimethamine.

Sulphadoxine/Pyrimethamine + Mefloquine : This single dose pill offered obvious advantages of convenience over more complex regimes but it has not been recommended for use for many years owing to widespread resistance to the components.

Quinine + Tetracycline / Doxycycline: This combination retains a high cure rate in many areas. Problems with this regime include the relatively complicated drug regimen, where quinine must be taken every 8 hours for 7 days. Additionally, there are significant side effects with quinine ('cinchonism') and tetracyclines are contraindicated in children and pregnant women (these groups should use clindamycin instead). With the advent of ACTs, quinine-based treatment is less popular than previously. It is given as quinine 10mg/kg doses every 8 hours and tetracycline 4mg/kg doses every 6 hours for 7 days.

According to WHO guidelines 2010, artemisinin-based combination therapies should be used in preference to amodiaquine plus sulphadoxine-pyrimethamine for the treatment of uncomplicated P. falciparum malaria (WHO, 2010).

2.3.5. Artemisinin-based Combination Therapies (ACTs)

Artemisinin has a very different mode of action than conventional anti-malarial, this makes it particularly useful in the treatment of resistant infections. However, in order to

prevent the development of resistance to this drug it is only recommended in combination with another non-artemisinin based therapy. It produces a very rapid reduction in the parasite biomass with an associated reduction in clinical symptoms and is known to cause a reduction in the transmission of gametocytes thus decreasing the potential for the spread of resistant alleles. At present there is no known resistance to artemisinin (though some resistant strains may be emerging) and very few reported side effects to drug usage.

Artesunate + Amodiaquine : This combination has been tested and proved to be efficacious in many areas where amodiaquine retains some efficacy. A potential disadvantage is a suggested link with neutropenia. It is recommended by the WHO for uncomplicated falciparum malaria. (WHO 2010). It is given as a fixed-dose combination recommended as artesunate 4 mg/kg and amodiaquine 10 mg/kg per day for 3 days.

Artesunate and Mefloquine : This has been used as an efficacious first-line treatment regimen in areas of Thailand for many years. Mefloquine is known to cause vomiting in children and induces some neuropsychiatric and cardiotoxic effects, interestingly these adverse reactions seem to be reduced when the drug is combined with artesunate, it is suggested that this is due to a delayed onset of action of mefloquine. This is not considered a viable option to be introduced in Africa due to the long half-life of mefloquine, which potentially could exert a high selection pressure on parasites. It's recommended by the WHO for uncomplicated *falciparum* malaria (WHO 2010). The standard dose required is artesunate 4 mg/kg plus mefloquine 25 mg/kg per day as a split dose of 15 mg/kg on day 2 and 10 mg/kg on day three.

Artemether+Lumefantrine : This combination has been extensively tested in 16 clinical trials, proving effective in children under 5 and has been shown to be better tolerated than artesunate plus mefloquine combinations. There are no serious side effects documented but the drug is not recommended in pregnant or lactating women due to limited safety testing in these groups. This is the most viable option for widespread use and is available in fixed-dose formulas thus increasing compliance and adherence. It's recommended by the WHO for uncomplicated *falciparum* malaria.

Artesunate + Sulphadoxine+Pyrimethamine : This is a well-tolerated combination but the overall level of efficacy still depends on the level of resistance to sulphadoxine and pyrimethamine thus limiting is usage. It is recommended by WHO for uncomplicated *falciparum* malaria (WHO 2010).

It is recommended in doses of 4 mg/kg of artesunate per day for 3 days and a single dose of 25 mg/kg of sulphadoxine/pyrimethamine.

Dihydroartemisinin-piperaquine : This combination been studied mainly in China, Vietnam and other countries in SE Asia. The drug has been shown to be highly efficacious (greater than 90%). It is recommended by the WHO for uncomplicated *falciparum* malaria (WHO 2010).

Artesinin/Piperaquine/Primaquine: This protocol involves three doses of Artequick, spaced a month apart. The first dose is accompanied by one of primaquine. An experimental program in the Comoros islands employed the protocol. At the outset, more than 90% of the inhabitants of some villages had malaria. On one island the number of cases fell by 95%. In 2012 on the second island, the number of cases fell by 97% (The Economist, 2014).

Pyronaridine + Artesunate : Manufactured by Shin Poong Pharmaceutical. Pyramax developed by Shin Poong Pharmaceutical and Medicines for Malaria Venture (MMV). This is the first fixed-dose artemisinin-based combination therapy to be granted a positive scientific opinion for efficacy, safety and quality from European Medicines Agency (EMA) under Article 58 for the treatment of *P. falciparum* and *P. vivax* in adults and children over 20 kg based on 5 multi-centre phase III trials conducted in Africa and South-East Asia. Pyramax is highly efficacious (greater than 97%) in both species and only ACT approved by stringent regulatory authority for treatment of both *P. falciparum* and *P vivax* by now.

2.3.6. Other Combinations

Several other anti-malarial combinations have been used or are in development. For example, Chloroproguanil-dapsone and artesunate appears efficacious but the problem of haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency is likely to prevent widespread use (Premji *et al,* 2009).

2.4. Epidemiology of Malaria

It is estimated that 350 – 500 million clinical cases of malaria occur annually. About 90% of all malaria deaths in the world today occur in Africa, south of the Sahara. Malaria kills at least 1 million people yearly, 90% of whom are estimated to be African children. Malaria kills an African child every second. Malaria has the highest association of any disease with poverty and the world's poorest are in malaria endemic regions of the world including Nigeria. Malaria contributes to anaemia in children and undermines their growth and development (UNICEF, 2003). It is a leading cause of low birth weight and contributes to high rates of maternal death.

Malaria is the most common cause of hospital attendance in all age groups in Nigeria. In Nigeria, malaria accounts for 30% of childhood mortality. About 50% Nigerians suffer from at least an episode of malaria each year (FMoH, 2004). In other words, about 70 million Nigerians suffer from at least an episode of malaria annually.

Malaria mortality among 1-4 years age group has been estimated at between 10 and 20 per thousand. In 1962 WHO Regional Office for Africa estimated that every year between 200,000 and 500,000 African children die from malaria (Pampana, 1969). Bruce-Chwatt (1969) estimated that figure at about one million. The latter figure has been extensively quoted ever since. Molineaux (1985) reviewed the impact on infant mortality of some malaria control projects, in particular those of Kisumu (Kenya) and Garki (Nigeria) and concluded that malaria was responsible for about 20 to 30% of infant mortality. Studies in the Gambia show a malaria mortality in the order of 6.3 per thousand per year in infants and 10.7 per thousand per year in children 1-4 years old (Greenwood *et al.,* 1987), representing 10% of deaths before one year of age and 25% of those in the 1-4 years age group.

There have, nevertheless, been indications that at least in some areas of Africa, general infant and malaria specific mortality may be declining, often independently of specific interventions and more in line with social development and general education. Studies in Congo and Burkina Faso in the late 1970's indicated that malaria specific mortality could be lower than expected in areas where some decades ago malaria constituted a major cause of infant mortality. The findings were attributed to the widespread, even if indiscriminate, use of antimalarial drugs, often at doses which may not be adequate to ensure parasite clearance, but may achieve clinical cure and prevent death, even if collectively they will increase the drug pressure over the overall parasite population and may, therefore, be contributing to the selection of resistant parasites (Trape *et al.*,

1987). The wide availability of antimalarial and other active drugs has also been blamed as a potential contributing factor to the general decline of infant mortality that was observed in the Kisumu area of Kenya, where between 1972 and 1976 overall infant mortality was reported to have declined between 157/1000 and 93/1000 while an effective malaria control programme using fenitrothion indoor house spraying was being conducted; later a slight decline in post neonatal mortality (from 73 to 67/1000) and a marked drop in mortality of children 1-4 years old (from 25 to 18/1000) were recorded between 1981-2 and 1982-3, following the implementation of a programme of community based antimalaria treatment. The bulk of such a decline was explained by the influence of a measles epidemic in 1981-2, the malaria specific mortality, being relatively low, did not show significant change in the year of intervention. Interestingly, this study appears to confirm in a small rural area the general observation that child mortality differentials can largely be explained by differences in maternal education, which will no doubt also influence use of medical care and drugs, but is more likely indicative of better hygiene and general living standards.

2.5. The Burden of Malaria on the Health System

Quantifying the burden of malaria is a challenge because the disease may be asymptomatic, present in an acute cerebral or deadly form or some forms in between. Several factors contribute to imprecise estimate. These include inadequate diagnosis, incomplete or lack of reporting, inability and/or inaccessibility of some febrile patients to formal health system, and similarities between some other diseases and malaria and their coexistence in malaria endemic regions.

Deaths due to malaria are approximately 1 million per annum globally and 90% of these occur in Africa (Ajayi *et al.*, 2008). This gives a proxy to the burden of malaria on the health system. However, these estimates fall short of the real burden because the

disease covers a wide range of continuum from asymptomatic infection to the severe acute illness or death. In most countries in Africa south of Sahara, most illnesses, including malaria, are treated at home or in the community before or without seeking care at a formal health facility. In Ethiopia (Kloos *et al.*, 1987), Ghana (Asemo-Okyere *et al.*, 1998), Niger (Chawla and Ellis, 2000) and Nigeria (Owumi and Raji, 2013) reported up to two-thirds of population with illness seek care outside the health system. Although malaria recorded in the health system represents only a small percentage, malaria is also a major contributor to hospital deaths among hospital in-patients with high case-fatality rates arising from late presentation, inadequate management, and lack of access to effective drugs either through inability to pay or unavailability. A growing complication is the scourge of fake, counterfeit and adulterated antimalarial drugs (Taylor *et al.*, 2001; Dondorp *et al.*, 2004; Aina *et al.*, 2007; Newton *etal.*, 2008; Ofori-Kwakye *et al.*, 2008; Onwujekwe *et al.*, 2009; Nayyar *et al.*, 2012; Tayo, 2013).

2.6. The Economic and Social Burden of Malaria

The high burden of malaria is a significant drawback to economic and social development in Nigeria. Malaria causes at least 20% of all deaths in children under 5years of age in Africa. In Nigeria, it is as high as 30% (FMoH, 2001). In Sub-Saharan Africa, malaria drained economies of more than $2 billion in 1997 (UNICEF, 2000). There is a bi-directional link between malaria and economic development. Thus, high prevalence of malaria impairs health and restrains economic growth and development. On the other hand, by improving health status, living conditions and access to effective prevention and treatment, economic growth and development reduce both the incidence and prevalence of malaria. Financial barriers limit access of the poor to health services, they usually live in remote areas, and are socially and culturally marginalized. The poorest of the poor are most affected (Barat*et al.*, 2004) since they live in dwellings

prone to mosquito proliferation and are less likely to afford health services and malaria interventions.

For most endemic countries in Africa, the high burden of malaria is responsible for an estimated average annual reduction of 1.3% in economic growth, US$12 billion loss, and serious social disruptions. Studies estimating the economic burden of malaria in endemic countries showed that the direct cost of a single episode of malaria to a household was US$6.87 in Ghana, US$4.8 in Uganda and US$4.5 in Mali. In Nigeria, it costs about US$1.0 to treat a malaria episode by self- medication before the change in policy from chloroquine to artemisinin combination therapy (ACT) which is considerably more expensive than the former (Worall *et al.,* 2004). It costs about US$10 to treat malaria by the use of orthodox health care provider when admission is not involved Estimates of the burden of malaria on the overall economies of Ghana, Mali, Nigeria and Uganda reveal that malaria impedes economic growth ranging from 0.067% in Uganda to as much as 3.8% in Nigeria (Okorosobo *et al.*, 2011; Tayo 2013) The Gross Domestic Product (GDP) loss due to malaria in Ghana (0.41%), Nigeria (3.8%) and Chad (8.9%) is quite substantial (Okorosobo *et al*., 2011). This translates to a GDP loss of US$9.272billion for Nigeria (Okorosobo *et al*., 2011).In Nigeria, Ghana and Mali, the burden of malaria on households are US$11.84, US$6.87 and US$17.5 respectively (Okorosobo *et al*., 2011).Jimoh *et al* (2007) found that households in Nigeria would be prepared to pay an average of about US$ 9.3 per month for the treatment of malaria. This is about US$ 3.6 in excess of the average expenditure they currently make on malaria treatment per month. Similarly, households are willing to pay on the average a sum of US$ 61 per month for the control of malaria, an excess of about US$ 22.6 over the cost they currently bear (protection, treatment and indirect costs), and it represents households' average valuation of their intangible costs of

malaria illness. This amount represents about US$ 5.1 per head per month and US$ 61.2 per year. In a country of about 160 million this translates to about US$ 6,000 million per annum. This is more than 12.0 per cent of Gross Domestic Product. This has a devastating effect on the economy of the country.

The value of days lost due to malaria is estimated at US$8.92 and US$8.84. Monthly expenditures on malaria prevention ranged from US$0.32 to US$10 in many African countries (Worall *et al*., 2004).

2.7. Roll Back Malaria

Recognizing that there are proven and effective interventions against malaria, the Roll Back Malaria (RBM) partnership was launched in 1998 by the WHO, the World Bank, the United Nations Children's Fund (UNICEF) and the United Nations Development Programme (UNDP), with the overall goal of halving the burden of malaria by 2010. The following core technical strategies for the sustainable control of malaria have been identified:

- Improved and prompt access to effective treatment,
- Increased use of insecticide-treated nets (ITNs) and other locally appropriate means of vector control.
- Early detection of, and response to malaria epidemics;
- Improved prevention and treatment of malaria in pregnant women in highly endemic areas (WHO/RBM, 2005).

African leaders are committed to ensuring that 80% of malaria episodes are adequately treated within 24 hours of onset of symptoms by 2010(WHO/RBM, 2005). However, treatment of malaria is challenged by inadequate health-care infrastructure in many parts of Africa (Kager, 2002). Health facilities are often resource-limited, and access to

care may be limited by distance, fees, inadequate staffing, and lack of essential medicines (Moerman *et al*., 2003; Ruebush, *et al*., 1995). The direct and especially indirect costs of seeking health care from formal facilities may be substantial, providing a major barrier for many households (Wiseman, *et al.*, 2006). Thus, febrile illnesses are commonly treated at home, frequently with drugs purchased from shops (McCombie, 1996). It is estimated that fewer than 20% of children with malaria in endemic areas are treated in formal health-care settings (Breman, 2001).

2.8. Change in Anti-Malaria Policy.

Recently, antimalarial treatment policies in Africa have undergone a major transition; most countries have adopted artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated malaria Whether ACTs can be successfully incorporated into HMM and used safely and effectively at home is a critical question (D'Alessandro *et al.*,2005; Pagnoni *et al.*, 2005). The cost of implementing ACTs in sub-Saharan Africa according to current prescribing practices has been estimated at US$ 1.6 – 3.4 billion per year, and the cost-effectiveness of deploying ACTs in HMM remains uncertain (D'Alessandro *et al.*, 2005). Quoted data supporting HMM policy are limited, and the impact of HMM on malaria-associated morbidity and mortality has not been fully established in most settings. The ideal regimen for use in HMM programmes is also not clear, and may vary by setting.

2.8.1. Challenges Associated With Change In Antimalarial Policy

The threat posed by failing, but relatively inexpensive antimalarial drugs such as chloroquine and sulphadoxine-pyrimethamine, led to an international effort to replace them with relatively more expensive but more efficacious artemisinin-based

combination therapies (ACTs) to manage uncomplicated malaria (White *et al.*, 1999; Attaran *et al.,* 2004; WHO, 2003). It is noteworthy, however, that a change in international therapeutic recommendations does not always translate to an immediate effective national policy change at country levels (Amin *et al.*, 2007).

The difficulties confronting national antimalarial drug policy change especially when it involves moving from an inexpensive failing drug such as chloroquine to an equally widely available, inexpensive but more efficacious drug such as sulphadoxine-pyrimethamine are well documented (Shretta *et al.,* 2000; Kamya *et al.*, 2002; Williams *et al.,* 2004; Mulligan *et al.,* 2006). These observations during the 1990s and early to mid-2000s highlighted the complexity of drug policy change and implementation for malaria case management in Africa.

Following the inception of Roll-Malaria, the Federal Ministry of Health has paid more attention to the scourge of malaria in order to reduce its debilitating effect on the masses especially children and pregnant mothers. Thus, it adopted the internationally agreed change in antimalarial drug policy. In 2005, chloroquine which was hitherto a first-line drug was removed from the official National Treatment Guidelines for Malaria and replaced with artemisinin-combination therapies (ACTs) artemether-lumefantrine and artesunate-amodiaquine (FMoH, 2005). The uptake of the change was met with scepticism for obvious reasons. Thus, advocacy was lacking hence many major stakeholders were not carried along. In addition, the new drugs, ACTs, were not readily available for several months after the ban on chloroquine and sulphadoxine-pyrimethamine.

2.9. Pharmacoeconomic Considerations of HMM.

Provision of ACTs in HMM has substantial economic and public health implications. Implementation of home- or community-based programmes based on non-ACT regimens (chloroquine or chloroquine plus sulfadoxine-pyrimethamine) was reported to be relatively affordable (Pagnoni *et al*., 1997; Onwujekwe *et al*., 2007), and a cost-effectiveness model found that provider training, community education and pre-packaging of chloroquine compared favorably with other malaria control measures (Goodman *et al.*, 1999). The system costs of implementing HMM are expected to be similar regardless of which regimen is used, however, the cost of deploying ACTs in HMM will certainly be higher than that of chloroquine. Although the effectiveness of HMM with ACTs is likely to be greater than with chloroquine, this has not been demonstrated. In addition, further evaluation of the cost-effectiveness of HMM, particularly using ACTs, would be instructive. Deployment of ACTs just within the public health sector already poses a significant challenge to many countries due both to cost and to limitations in the global supplies of artemisinin compounds (Malik *et al.*, 2006; Zurovac *et al.*. 2007) and the costs and benefits of further deployment of ACTs in HMM programmes should be assessed.

Presumptive treatment of all childhood fevers in Africa would greatly increase ACT demand and drug pressure, even if just a proportion of fevers were actually treated. A number of studies suggest that increased antimalarial use speeds the emergence and spread of parasite resistance (Talisuna *et al.,* 2004; Valley *et al*., 2007; O'Meara *et al.*, 2006). Instead of deploying a single ACT regimen as first-line treatment in both health facilities and HMM, use of different regimens in different settings may be an alternative approach. Early modeling work suggests that using more than one ACT in a region, e.g.

administering different ACTs in facilities and in HMM, may slow development of resistance, although this theory requires further investigation (Laxminarayan *et al.*, 2006). Poor patient adherence to treatment is also likely to contribute to the development of parasite resistance, through exposure of parasites to sub therapeutic drug levels (White and Olliaro, 1996; Price and Nosten, 2001). Use of pre-packaged drugs, as promoted for HMM, has been shown to improve adherence (Yeboah-Antwi *et al.*, 2001; Ansah *et al.*, 2001) which may deter parasite resistance. The impact of widespread presumptive use of ACTs in HMM programmes on the development of drug resistance requires further study.

2.10. Community-Based Approach to Home Management of Malaria.

A community-based project was conducted in Kenya (1981 – 1983) in a hyper- to holo-endemic area near Lake Victoria (Spencer *et al*., 1987). All households were registered, and the community was divided into three areas, two interventional, and one control. Community Health Workers (CHWs) were trained to give chloroquine free of charge "to every person who came for treatment saying they had malaria," and to refer ill patients. Each household was revisited at six to nine month intervals and information on births, deaths, and migration was recorded. Biannual surveys were also conducted in randomly selected villages to assess parasitaemia and antimalarial antibodies. Despite high utilization, presumptive treatment with chloroquine was found to have no impact on malaria-specific or overall mortality. Further, there was no change in parasite prevalence or serologic markers. The authors attributed the lack of effect to the high level of presumptive treatment within the community prior to the onset of the programme.

In The Gambia (1982-85), a community-based programme was conducted in an area with seasonal transmission (Greenwood *et al*., 1988), with follow-up assessments in 1986–87 (Menon *et al*., 1990). In the initial evaluation, presumptive treatment of fever with CQ was found to have no impact on morbidity or mortality. A similar study was conducted in a meso-endemic area on the western shore of Lake Kivu Zaire (Democratic Republic of Congo) between 1985 and 1987 (Delacollette *et al*., 1996). The intervention was associated with a decrease in malaria morbidity: a two-fold reduction in mean malaria prevalence and incidence, and a five- to six-fold decrease in parasitological indices were observed.

The impact of community-based provision of prompt antimalarial treatment on the risk of progression to severe disease was studied in north-western Burkina Faso (1994-95) (Pagnoni, *et al*., 1997). The intervention involved teaching mothers to recognize malaria episodes and providing pre-packaged CQ through CHWs. A "core group" of mothers and CHWs received training from local nurses in the diagnosis and treatment of uncomplicated malaria, and were expected to train other mothers in the village. Emphasis was placed on entrusting mothers with the decision to treat their children. This study confirmed the feasibility and affordability of community-based presumptive treatment, and suggested a morbidity benefit. Empowering mothers as decision-makers for diagnosis and treatment, and the cost-recovery scheme of the programme, were considered to be strengths of the intervention.

An Ethiopian (1996-1998) trial examined the effect of "teaching mothers to promptly provide antimalarials to their sick children at home," as compared to health facility-based treatment, on under-5 mortality (Kidane and Morrow, 2000). This widely-cited study found a reduction in the under-5 mortality rate of 40.6%.

An observational study was conducted in south-eastern Burkina Faso, an area with hyper-endemic seasonal malaria (Sirima *et al.,* 2003). A "core group of opinion leaders," mostly older mothers, and CHWs were trained in diagnosis of malaria, referral of cases, and treatment with pre-packaged chloroquine and aspirin. Of 1806 children receiving prompt treatment with pre-packaged chloroquine, 93 (5%) progressed to severe malaria, compared to 153 of 1396 (11%) of children who did not receive this treatment (risk ratio 0.47, 95% CI 0.37 – 0.60, $p < 0.0001$). The authors addressed the possible impact of non-differential misclassification, recall bias, lack of parasitological confirmation of disease, and confounding factors on their findings, concluding that these were unlikely to affect their positive results. They noted that the study only provided evidence on risk of progression to cerebral malaria, not other clinical forms of malaria, including severe anemia.

2.11. Home Management of Uncomplicated Childhood Malaria

To improve access to antimalarial drugs, the World Health Organization is promoting home-based management of malaria (HMM) as a major strategy for Africa (WHO, 2004). HMM involves presumptively treating febrile children at or near home with antimalarial drugs distributed by trained members of the community (WHO, 2004; 2005). Community distributors provide medications and educate primary caregivers about treatment of malaria, administration of antimalarial drugs, and recognition of severe illness. Emphasis on prompt treatment and distribution of pre-packaged antimalarials are strengths of the HMM strategy (Yeboah-Antwi *et al*., 2001; Ansah *et al*., 2001; Ajayi *et al*., 2008).

Prompt treatment with effective antimalarials is a cornerstone of malaria control in Africa. HMM has the potential to improve treatment delivery and decrease malaria-

associated morbidity and mortality. However, the HMM strategy is a major undertaking, and its implementation should be based on sound evidence of public health benefit. To assess the current evidence base for HMM, the following is a review of published studies that evaluated the health impact of community- and home-based treatment for malaria in Africa. These studies were conducted in diverse epidemiological settings in five countries over a span of 18 years. Heterogeneity of the evaluations, including variability in study design, precluded meta-analysis. All studies were conducted in rural areas, and most were done in settings with seasonal malaria transmission. Of the two trials conducted in perennial transmission areas, one in Kenya showed no obvious effect of the intervention (Spencer *et al*., 1987a; Spencer *et al*., 1987b), while the other in the Democratic Republic of Congo showed a decrease in malaria morbidity but no impact on mortality (Delacollette *et al*., 1996). All studies evaluated presumptive treatment with CQ, and only two studies (both in Burkina Faso) reported using pre-packaged drugs, a key element of the HMM strategy. Of the four studies that included mortality endpoints, only one showed a benefit (Kidane and Morrow, 2000). Data showing an impact of community-based programmes on malaria morbidity are also relatively sparse with only one study showing a decrease in malaria prevalence and incidence (Delacollette*et al*., 1996), and one demonstrating a decreased risk of progression to severe (essentially cerebral) malaria (Sirima *et al*., 2003). Thus, current evidence demonstrating the health benefit of home- and community-based presumptive treatment of fever with antimalarials is limited, and does not necessarily support widespread implementation of HMM. The use of guideline with adequate training significantly improved correctness of malaria treatment with chloroquine at home (Ajayi *et al*., 2008).

The WHO has advocated scaling up home-based programmes in malaria-endemic countries (WHO, 2004). This is supported by the positive results of the two studies (Kidane and Morrow, 2000; Sirima *et al*., 2003). As of 2004, three countries in Africa (Eritrea, Ethiopia and Uganda) were implementing the full HMM strategy with a non-ACT regimen, while other countries were incorporating some components of the strategy (WHO, 2005). In Uganda, HMM was initiated with pre-packaged CQ plus sulfadoxine-pyrimethamine (Homapak), but artemether-lumefantrine (AL) has recently been introduced in the HMM programme in northern districts, and widespread introduction of AL is expected in the future.

2.11.1. Potential Downsides to Presumptive Home Treatment of Malaria.

There are potential downsides to presumptive treatment at home. Use of antimalarials to treat all febrile episodes, even if administered correctly, may delay treatment of other illnesses (Kallander *et al*., 2006). In addition, over-treatment with antimalarials could promote drug resistance (Duong *et al*., 2004; Talisuna *et al*., 2004) and is likely to have substantial economic consequences (Snow *et al*., 2005; Talisuna *et al.*, 2004).

CHAPTER THREE

3.0. Methods

3.1. Study Setting

The study setting was Lagos State, situated in the South-West Zone of the Federal Republic of Nigeria. It is bordered in the west by The Republic of Benin, in the east and the north by Ogun State and in the south by the Atlantic Ocean. It is the home of almost every tribe in Nigeria. Lagos was the Federal capital until the movement to Abuja in the late 1980s to early 1990, despite this, it is still the commercial capital of the country. It has twenty (20) Local Government Areas (LGAs) (Nigeria Constitution, 1999) (Fig. 3.1).

Four LGAs (Alimosho, Ikeja, Mushin and Ajeromi-Ifelodun) (Fig. 3.1) were randomly selected by balloting. For the purpose of this study, an advocacy visit was first made to the traditional rulers, who chaired the meeting involving community leaders, religious leaders, women leaders and the local government area officers of the study areas to intimate them with the proposed work.

During the meeting, the aim, objectives, modalities and possible outcomes of the study were explained to them. Possible application of the outcomes in malaria policy formulation was also highlighted. This was to make them feel involved as partners.

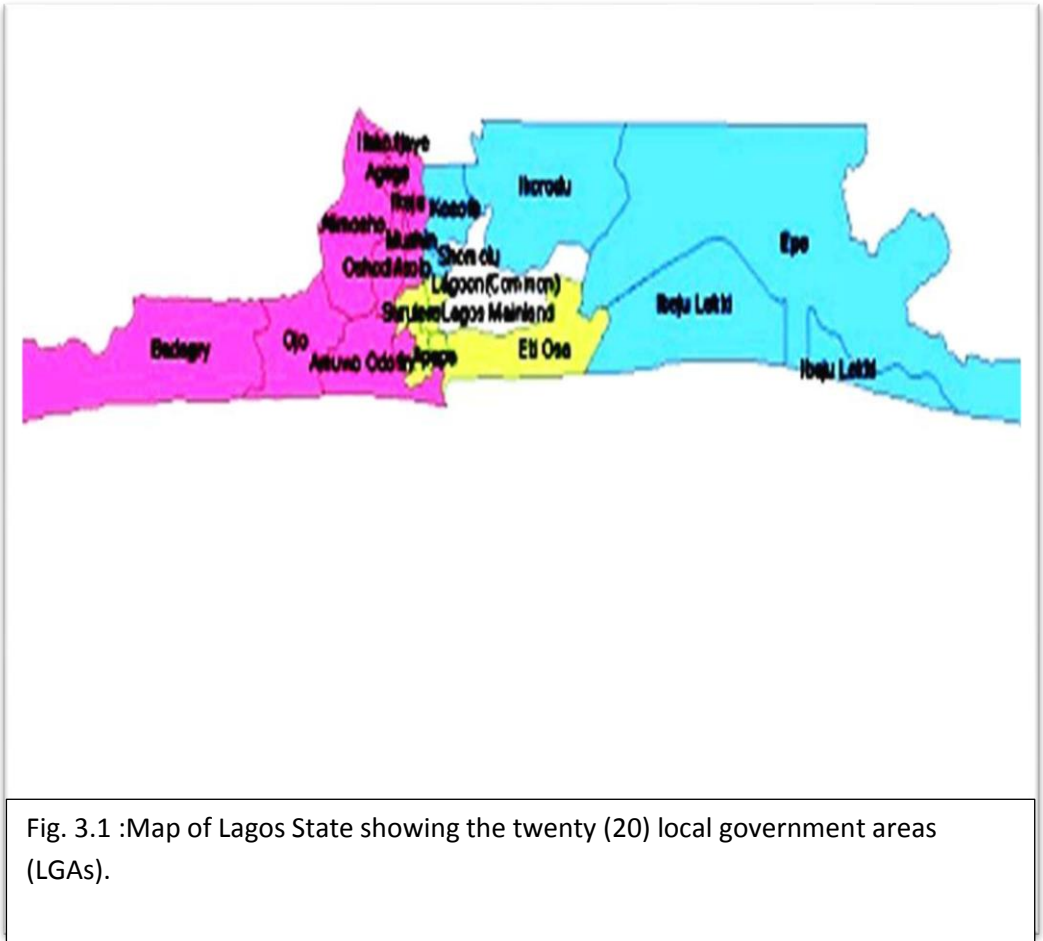

Fig. 3.1 :Map of Lagos State showing the twenty (20) local government areas (LGAs).

3.2. Study Design and Measurement

The instrument used was either self-administered (literate respondents) or interviewer-administered (non-formal education respondents). In the latter case, the questionnaires were explained and interpreted in Yoruba and/or Pidgin English as appropriate. The Nigerian Pidgin is an English-based pidgin and Creole, language spoken as a *lingua franca* across Nigeria and many West African countries as far as Sierra Leone. The language is commonly referred to as "*Pidgin*" or "*Broken*". It is distinguished from other creole languages since most speakers are not true native speakers, although many children do learn it at an early age. It can be spoken as a pidgin, or a creole by different speakers, who may switch between these forms depending on the social setting. It was explained that our mission was not for tax and/or related purposes. Their names, addresses, telephone numbers and e-mail addresses (willing respondents) were recorded for the purpose of further studies and feedback of findings and observations only.

3.3. Ethical Consideration

The respective Health Department of each local government area was approached for permission to operate within their LGA. This was given after the experimental design has been explained. Although the study did not involve any invasive technique, respondents were fully briefed and their consent obtained before they were admitted into the study.

3.4. Selection of Study Participants

3.4.1 Selection of Local Governments Areas. For the purpose of this study a map of Lagos State was obtained (Fig. 3.1). Four (4) of the 20 LGAs were selected by convenience sampling method. The selected LGAs were Alimosho, Ikeja, Mushin and Ajeromi-Ifelodun.

3.4.2 Selection of Study Participants. Each LGA was divided into four (4) zones (East, West, North and south) giving a total of 16 zones. From each zone, thirty (30) mothers and (30) fathers were selected by convenience sampling. Fathers in this study fell into two categories. In the first category were fathers that lived with the mothers of the children whether as husbands or as partners. The second category consisted of fathers that did not live with their wives or mothers of their children.

Overall, 30 mothers and 30 fathers = 60 respondents per zone x 16 zones) making a total of 960 potential respondents were selected.

3.5 Inclusion Criteria

3.5.1 Inclusion Criteria for Mothers

- Child-bearing age mothers (19 – 45 years) (WHO's definition of child-bearing age is 15 – 49).
- Mothers must be nursing, at least, a child under 5 years old.
- They must be willing and available to participate throughout the study period.

3.5.2 Inclusion Criteria for Fathers

- Fathers who had, at least, a living child under 5 years old

- Must be willing and available to participate throughout the study period.

3.6 Exclusion Criteria

- Medical practitioners, pharmacists, nurses, midwives and medical laboratory scientists because they already had knowledge of malaria and its management.
- Mothers and fathers who had no surviving child under 5 years old.
- Unwillingness to give oral consent.

3.7 Determination of Sample Size

The population figures of Lagos State from both Federal and State governments are conflicting (15 and >20 million respectively). The required sample size (ss) of 960 mothers and fathers was determined using the formula:

$$ss = Z^{2*}(p)^{*}(1\text{-}p)/c^{2}$$

Where: Z = Z value (e.g. 1.96 for 95% confidence level)

p = percentage picking a choice, expressed as decimal (0.5 used for sample size needed)

c = confidence interval, expressed as decimal (e.g. 0.05 = ±5).

3.8 Data Source and Development of Study Instrument

The instrument (questionnaire) was designed based on the objectives of the study. To determine the demography, knowledge, attitude and practice of respondents, mothers' perception of fathers as care givers in HMM, drugs use in HMM, source of antimalarial drugs used in HMM, determinants of the choice of drugs, drug availability and access to drugs. The instrument was pre-tested in the same LGAs but using different subjects of equivalent demography to ascertain that the final respondents understood the

questionnaires which are a means of standardization. After the pre-test, appropriate corrections were made before final administration of the questionnaires which was validated using Cronbach's alpha (Cronbach 1951).

3.9 Effect of Education on the Various Parameters Studied

The effects of educational status of respondents were studied on their understanding, knowledge and practice of home management of uncomplicated childhood malaria, referral to an organized healthcare facility (as and when necessary), the choice of drugs to use in the treatment, and efficacy of the drug in a previous malaria episode. Respondents were stratified into non-formal-, primary-, secondary- and tertiary-education groups.

3.10 Factors Influencing Access To Drugs In HMM

A set of study was designed to investigate the factors influencing access to antimalarial drugs in home management of uncomplicated childhood malaria. Access was defined as availability and cost in this study. It was not intended to incorporate factors such as affordability in this study. Hence, to all intent and purposes, factors influencing access in this study were defined to include, availability, cost, packaging, brand of the drug, and rational use (previous efficacy of the drug, that is, in a previous episode of malaria suffered by the child, parent, and/or others that may influence decision of the care-giver).

3.11 Data Analysis

Results were expressed as percentage of total. Results were analysed with Statistical Package for Social Sciences (SPSS) Version 17.0. Where appropriate, they were expressed as means, standard deviation and standard error of the mean. In some

instances, Null hypothesis and Chi-square tests were done, likelihood ratio and linear-by-linear association were calculated. In some cases, Fisher's Exact Test was also done. $P<0.05$ was taken as the level of statistical significance.

CHAPTER FOUR

4.0 Results

4.1 Demography

A total of 960 questionnaires were sent out, 809 (84%) were completed and returned. All the returned questionnaires were used. The 809 was made up of 485 from mothers and 324 from fathers. Demographic profiles of the respondents were collected. Table 4.1 shows the analysis of the demography.

There was a total of 809 made up of 326 (18-30 years old, i.e, 40%), 380 (31-40 years, i.e, 47%), 103 (41 years and above, i.e, 13%) respondents (Table 4.1). Judging from the mean score, the average 1.72 falls upwards above the bench mark (2.0, whereby 1>2), thus the age range will fall within 31-40 years of age, with 1.688-1.770 confidence interval. The indication of this was that if the survey was repeated 100 times over a period of time, there was a 95% confidence (remaining 5% as an error) that the mean score would fall within 1.688-1.770. This showed that the average age of caregivers was within 18-40 years range.

4.1.1. Gender Representation

The total number of mothers was 485 (60%), and fathers 324 (40%) respectively of the total respondents (Table 4.1). The mean score was 1.40, which was above the bench mark (1.50, whereby 1>2) indicating that majority of the respondents were mothers. In addition, there was a 95% certainty that in further surveys with all other factors being equal (unbiased), our mean score would fall within range 1.37-1.43 which is still above the bench mark. This means majority of our respondents will almost always be mother

Table 4.1. Demography of Respondents

Age (years)	Respondents	Percent (%)	Lower bound (Cl-95%)	Upper bound (Cl-95%)	Mean score of Respondents
18 – 30	326	40	1.68	1.77	1.724 (n = 809)
31 – 40	380	47			
More than 41	103	13			
Gender			1.37	1.43	1.4 (n = 809)
Mother	485	60			
Father	324	40			
Children			1.46	1.55	1.503 (n = 809)
One	475	59			
Two	276	34			
Three	43	5			
Four	15	2			
Education					
Primary	165	20			
Secondary	382	47			
Tertiary	191	24			
Non-formal	71	9			

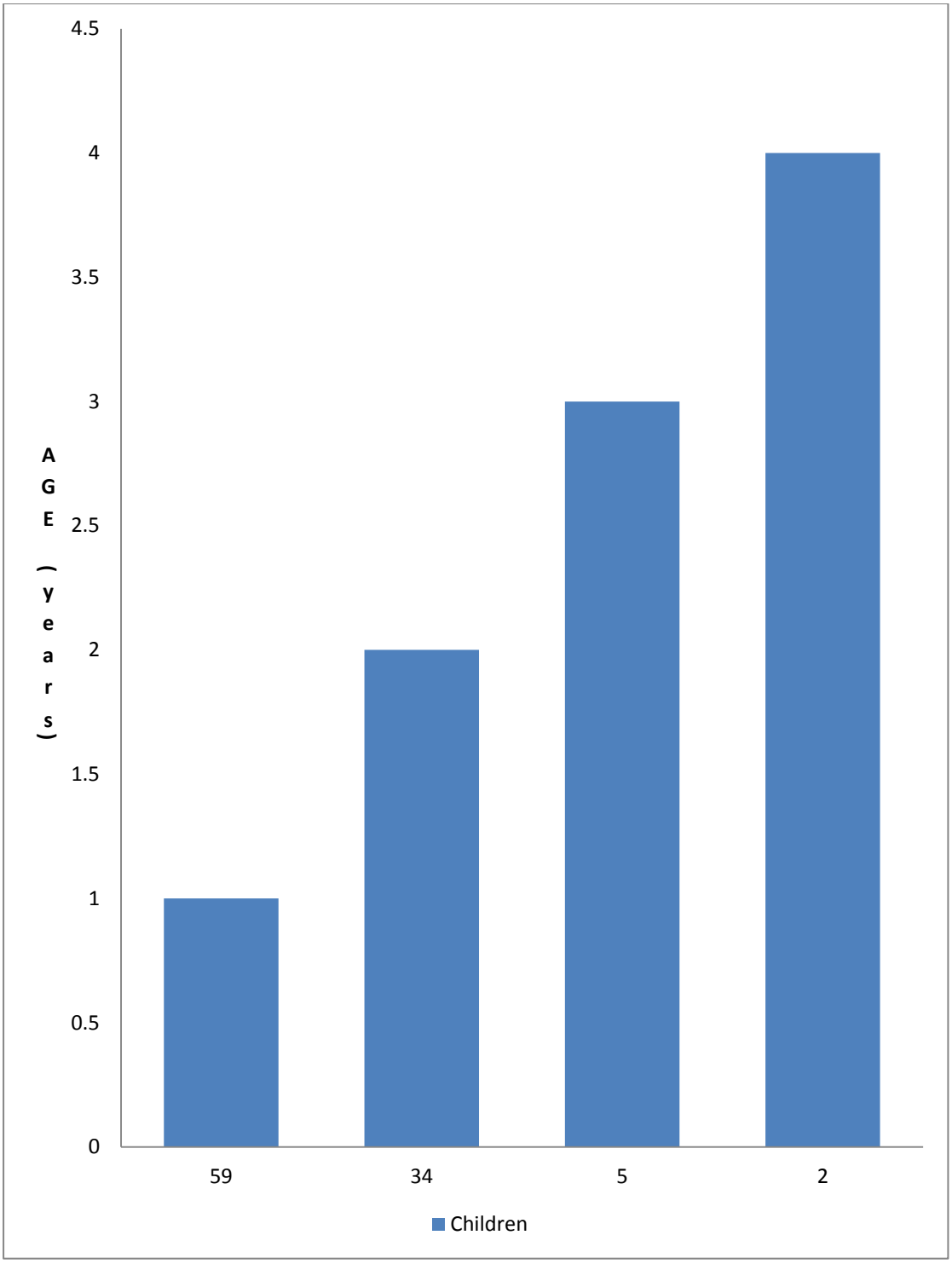

Fig. 4.1. Total per cent of respondents expressed according to number of children under 5 years old.

4.1.2. Number Of Children Under- 5

More than half of the respondents, 475 (59%) had one child under 5 years old, 276 (34%) had two children under 5 years old, 43 (5%) three children under 5 years old, and 15 (2%) had 4 children under 5 years old (Fig. 4.1). None of the respondents had more than 4 children. With an average score of 1.503 this is a strong indication that majority of respondents had one or two children under 5 years old. At 95% the mean score fell between 1.46 and 1.55.

4.1.3. Educational Background

The total population of respondents was stratified according to their educational status. It was found that while only 9% had no formal education, 20%, 47% and 24% respectively had primary, secondary and tertiary education (Fig. 4.2).

When the respondents were stratified according to their gender and educational background, it was found that the educational status of mothers and fathers was almost even except that more fathers had tertiary education than mothers, while more mothers had primary education than fathers (Fig. 4.3).

4.2. Knowledge And Practice Of Mothers And Fathers On Malaria

In this section, the knowledge of mothers and fathers on malaria was tested on the causes, prevention, signs and treatment of malaria: How do mothers and fathers understand the causes of malaria? Is their educational status a factor in determining their understanding of the cause of malaria? The bivariate Table 4.2.below gives an insight to our analysis. A total of 37, 15, 756, and 5 respondents respectively chose flies, bees, mosquitoes and juju respectively as the cause of malaria, while 10 did not indicate any cause. A Chi-square test statistics was done to compare these two variables

using Statistical Packages for Social Sciences (SPSS) Version 17.0. Literate respondents had a better knowledge of the causes of malaria than those with no formal education.

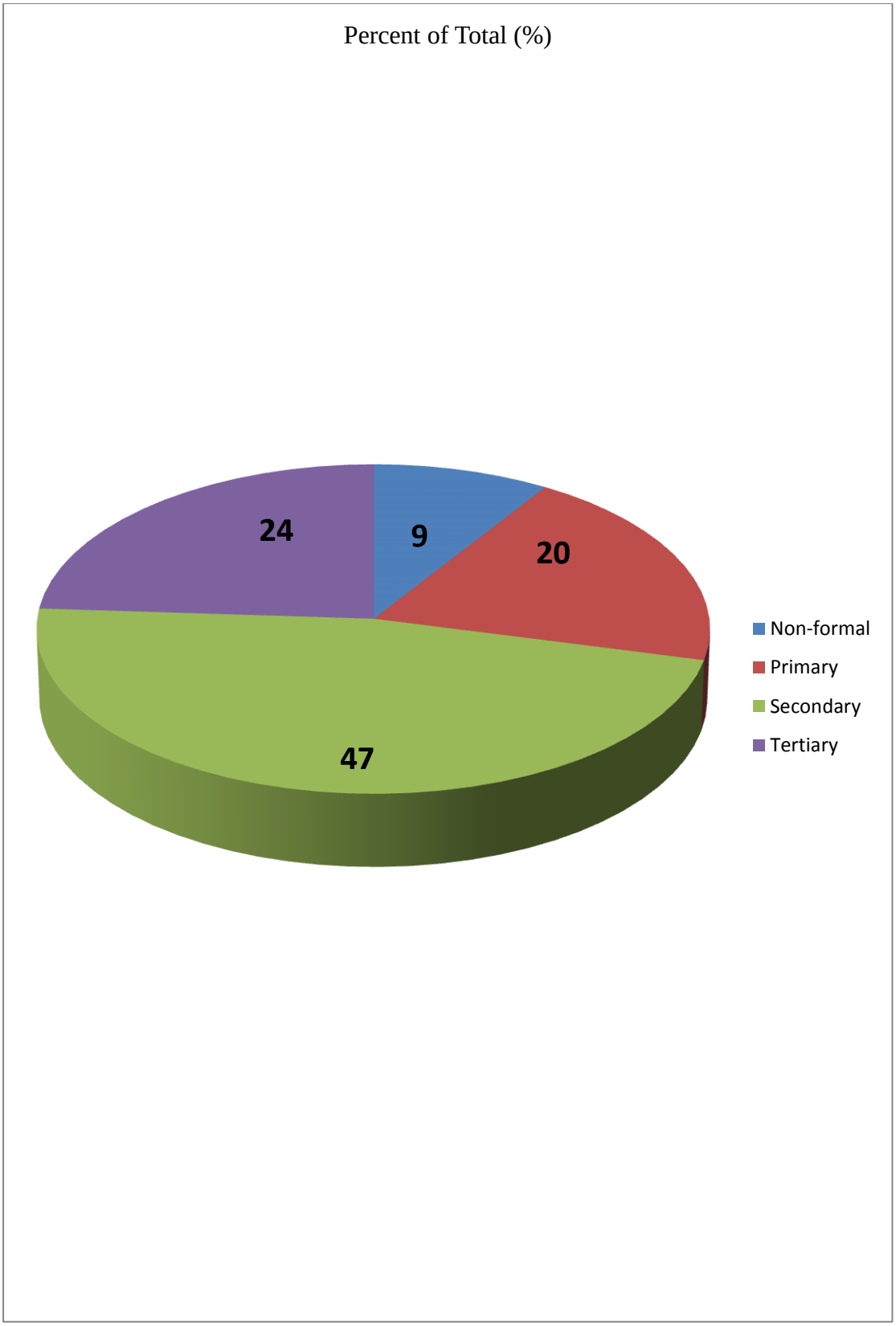

Fig. 4.2. Population of respondents expressed according to their educational status.

Table 4.2.Effect of education on respondent' understanding of causes of malaria.

Cause of malaria	**Educational background**				
	Primary	Secondary	Tertiary	Non-Formal	Total
Flies	8	14	4	11	37
Bees	4	3	7	1	15
Mosquito	152 (92%)	365 (96%)	182 (95%)	57 (80%)	756
Juju	1	1	3	0	5
Don't Know	5	3	0	2	10
Total	165	382	191	71	
% of Total Respondents	20	47	24	9	100

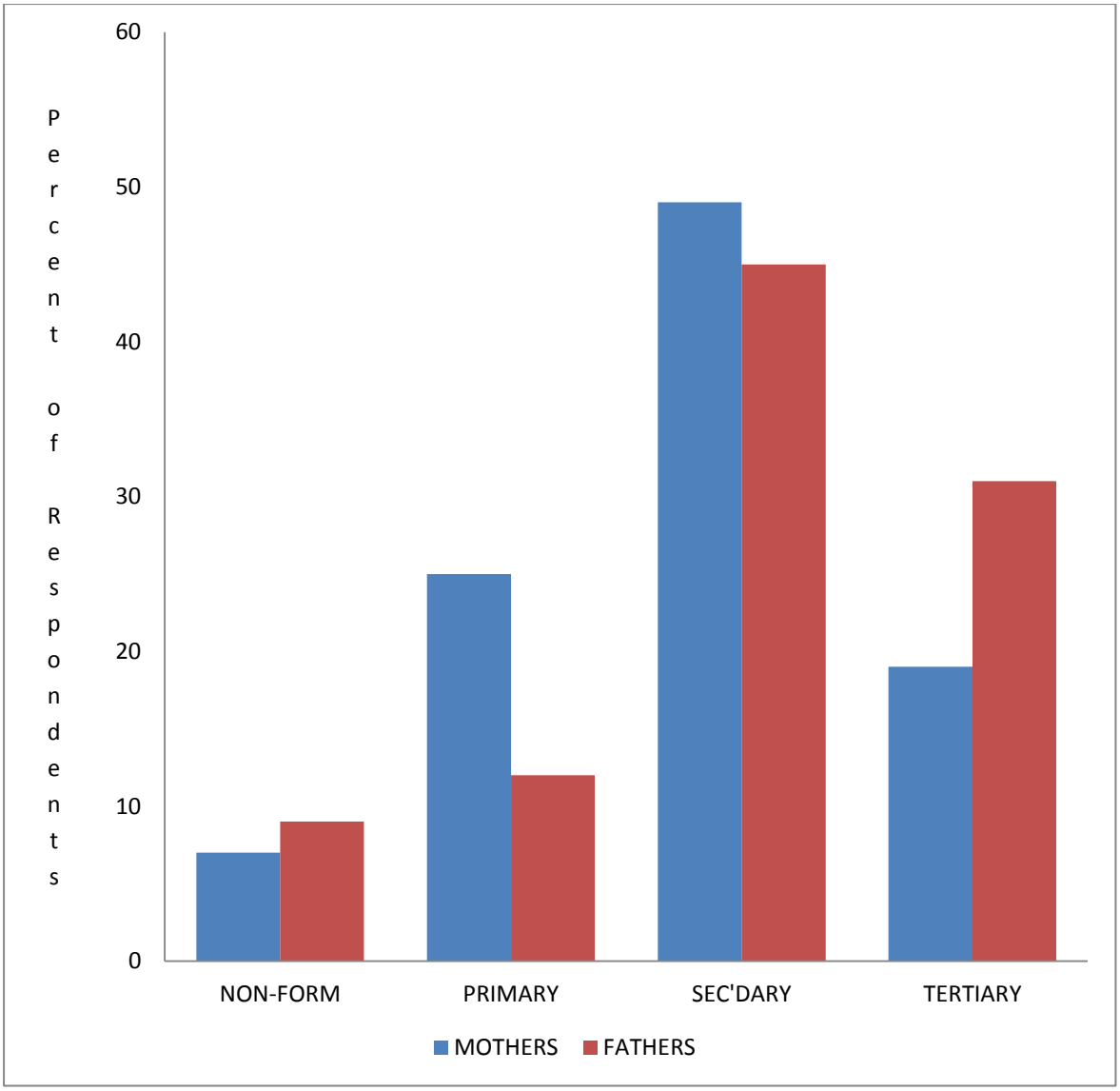

Fig. 4.3. Stratification of respondents according to their gender and educational status.

Key : N-F = non-formal education,

PRY = primary education,

SEC = secondary education

TER = tertiary education.

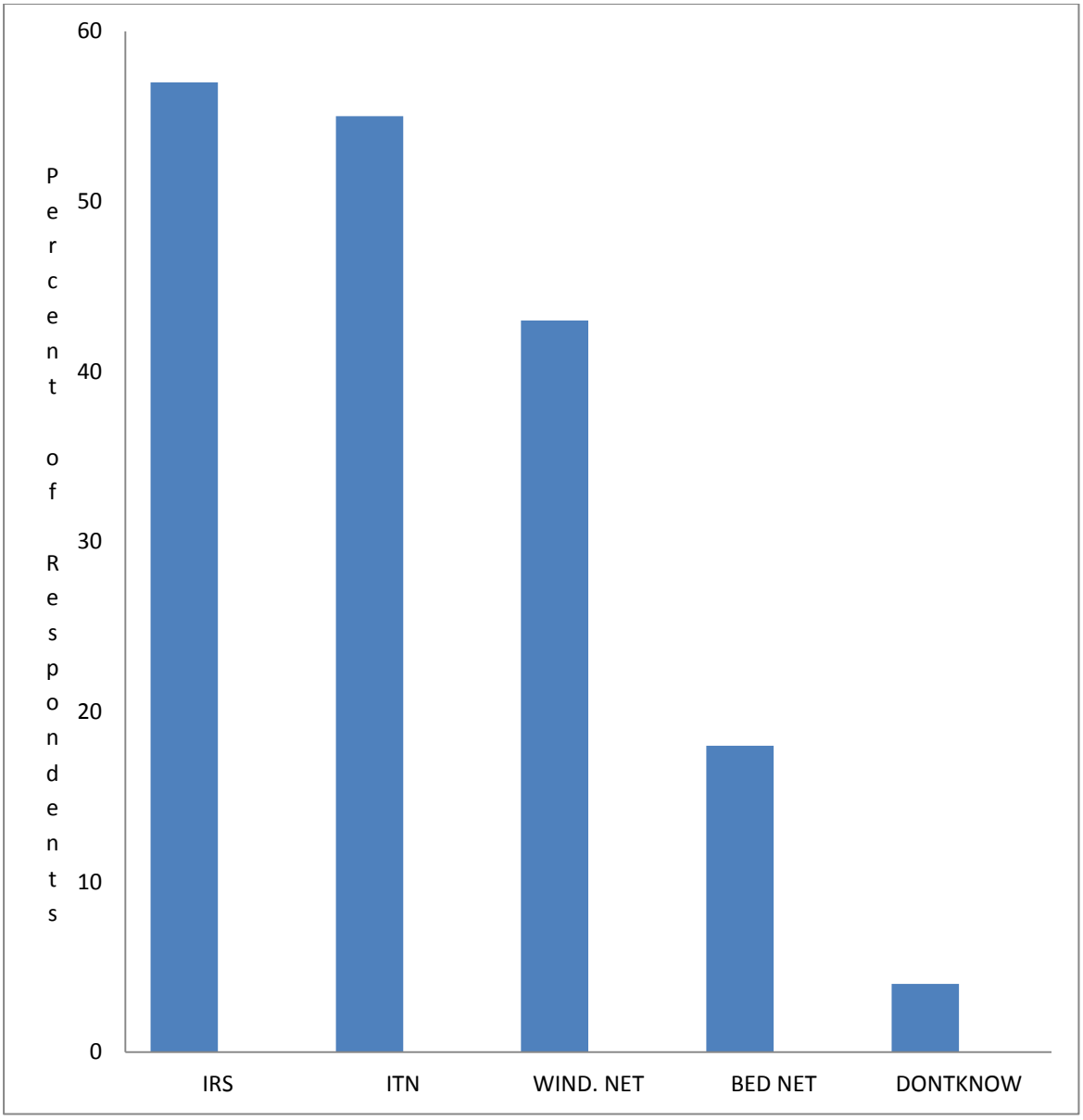

Fig. 4.4 Knowledge of respondents on the choice of prevention of malaria expressed as %.

Key:

ITN = Insecticide treated net,

IRS = Indoor residual spray,

WIND.NET = Window net.

4.2.1 Choice Of Method Of Preventing Malaria By Mothers And Fathers Involved In HMM.

Majority of the respondents (56%) chose IRS, ITN (55%) and window net (43%) as the methods of preventing malaria (Fig. 4.4). The difference between IRS and ITN was not statistically significant ($P > 0.05$), however, there were statistically significant differences between IRS, ITN and the other choices ($P < 0.05$).

The effect of the educational status of respondents on their choice of preventive method of malaria is shown in Fig. 4.5. Educational status positively influenced the choices of bed net, ITN and window net, however, the choice of IRS was not dependent on their educational status. The order of preference was as follows: non-formal education: IRS > ITN = Window net >> bed net; primary education: ITN > IRS = window net >> bed net; secondary education: ITN > IRS > window net >> bet net; and tertiary education: ITN = IRS > window net >> bed net (Fig. 4.5).

A Chi-square test was done and the result indicated that educational status and method of malaria prevention were interdependent.

4.2.2. Knowledge Of Mothers And Fathers Of The Symptoms Of Malaria

Of the respondents, 68%, 46%, 45%, 28%, 14%, 7%, 3%, and 2% chose fever, chills/rigors vomiting, pallor, dehydration and diarrhoea as the symptoms of malaria respectively (Fig. 4.6). There were statistically significant differences between fever and each of the other symptoms ($P < 0.05$), chills/rigours and vomiting and the other symptoms ($P < 0.05$), pallor and dehydration and diarrhoea ($P < 0.05$). This indicated

that majority had knowledge of fever as an early symptom of malaria. Chills and rigours, pallor and vomiting are also signs of malaria.

The educational status of respondents significantly influenced their knowledge of the symptoms of malaria (Fig. 4.7). Thus, secondary and tertiary education groups demonstrated better knowledge of the symptoms than the primary and the non-formal education groups ($P < 0.05$).

4.2.3 Knowledge Of Mothers And Fathers On The Meaning Of Home Management Of Uncomplicated Childhood Malaria.

Majority of respondents (69%) knew the concept of home management of uncomplicated childhood malaria (Table 4.3). The remaining 31% did not know. The results were not analysed based on gender as the purpose was to determine their knowledge.

The educational status of respondents did not consistently influence their knowledge (Fig. 4.8).

The order of preference was paracetamol (65%), anti-malarial drugs (37%), tepid sponging (26%), bathing (11%), fanning (5%), antibiotics (6%), herbs (3%) and 2% preferred oral rehydrate solution. The differences between paracetamol and the other methods, antimalarials and the other methods, tepid sponging and other methods were significantly different ($P < 0.05$).

4.2.4. Preferred Treatment Of Malaria

The choice of paracetamol ranked highest followed by antimalarial drugs, tepid sponging, fanning, antibiotics, herbal remedies, bathing and oral rehydration solution among the preferred (Fig. 4.9).

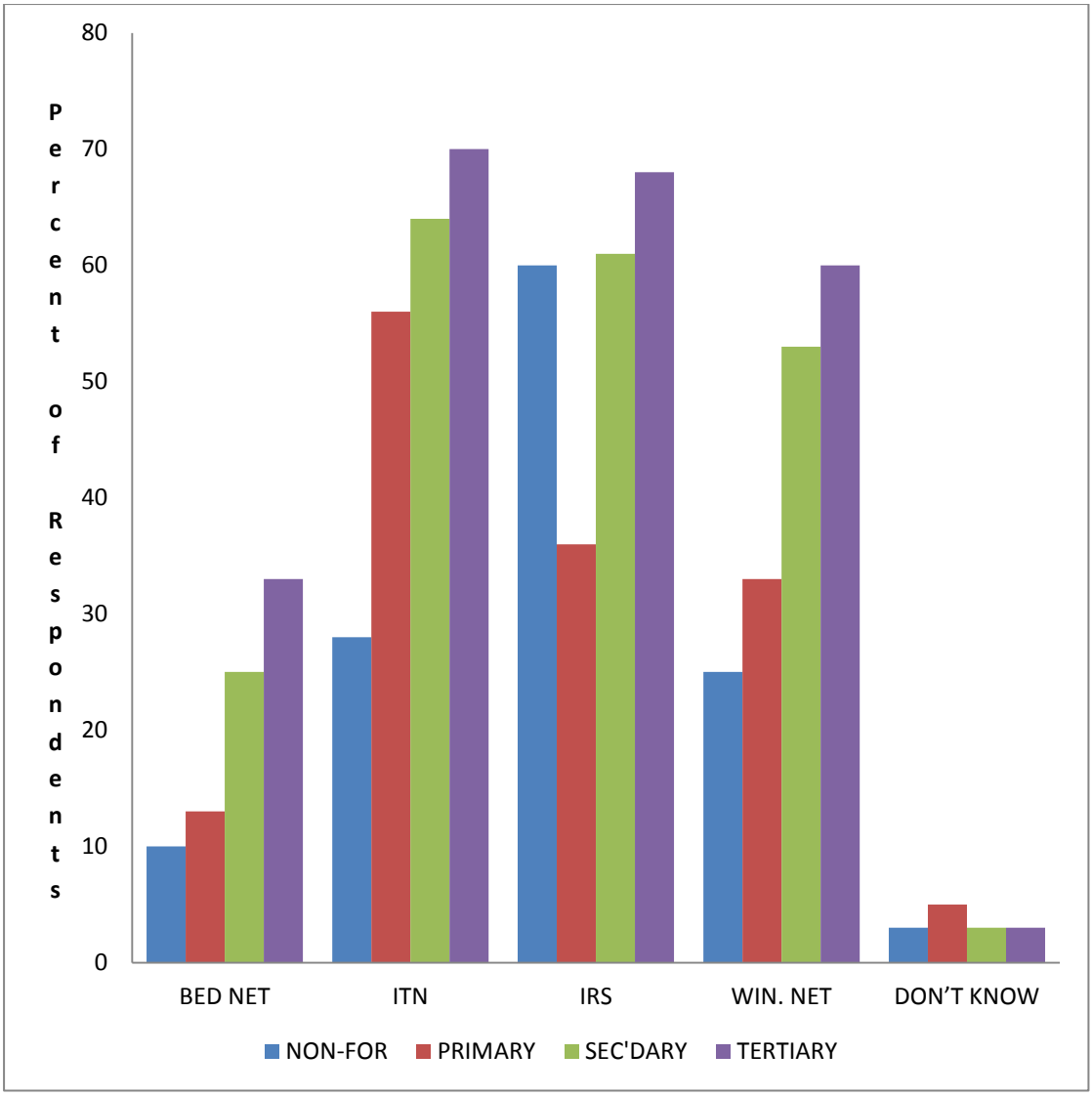

Fig. 4.5 Effect of educational status on the choice of prevention of malaria by respondents.

KEYS: ITN = Insecticide treated net,

WIN. NET = Window net

IRS = Indoor residual spray.

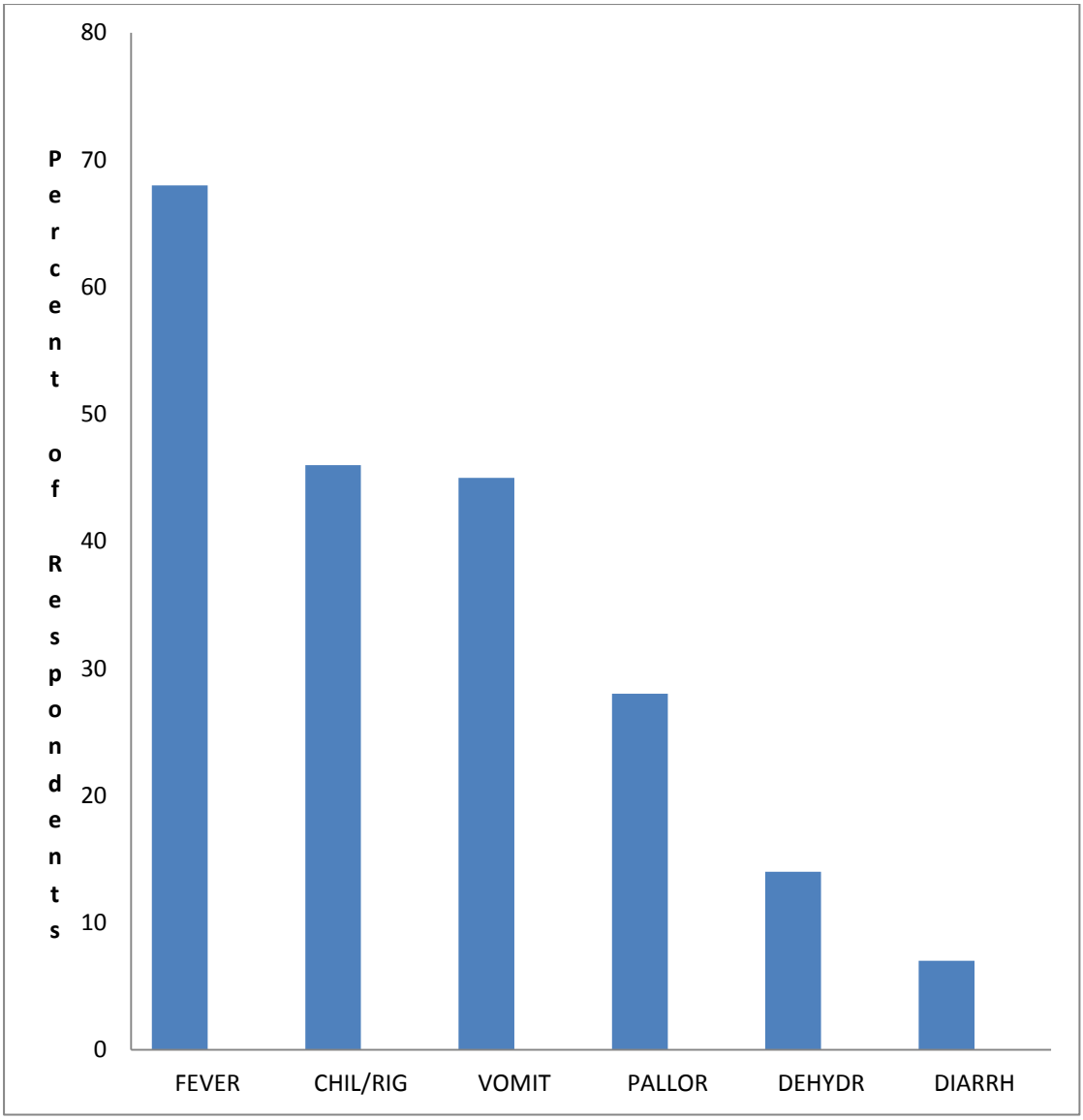

Fig.4.6. Knowledge of respondents on the signs of malaria.

Key:

CHIL/RIG = Chills/Rigour

VOMIT = Vomiting

DEHYDR = Dehydration

DIARRH = Diarrhoea

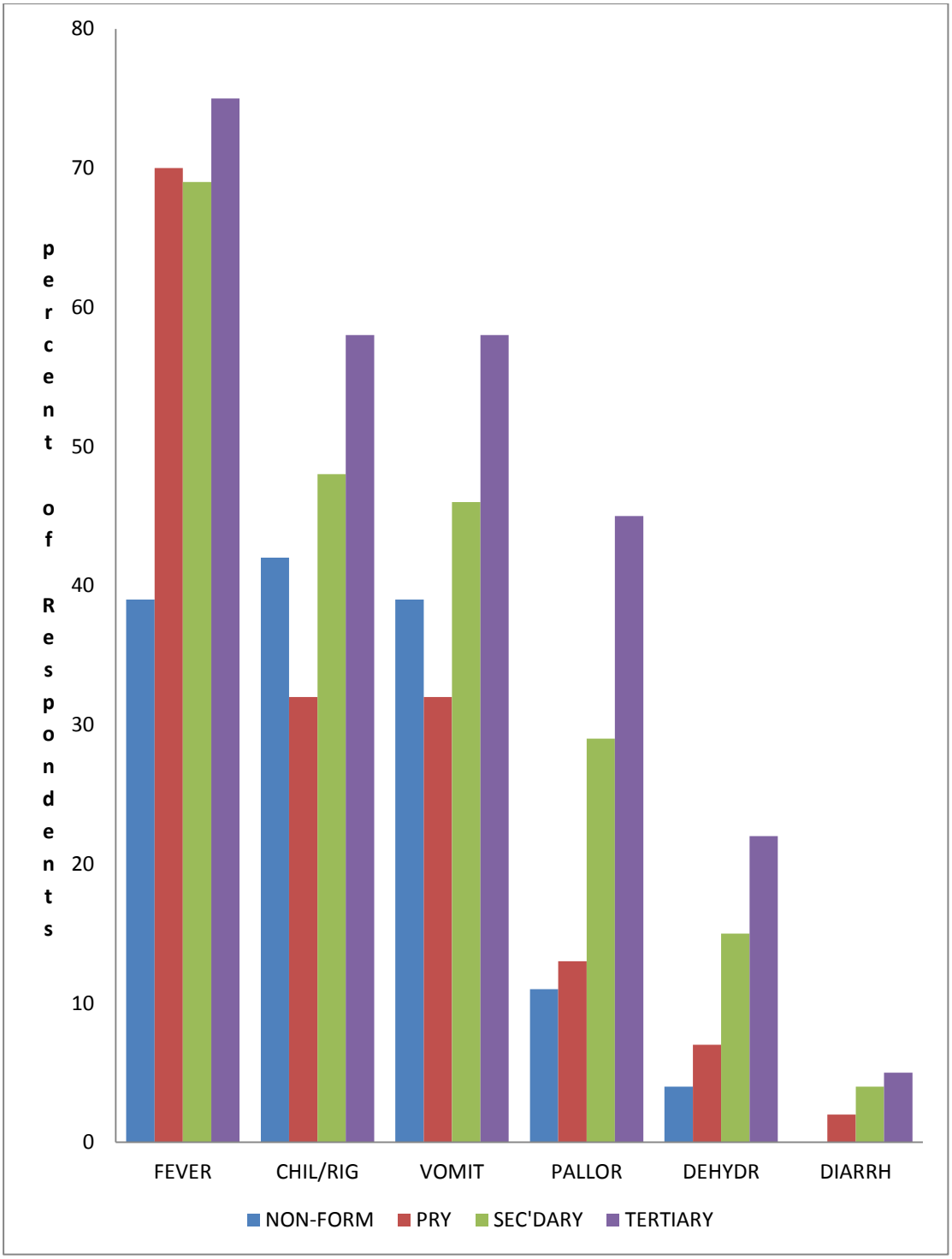

Fig. 4.7 Influence of the educational status of respondents on their knowledge of the symptoms of uncomplicated malaria.

Table 4.3 Knowledge of mothers and fathers of the meaning of home management of uncomplicated childhood malaria.

Home management of uncomplicated malaria is:	**Count**	**Per cent (%)**
Calling doctor to the house to treat the patient	**48**	**6**
Parents treating child's malaria at home	**556**	**69***
Taking child from home to the hospital for treatment	**317**	**39**
Parents giving antimalarial medicines at home	**562**	**69***
Taking child to the health centre for injection	**184**	**23**
No Response	**72**	**9**

Key: * = Correct answers.

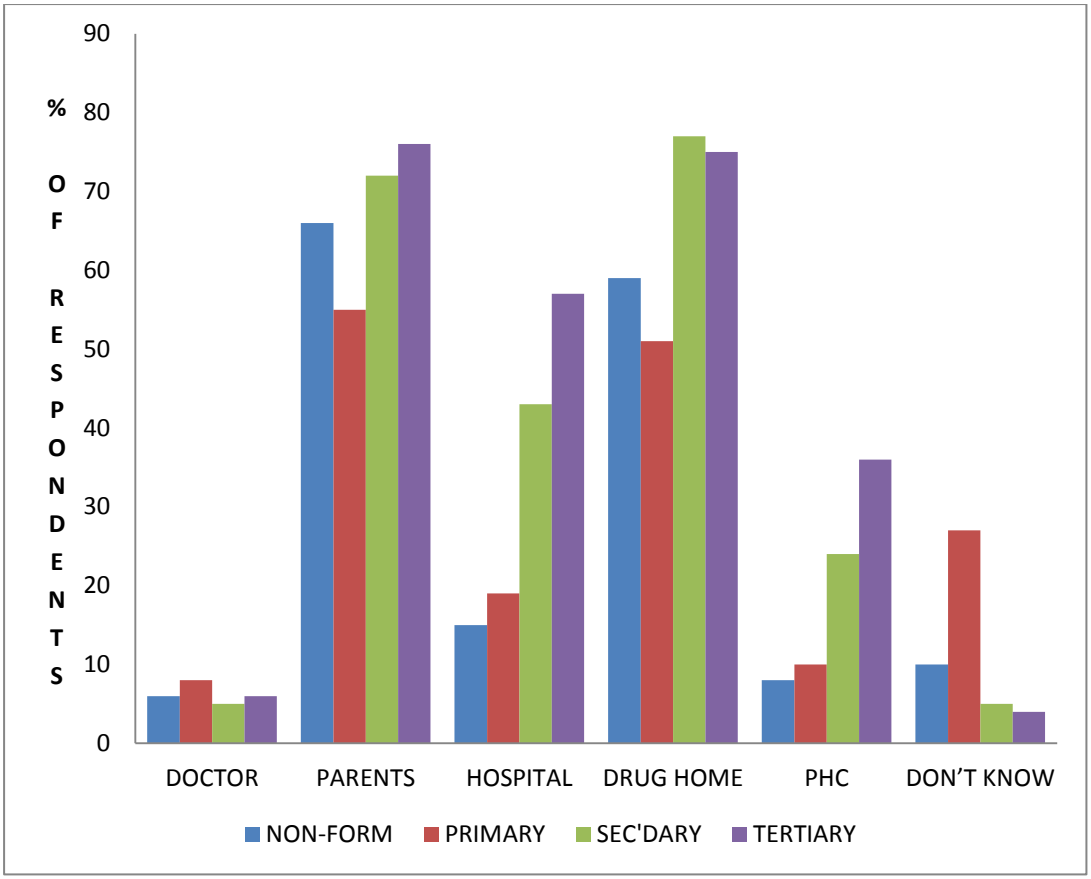

Fig. 4.8 Effect of the educational status of respondents on their knowledge of home management of malaria.

Key: DOCTOR: Calling a doctor to the house to treat patient.

PARENTS: Parents treating child's malaria at home.

HOSPITAL: Taking patients from home to the hospital for treatment

DRUG HOME: Parents giving antimalarial medicines at home.

PHC: Taking child to the health centre for injection.

DON'T KNOW: Those whose response was "Don't Know".

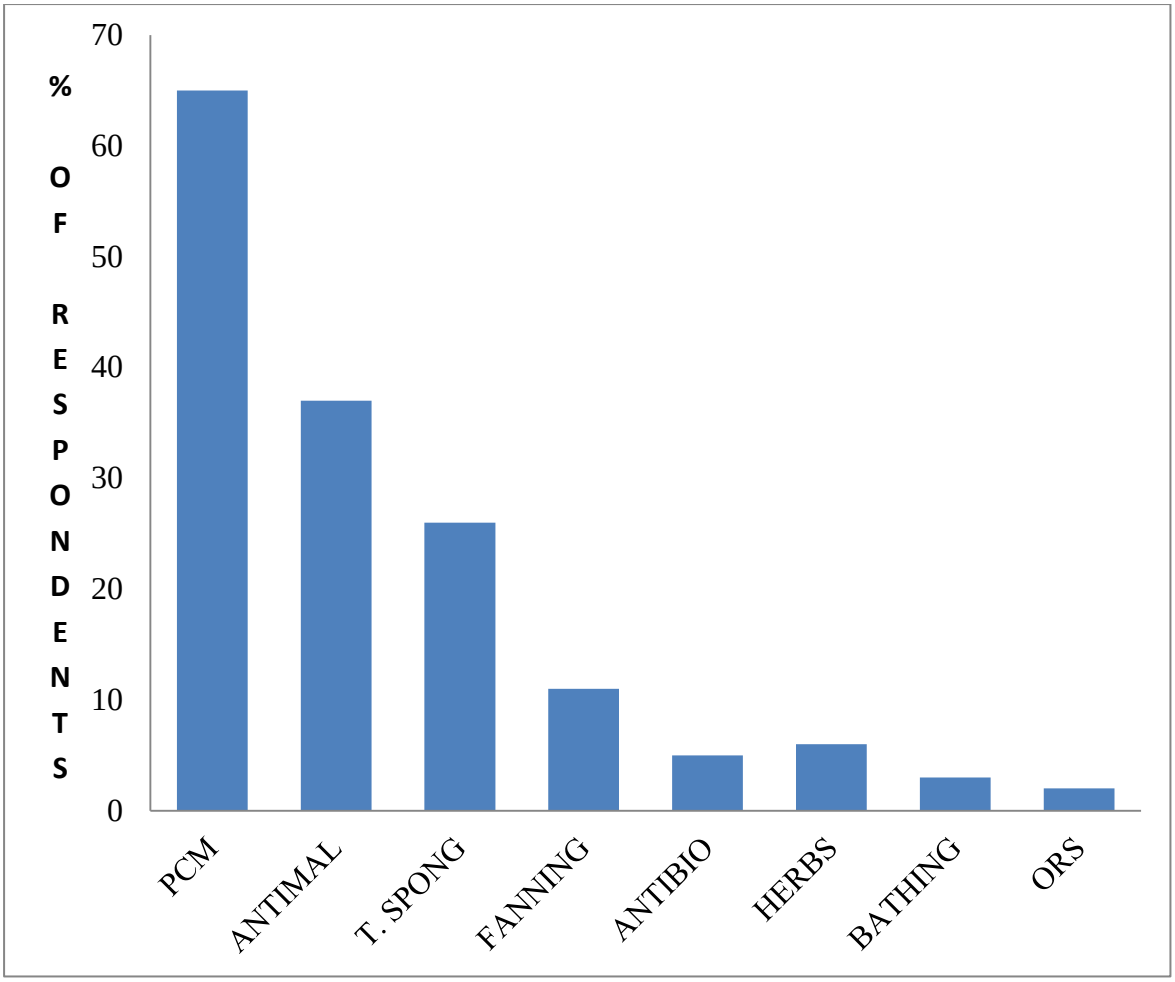

Fig.4.9. is a representation of respondents' answers to the question above. "What is your preferred method of treatment of malaria?"

KEY: PCM = Paracetamol,

ANTIMAL = Antimalarial drugs,

T. SPONG. = Tepid sponging,

ANTIBIO = Antibiotics,

ORS = Oral rehydrate solution.

The **e**ducational status of respondents positively influenced their preference for paracetamol (NF < 1^0 < 2^0 = 3^0) and tepid sponging as preferred choices in the treatment of uncomplicated childhood malaria (Fig. 4.10). The trend with antimalarials was, however, not dependent on the educational attainment of respondents because there was no statistically significant difference (P > 0.05) between the three educated groups. However, there was a statistically significant difference between the non-formal and the educated groups (P < 0.05).

4.2.5 Time Interval Between Noticing The Symptoms And Commencement Of Treatment With Drugs

How soon after noticing symptoms of malaria and commencement of treatment with drugs was determined for all respondents. Majority (60%) commenced treatment between 0 and 1.0 hour after noticing signs, 45% after 1.1 – 6 hour, 10% after 6.1 – 12 hour, 8% after 12.1 – 24 hour, 12% after 24.1 – 48 hour and 3% after 48 hour (Fig. 4.11). Overall, about 97% of the respondents commenced treatment within 48 hours of noticing signs of malaria.

The time intervals were weighted and scored (Fig. 4.11). The number of respondents was expressed as %, for example, 292 mothers out of a total of 485 = 60%. Very early commencement (0-1h) of treatment was practised by 60% of mothers and 61% of fathers, early commencement (1-6h) by 25% and 20% of mothers and fathers respectively. The responses were independent of their educational status. Average score of 5.294845 (mothers) and 5.191358 (fathers) indicated that the response of mothers and fathers were even, with their average response falling between 0-6h. The distribution across education also showed that the average scores were almost even with each of the mean score falling above 7-12h. The indication of this was that majority of

the respondents commenced treatment within 12 hours of noticing any sign of malaria. With a standard deviation of 1.203778, the opinions were clustered, not many opinions dispersed away from the mean score

4.2.6. Frequency Of Noticing An Improvement After Drug Treatment

As shown in Table 4.4, both mothers and fathers noticed improvements all the time and almost every time. These constituted 70% and above of the respondents. These responses were independent of their educational status. With a total mean score of 5.724351, there was a strong indication that the majority had responses above "Sometimes (5.0)"

4.2.7. Frequency Of Noticing No Improvement After HMM.

There were occasions when no improvement was noticed by mothers and fathers in HMM after drug treatment. The results were in two parts. The first part was from all the respondents pooled together irrespective of gender and educational status (Fig. 4.13). The second part was stratified according to their educational background so as to determine the influence of education on their ability to notice or identify non-improvement (Fig. 4.14).

Only 2% of the respondents always noticed no improvement after treatment. An average of 47% occasionally noticed no improvement while 39% never noticed no improvement (Fig. 4.13). If the "always" and the "frequently" are merged, the population that noticed no improvement would still be 11%. This value is still very low compared to the others. However, it is therapeutically important because it means about 10% of those treated were likely to progress to complicated malaria if they were not referred.

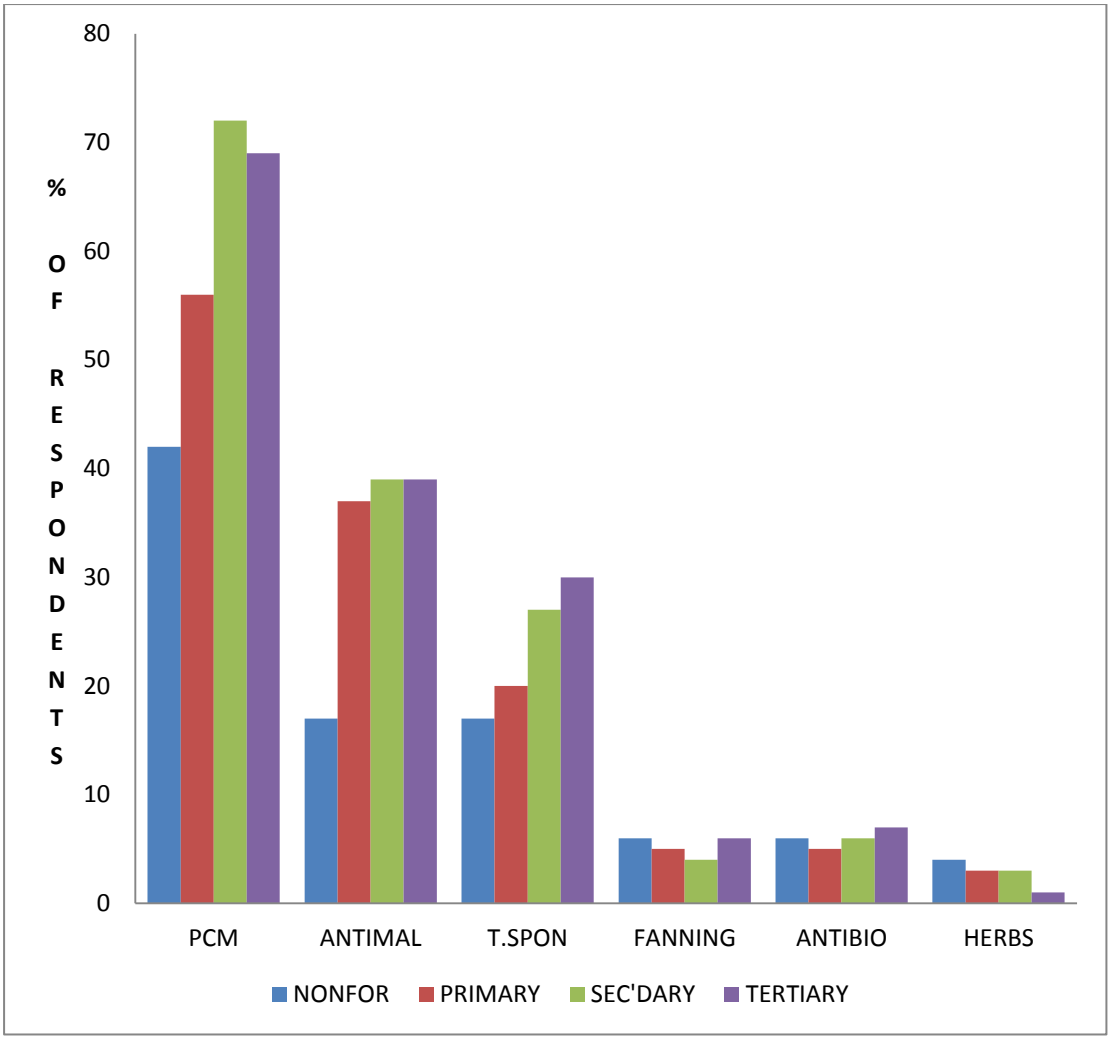

Fig. 4.10. Effect of educational background of respondents on their preferred treatment of malaria.

KEY: PCM = Paracetamol,

ANTIMAL = Antimalarial drugs,

T. SPON. = Tepid sponging,

ANTIBIO = Antibiotics,

ORS = Oral rehydrate solution.

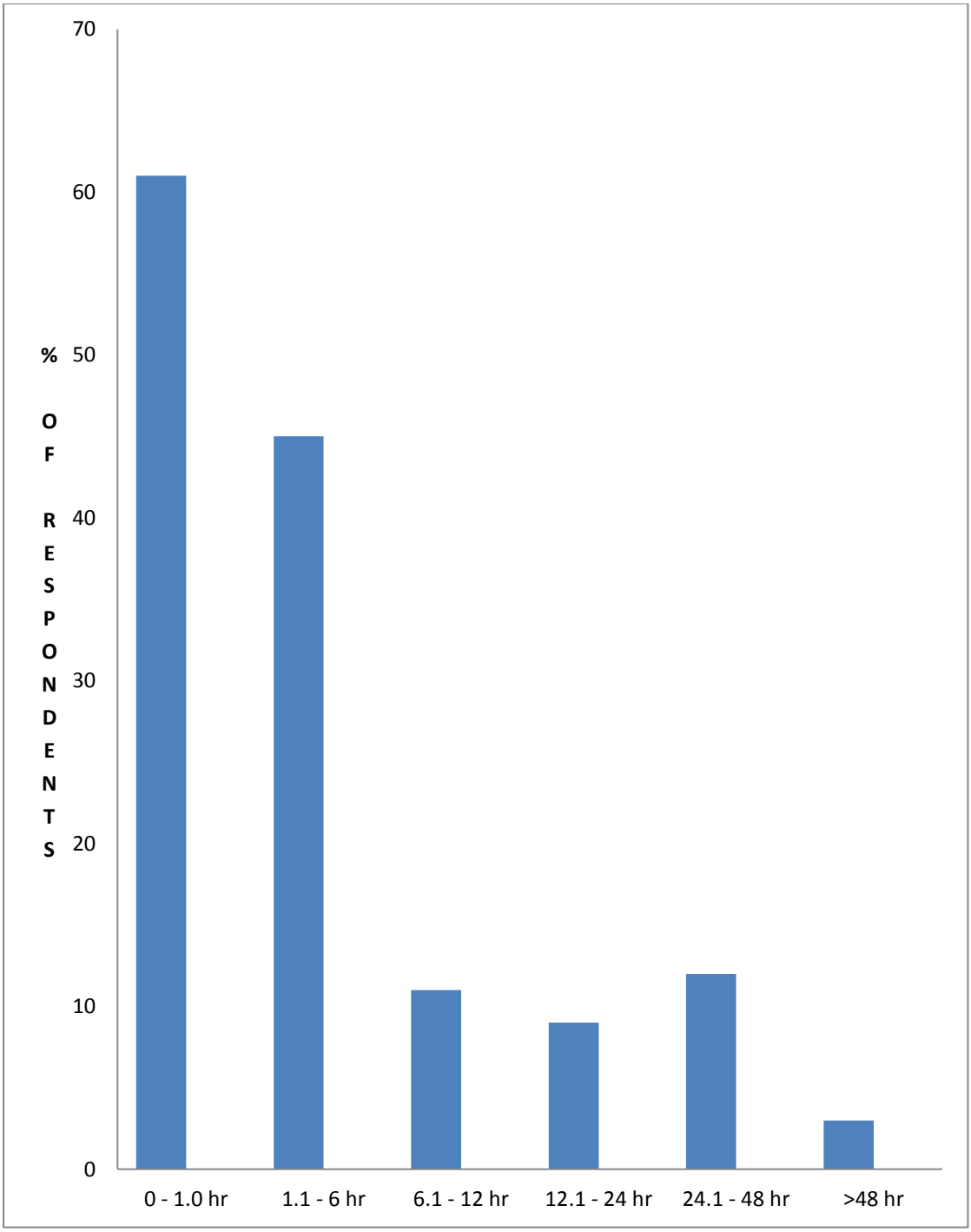

Fig. 4.11. Time interval between noticing the symptoms of malaria and commencement of treatment with drugs.

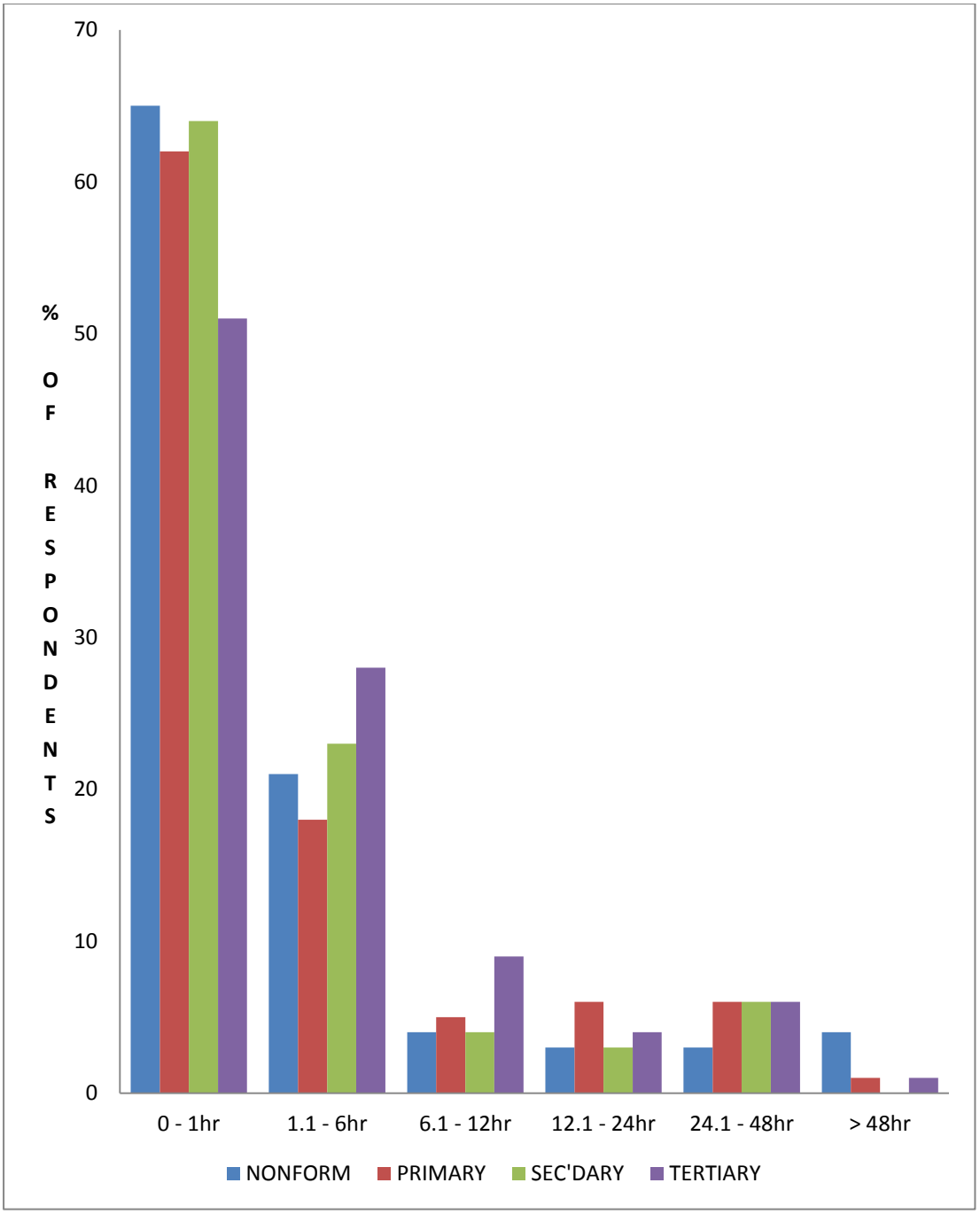

Fig. 4.12. Effect of educational status of respondents on time interval between noticing the signs of malaria and commencement of treatment with drugs.

Table 4.4.Frequency of noticing an improvement after treatment.

	Gender	Educational Background					
Improvement	**Mothers**	**Fathers**	**Primary**	**Secondary**	**Tertiary**	**Non-formal**	**Total**
All the time (7)	190 (39)	118 (36)	51 (31)	161 (42)	79 (41)	17 (24)	308
Almost every time (6.0)	166 (34)	118 (36)	59 (36)	127 (33)	59 (31)	39 (55)	284
Sometimes (5)	76 (16)	42 (13)	28 (17)	53 (14)	31 (16)	6 (8)	118
Rarely (4.0)	27 (6)	25 (8)	15 (9)	25 (7)	10 (5)	2 (3)	52
Very rarely (3)	12 (2)	10 (3)	5 (3)	6 (2)	9 (5)	2 (3)	22
Don't Know(2)	14 (3)	11 (3)	7 (4)	10 (3)	3 (2)	5 (7)	25
Total	485	324	165	382	191	71	809
Std. Dev.	1.45831	1.49252	1.56020	1.418485	1.429755	1.60055	1.4715
Std. Error	0.06622	0.08292	0.12146	0.072576	0.103453	0.18995	0.0517
Mean Score	5.74845	5.68827	5.48485	5.835079	5.764398	5.57747	5.7244
Lower bound (95%)	5.61866	5.52575	5.24678	5.69283	5.56163	5.20516	5.62295
Upper bound (95%)	5.87824	5.85079	5.72291	5.97732	5.967166	5.94976	5.82575

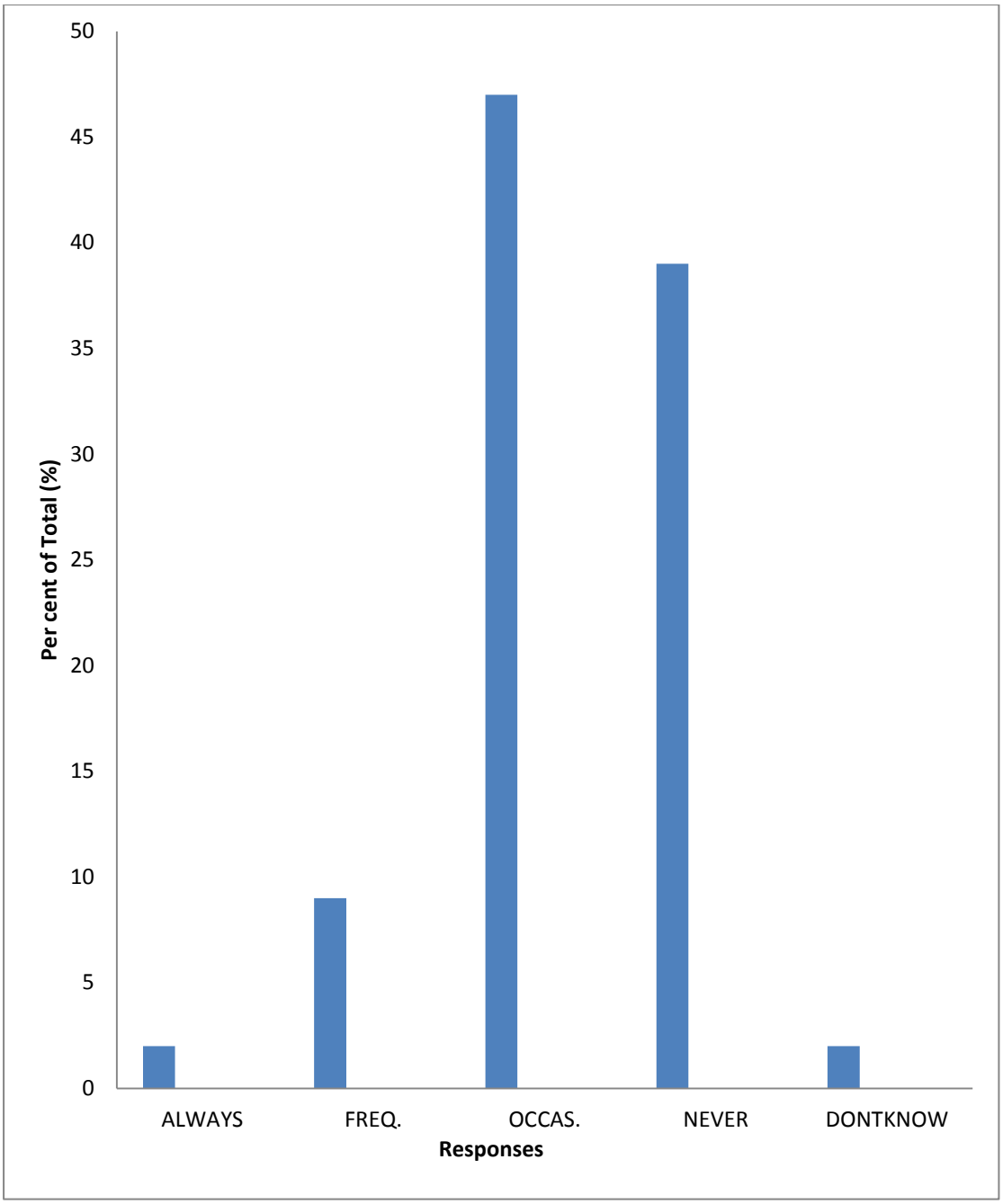

Fig. 4.13. Responses on how often they noticed no improvement after drug treatment in home management of childhood uncomplicated malaria.

Key:

FREQ = Frequently, OCCAS = Occasionally

There was no significant difference between the four groups as to whether they always noticed no improvement ($P > 0.05$), however, the primary education group seemed to notice no improvement more occasionally than the other groups ($P < 0.05$) (Fig. 4.14). Among those who occasionally noticed no response, the non-formal education group ranked highest ($P < 0.05$). Among the educated groups the order was tertiary > secondary > primary. The differences were statistically significant ($P < 0.05$). In other words, the educational status of these groups had an effect on their responses. Among those that never noticed an improvement, the order was non-formal education < primary = secondary > tertiary education groups.

4.2.8. Action Taken When No Improvement Was Noticed.

As shown in Fig. 4.15, majority of respondents 45% went to the hospital when they noticed there was no improvement after treatment, 28% went to primary health care clinic, 17% went to pharmacy, 6% to herbal practitioner while the remaining (4%) did not go to any of the above healthcare facilities (Fig. 4.15). Overall, (45 + 28) = 73% went to formal healthcare facilities when they noticed no improvement. As high as 27% did not go to where they could access appropriate healthcare service.

4.2.9. Effect Of Educational Background On The Actions Taken By Respondents When There Is No Improvement After Treatment.

The effect of the educational status of respondents was studied a determinant of the actions they took when there was no improvement after treatment.

As shown in Fig. 4.16, there seemed to be a reversed relationship between educational status and the decision to go to healthcare facilities in treatment failure. Thus, 80% of

non-formal education, 45% of primary, 20% of secondary went to the hospital; 20% of non-formal, 15% of primary and 8% of secondary went to pharmacy.

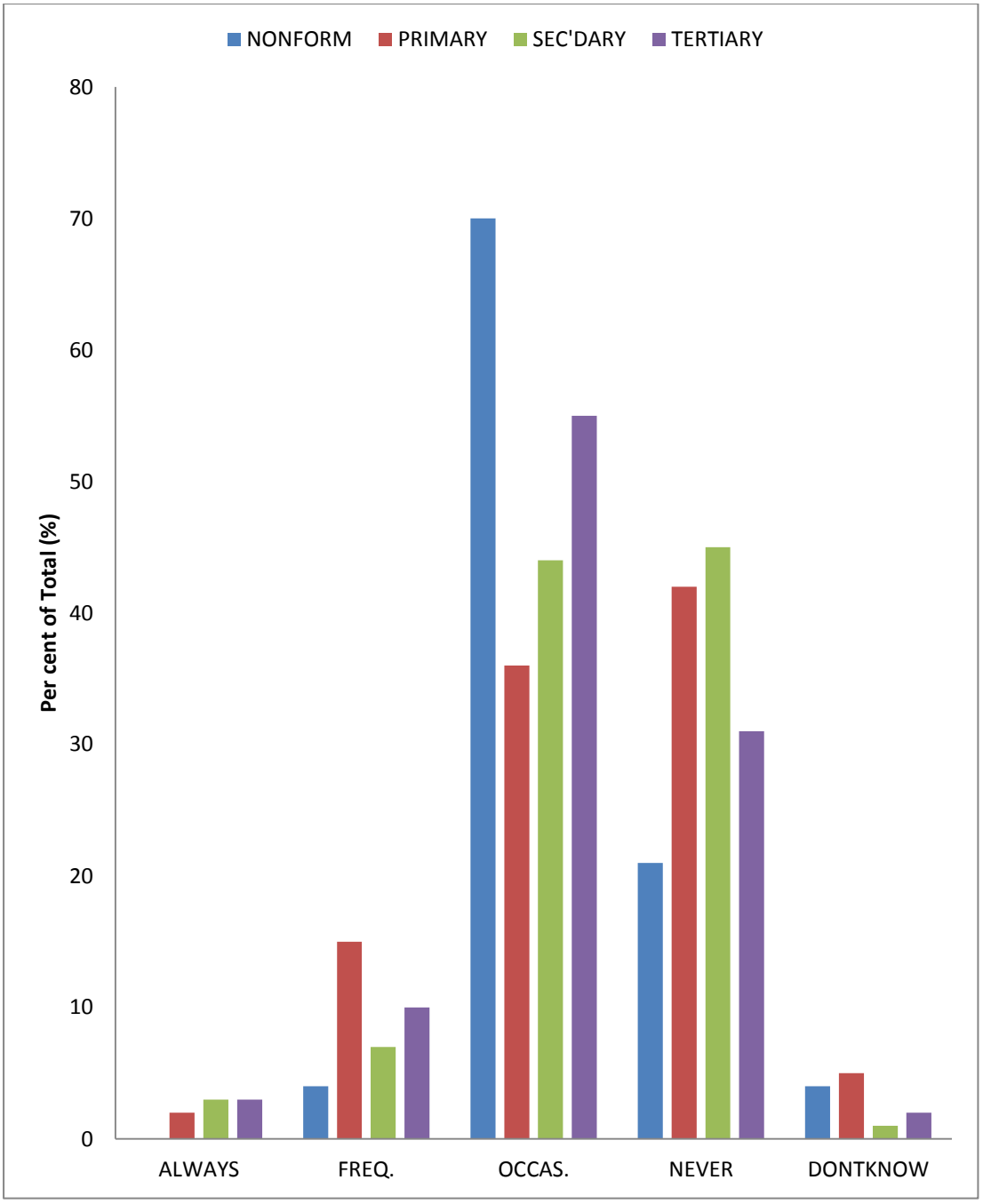

Fig. 4.14. Influence of educational status of respondents on how often they noticed no improvement after treatment.

KEY:

FREQ = Frequently

OCCAS = Occasionally.

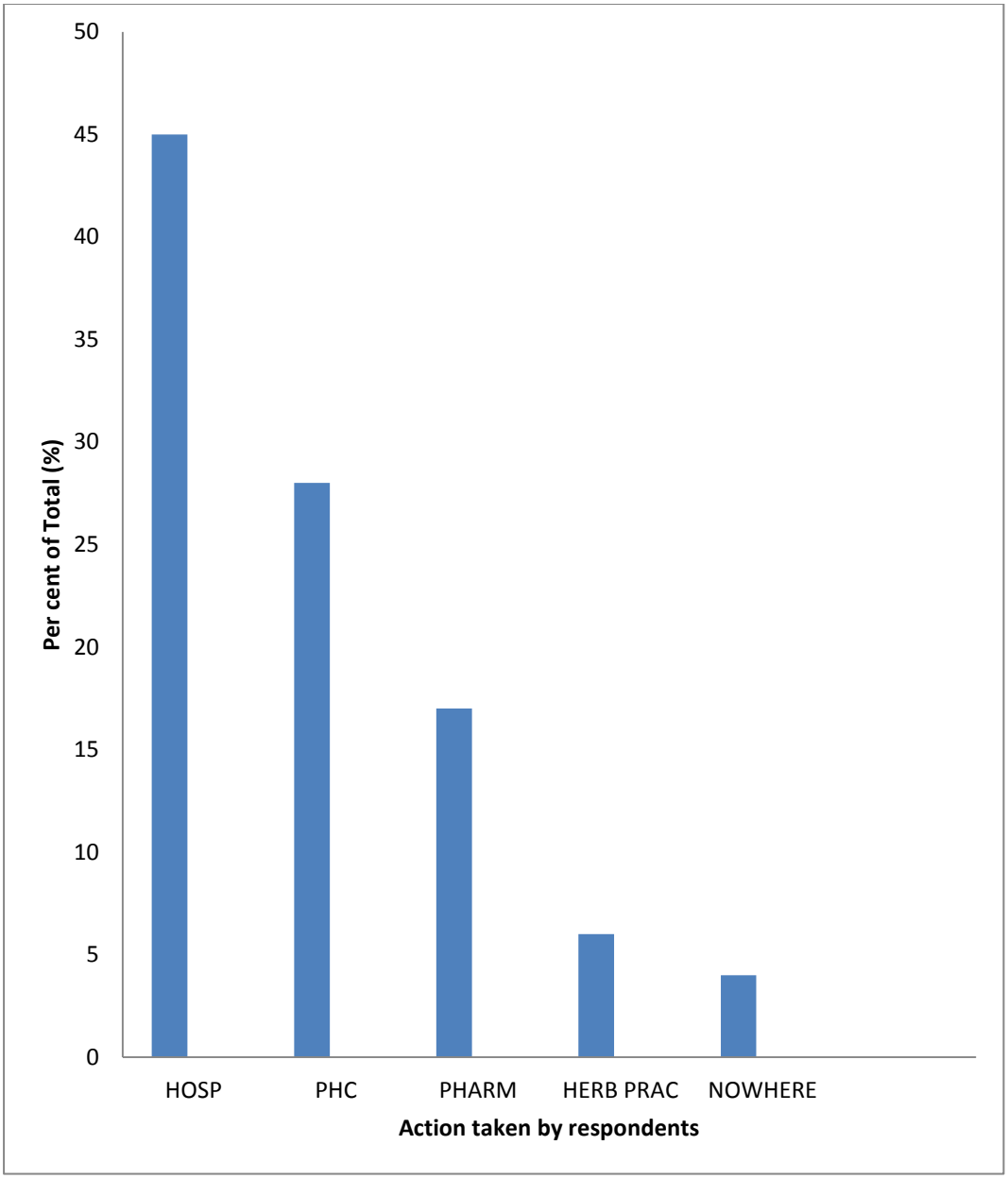

Fig. 4.15.Action taken when no improvement was noticed after treatment.

KEY:

HOSP = Hospital

PHC = Primary Health Care Centre

PHARM = Pharmacy outlet

HERB PRAC. = Herbal practitioner.

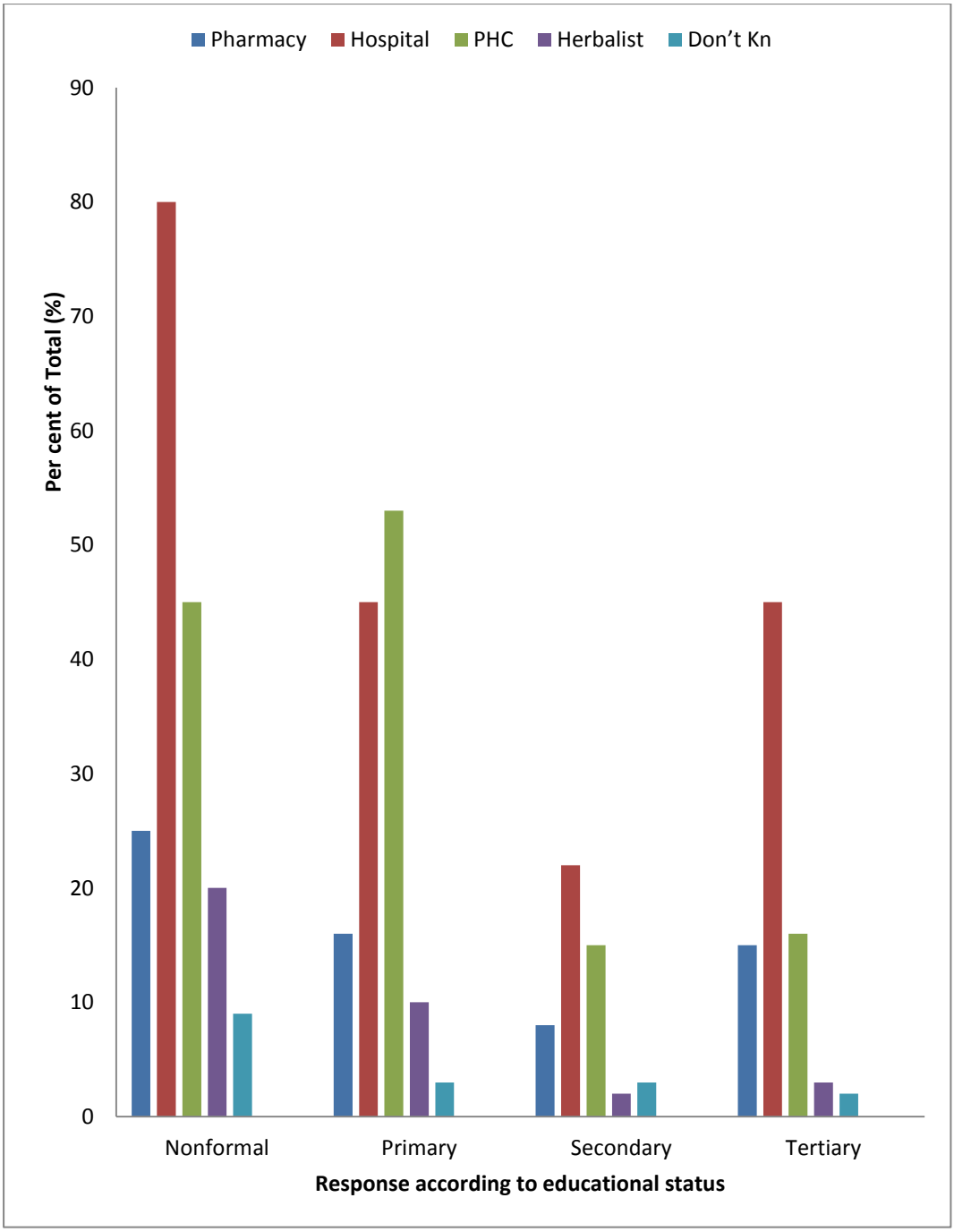

Fig. 4.16. Effect of educational background on the action taken by respondents when there was no improvement after treatment.

KEY:

PHC = Primary Health Care centre,

Don't Kn = Don't know.

4.2.10. Frequency At Which The Following Signs/Symptoms Of Severe Malaria Were Noticed.

Malaria can be complicated (severe) or uncomplicated. It was therefore necessary to determine if respondents understood the differences between the two. This would demonstrate whether they were dealing with uncomplicated childhood malaria or not. They were tested on some of the physical signs (convulsion, stiff neck, loss of consciousness, severe fever (>38.5^{0}C), drooling of saliva, yellow skin and eyes) of complicated malaria.

Table 4.5 shows that each of the average score of the signs noticed falls below occasionally, indicating that not many respondents noticed all these signs of severe malaria. These results confirmed that an average of over 80% of respondents were actually managing uncomplicated childhood malaria at home.

4.2.11 Action Taken By Respondents When These Signs Were Noticed.

It was expedient to find out the action taken by respondents any time they noticed any of the above signs because of the probable case of complicated malaria.

In order of priority, the actions taken by respondents are as follows: child was taken to the hospital > child taken to a primary health centre (PHC) >>> medication was changed > child taken to pharmacy (the reasons for this was connected to change of medicine and advice) >> herbal remedy was used (Fig. 4.17). A disturbing finding was the almost 10% that took no action at all.

The decision to go to the hospital was a function of their educational background (Fig. 4.18). Thus, the order was tertiary education > secondary education > primary education > non-formal education respondents (Fig. 4.18). The difference in each case

was significant ($P < 0.05$). Among those who decided to go to PHC, the order was non-formal = secondary education > primary = tertiary education groups.

4.2.12. Educational Intervention To Correct The Actions Taken By Some Respondents.

Those respondents that went to the pharmacy, gave medicines, herbs or took no action at all were a cause for concern. An intervention was immediately conducted to correct them in case of the future. This took the form of an educational intervention in which the progression of malaria from uncomplicated to complicated if there was a treatment failure was carefully explained. In addition, the signs/symptoms of complicated malaria were clearly explained to them and the consequences if the condition remained untreated successfully. They were specifically taught not to go to any other health post other than a hospital and in the absence of a hospital nearby, they should go to a PHC immediately.

Table 4.5. Frequency of noticing the following signs/symptoms,

Frequency	Convulsion	Stiff neck	Loss of conscious-ness	Severe fever	Drooling of saliva	Yellow eye/skin
Always (5.0)	21	10	10	39	25	44
Frequently (4.0)	39	8	19	58	28	32
Occasionally (3)	11	26	41	136	27	35
None (2.0)	727 (90%)	738 (91%)	724 (89%)	568 (70%)	718 (89%)	696 (86%)
Don't know (1)	11	27	15	8	11	5
Mean score	2.174289	2.055624	2.116192	2.44620	2.181706	2.268232
Std. Dev.	0.650994	0.462046	0.511112	0.83689	0.656545	0.769783
Std. Error	0.022888	0.016245	0.017970	0.02943	0.023083	0.027064
Lower bound (Cl-95%)	2.129429	2.023785	2.080972	2.38856	2.136463	2.21518
Upper bound (Cl-95%)	2.219149	2.087464	2.151413	2.5039	2.226948	2.321278

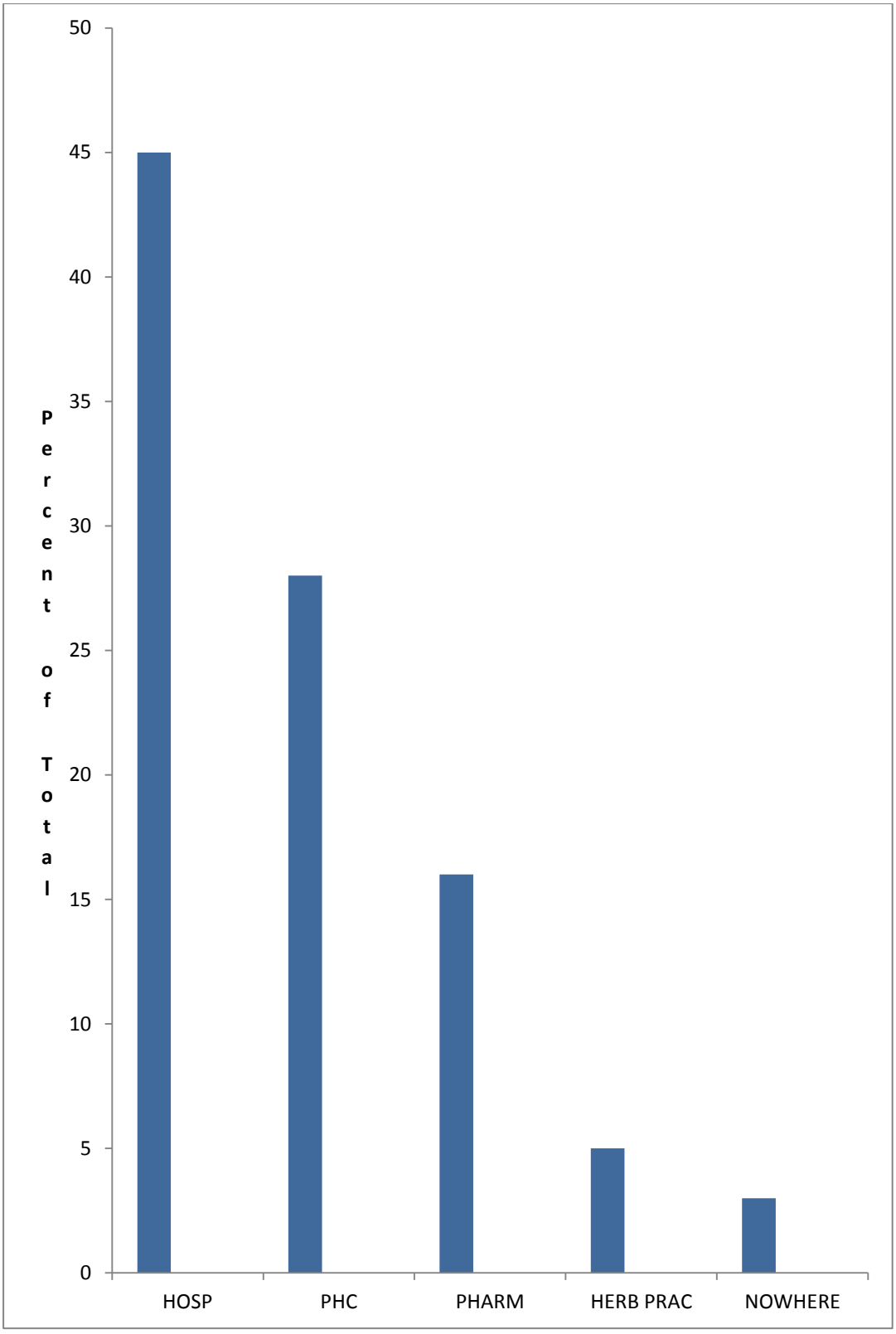

Fig. 4.17. Action taken by all respondents when the signs/symptoms above were noticed in home management of uncomplicated childhood malaria.

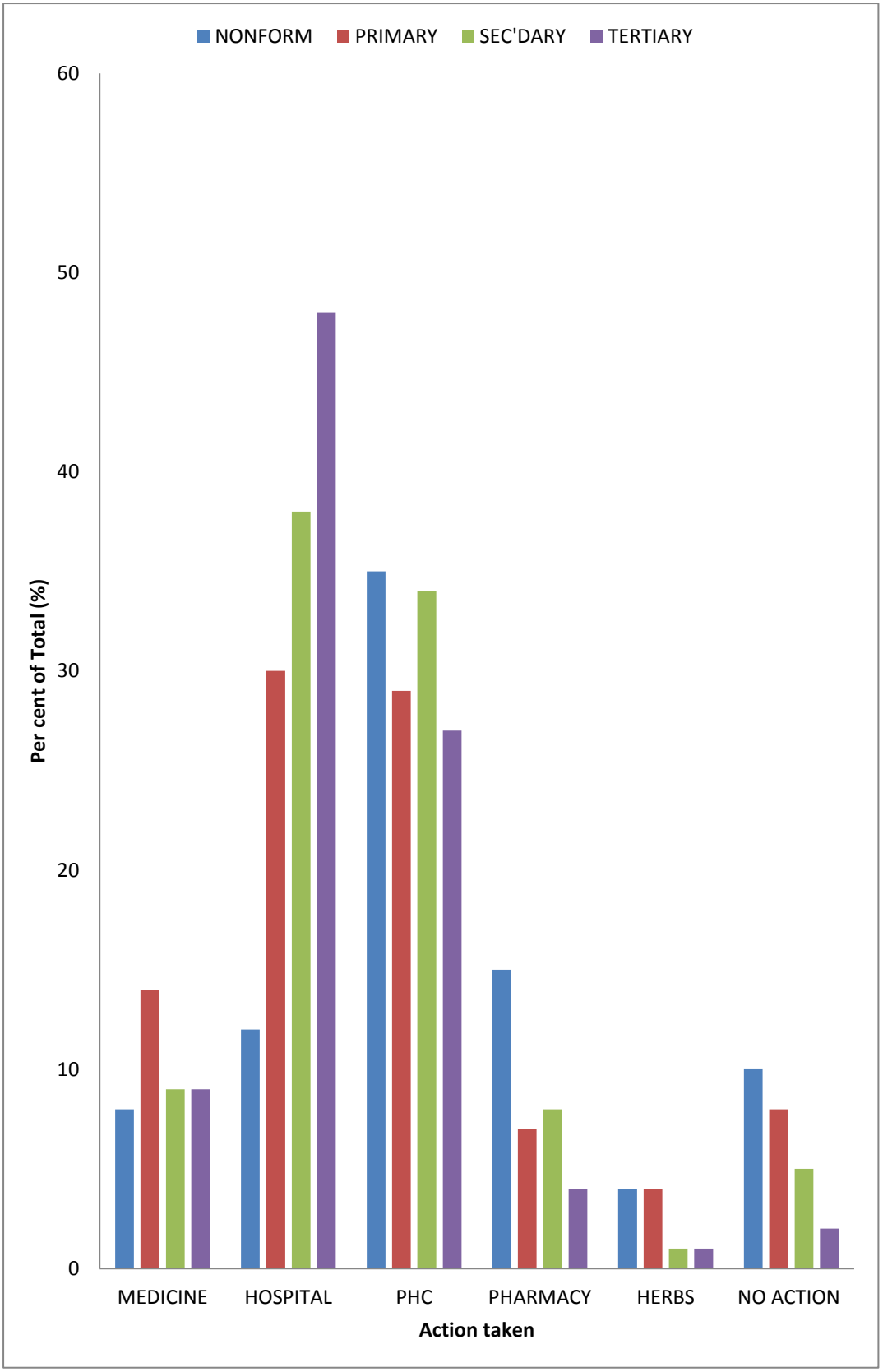

Fig. 4.18. Effect of educational background of respondents on the actions taken after noticing the sign/symptoms described above

4.3. Mothers' Perception On Fathers' As Care Givers In HMM.

In this section the perceptions by mothers of fathers as care givers in home management of uncomplicated childhood malaria was studied and analysed.

4.3.1 Mothers That Lived With Their Children's Fathers

The total population of mothers was 485 (100%). Most of them 427 (88%) lived with the fathers of their children. The remaining 58 (12%) did not live with the fathers of their children (Fig. 4.19). It was not the intention of this study to ask questions that were too personal and/or private, hence, it was not established if these men were their husbands as it was sufficient to know that they lived together because of the design of this work.

Education seems to have a positive effect on whether on or not mothers lived with the fathers of their children. Thus, while 70% of non-formally educated mothers lived with the fathers of their children, as high as 90% of the formally educated mothers lived with the fathers of their children (Fig. 4.20). The difference was statistically significant ($P < 0.05$). On the other hand, among mothers not living with the fathers of their children, the non-formally educated topped the list with 29% while the educated mothers were significantly less in numbers ($P < 0.05$).

4.3.2 Frequency At Which Fathers Practise Home Management Of The Children During An Episode Of Uncomplicated Malaria As Expressed By Mothers.

Majority of the fathers (64%) always and 19% frequently practised home management of uncomplicated childhood malaria (Table 4.6). Only 4% of the fathers never practised

home management of uncomplicated childhood malaria. The average mean score of 4.405152 means that the average response fall above frequently, in other words, majority always practised home management of the children during an episode of malaria. The upper bound and lower bound of 4.491728and 4.318577 are indications that if this survey is repeated 100 times, it is 95% likely to have the means score falling into this range.

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4.3.2.1. Effect Of Educational Background Of Fathers On The Frequency Of Practising HMM As Described By Mothers.

The frequency with which fathers practised home management of uncomplicated childhood malaria was independent of their educational status. Fathers with no-formal education always practised HMM more than fathers with secondary education (Fig. 4.21). Hence, increase in educational status did not necessarily influence the practice of HMM by fathers.

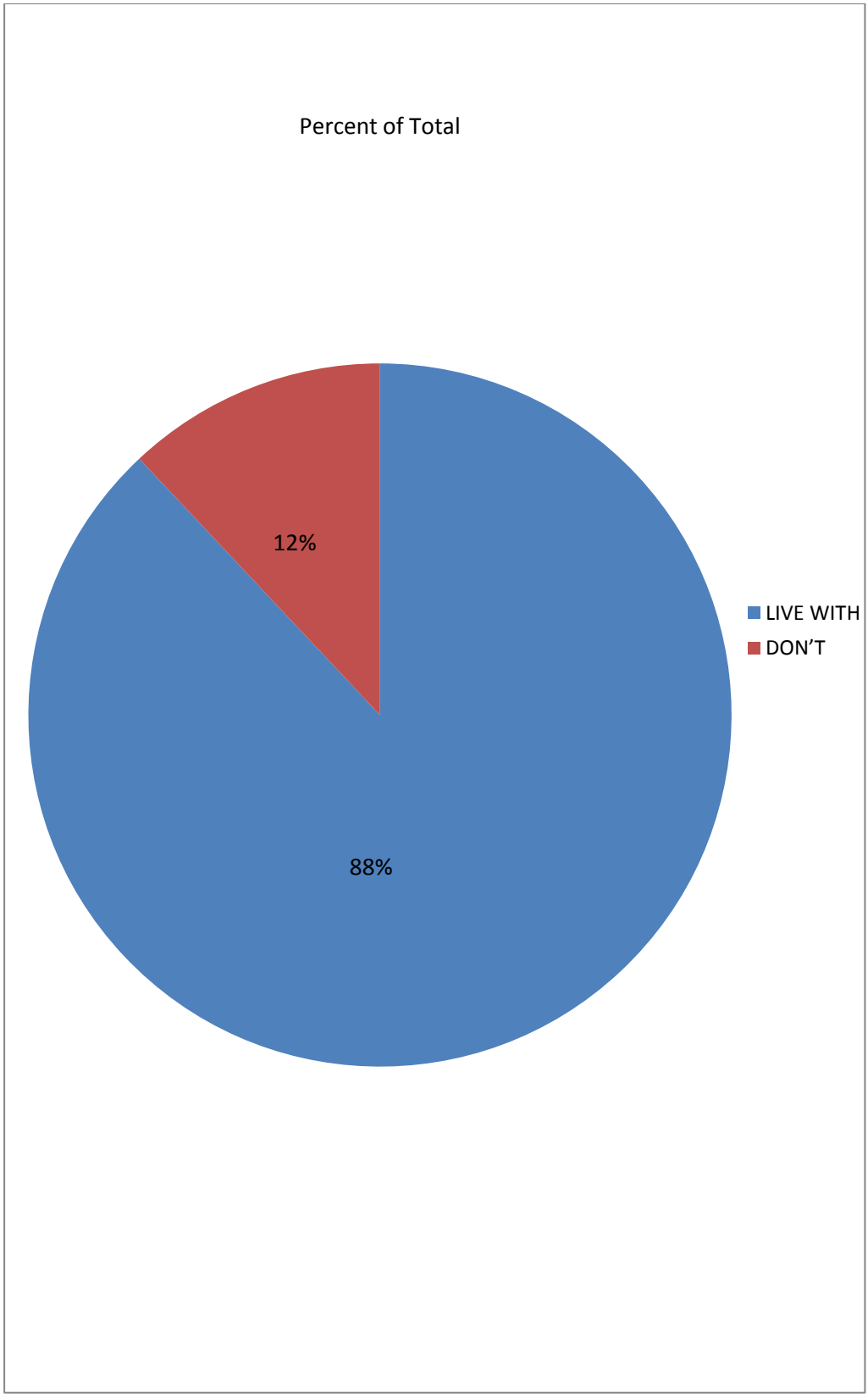

Fig. 4.19. Distribution of the population of mothers living with the fathers of their children.

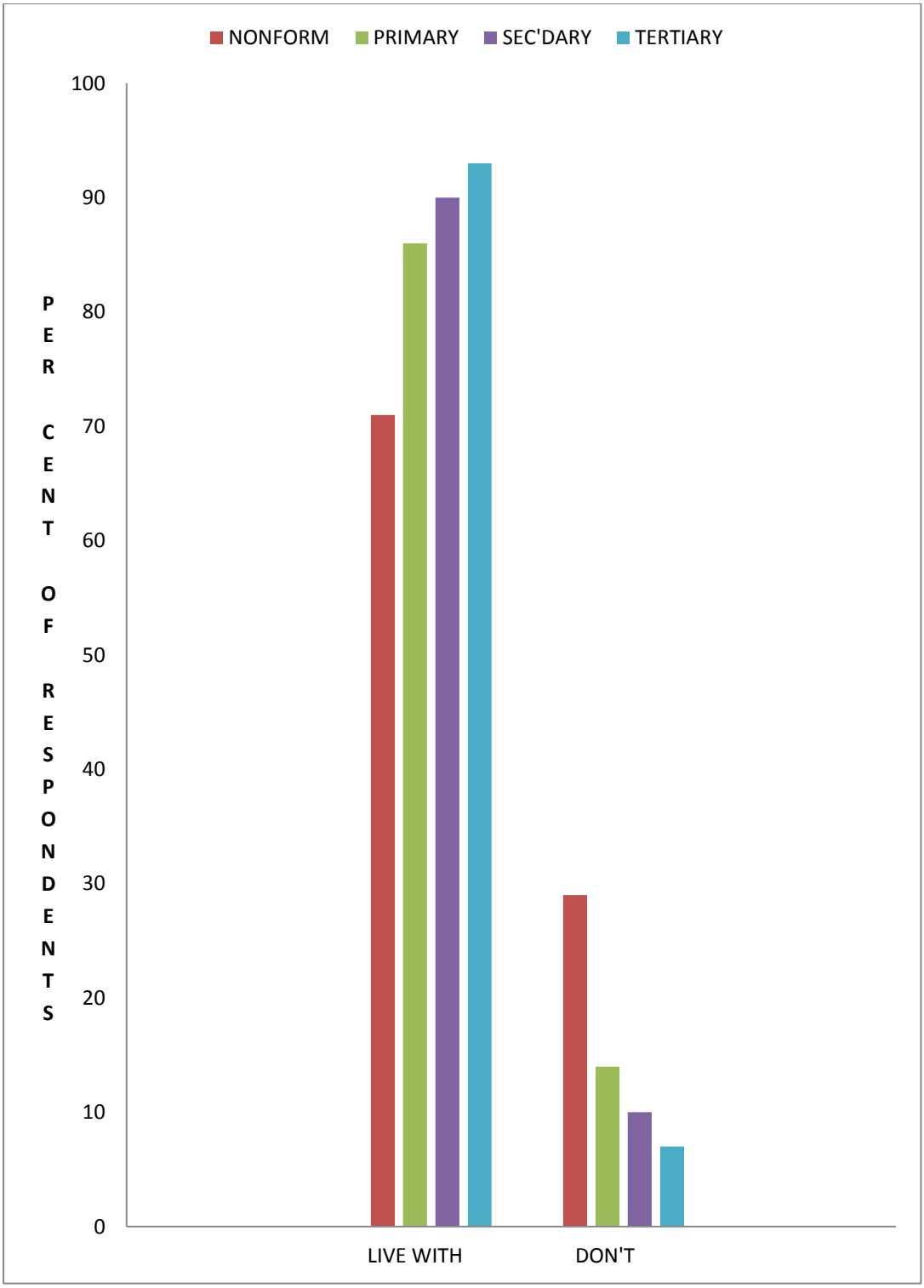

Fig. 4.20. Distribution of mothers living with the fathers of their children according to their educational background.

Table 4.6. Practice of home management of uncomplicated childhood malaria by fathers as expressed by mothers.

Frequency	Score	Respondents	Percent (%)
Always	5.0	272	64
Frequently	4.0	80	19
Occasionally	3.0	54	12
Never	2.0	18	4
Don't know	1.0	3	1
Total		427	100
Mean score		4.405152	
Std. Dev.		0.912753	
Std. Error		0.044171	
Lower bound (Cl-95%)		4.318577	
Upper bound (Cl-95%)		4.491728	

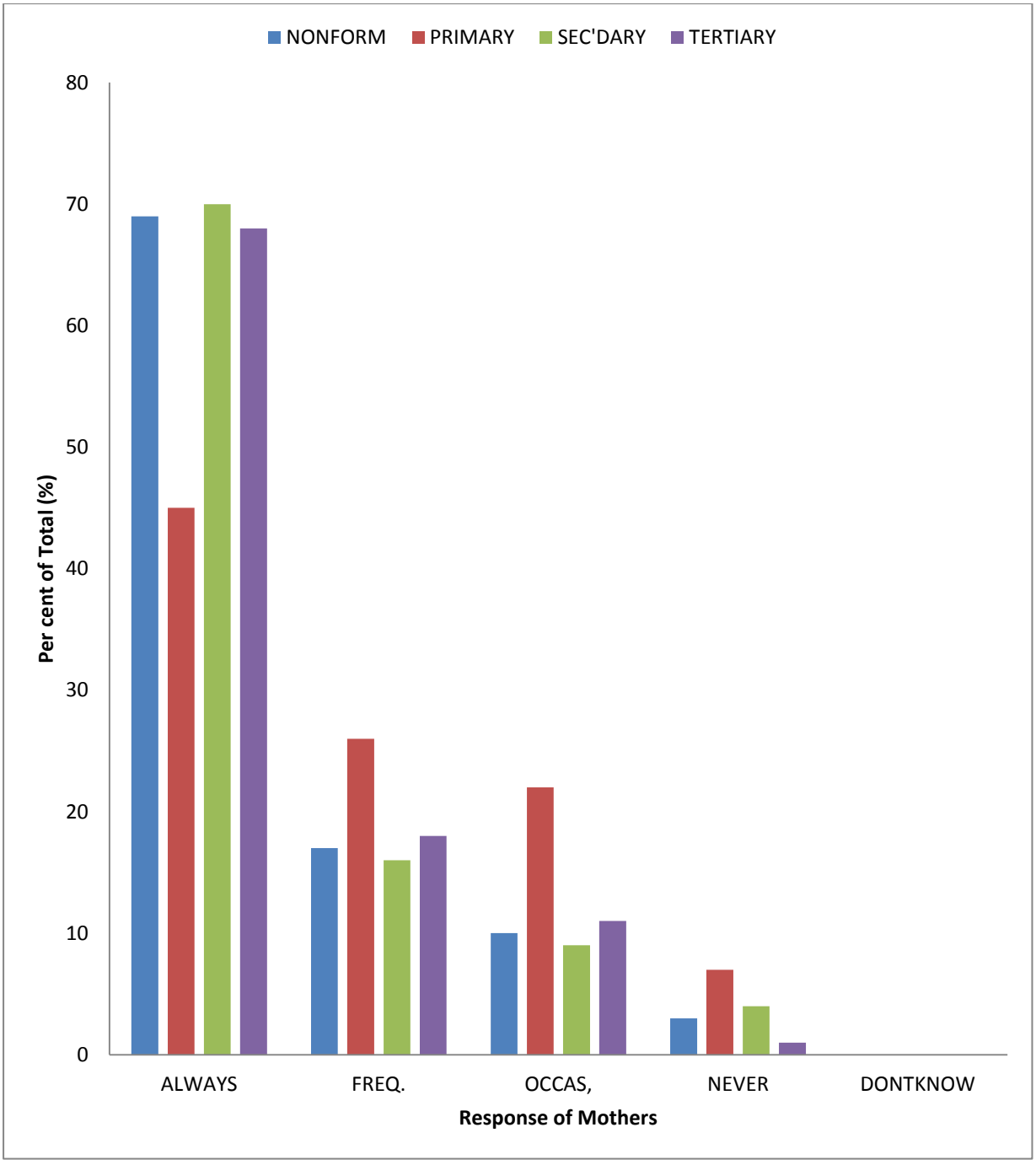

Fig. 4.21. Effect of educational status of fathers on the frequency of their home management of uncomplicated childhood malaria.

KEY:

FREQ. = Frequently

OCCAS. = Occasionally

4.3.3 What Fathers Did Most In Home Management Of Uncomplicated Childhood Malaria As Described By Mothers.

Although mothers unequivocally reported that the fathers of the children generally practised home management of uncomplicated childhood malaria, it was important to determine what they actually did most during such management in the home.

Results from such study are presented in two parts. One deals with the overall responses of mothers irrespective of the educational background of fathers (Fig. 4.22). The other part deals with the effect of education on fathers' involvement in HMM (Fig. 4.23).

From the results, the rank order of activities that fathers performed most in home management of uncomplicated childhood malaria is drug administration >> cloth removal > tepid sponging > fanning/cooling = giving oral rehydrate solution (Fig. 4.22). With about 70% of respondents administering drugs, there was need to investigate this further. Such investigations are reported in the appropriate sections (see under Drug Use in HMM).

Educational status of fathers did not have any significant influence on what fathers did in home management of uncomplicated childhood malaria, hence, the rank order of drug administration which was the most important among what they did was non-formal education = primary education = secondary education = tertiary education fathers (Fig. 4.23). Tepid sponging and removal of clothes ranked next to drug administration even though the latter was significantly more ($P < 0.05$) than the former.

4.3.4. Referral To A Health Care Worker By Fathers When Malaria Persisted

As shown in Table 4.7, 76% of fathers always and/or frequently referred children to health care worker when the malaria persisted with the average score of 4.1 falling slightly above frequently. Some fathers did occasionally (13%) and 9% never did. These were counselled on the need to always refer because they had no expertise to continue treatment, neither were they licensed so to do. In addition, they were counselled to always consider the life of their children first. Every unresolved case should be referred for medical intervention immediately.

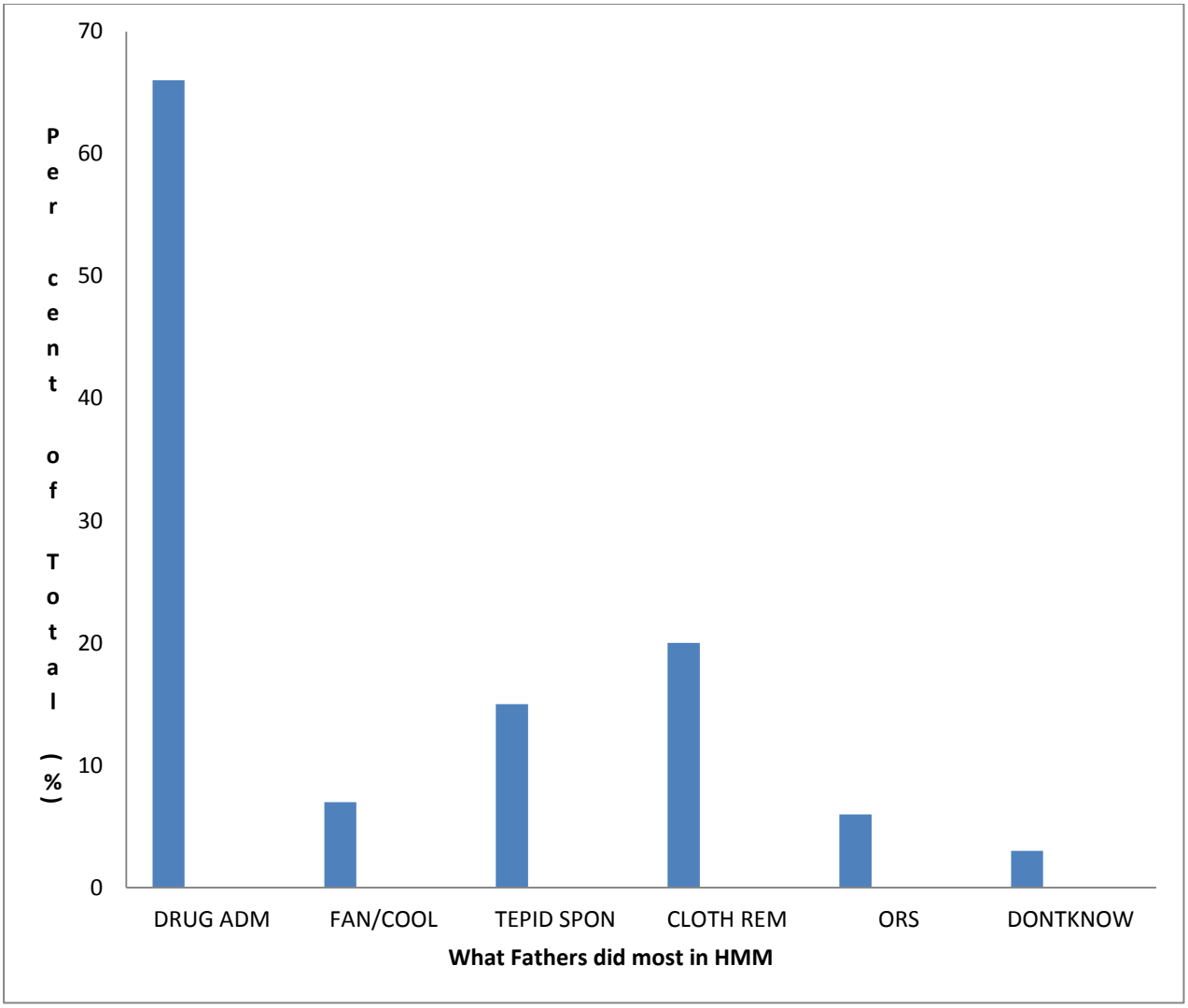

Fig. 4.22. Activities fathers do most in home management of uncomplicated childhood malaria.

Key:

DRUG ADM: drug administration,

FAN/COOL: fanning and/or cooling the child,

TEPID SPON: tepid sponging the child,

CLOTH REM: removal of cloth,

ORS: oral rehydrate solution.

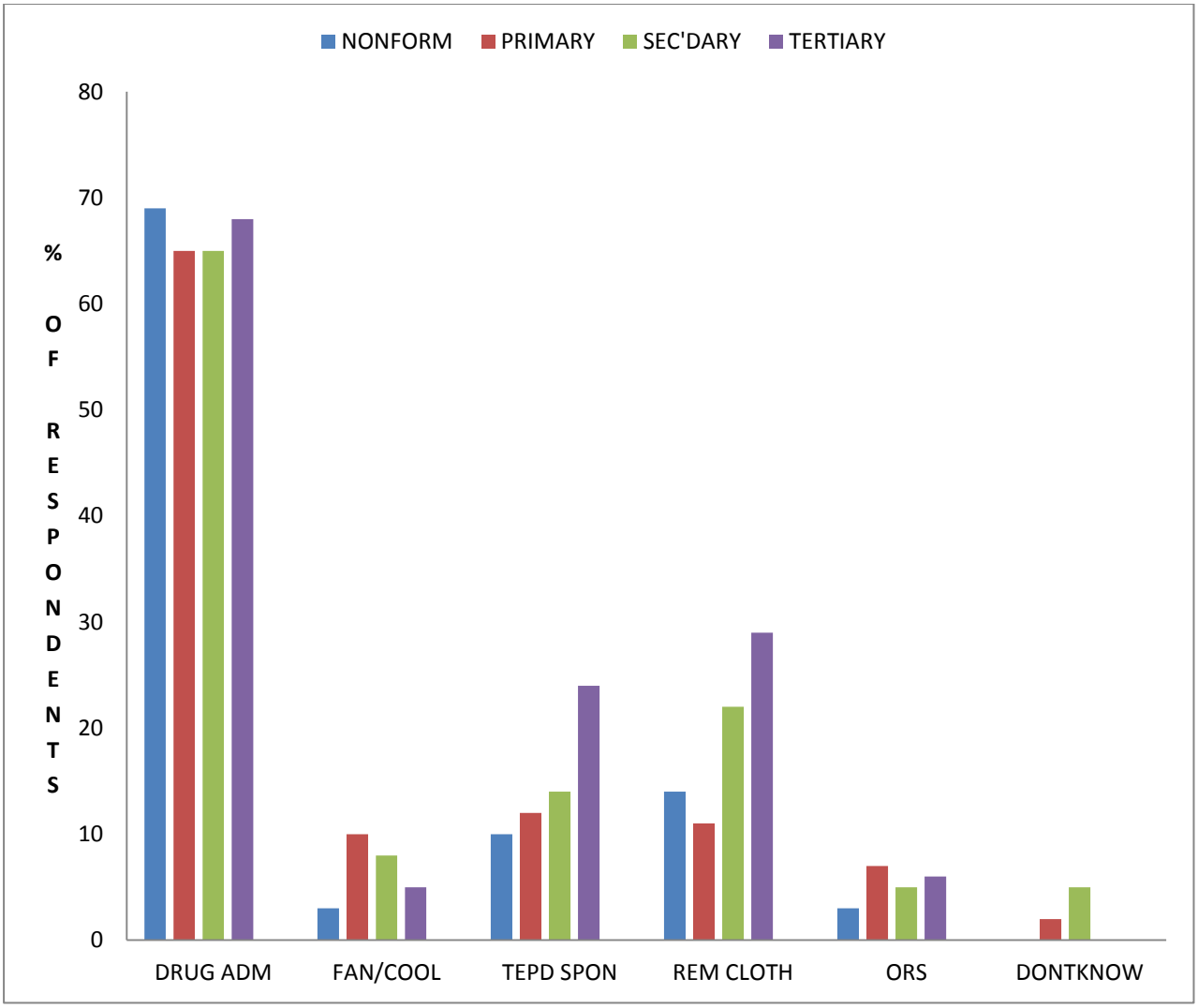

Fig. 4.23 Influence of the educational status of fathers on what they did in home management of uncomplicated childhood malaria as described by mothers.

KEY:

DRUG ADM. = Drug administration

FAN/COOL = Fanning/Cooling child

TEPD SPON = Tepid sponging

REM. CLOTH = Removal of cloth

ORS = Oral rehydrate solution.

4.3.5. Participation Of Fathers In HMM When Mothers Were The Care Givers.

In addition to establishing that fathers practised HMM on their own, their participation as helpers when mothers were the care givers was studied. In addition, the role of education on the participation of fathers was determined.

About 60% of mothers reported that the fathers of their children always participated in home management of uncomplicated childhood malaria when they (mothers) were the care givers. On the other hand, only 16% and 18% said fathers frequently and occasionally respectively participated (Fig. 4.24). The difference between those that always did and the other groups was statistically significant ($P < 0.05$). At the other extreme are the 7% women who never enjoyed such participation from the fathers of their children.

Fathers' educational status was not a determinant of their participation in home management of uncomplicated childhood malaria when mothers were the care givers. Thus, 72%, 39%, 66% and 63% of non-formal education, primary, secondary and tertiary education fathers respectively always participated when mothers were the care givers in home management of uncomplicated childhood malaria (Fig. 4.25). There was no significant difference between non-formal education, secondary and tertiary education ($P > 0.05$) compared with primary education group which was significantly different ($P < 0.05$) from the other groups. Population of fathers that frequently and/or occasionally participated was significantly lower than those that always did ($P < 0.05$). Less than 8% of fathers never participated.

Over 60% of fathers always reminded mothers to give medicines in the home management of uncomplicated malaria. There was, however, a statistically significant

difference in the response of both non-formal education and/or primary, secondary and tertiary educated respondents ($P < 0.05$). When the results of the two groups (always and frequently) were combined, approximately 90% of the total respondents of 427 reminded mothers to give medicines to their children in HMM.

4.3.6. Other Supports Fathers Give In HMM To Mothers As Care Givers.

In addition to drug administration in malaria, other adjuvants can be administered to ensure that the child is comfortable. The burden of the care can be heavy on the mother alone unless there is extra help. For this reason, other supports given by fathers were also investigated. Such supports are fanning/cooling the child, cleaning child's vomit, tepid sponging the child, preparing oral rehydrate solution, giving the oral rehydrate solution to the child, clearing and cleaning child's stool, carrying the child, and encouraging the mother that the child will be well.

The support given by fathers varied considerably. The order of magnitude is: carry child at night when he/she is sleepless > encourage mother that child will be well > gives medicine to the child > cleans vomit when child throws up + tepid sponge child to cool body temperature > cleans stool when child defecates > gives oral rehydrate solution > prepare oral rehydrate solution (Fig. 4.27).

Table 4.7. How often fathers referred their children to a health care worker in treatment failure.

Frequency		Respondents	Per cent (%)
Always	5.0	228	53
Frequently	4.0	99	23
Occasionally	3.0	56	13
Never	2.0	37	9
Don't Know	1.0	7	2
Total		427	100
Mean Score		4.180328	
Std. Dev.		1.062722	
Std. Error		0.051429	
Lower Bound (95% Cl)		4.079528	
Upper Bound (95% Cl)		4.281128	

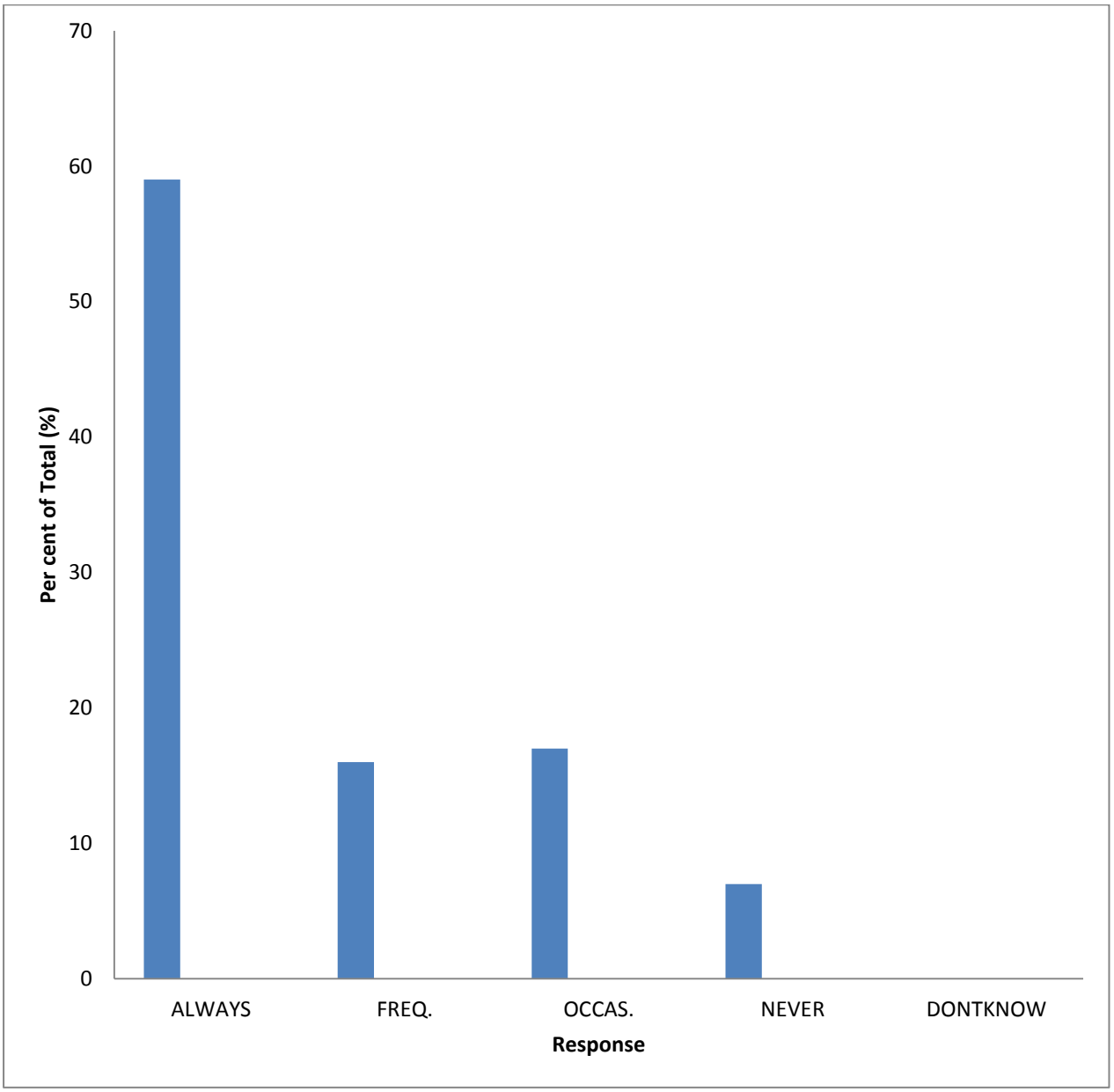

Fig. 4.24. Frequency with which fathers participated in HMM when mothers of their children were the care givers.

KEY:

FREQ. = Frequently

OCCAS. = Occasionally.

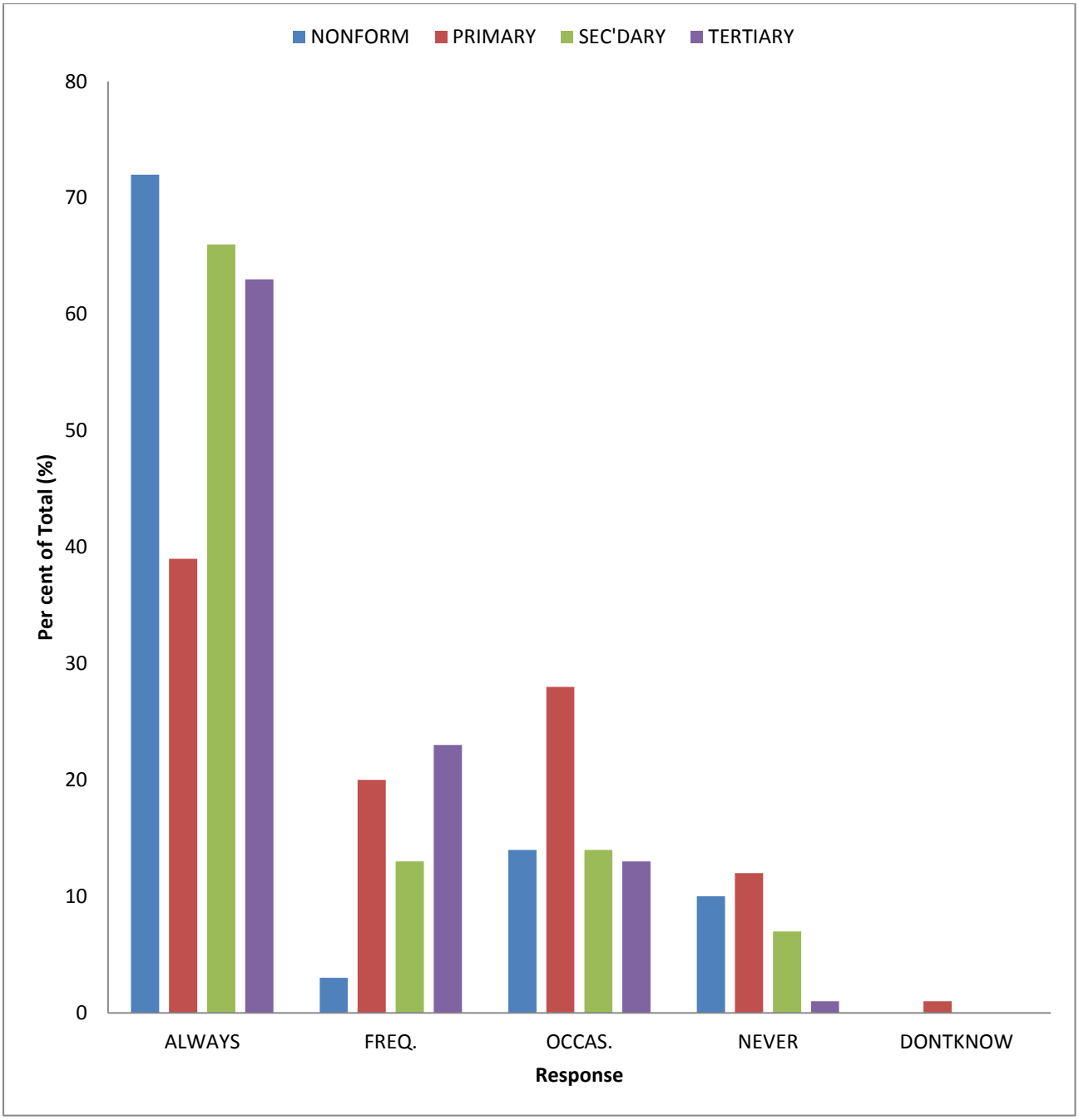

Fig. 4.25. Influence of educational status of fathers on how often they participated in home management of uncomplicated malaria when mothers were the care givers.

Key:

FREQ: Frequently

OCCAS: Occasionally

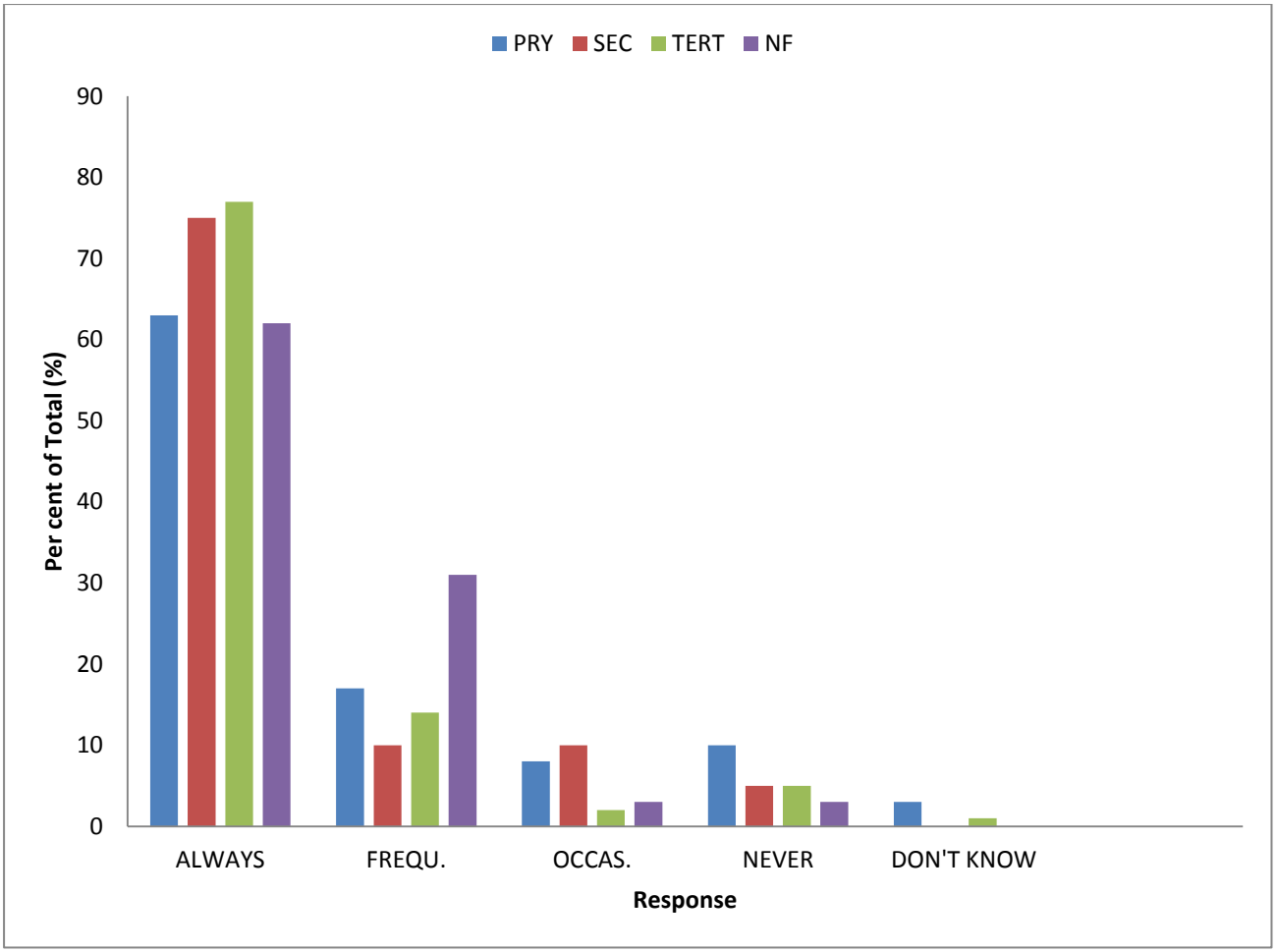

Fig. 4.26. How often fathers reminded mothers to give medicines to their children in home management of uncomplicated malaria.

KEY:

FREQU = Frequently

OCCAS = Occasionally

PRY = Primary education

SEC. Secondary education

TERT = Tertiary education

NF = Non-Formal.

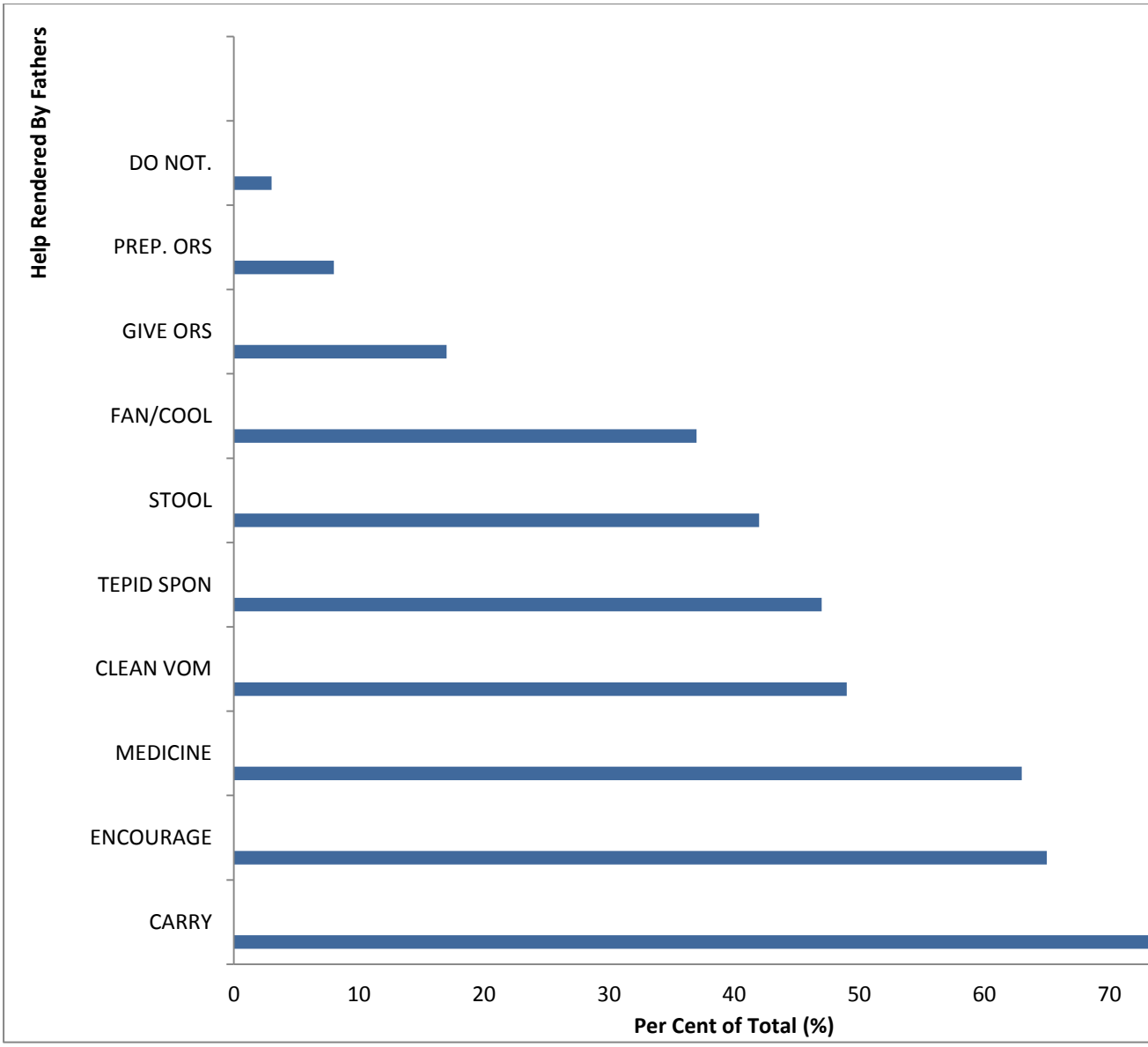

Fig. 4.27. Other supports fathers gave to mothers in HMM.

Key: ENCOURAGE: encourage mother that child will be well.

CARRY: carry child at night when he/she was sleepless.

STOOL: clean stool when child defecated.

GIVE ORS: gave child oral rehydrate solution.

PREP ORS: prepared Oral rehydrate solution. DO NOT = do nothing

MEDICINE: gave medicine TEPID SPON: tepid sponged child

CLEAN VOM: cleaned vomit FAN/COOL: fanned and/or cooled the child.

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4.3.7. Mothers' Overall Assessment Of Fathers' Intervention In HMM

In this section, mothers were asked to assess the overall participation of fathers in home management of uncomplicated childhood malaria. Results here are presented in two parts. The first part deals with the general assessment of all mothers, while the second part deals with the influence of education on the overall assessment.

About 44%, 35% and 13% of mothers rated the intervention of fathers in home management of uncomplicated childhood malaria as excellent, good and fair respectively (Fig. 4.28). The difference between the 3 groups was statistically significant ($P < 0.05$). Only about 7% rated fathers' intervention as poor. Indeed, if the excellent and good are pooled together, the result would be about 80% of mothers.

Tertiary education mothers rated their children's fathers' intervention as excellent > secondary education mothers = primary education mothers = non-formal education mothers respectively. The difference between the tertiary education group and the other 3 groups is statistically significant ($P < 0.05$). The groups that rated fathers as good are education-dependent in the following order: non-formal < primary < secondary (Fig. 4.29). The difference between the groups was statistically significant ($P < 0.05$). Among those that rated fathers' intervention as poor, non-formal education group was significantly higher than the other three groups ($P < 0.05$).

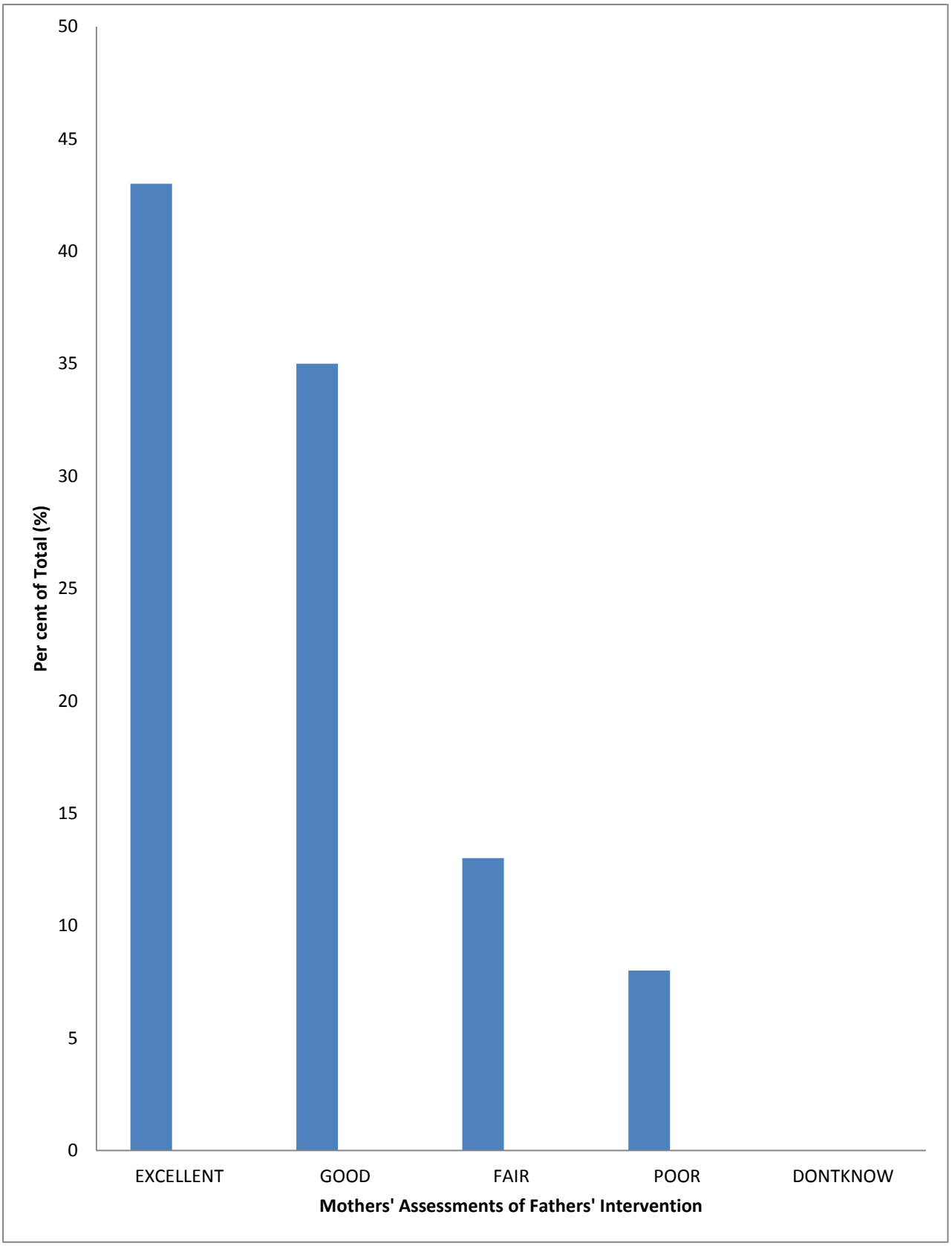

Fig. 4.28. Assessment by mothers of fathers' intervention in HMM.

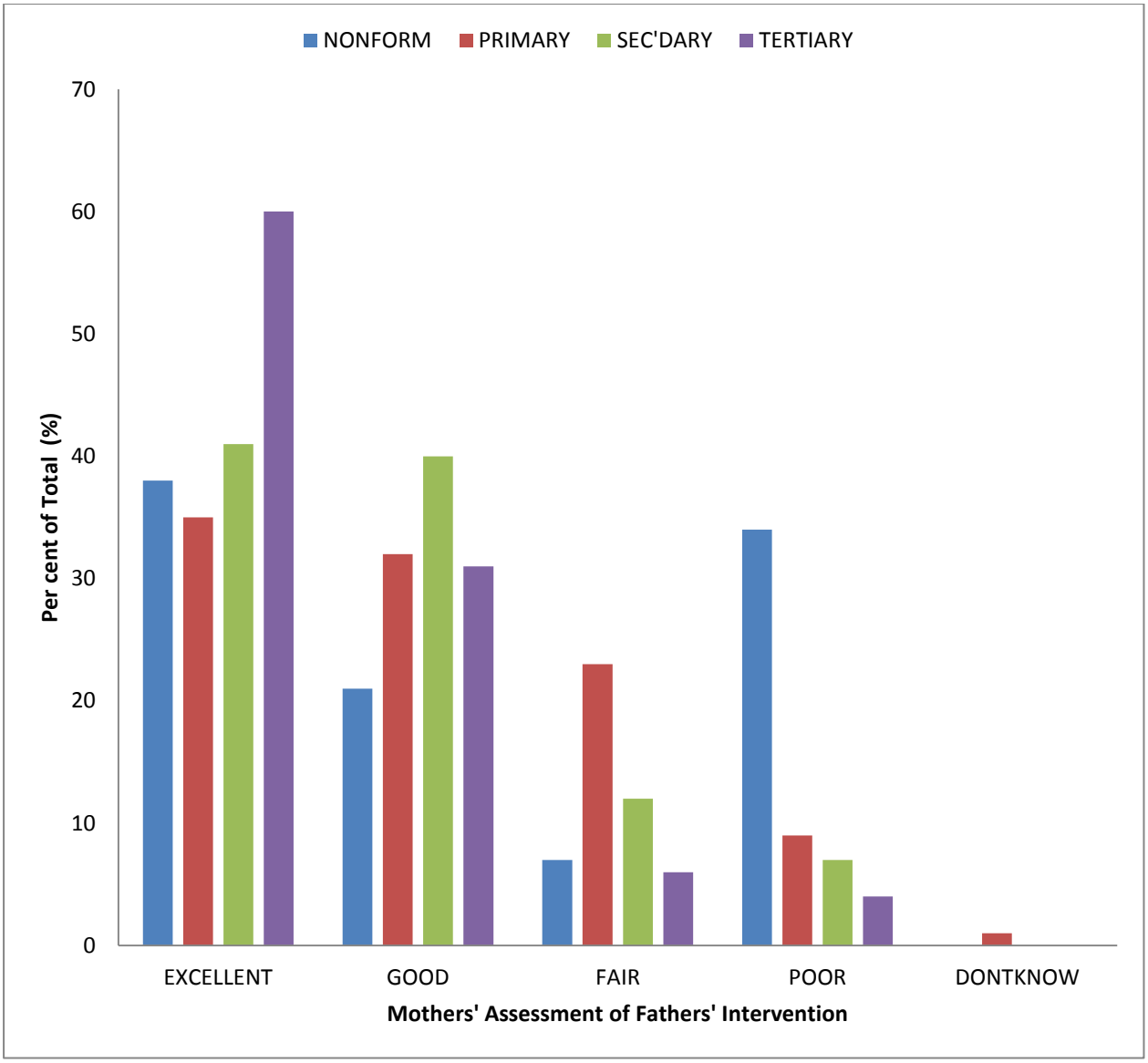

Fig. 4.29. Effect of educational status of mothers on their assessment of fathers' intervention in HMM.

KEY:

NON-FORM. = Non-formal education

PRIMARY = Primary education

SEC'DARY = Secondary education

TERTIARY = Tertiary education.

4.4.0. Drugs Used In Home Management of Uncomplicated Childhood Malaria

This section deals with drugs used in home management of uncomplicated childhood malaria.

The order of preference of drugs used in home management of uncomplicated childhood malaria was A-L >> PCM >> CQ >> HER> A-A > QU > A-M > A-P = S-P > A-SP. (Table 4.8). It is noteworthy that chloroquine (CQ) was still in wide use (22%) by respondents despite the ban on the drug (FMoH, 2005). Paracetamol (PCM), an antipyretic with no known antimalarial action, was second to artemether-lumefantrine. To all intents and purposes, paracetamol is not considered in this work as an antimalarial drug. Its high rating was most probably due to its antipyretic effect which respondents mistook for antimalarial effect.

4.4.1 Effect Of Gender And Educational Status Of Respondents On Drug Selection In HMM.

The Nigerian antimalarial market has an abundance of innovator, branded generic and generic products that it is often said that product selection may be confusing. It was thought desirable to investigate the effect of educational background of respondents on drug selection in home management of uncomplicated childhood malaria. In addition, the influence of gender on such selection was studied. In this study, antimalarial drugs are defined as drugs available and used for malaria treatment. Such drugs may be officially or unofficially recommended by the National Malaria Treatment Guidelines of the Federal Ministry of Health (2005).

Gender had no effect on drug selection in home management of uncomplicated childhood malaria (Fig. 4.30). All the drugs used were selected equally by both fathers and mothers. Selection of drugs cut across the official (artemether-lumefantrine, artesunate-amodiaquine) and the others that were not listed as official drugs in Nigeria.

Selection of artemether-lumefantrine in home management of uncomplicated malaria was dependent on the educational status of respondents. Thus, tertiary educated > secondary educated > primary educated = non-formal educated (Fig. 4.31). The differences were statistically significant ($P < 0.05$). Selection of chloroquine followed an interesting pattern. Thus, non-formal < primary > secondary > tertiary educated groups. The higher the educational status, the less the preference for chloroquine. The differences were statistically significant ($P < 0.05$).

Table 4.8. Frequency distribution of drugs used by mothers and fathers in HMM.

Frequency	Respondents (n = 809)									
	A-L	A-A	A-M	A-S	A-P	CQ	SP	QU	HER	PCM
Always (5.0)	290	28	16	4	5	101	4	22	43	222
Frequently (4.0)	29	8	2	2	0	41	2	19	7	9
Occasion-ally (3.0)	38	15	7	4	10	31	3	6	2	19
Never (2.0)	1	0	1	0	0	2	2	1	0	4
Don't Know (1.0)	6	1	1	1	1	1	4	1	2	2
TOTAL	364 (45%)	52 (6%)	27 (3%)	11 (1%)	16 (2%)	176 (22%)	15 (2%)	49 (6%)	54 (7%)	256 (32 %)
Mean Score	4.637	4.192	4.148	3.727	3.50	4.358	3,0	4.225	4.648	4.78
Std. Dev.	0.810	0.991	1.167	1.272	1.155	0.850	1.604	0.896	0.872	0.73
Std. Error	0.043	0.137	0.225	0.384	0.289	0.064	0.414	0.128	0.119	0.05
Lower Bound (Cl-95%)	4.554	3.923	3.708	2.976	2.934	4.232	2.189	3.974	4.416	4.65
Upper Bound (Cl-95%)	4.721	4.462	4.588	4.479	4.066	4.484	3.812	4.475	4.881	4.83

Key:

A-L = Artemether-Lumefantrine

A-A = Artesunate-Amodiaquine

A-M = Artesunate-Mefloquine

A-S = Artesunate-Sulphadoxine Pyrimethamine

A-P = Artesunate-Piperaquine

CQ = Chloroquine

QU = Quinine

HER = Herbal remedies

PCM = Paracetamol.

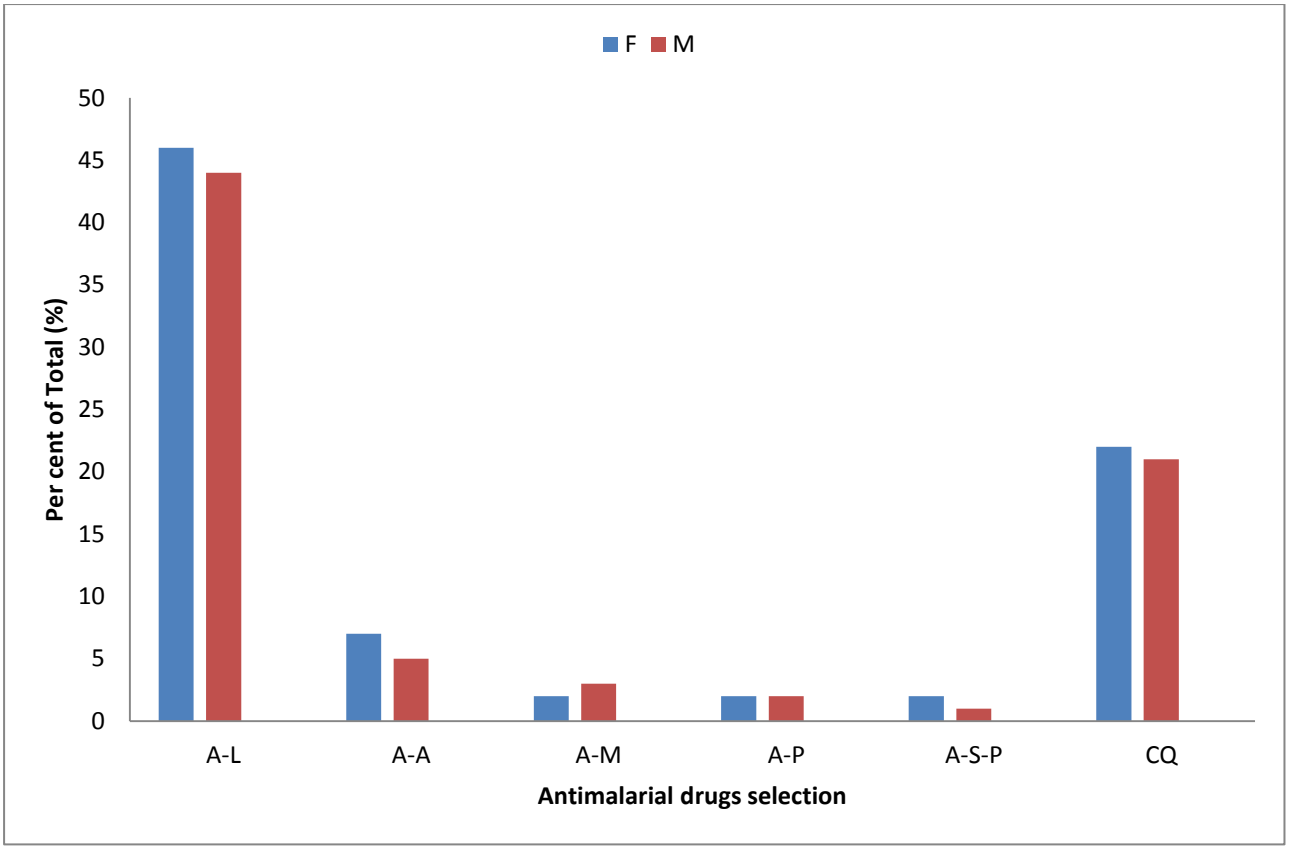

Fig. 4.36.Effect of gender on antimalarial drug selection in HMM.

KEYS:

A – L = artemether-lumefantrine

A – A = artesunate-amodiaquine

A – M = artesunate-mefloquine

A – S – P = artesunate-sulphadoxine-pyrimethamine

A – P = artesunate-piperaquine

CQ = chloroquine

F = Female (Mothers)

M = Male (Fathers).

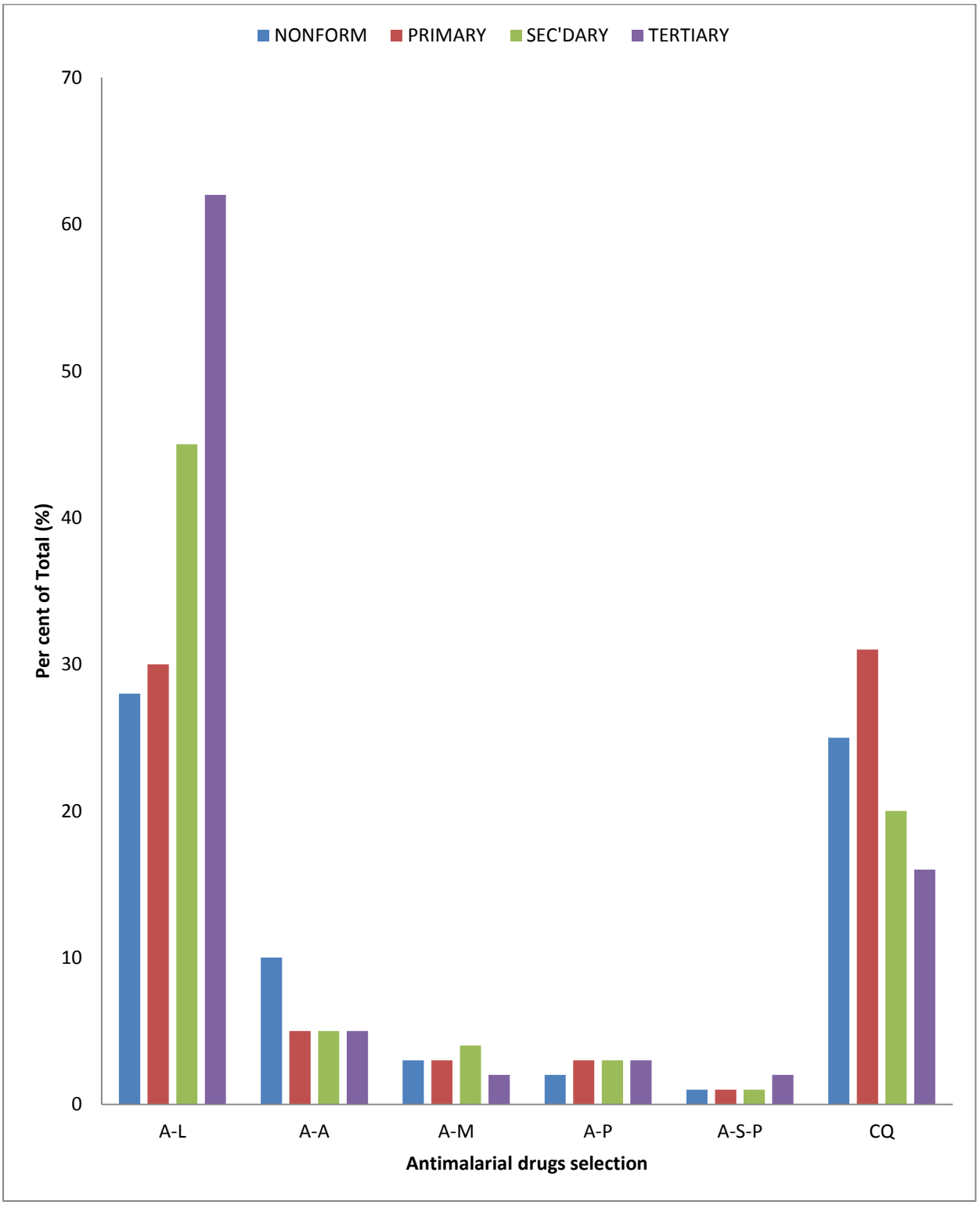

Fig. 4.37. Effect of educational status on the selection of antimalarial drugs in home management of uncomplicated childhood malaria.

4.4.3. Sources Of Drugs Used In Home Management Of Uncomplicated Childhood Malaria By Fathers And Mothers.

The use of antimalarial drugs in HMM was studied with reference to how often they were sourced from the pharmacy, doctor's clinic, health centre and the "chemist". Results from such study are presented in this section.

Fig. 4.32 shows the mean score distribution of the sources of the various drugs used in home management of uncomplicated childhood malaria. Most of the respondents obtained the drugs from pharmacy outlets. Artemether-lumefantrine followed the pattern pharmacy > doctor > primary health care > "chemist" > traditional medical practitioner. An unexpected finding is that all the drugs were also sourced in varying proportion from traditional medical practitioners, just herbal remedies were also sourced from pharmacy, doctor and other outlets. The difference between pharmacy as a source and the other sources is significant ($P < 0.5$).

4.4.3.1. Influence Of The Educational Status Of Respondents On Their Choice Of The Source Of Antimalarial Drugs In Home Management Of Uncomplicated Childhood Malaria.

Majority of the respondents (over 60%) always obtained their artemether-lumefantrine from pharmacy outlets (Fig. 4.33). However, when the respondents are stratified according to their educational background, the influence of education is quite tremendous. Thus, those with no formal education, 52%, those with primary education, 62%, while the respondents with secondary and tertiary education had 79% and 82% respectively. There was a statistically significant difference between the non-formal and the primary education respondents ($P < 0.05$). In addition, both the non-formal and the

primary education respondents' results were significantly different from those with secondary and tertiary education ($P < 0.05$). Overall, the educational status of respondents influenced their choice of pharmacy outlet as a source for artemether-lumefantrine.

Majority of the respondents with primary and secondary education (70% and 65%) always obtained their artesunate-amodiaquine from the pharmacy, while 45% and 50% of tertiary-educated and non-formally educated respondents respectively obtained theirs from the pharmacy (Fig. 4.34). It is noteworthy that 50% of non-formally educated respondents, 27%, 22% and 20% of tertiary-, secondary- and primary-educated respondents respectively, never obtained artesunate-amodiaquine from the pharmacy.

With the exception of respondents with non-formal education (16%), all the others (primary 60%, secondary 69% and tertiary 86%) always obtained chloroquine from the pharmacy (Fig. 4.34). The differences between non-formal and the other three groups are significantly different ($P < 0.05$). Also there was a statistically significant difference between primary, secondary and tertiary ($P < 0.05$). Among the non-formally educated respondents, 32%, while 22%, 14% and 13% of primary, secondary and tertiary-educated respondents respectively never used the pharmacy as a source of chloroquine. Thus, the educational status of respondents influenced their choice of pharmacy as a source of chloroquine.

Other drugs used by respondents include paracetamol and multivitamins. Overall, they were mainly obtained from the pharmacy always (Fig. 4.36). However, between 18% and 41% never obtained these drugs from the pharmacy.

The results obtained with those who always used a doctor as a source of the artemether-lumefantrine was dependent on the educational background, thus, non-formal education

(11%), primary education (25%), secondary education (41%) and tertiary education (57%) (Fig. 4.37). Correspondingly, 53%, 43%, 28% and 25% respectively of non-formal, primary, secondary and tertiary educated respondents never used a doctor as a source of the drug in home management of uncomplicated childhood malaria. The differences between the groups that always used a doctor as a source of the drug were statistically significant ($P < 0.05$). Additionally, the differences between the groups that never used a doctor as the source were also statistically significant ($P < 0.05$).

The results show that most of the respondents never obtained artesunate-amodiaquine used in home management of uncomplicated childhood malaria from a doctor. Pooled results from 3 educated groups, show that about 45% went to the doctor for this drug. Indeed, 50% of primary, 39% of secondary, 26% of tertiary and 38% of non-formal education group never obtained this drug from a doctor (Fig. 4.38). The non-formal education group recorded a relatively high per cent of "don't know" in this section.

Many of the respondents (about 50%) never obtained chloroquine from the doctor. In spite of this, it is significant to note that as high as 40% of tertiary educated respondents, always obtained chloroquine in HMM from the doctor (Fig. 4.39). This value is significantly higher than those obtained for the other groups ($P < 0.05$).

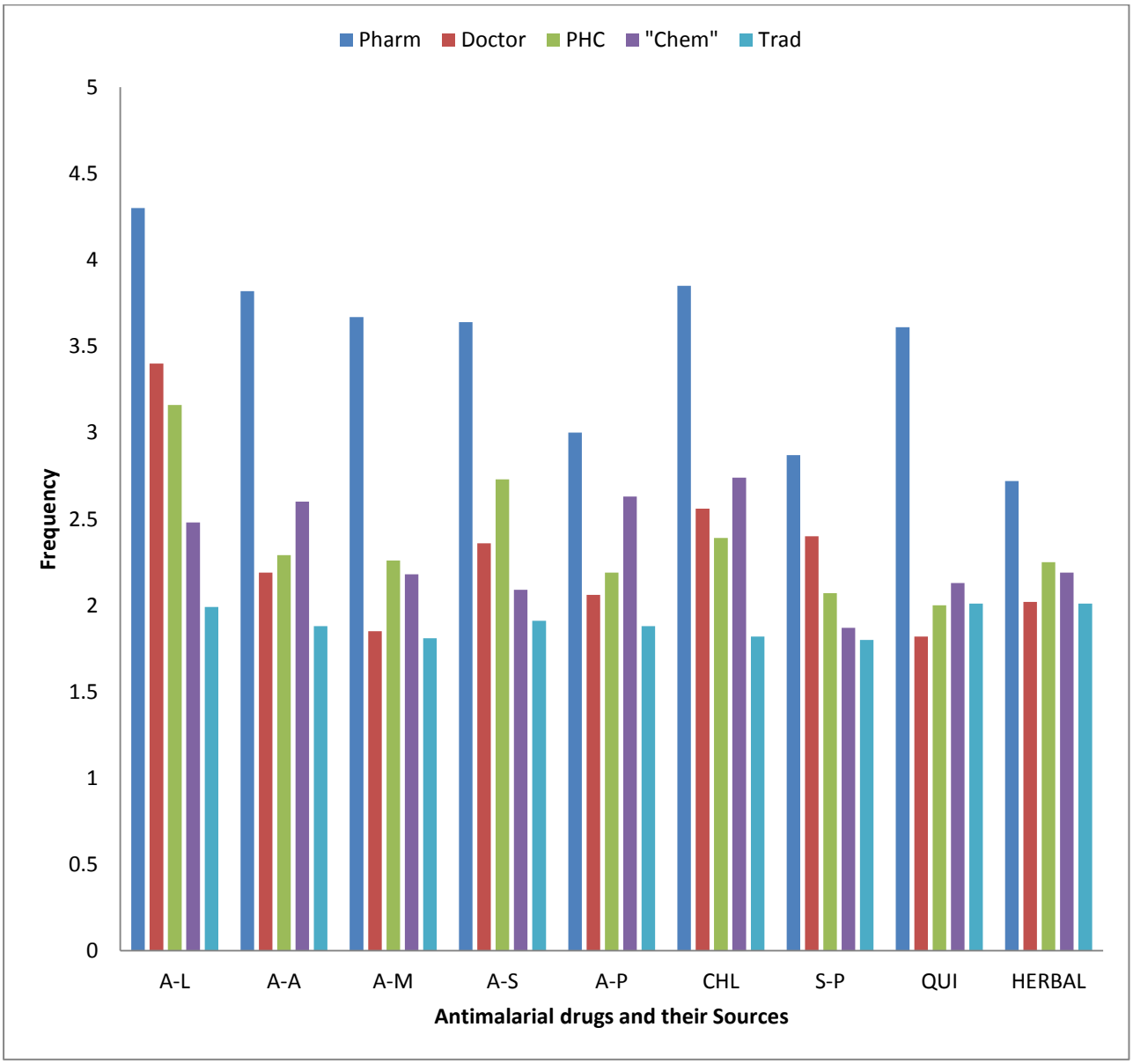

Fig. 4.32. Sources of drugs used in home management of uncomplicated childhood malaria by respondents.

KEY: A-L = artemether-lumefantrine, A-A = artesunate-amodiaquine, A-M = artesunate-mefloquine, A-P = artesunate-piperaquine, CHL = chloroquine, S-P = sulphadoxine-pyrimethamine, QUI = quinine, HERBAL = herbal remedies. Scores: Always = 5.0; Frequently = 4.0; Occasionally = 3.0; Never = 2.0; Don't Know = 1.0.

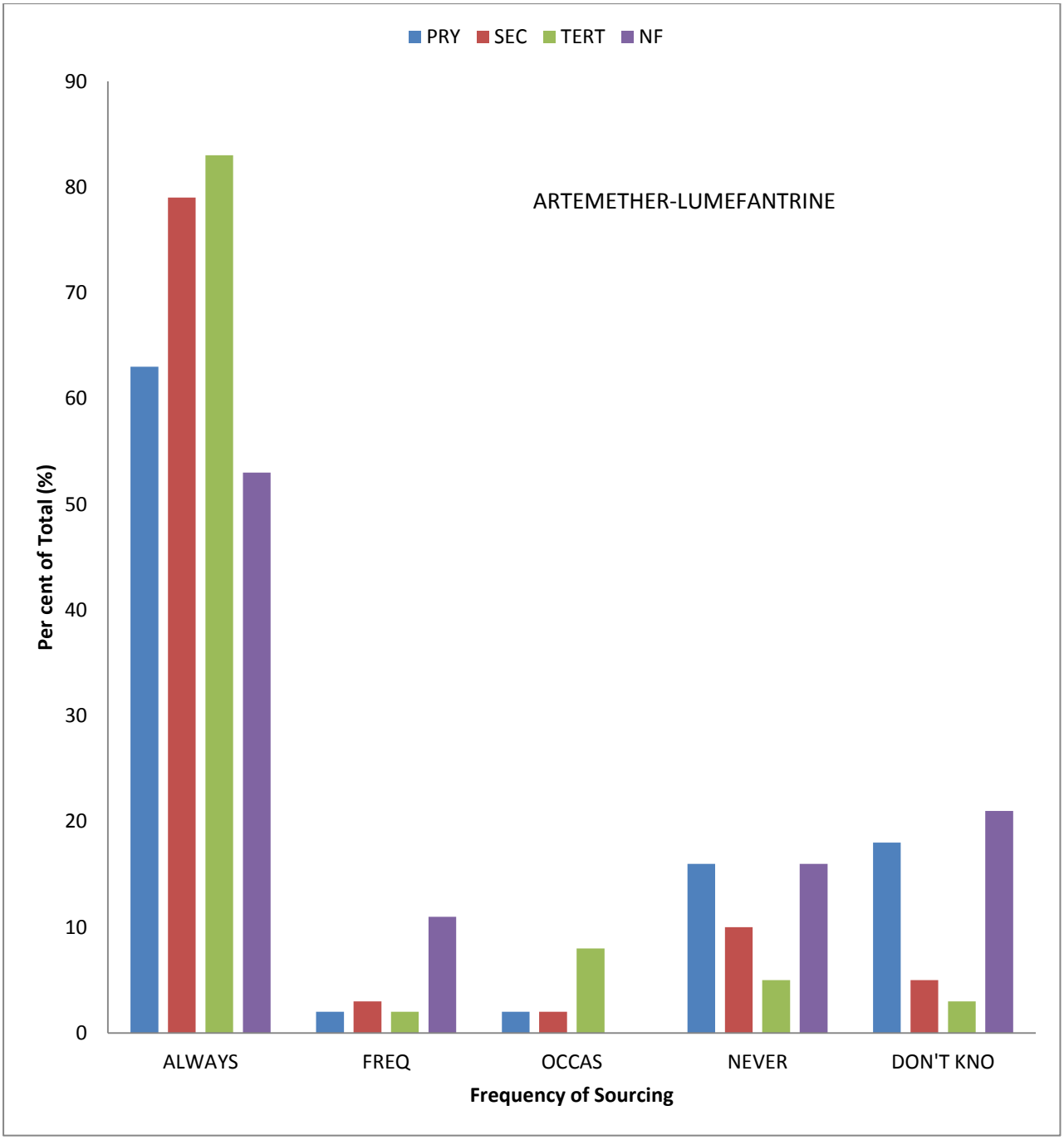

Fig 4.33. Pharmacy as a source of artemether-lumefantrine in home management of uncomplicated childhood malaria according to educational background of respondents.

KEY: FREQ = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC = Secondary education, TERT = Tertiary education,

NF = Non-formal education.

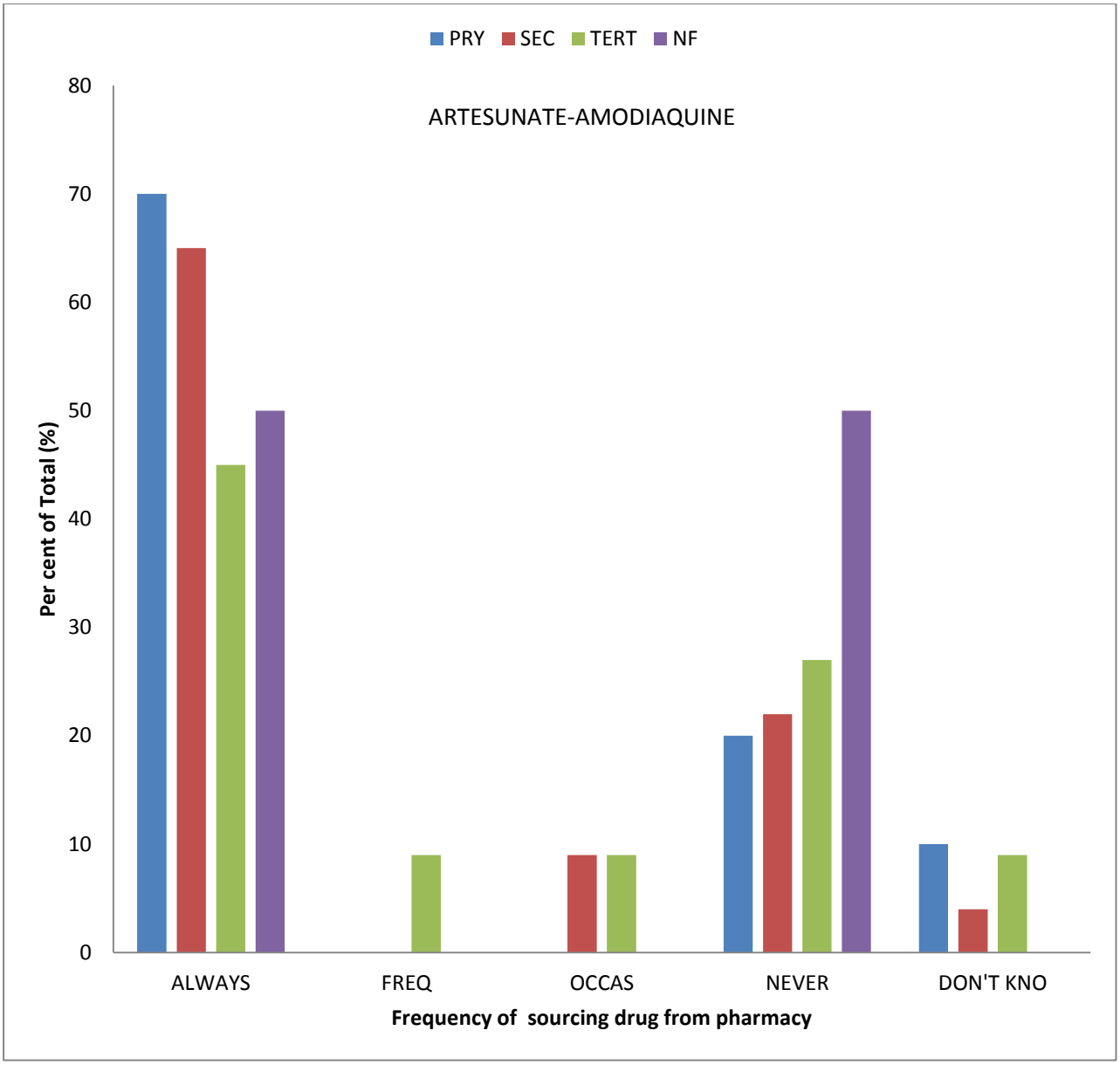

Fig. 4.34. Influence of educational status on respondents' choice of pharmacy as a source of artesunate-amodiaquine used in home management of uncomplicated childhood malaria.

KEY: FREQ = Frequently, OCCAS = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC = Secondary education, TERT = Tertiary education, NF = Non-formal education.

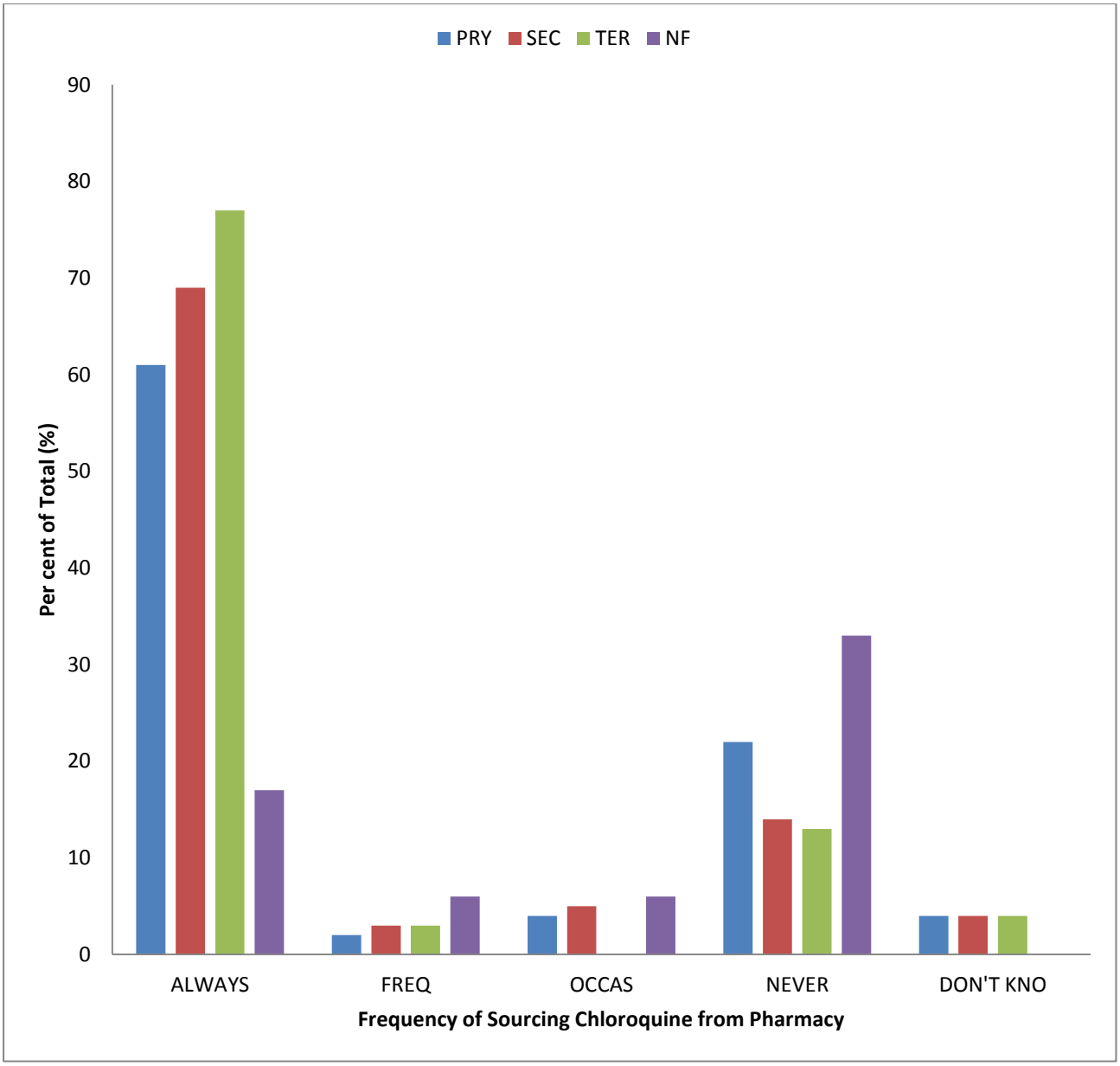

Fig. 4.35. Effect of educational background of respondents on the choice of pharmacy as a source of chloroquine in HMM.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

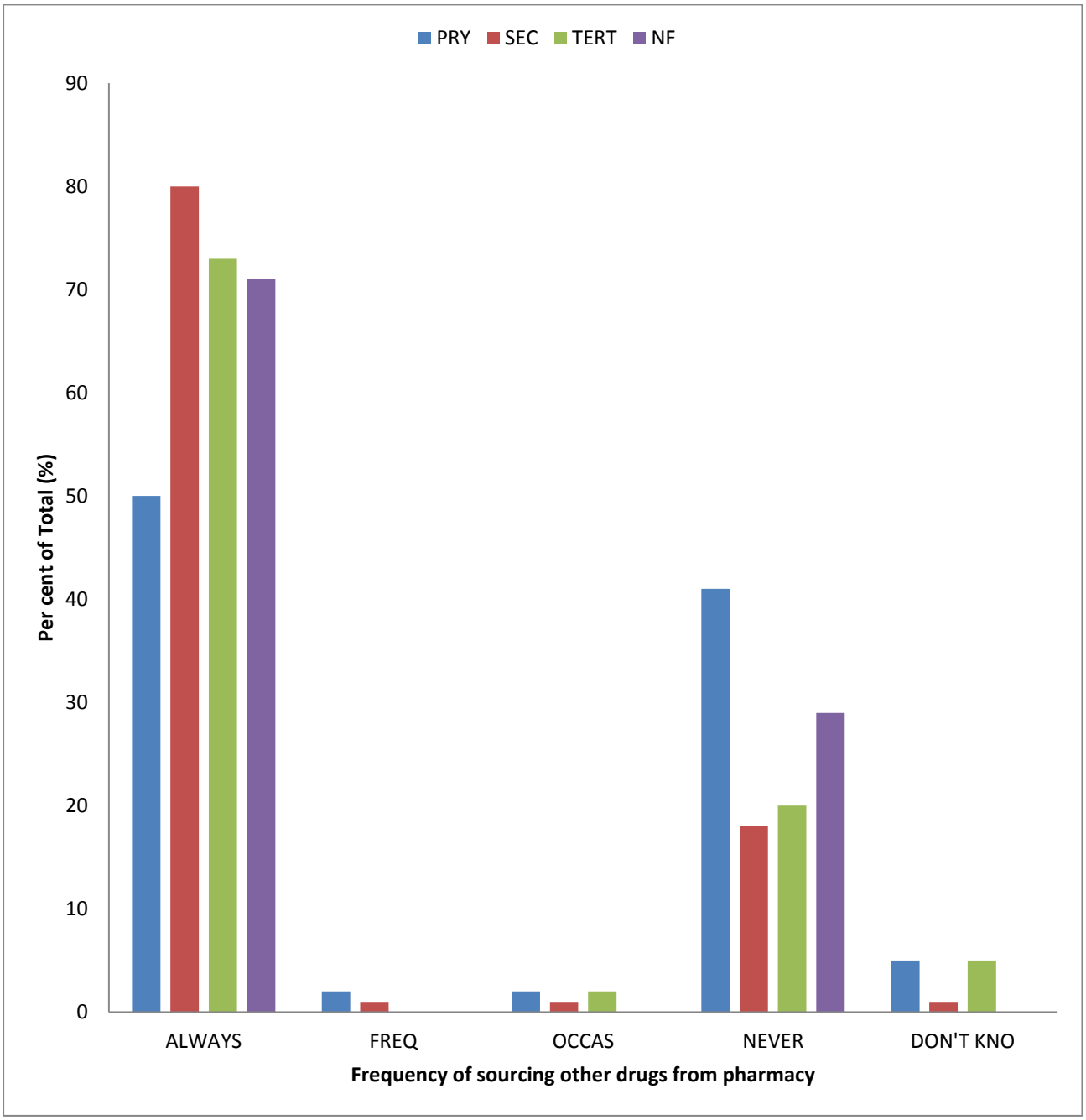

Fig. 4.36. Pharmacy as a source of other drugs used in home management of uncomplicated childhood malaria: influence of educational status of respondents.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

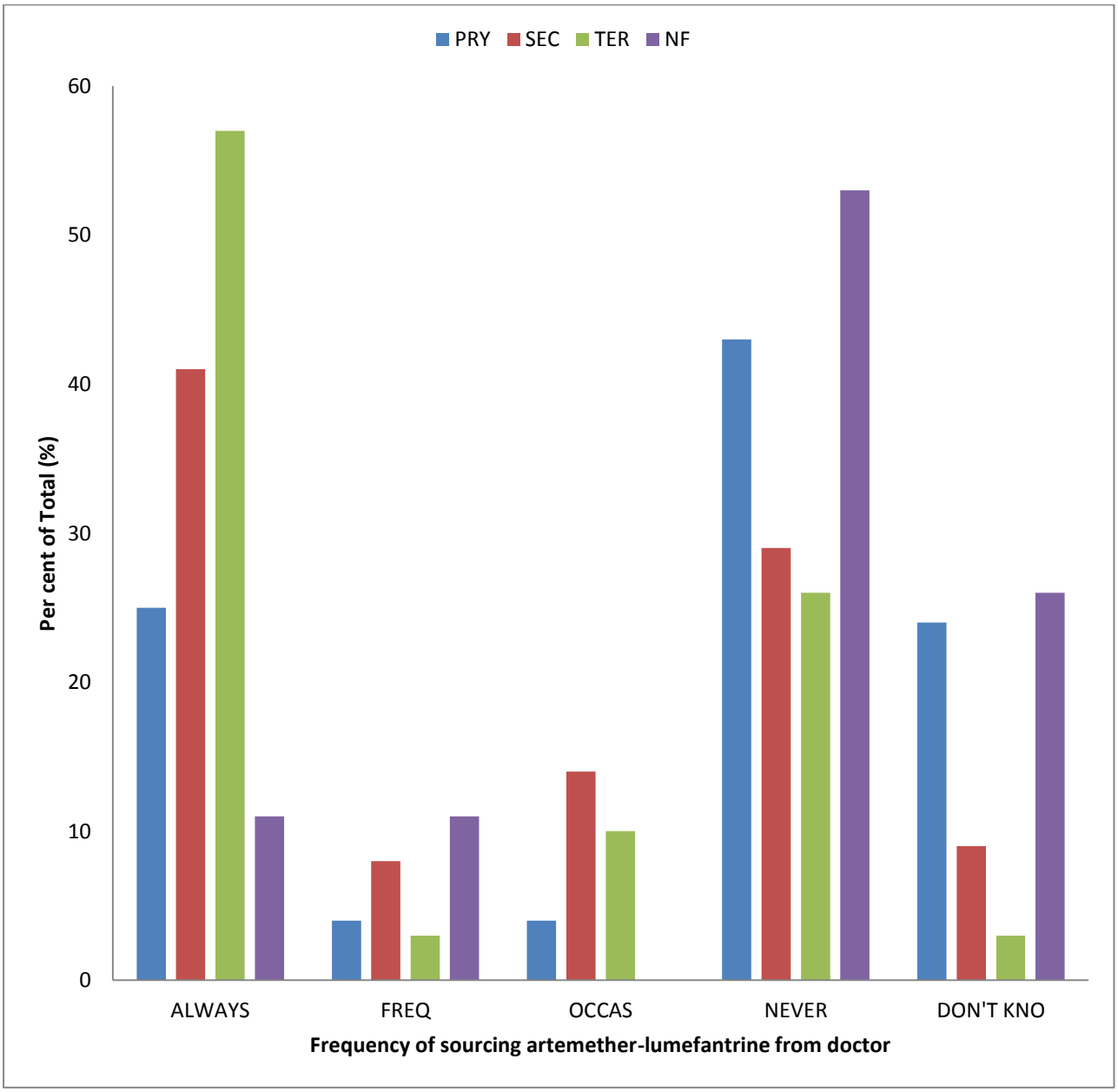

Fig. 4.37. Effect of education on the choice of a doctor as a source of artemether-lumefantrine used in home management of uncomplicated childhood malaria by respondents.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal educati

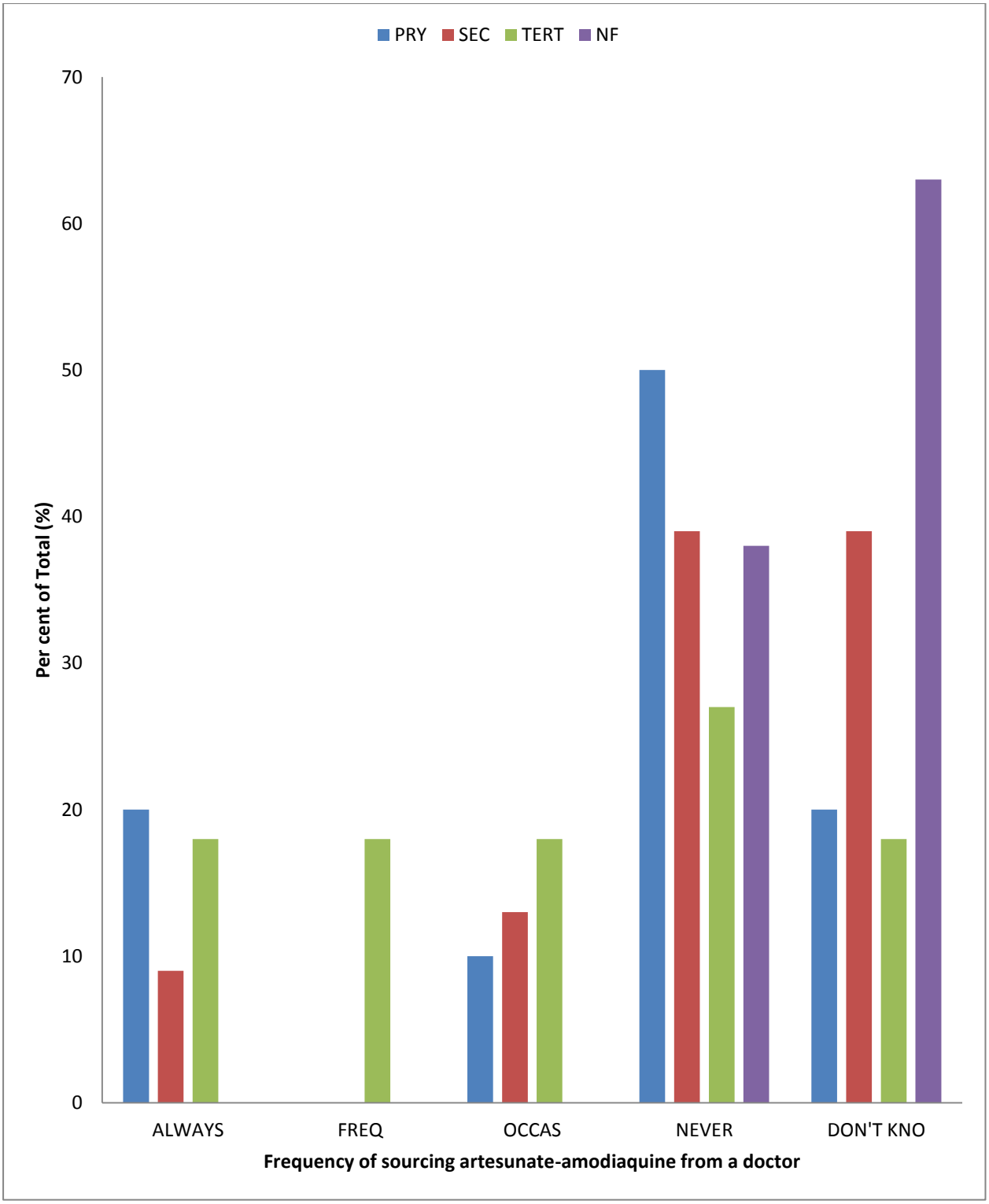

Fig. 4.38. Influence of education on the choice of a doctor as the source of artesunate-amodiaquine used in home management of uncomplicated childhood malaria by respondents.

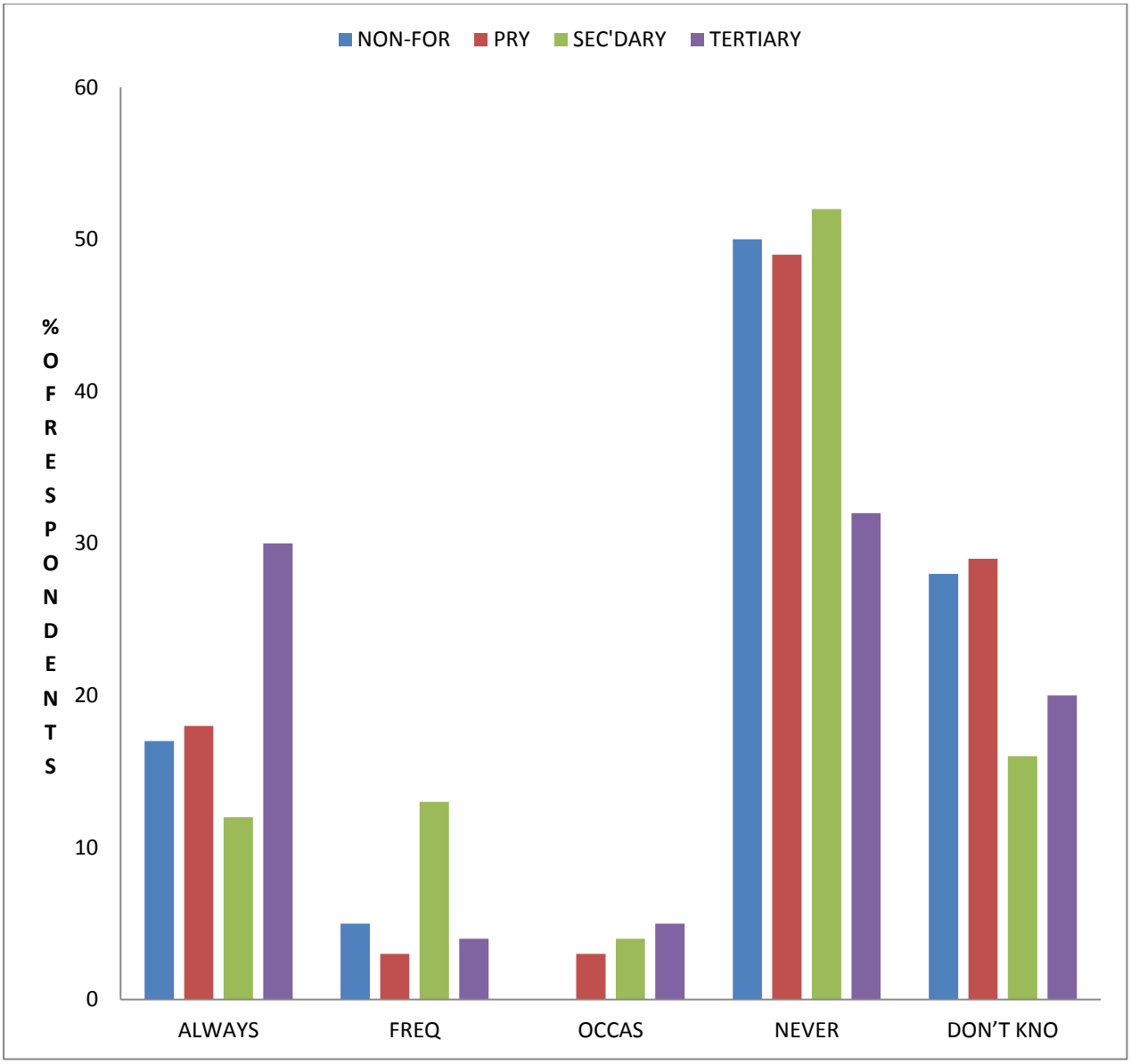

Fig. 4.39. Doctor as a source of chloroquine used in home management of uncomplicated childhood malaria: effect of the educational status of respondents.

Results are expressed as % of total number of respondents in an educational status group.

4.4.4 Factors Determining Access To Drugs Used In Home Management Of Uncomplicated Childhood Malaria

4.4.4.1. Availability Of Antimalarial Drugs As A Determinant Of Access To Treatment.

The success of any drug therapy depends, in part, on the availability of the required drugs and its affordability. The results show that artemether-lumefantrine was always available when needed by primary (32%), secondary (69%), tertiary (78%) and non-formal (62%) educated respondents in home management of uncomplicated childhood malaria (Fig. 4.40). The value for respondents with primary education was significantly lower ($P < 0.05$) lower than those of the other groups. Availability of the drug was reasonably good because less than 10% in each group never found artemether-lumefantrine. The differences between primary education group and the other groups were statistically significant ($P < 0.05$). In addition, there was a statistically significant difference between the non-formal education group and the secondary education group, and the non-formal education group and the tertiary education group ($P < 0.05$).

Similar results were obtained for artesunate-amodiaquine.

Chloroquine was always available to non-formal (39%), primary (27%), secondary (30%) and tertiary (47%) educated respondents (Fig. 4.41). There was a statistically significant difference between primary and secondary education and the other groups ($P < 0.05$). Similar responses were recorded by respondents for frequent availability of the drug: non-formal (17%), primary (25%), secondary (36%) and tertiary (27%) educated respectively (Fig. 4.41). The differences were statistically significant ($P < 0.05$).

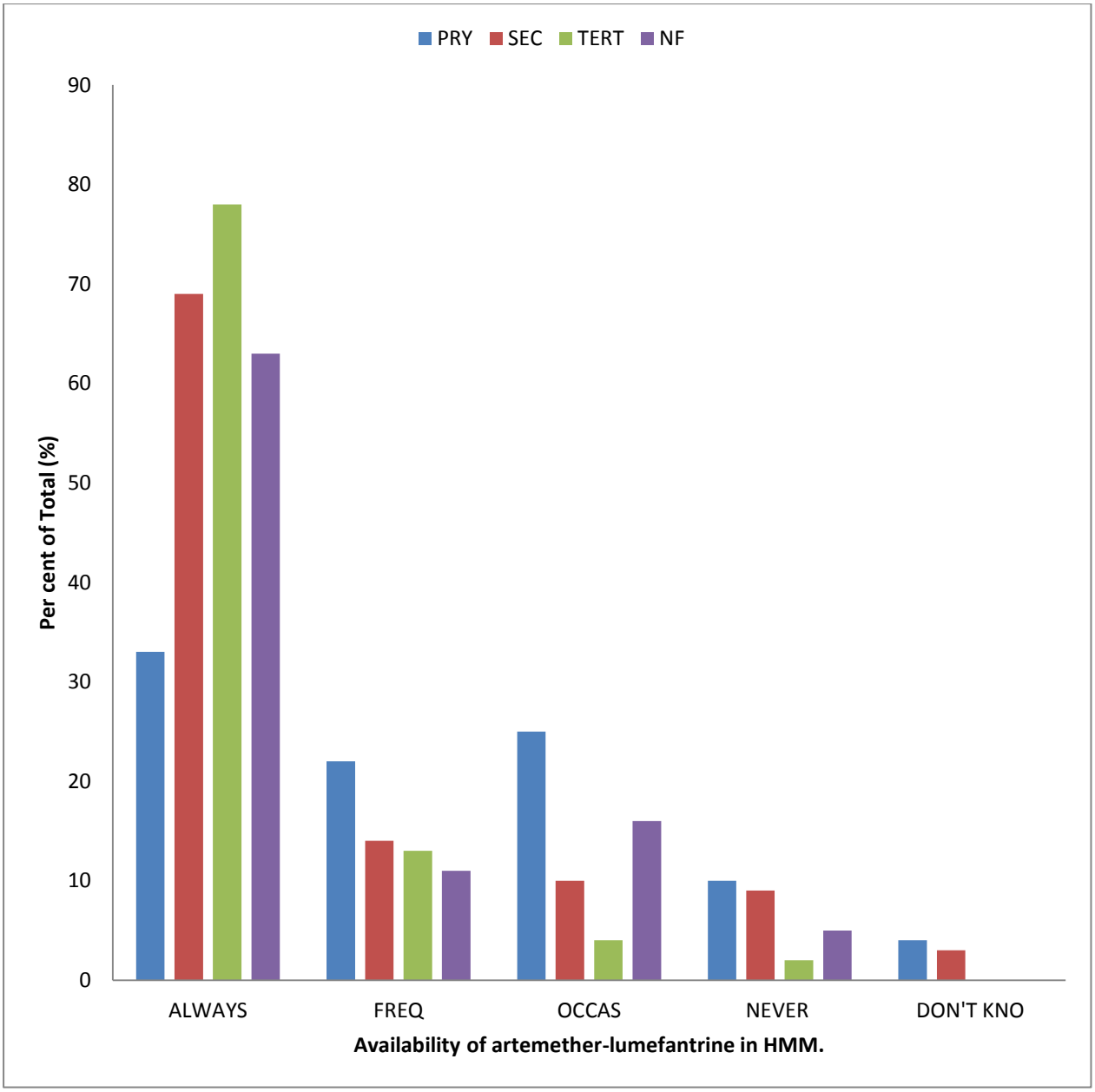

Fig. 4.40. Availability of artemether-lumefantrine as a determinant of access to therapy in HMM.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

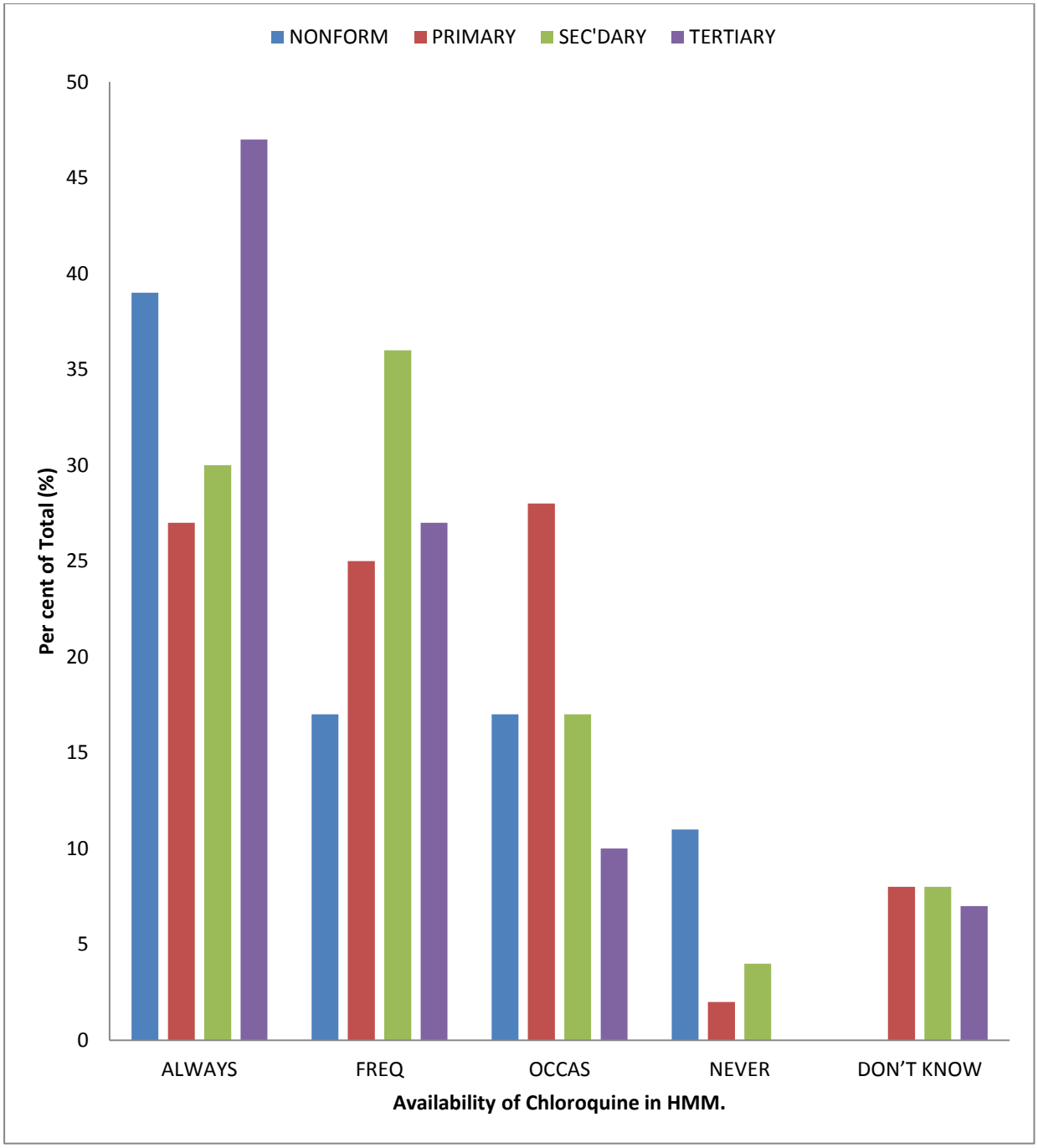

Fig. 4.41. Availability of chloroquine as an indicator of access to therapy in home management of uncomplicated childhood malaria by respondents.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRIMARY = Primary education, SEC'DARY. = Secondary education, TERTIARY. = Tertiary education, NON FORM. = Non-formal education

4.4.4.2. Brand Of Drug As A Determinant Of Access To Therapy In HMM.

In this section, effect of brand was studied on access to therapy. Respondents had more than one brand of the drug available at the point of purchase of the drug to choose from. Brand is used here to include innovator brand and branded generics.

The influence of brand of artemether-lumefantrine in determining access to treatment was dependent on the educational background of respondents. Thus, non-formal (5%), primary (24%), secondary (43%) and tertiary (59%) educated respondents always considered brand before obtaining artemether-lumefantrine for use (Fig. 4.42). There was a statistically significant difference in the responses of the educational groups ($P < 0.05\%$). In these groups, brand was always a determinant of access. In addition, brand also featured as a frequent determinant of access in a further 20% of the respondents.

On the other hand, brand of artesunate-amodiaquine was not always a determinant of access to therapy except among tertiary educated respondents. Most of the respondents never considered brand as a determinant of access to therapy. In addition, brand of artesunate-sulphadoxine-pyrimethamine was not always or frequently a determinant of access to therapy in home management of uncomplicated childhood malaria.

Some respondents (about 30%) never considered brand as a determinant of access to therapy in HMM. About 25% however, frequently considered brand a determinant of access to therapy. Only a few respondents (about 15%) always considered brand of chloroquine a determinant of access in home management of uncomplicated childhood malaria (Fig. 4.43).

The case with quinine was different. Brand was never an issue in access.

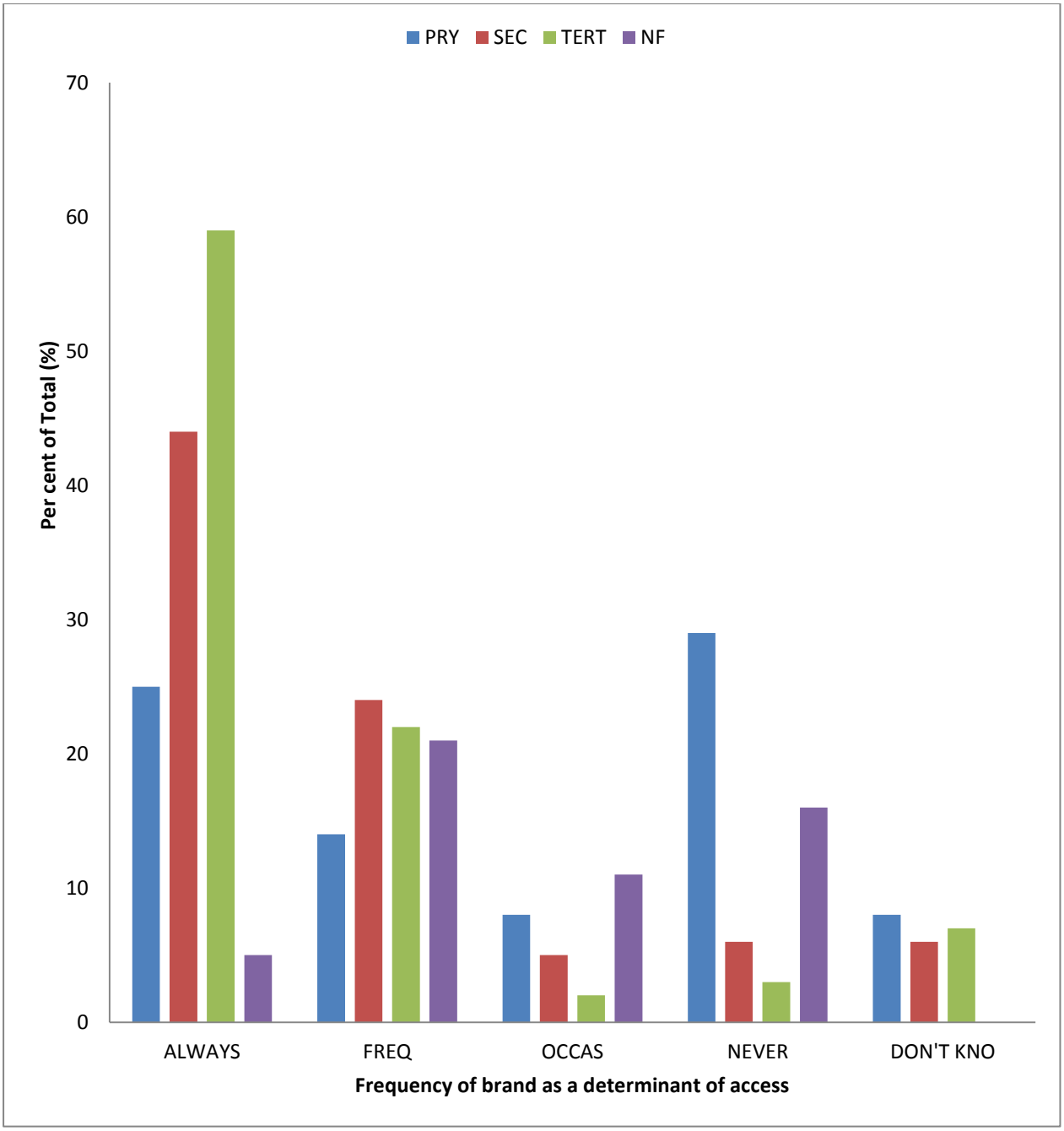

Fig. 4.42. Brand of artemether-lumefantrine as a determinant of access to therapy in home management of uncomplicated childhood malaria.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal educ

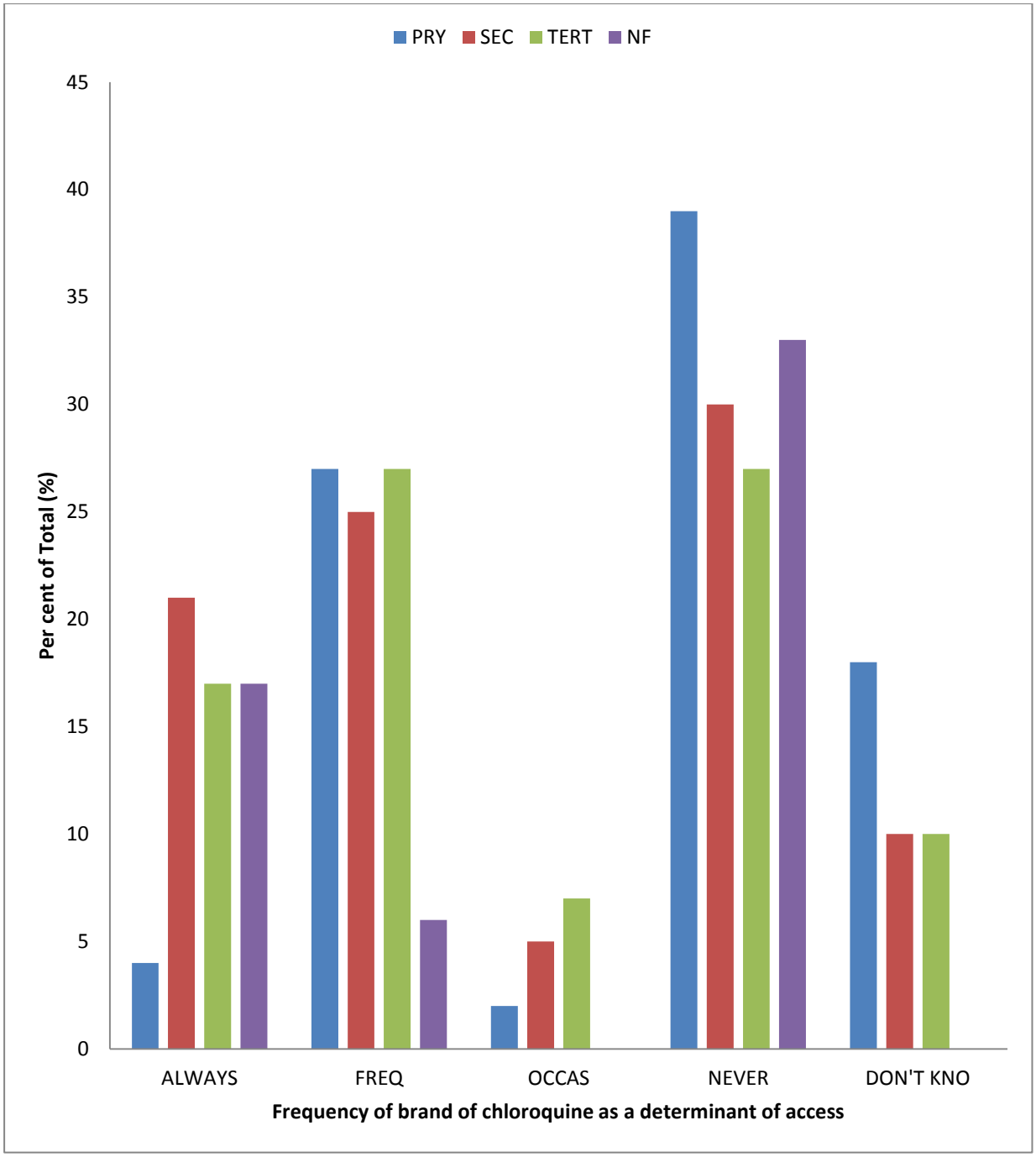

Fig. 4.43. Brand of chloroquine as a determinant of access to therapy in home management of uncomplicated childhood malaria.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

4.4.4.3. Cost As A Determinant Of Access To Therapy In Home Management Of Uncomplicated Childhood Malaria.

Cost refers to respondent's direct comparison of the prices of antimalarial drugs available at the point of purchase.

Educational background of respondents influenced significantly their choice of cost as a determinant of access to therapy in home management of uncomplicated malaria. Hence, non-formal (16%), primary (35%), secondary (52%) and tertiary (58%) educated respectively always considered cost as a determinant of access (Fig. 4.44). The differences between non-formal, primary, secondary and tertiary educated respondents were statistically significant ($P < 0.05$). Most of the non-formal education group (62%) considered cost as a frequent determinant to access, while about 20% each of the other groups frequently considered cost as a determinant of access to therapy. Similar results were obtained with artesunate-amodiaquine to a lesser magnitude.

Artesunate-sulphadoxine-pyrimethamine and artesunate-piperaquine results were very similar even though the magnitude of responses was significantly less ($P < 0.05$).

Cost of chloroquine was always a determinant of access to therapy by 50%, 35%, 28% and 14% respectively of respondents with tertiary, secondary, non-formal and primary education (Fig. 4.45). The differences between the responses of the groups were statistically significant ($P < 0.05$).There was no significant difference between respondents with non-formal and those with secondary education ($P > 0.05$). Except for 17% respondents with tertiary education that frequently considered cost as a determinant to access, 50%, 33% and 60% of those with primary, secondary and non-formal education respectively frequently did. The differences between the groups were statistically significant ($P < 0.05$).

Results obtained for quinine were not significantly different from those of chloroquine ($P > 0.05$).

Irrespective of the educational status of respondents, over 60% frequently considered cost of suphadoxine-pyrimethamine, artesunate-sulphadoxine-pyrimethamine and artesunate-piperaquine as a determinant of access to therapy.

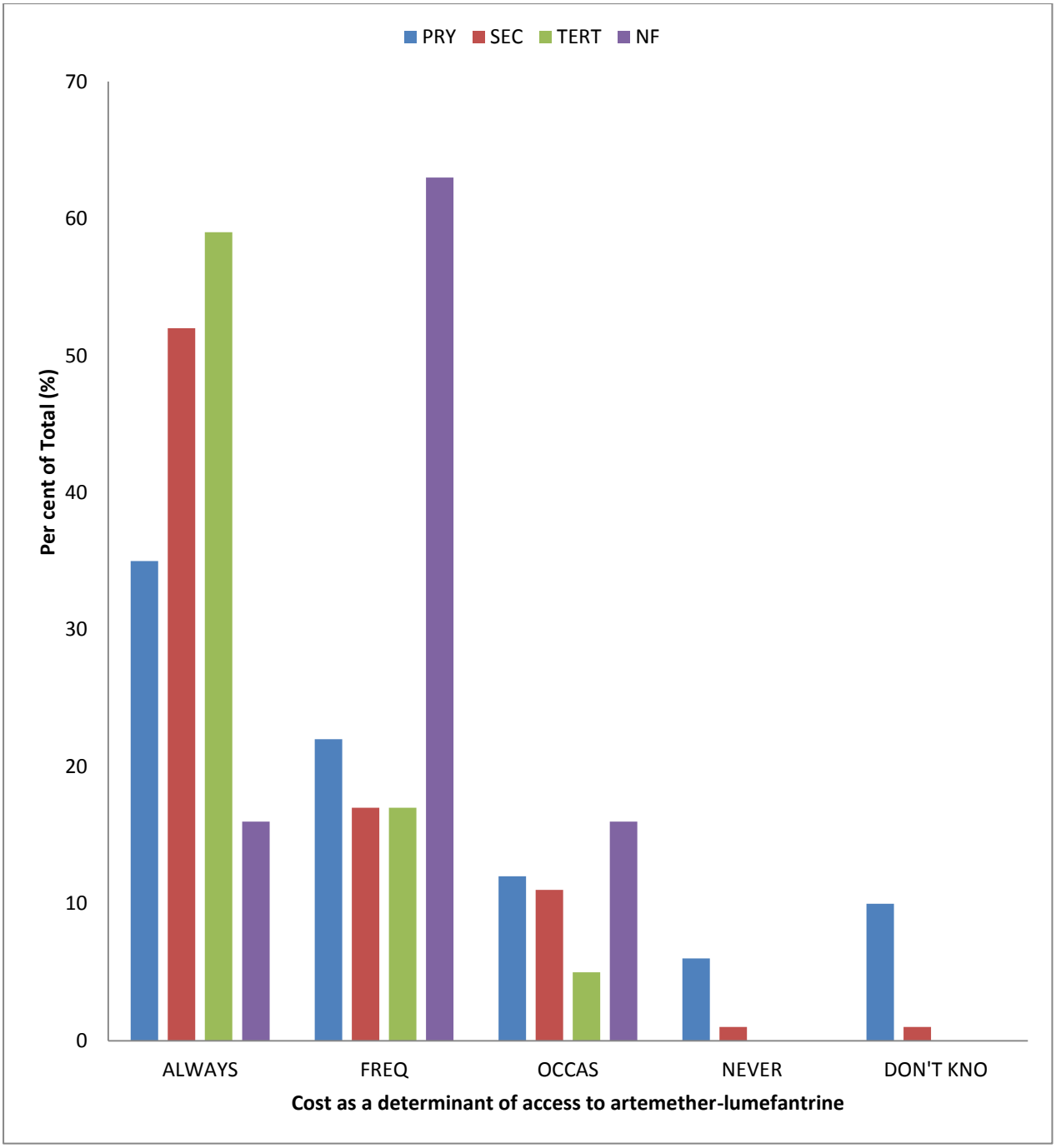

Fig. 4.44. Cost of artemether-lumefantrine as a determinant of access to therapy in HMM.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

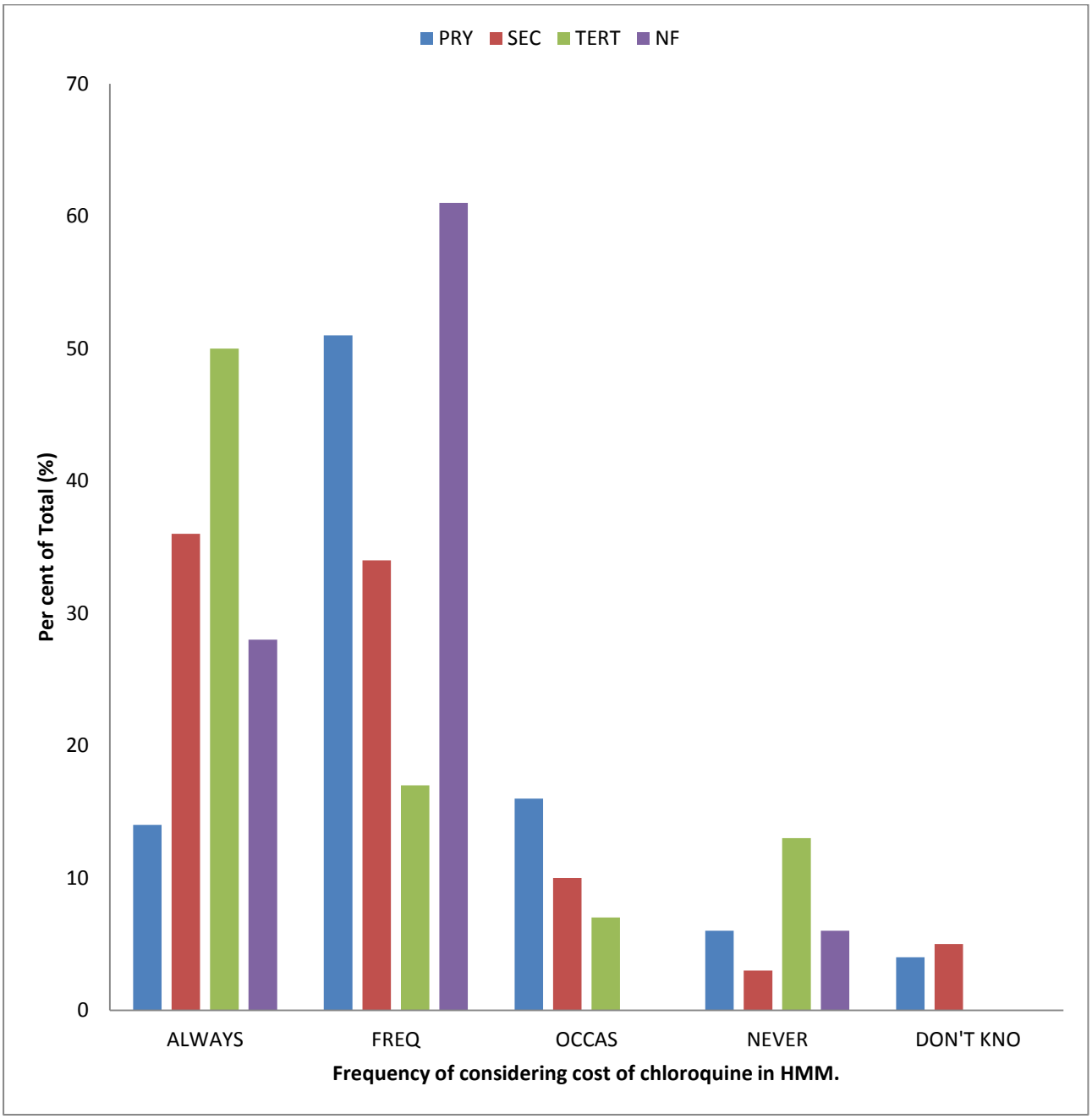

Fig. 4.45. Cost of chloroquine as a determinant of access to therapy in home management of uncomplicated childhood malaria.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

4.4.4.4. Packaging Of The Medication As A Determinant Of Access To Therapy.

In this section, the influence of packaging of drugs used in HMM by respondents was studied. Packaging here refers to external packaging.

Packaging of artemether-lumefantrine was always a major determinant of access in HMM. The influence of packaging was dependent on their educational status. Thus, 10%, 28%, 46% and 70% were recorded for non-formal, primary, secondary and tertiary educated respondents respectively (Fig. 4.46). The differences between the groups were statistically significant ($P < 0.05$). The results obtained for those who frequently, occasionally or never considered packaging as a determinant of access were generally not greater than 20%. Among those with primary education, about 36% did not know, that is, they had no opinion.

To a varying extent, packaging of chloroquine was always a consideration by 12% to 27% of respondents in its access for treatment in home management of uncomplicated childhood malaria (Fig. 4.48). A similar per cent of the respondents frequently considered packaging of the drug as a determinant of access. A significantly lower per cent never considered packaging a determinant, while many had no opinion.

Similar results were obtained for quinine, however, the per cent that never considered packaging an access determinant was greater. In this respect, the differences between chloroquine and quinine were significant ($P < 0.05$).

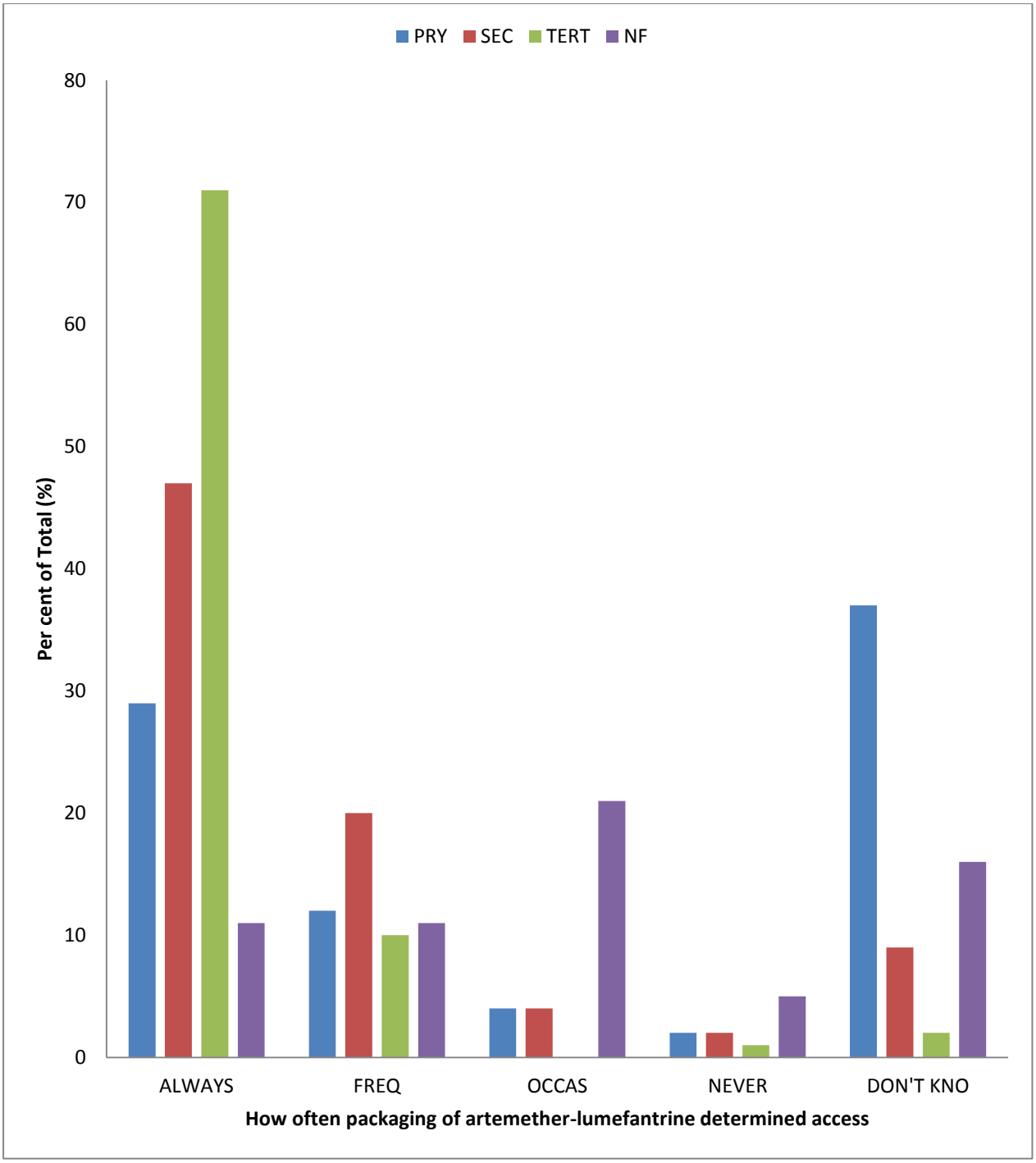

Fig. 4.46. Influence of packaging of artemether-lumefantrine on access to therapy in home management of uncomplicated childhood malaria.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

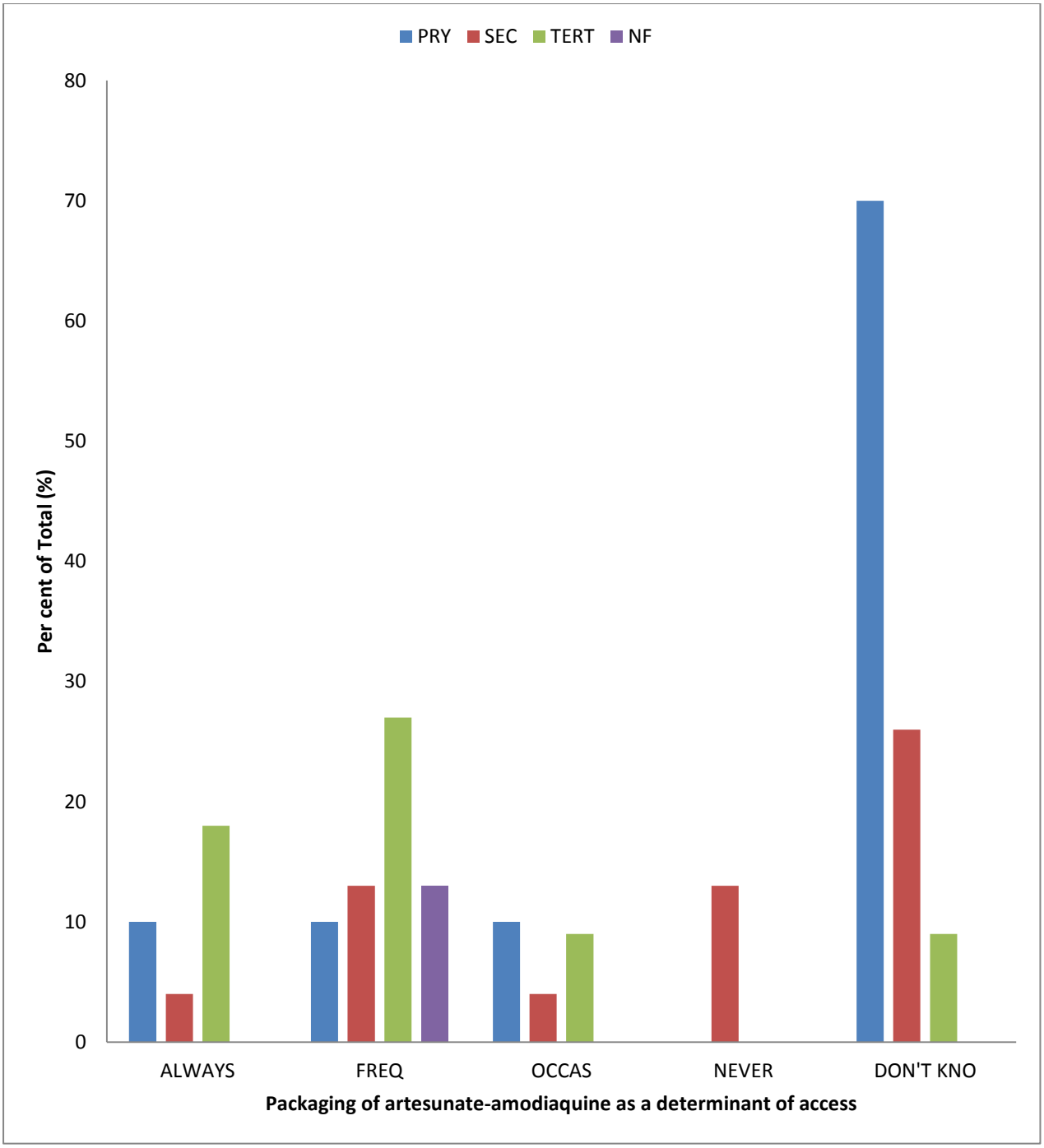

Fig. 4.47. Effect of packaging on the access to artesunate-amodiaquine in home management of uncomplicated childhood malaria.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

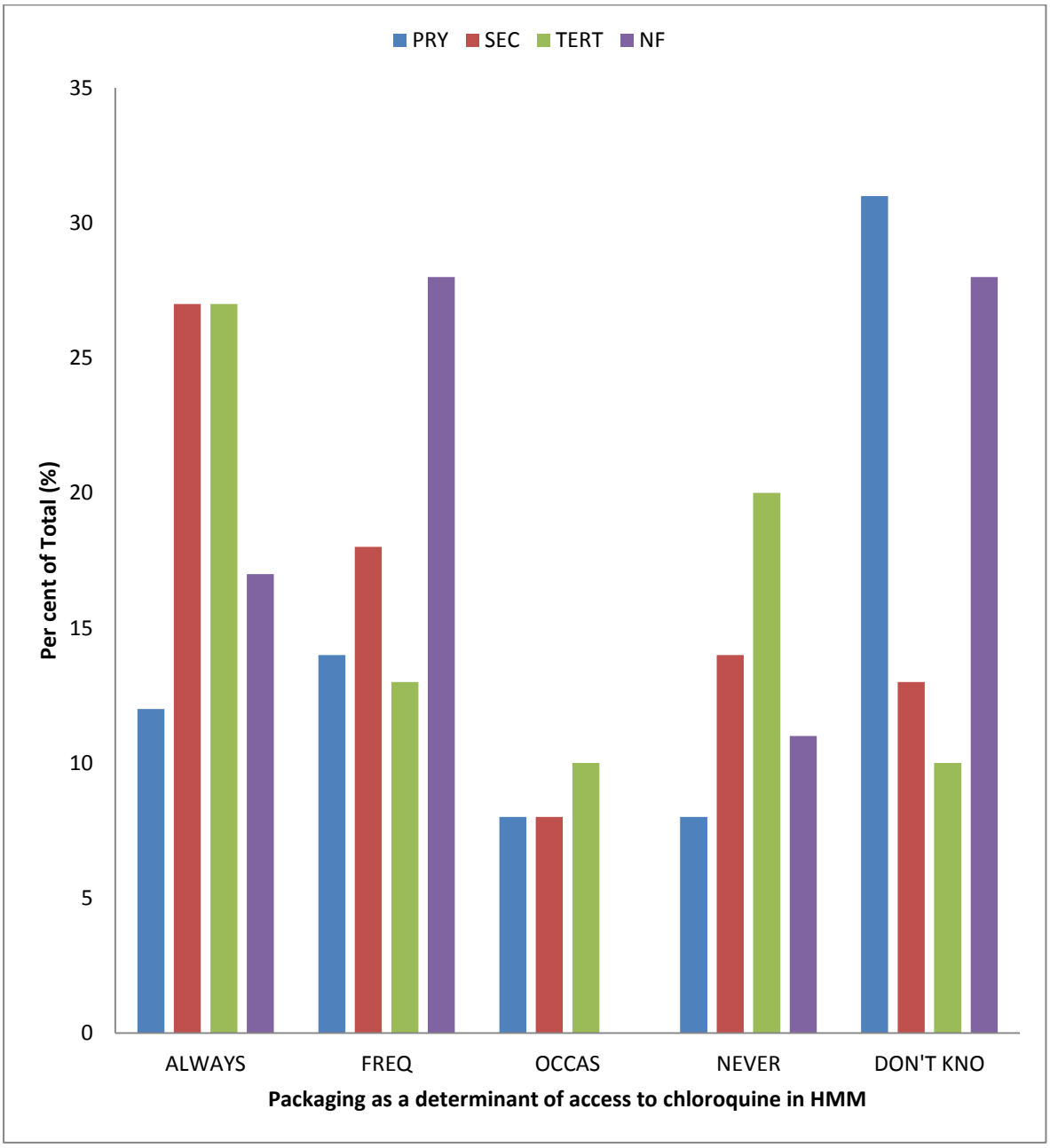

Fig. 4.48. Effect of packaging as a determinant of access in home management of uncomplicated childhood malaria.

KEY: FREQ. = Frequently, OCCAS. = Occasionally, DON'T KNO = Don't know, PRY = Primary education, SEC. = Secondary education, TERT. = Tertiary education, NF = Non-formal education.

Unlike chloroquine which has been banned in Nigeria, quinine is an approved drug reserved for cerebral malaria in The National Treatment Guidelines for Malaria.

4.4.4.5. Previous Efficacy Of Drugs As A Factor Influencing Access In HMM.

In this section, the influence of previous efficacy of drugs used in HMM as a determinant of access to drugs by respondents was studied. Previous efficacy in this case was either in the child, the respondent or other people that had communicated with the respondent. This was done in two parts: the responses of all participants irrespective of their educational background, and their responses stratified according to their educational background.

Previous exposure to artemether-lumefantrine always influenced access to treatment in home management of uncomplicated childhood malaria. This was dependent on the educational status of respondents. Hence, of the respondents with no formal education, those with primary, secondary and tertiary education were15%, 35%, 58% and 69% respectively always considered previous efficacy of artemether-lumefantrine as a factor influencing access to treatment (Fig. 4.49). The differences in responses between the groups were significantly different ($P < 0.05$). About 20% of all responses frequently considered previous efficacy of artemether-lumefantrine a factor influencing access to treatment in home management of uncomplicated childhood malaria.

Fig. 4.50 represents the pooled results of all respondents. Previous efficacy of artesunate-amodiaquine was always a factor influencing access in 36% of the respondents irrespective of their education and sex. One-third of the respondents never considered previous efficacy a determinant to access. On the other hand, 15% either frequently or occasionally considered previous efficacy as a determinant of access to

the drug. The differences between those that always did and those that either frequently and/or occasionally did were statistically significant ($P < 0.05$). Those that never did were significantly more than those that either frequently and/or occasionally did ($P < 0.05$). On the other hand, the difference between those that always did and those that never did was not significant ($P > 0.05$).

About 40% of the respondents always considered previous efficacy as a factor influencing access to chloroquine, while 19% and 16% either frequently or occasionally considered it a determining factor (Fig. 4.51). The difference in between the group that always did and the groups that frequently and/or occasionally did was statistically significant ($P < 0.05$). On the other hand, 14% of the respondents never considered previous efficacy a determinant to access in HMM.

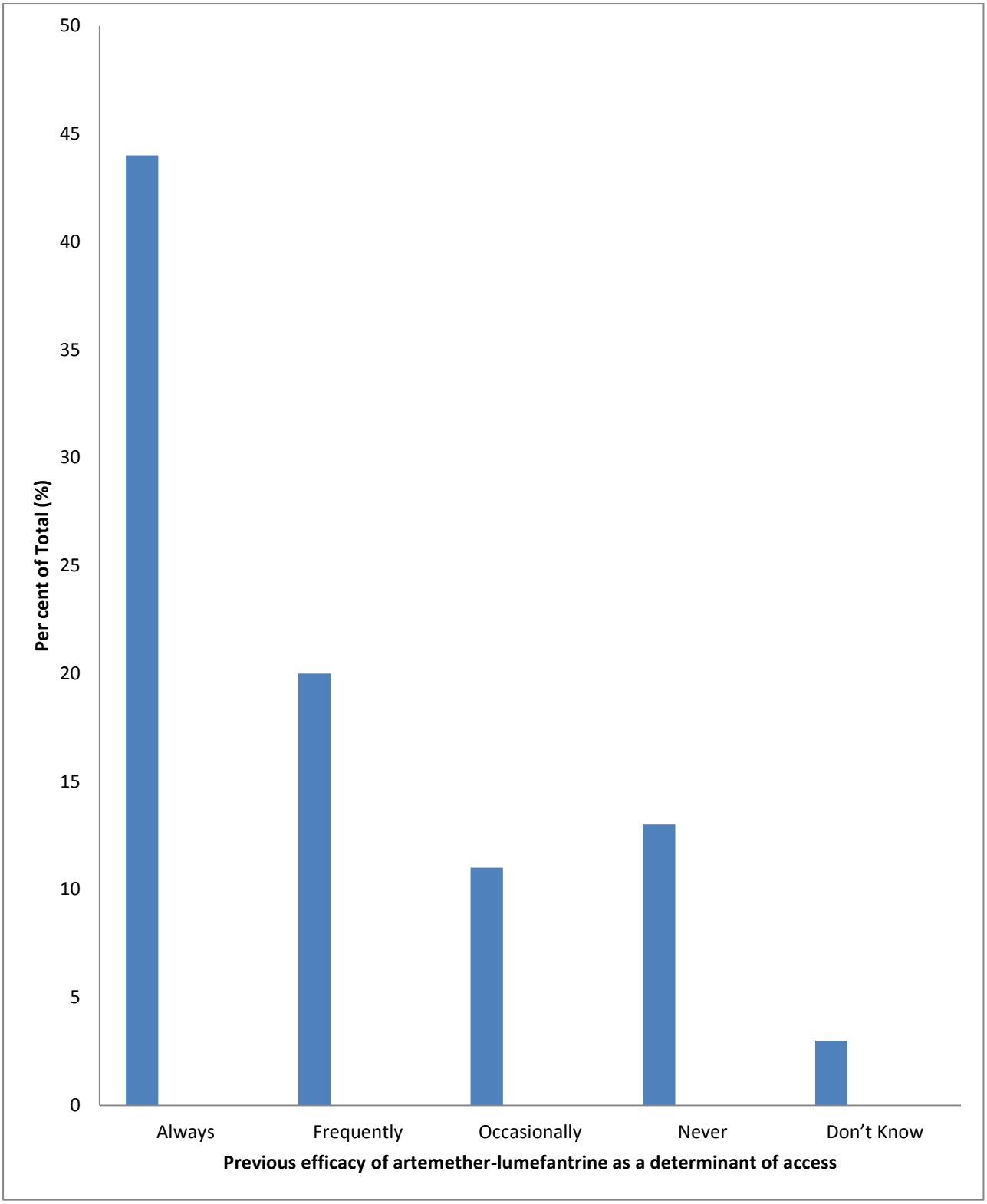

Fig. 4.49. Influence of previous efficacy of artemether-lumefantrine on its access in HMM.

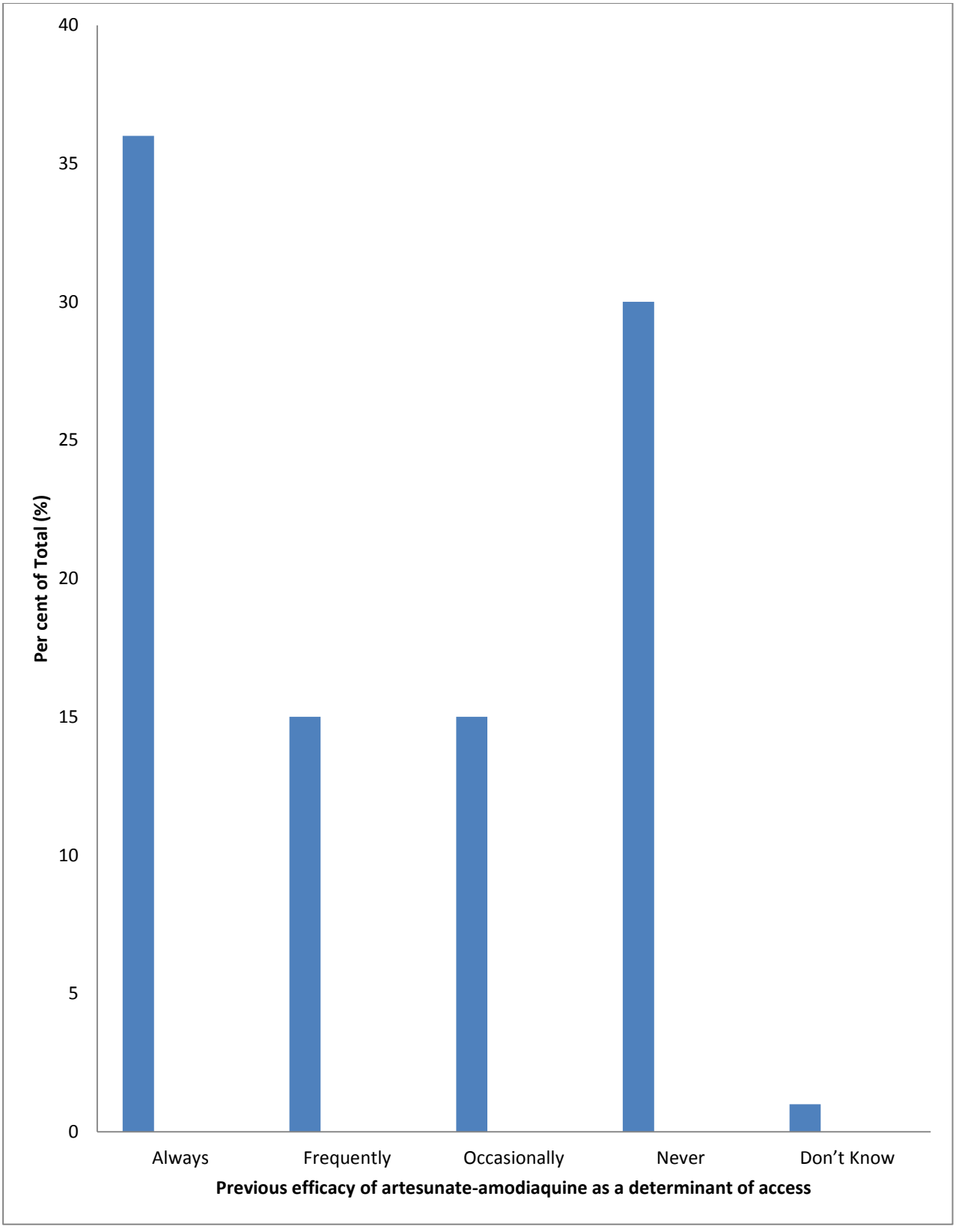

Fig. 4.50. Previous efficacy of artesunate-amodiaquine as a determinant of access to treatment in HMM.

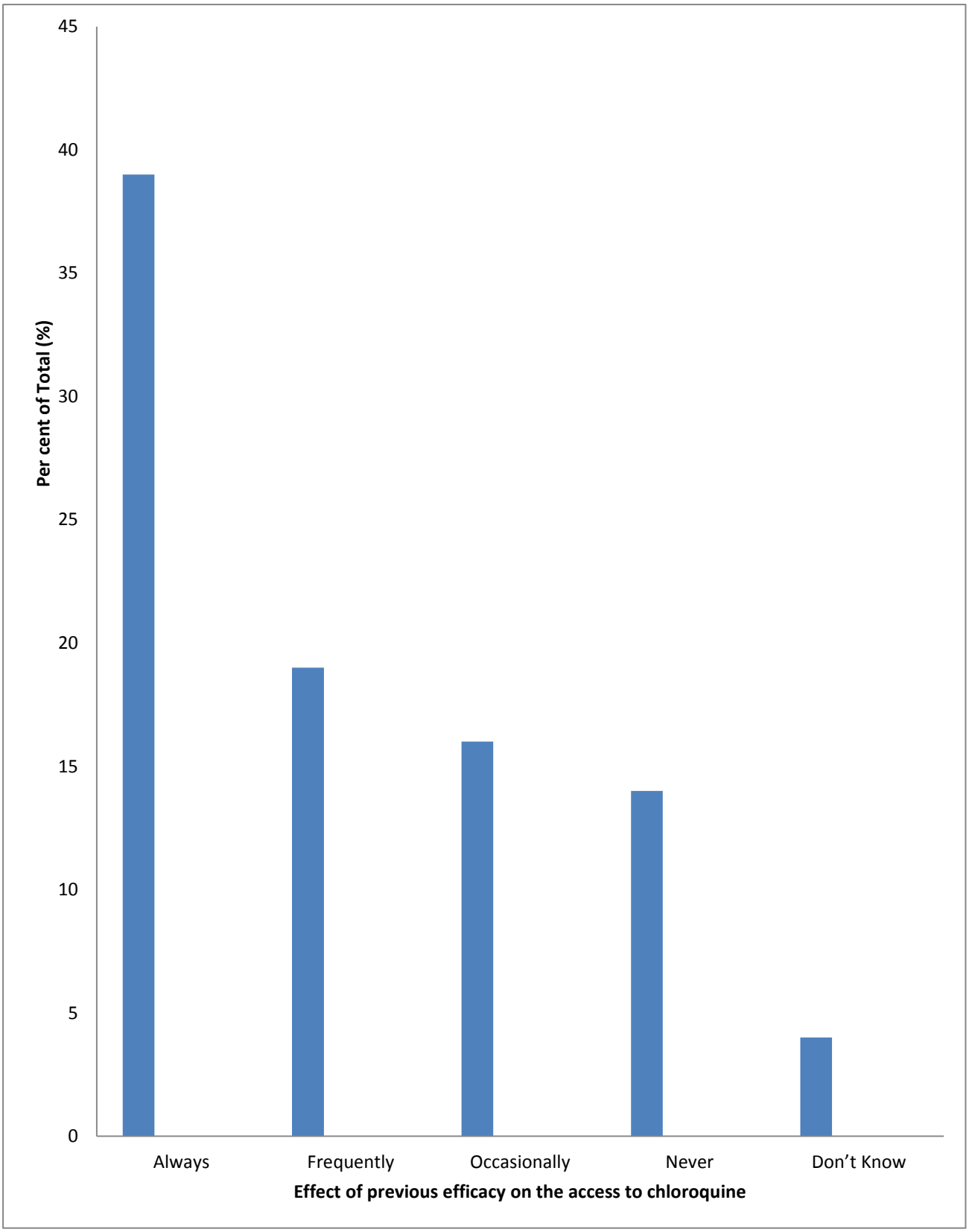

Fig. 4.51. Previous efficacy of chloroquine as a factor influencing access in the treatment of uncomplicated childhood m

CHAPTER FIVE

5.0 Discussion

5.1. Practice of Home Management of Uncomplicated Childhood Malaria by Mothers and Fathers

The study was designed to determine the knowledge, understanding, practice and drug use in home management of uncomplicated childhood malaria by mothers and fathers in Lagos State, Nigeria, because malaria ranks high as a killer of Nigerian children under 5 years old (U_{-5}) (Bruce-Chwatt, 1952; Salako *et al.*, 2001; Adebayo and Fahrmeir, 2005; Aigbe and Zannu, 2012). Every single day, Nigeria loses about 2,300 under-five year olds and 145 women of childbearing age. This makes the country the second largest contributor to the under–five and maternal mortality rate in the world (UNICEF 2012).

Underneath the statistics lies the pain of human tragedy, for thousands of families who have lost their children. Even more devastating is the knowledge that, according to recent research, essential interventions reaching women and babies on time would have averted most of these deaths.

Although analyses of recent trends show that the country is making progress in cutting down infant and under-five mortality rates, the pace still remains too slow to achieve the Millennium Development Goals of reducing child mortality by a third by 2015 (Adeyele and Ofoegbu 2013).

Preventable or treatable infectious diseases such as malaria, pneumonia, diarrhoea, measles and HIV/AIDS account for more than 70 per cent of the estimated one million under-five deaths in Nigeria (UNICEF 2012).

Indeed, according to WHO (2007), the overall childhood mortality in Nigeria is 194 per 1,000 births, much of which can be attributed to malaria.

The inclusion of fathers in this study was an innovation because fathers do not traditionally feature in home care of children in many cultures, including Nigerian cultures. Indeed, most studies on care of children have been done using mothers because throughout human history and across cultures, women have typically assumed primary caregiving responsibility for children (Geary, 2000; Hrdy, 1999). Until recently, men's image as fathers was that of a parent with no close relationship to his children, particularly not if they were newborn or very young (Madsen, 2007).

Majority of the mothers (59%) had one child. Indeed, the number of children per mother in this study was below national average which is 5.7 (NDHS, 1999). This may be explained by the high educational status of respondents. In this study, only 9% of respondents had no formal education while as high as 47% and 24% had secondary and tertiary education respectively.

Respondents' knowledge of the cause of malaria was good as many chose fever. This may explain why they commenced treatment for malaria presumptively. Their responses were independent of their educational background. It is noteworthy that the Lagos State Government Malaria Research Committee has created substantial awareness of malaria prevention and control in recent times. Preventive methods of malaria were well understood among respondents. Thus, IRS = ITN > window net >> bed net. The state-wide activities of Lagos State Malaria Research Committee (Wright *et al*, 2013) may have empowered respondents in this respect. Neither gender nor the educational status of respondents influenced their knowledge of cause of malaria. This may be explained by the fact that malaria has become a "household" word and people

readily associate it with mosquito bite. Indeed, this is confirmed by the prevention methods chosen by respondents. It is noteworthy that the choice of IRS as a leading preventive measure could be attributed to the recent aggressive indoor residual spray campaign of the Lagos State Government's Malaria Research Committee (Wright *et al*., 2013).

Fever ranked highest among other signs of malaria. This is expected because it is generally the most easily noticeable sign. Indeed, the choice of fever was not dependent on their educational status. However, their choices of chills/rigour, vomiting, dehydration and diarrhoea were dependent on their educational background. In a similar study in Ghana, it was found that 96.9% and 75% of respondents knew the symptoms and causes of malaria respectively (Aborah *et al.,* 2013).

Home management of uncomplicated childhood malaria involves presumptively treating febrile children at or near home with antimalarial drugs (WHO, 2004, 2005; Adjei *et al.,* 2008; Ajayi *et al*., 2008). Majority (70%) of respondents understood the concept of home management of uncomplicated childhood malaria. Despite this relatively high percentage, there is need for more advocacy to empower the populace because quite unexpectedly, between 42% and 57% of primary and tertiary educated respondents thought home management of uncomplicated childhood malaria was taking the child to the hospital. This understanding was independent of gender, however, educational status seemed to influence it. The higher the educational status, the better their understanding. It seemed probable from this study that before the WHO concept was advanced, parents had been practising home management of uncomplicated childhood malaria or home management of childhood malaria as a measure to prevent childhood mortality. The ultimate, however, is to have all mothers and fathers understand and practise home management of uncomplicated childhood malaria. There

is therefore need for enlightenment and advocacy highlighting the benefits, while emphasizing the need for referral in unresolved cases. Home management of uncomplicated childhood malaria must be done promptly to prevent progression into complicated (severe) malaria which may be fatal. Prompt diagnosis and effective treatment may save lives, but many children still die from severe malaria despite efforts to improve health services and encourage families to seek treatment through health facilities. Many children living far away from health care units die while travelling to the nearest hospital (Arnaud *et al.,* 2005). These deaths due to malaria usually occur in the first 24 hours of hospital admission which highlights the need for early diagnosis, prompt and appropriate management (Arnaud *et al,* 2005). It is clear that unless effective management of malaria is introduced early at the point of first consultation, the huge burden of morbidity and mortality cannot be arrested.

Self-treatment at home, a form of home management of uncomplicated malaria, is the major action taken to manage malaria. Deressa *et al.,* (2003), based on their experience, in a rural community in southern Ethiopia coupled with the works of Mwenesi *et al*., (1995) and Deming *et al.,* (1989) in Kenya and Togo respectively, advocated that efforts should be made to improve the availability of effective antimalarial drugs to communities in rural areas with malaria, particularly through the use of community health workers, mother coordinators, drug sellers and shop owners.

Results obtained in this study indicated that, at least, 80% of respondents were managing uncomplicated malaria because they did not notice convulsions, stiff neck, loss of consciousness, drooling of saliva and/or yellow eye/skin, which are signs of complicated malaria. They also noticed improvement most of the time. When no improvement was noticed they went to a hospital and/or a primary healthcare centre. Those that noticed any of the signs of complicated malaria sought help mainly from the

hospital and primary healthcare centre. About 16% of them sought help from the wrong sources, namely, buying medicines, pharmacy and herbal remedies. The remaining 9% took no action. These are among the downsides of home management of uncomplicated childhood malaria. It is therefore desirable that public enlightenment should accompany home management of uncomplicated childhood malaria with emphasis on immediate referral to appropriate centres in unresolved cases.

Drug administration as a preferred intervention in home management of uncomplicated childhood malaria by mothers and fathers ranked highest. Indeed, it was noted that the antipyretic, paracetamol, with no documented antimalarial action, ranked higher than the known antimalarial drug, artemether-lumefantrine. This may be indicative of the reduction in pyrexia by paracetamol which respondents noticed. Such action does not mean that parasitaemia has been reduced. Oshikoya and Senbanjo (2008) found that paracetamol was preferred by mothers in treating malaria in their children even above antimalarial drugs, including artemisinin combination therapy.

The use of paracetamol without concurrent use of antimalarial drugs calls for concern. This practice was exhibited independent of their educational status. Respondents obtained reduction in body temperature which was mistaken for an antimalarial effect. A reduction in pyrexia does not mean that there is a reduction in parasitemia, therefore, there may be a progression to complicated (severe) malaria even when outwardly pyrexia has subsided. Kwiatkowski (1989); Long *et al*., (2001) reported that febrile temperatures inhibited *P. falciparum* growth in erythrocytic culture *in vitro*, however, periodic fluctuations of temperature such as occur in natural infection, are capable of synchronizing the parasite population (Kwatkowski, 1989).

Two very significant findings of this study were that home management of uncomplicated childhood malaria (HMM) was practised by mothers and fathers in Lagos State and that artemisinin-combination therapy (ACT) drugs were used in compliance with the National Treatment Guidelines for Malaria. These results have significance in that they may be used as a template for a countrywide study to complement government efforts to attain Millennium Development Goal Number 4 to reduce childhood mortality and morbidity. Infant and Under-5 mortality rates in Nigeria are high, 75 and 157 deaths per 1,000 live births respectively in 2008 (Aigbe and Zannu, 2013).

Artemether-lumefantrine, one of the two official ACT antimalarial drugs is the most used, followed by paracetamol (antipyretic, with no antimalarial action) and the antimalarial drug, chloroquine, which was banned in 2006. Artesunate-amodiaquine the other official antimalarial drug, was hardly used in HMM in this study. The use of the official drugs (ACTs) has not been documented in HMM in Nigeria.

In agreement with WHO (2004) recommendation, majority of respondents commenced treatment almost immediately. This is very encouraging because one of the keys to success in home management of uncomplicated childhood malaria is prompt intervention to prevent progression into complicated malaria. Although about 73% referred to healthcare facilities in unresolved cases, 27% did not. Indeed, some went to pharmacies and herbal outlets. This is not appropriate because neither the pharmacy nor the herbal practitioner's outfit is equipped for detailed clinical intervention that is required in such a case. This is one of the downsides of HMM which must be addressed through public enlightenment and regulatory intervention. In this study, educational intervention was administered immediately to ensure that immediate referral is done in

unresolved cases in the future. The nature of this study did not permit an investigation of the effect of such intervention on future unresolved cases.

5.2. Mothers' Perception Of Fathers' Practice Of HMM

Fathers took active part in HMM on their own in addition to their active role when mothers were the care givers. They were supportive of mothers' intervention. Their support was not always dependent on their educational background. Drug administration was the major help they gave to mothers together with emotional support. This is very commendable because without such support, the mother could be distraught. Mothers also reported that fathers reminded them always to give medications and other needed attention. Overall, mothers' assessment of fathers' intervention was excellent. This assessment was dependent upon their educational status.

Until recently, men's image as fathers was that of a parent with no close relationship to their children, particularly if they were new-born or very young (Madsen, 2007). The present study is innovational in the average Nigerian cultural setting that seems to "exempt" fathers from domestic activities and child care.

5.3. Drugs Used In Home Management Of Uncomplicated Childhood Malaria.

The Nigerian drug market has a large pool from which selection is made. Based on this, drug selection may be an uphill task. In this study, while gender had no effect on product selection, the educational status of respondents was a major determinant of the choice of artemether-lumenfantrine. Thus, its choice or preference increased with education. On the other hand, the lower the educational status of the respondent, the

more he/she chose chloroquine. These two results indicated that education was a major determinant of the choice of drugs. It is reasonable to speculate that the higher their educational status, the more respondents became aware of the officially approved, artemether-lumefantrine, and the banned drugs, chloroquine, respectively.

It was important to determine the source(s) of antimalarial drugs used in home management of uncomplicated childhood malaria in Lagos State for obvious reasons. There are many unofficial (unregulated) sources in Nigeria. These include itinerant drug sellers, market women, and *maiguards* (gate men in residential quarters) and many others. Quite a large number of these cannot read and understand the instructions for use of the drugs they hawk/sell, hence the issue of detecting expired or unwholesome products is not a consideration as far as they are concerned. It is known that fake and counterfeit drugs are a major problem in Nigeria (Akunyili, 2004; Akinyandenu, 2013). Indeed, according to WHO in 2011, 64% of Nigeria's imported antimalarial drugs were fake (The Economist, 2012).

In the present study, the pharmacy was the major source of drugs used by respondents. Other sources included medical doctors ≥ primary health care centres >"chemists" > traditional herbal practitioners. ("Chemists" in this study are patent and proprietary medicines vendors (PPMV) and unlicensed medicines sellers who usually did an apprenticeship over a period of 3 – 5 years). Although the present study did not conduct tests for active contents, and other official tests to determine the genuineness of the drugs, the fact that they were majorly from pharmacies was taken as an indication of absence of fake and/or counterfeit products. Legal and professional disciplinary actions await pharmacists that sell, distribute and/or store fake and counterfeit products. These may include heavy fines, imprisonment and loss of professional licence to practice. Onwujekwe et al., (2009) found that care givers in malaria in a rural setting in Eastern

Nigeria obtained their drugs from patent medicines vendors mainly. The difference between the two studies could be attributed to the study setting and the fact that in rural parts of Nigeria, there are more patent medicines vendors than professional pharmacy outlets. In a study involving three States (Enugu, Kaduna and Oyo), it was found that 72% and 90% patent medicines vendors stocked chloroquine and sulphadoxine-pyrimethamine respectively while only 9% of them stocked ACTs (Oladepo *et al*, 2007).

In the present study, herbal preparations were not patronized to a significant extent. This must be interpreted with caution because of the urban setting and the sample population. Majority (71%) of the respondents have, at least, secondary education. On the other hand, Olorunniyi and Morenikeji (2013) found that herbal medicines are widely used in the treatment of malaria in a rural setting in Ekiti State. In the latter case, access to herbal practitioners may be easier than in the former case.

5.4. Factors Influencing Access To Drugs In Home Management Of Uncomplicated Childhood Malaria.

One of the determinants of success in the management of diseases and infections is access to efficacious and quality drugs. Access to drugs is a function of availability and affordability. Indeed, Frost and Reich (2008) defined access thus:

ACCESS = Availability + Affordability + Adoption and Appropriate Use.

Affordability in this work was determined as Cost for convenience, while previous efficacy of a drug was taken as an index of its Adoption and Appropriate Use. In addition, brand and packaging as access determinants were also studied. Most of the drugs were always available except quinine and artesunate-piperaquine. Cost was a

major determinant of access to artemether-lumefantrine. This is not surprising because the average cost per adult treatment of malaria with chloroquine and artemether-lumefantrine are US$0.1 and US$>2.0 respectively (Panosian 2005; Ondari 2013).

5.5 Summary Of Findings

This study indicated that mothers and fathers in Lagos State practise home management of uncomplicated childhood malaria. It was evident from the results that they were dealing majorly with uncomplicated childhood malaria since the signs of complicated malaria were not manifested significantly. Respondents used artemisinin-based combination therapy (ACT), artemether-lumefantrine and artesunate-amodiaquine, in compliance with the National Treatment Guidelines for Malaria. In addition, chloroquine which has been removed from the official list was used as well. It was found that the antipyretic, paracetamol, was also used.

Mothers rated the intervention of fathers very highly. Even when mothers were the care givers, fathers rendered useful assistance to the satisfaction of mothers. Both mothers and fathers referred unresolved cases to the hospital or primary health care centre.

The work also indicated that drugs used in home management of uncomplicated childhood malaria by mothers and fathers in Lagos State were mainly obtained from pharmacies.

Access to drugs used in home management of uncomplicated childhood malaria was determined by availability, brand, cost, packaging and previous efficacy of the drug. The educational status of respondents influenced these determinants for artemether-lumenfantrine and chloroquine consistently. Educated respondents seemed to prefer artemether-lumefantrine more than chloroquine while the non-formal education group used chloroquine more than the former.

CHAPTER SIX

6.0 Conclusion

Home management of uncomplicated childhood malaria is practised by mothers and fathers in Lagos State using artemisinin-based combination therapy (ACTs) in compliance with the National Treatment Guidelines for Malaria. Unresolved cases were referred to formal healthcare facilities.

Paracetamol is widely used as either adjuvant or alone, however, its antipyretic effect may be mistaken or misinterpreted as antimalarial when used alone. The most used among the ACTs is artemether-lumefantrine. Artesunate-amodiaquine, the other official is not commonly used. On the other hand, chloroquine, an antimalarial drug that has been withdrawn from the official list, is still widely used in home management of uncomplicated childhood malaria.

Pharmacy outlets ranked highest as source of drugs used in this study. Access to drugs in home management of uncomplicated childhood malaria is a function of availability, cost, previous efficacy, brand and packaging.

The study demonstrates the need for advocacy to empower mothers and fathers in home management of uncomplicated childhood malaria and immediate referral in unresolved cases as a means of achieving Millennium Development Goal Number 4, that is, reduction of childhood mortality. The need to use antipyretics as adjuvants and not to use them alone in malaria is emphasized. In addition, drugs used in HMM must be from authentic professional sources.

6.1 Contributions to Knowledge

The study has contributed to knowledge in the following ways:

1. This is the first documented finding of the practice of home management of uncomplicated childhood malaria by fathers in Nigeria, to the best of my knowledge.
2. It is among the few documented finding of the practice of home management of uncomplicated childhood malaria using ACTs in Nigeria to the best of my knowledge.
3. The study identified that contrary to the National Treatment Guidelines for Malaria, chloroquine, a banned drug, is still widely used.
4. It showed that artesunate-amodiaquine, a first line antimalarial drug is hardly used in home management of uncomplicated childhood malaria in Lagos State.
5. Demonstrated the need to emphasize referral to healthcare facilities in unresolved cases in HMM.
6. Proposed the need for caution in using antipyretics in HMM without concurrent antimalarial drugs.

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APPENDICES

INSTRUMENTS USED

MOTHERS AND FATHERS AS CARE GIVERS IN HOME MANAGEMENT OF UNCOMPLICATED CHILDHOOD MALARIA IN LAGOS STATE, NIGERIA.

APPENDIX I: RESPONDENT'S DEMOGRAPHY

(Tick the appropriate answers)

Name:……..

Address:……

……

……

Local Govt.

Area……

Tel: ……

Age: 18- 30years 30- 40years >40years

Are you a mother (Yes/No) or a father ? (Yes/ No)

No of children under 5years: 1 2 3 4

Education Background: No formal Primary Secondary Tertiary

Please state Yes or No:

Father living with Mother ……..

APPENDIX II

KNOWLEDGE OF MALARIA.

Choose the Correct Option.

Malaria is caused by: a) Flies b) Bees

c) Mosquitoes Parasite d) Juju e) Don't know

Prevention of Malaria is by: a) Bed Nets b) Insecticide Treated Nets

c) Indoor Residual Spray d) Window Net e) Don't Know

The symptoms of Malaria Include a) Fever b) Vomiting

c) Abdominal Pain d) Diarrhoea e) Cough

f) Restlessness or Irritability g) Don't know

h) Others, please specify……..

The signs of malaria include a) Fever b) Pallor

c) Dehydration d) Chills/Rigors e) Vomiting

f) Diarrhoea g) Don't know

h) Others please specify……

Which of the following signs have you ever recognized in childhood malaria?

a) Fever b) Pallor c) Dehydration

d) Chills/Rigors e) Vomiting f) Diarrhoea

g) Don't know h) Others, specify……

APPENDIX III

TREATMENT OF MALARIA

Which treatment do you usually prefer?

a) PCM b) Antimalarial c) Tepid Sponging
d) Fanning e) Antibiotics f) Others

(Please specify)……

How soon after you noticed the signs did you commence the treatment?

a) 0- 1hr b) 1-6hrs c) 7-12hrs d) 12-24hrs

e) 24-48hrs f) >48hrs

How often after treatment did you notice improvement after an episode of malaria?

a) Always b) Frequently c) Occasionally d) Never
e) Don't know

How often do you notice no improvement after each episode of malaria?

a) Always b) Frequently c) Occasionally

d) None e) Don't Know

What did you do when you noticed no improvement in the child's condition (during the day) after you have administered treatment in the home? Went to :

a) Pharmacy b) Primary Health Centre (PHC)

c) Doctor d) Hospital e) Herbal f) None

What did you do when you noticed no improvement in the child's condition (during the night) after you have administered treatment in the home? Went to :

a) Pharmacy b) PHC c) Doctor

d) Hospital e) Herbal f) None

How often did you notice an improvement?

a) All the time (100%) b) Almost every time 70-99%

c) Sometimes 50-69% d) Rarely 35-49%

e) Very rarely <35% f) Never (0%)

How often did you notice the following in your child during malaria?

	Always	**Frequency**	**Occasionally**	**Never**	**Don't know**
Convulsion (fits)					
Neck Stiffness					
Loss of Consciousness					
Severe Fever					
Drooling of Saliva					
Yellowness of eyes/skin					

What did you do?

a) Change Medication?

b) Refer to the hospital?

c) Go to Health Centre?

d) Back to Pharmacy?

e) Back to Chemist ?

f) Don’t Know ?

g) Did nothing?

h) Others, please specify……

APPENDIX IV

MOTHER'S PERCEPTION OF FATHERS AS CARE GIVERS IN HMM

1. Do you live with your husband/partner? Yes/No ☐
2. How often does he participate in home care of the children when they are sick?

   a) Always ☐ b) Frequently ☐ c) Occasionally ☐

   d) Never ☐ e) Don't know ☐

3. How often does he practice home care of the children when they are sick in your absence?

   a) Always ☐ b) Frequently ☐ c) Occasionally ☐

   d) Never ☐ e) Don't know ☐

4. How often does he practice home care of the children during an episode of malaria?

   a) Always ☐ b) Frequently ☐ c) Occasionally ☐

   d) Never ☐ e) Don't know ☐

5. How do you rate his intervention?

   a) Excellent b) Good c) Fair d) Poor

   e) Don't know

6. Tick the intervention strategy (ies) he uses most.

   a) Drug Admin b) Fanning/Cooling c) Tepid Sponging d) Removal of Clothes e) Giving ORS

7. How often does he refer to a Health Care Worker when the malaria persists? a) Always b) Frequently c) Occasionally

d) Never e) Don't know

8. How often does he help/participate in Home Management of Malaria when you are the care-giver?

a) Always b) Frequently c) Occasionally

d) Never e) Don't know

9. How often does he remind you to give medicines to the child when due in Malaria?

a) Always ☐ b) Frequently ☐ c) Occasionally ☐

d) Never ☐ e) Don't know ☐

10. Tick other support(s) he gives you during HMM :

- Fanning/Cooling

- Clearing/Vomit

- Tepid Sponging

- Giving medicines

- Preparing Oral Rehydrate Solution (ORS)

- Giving Oral Rehydrate Solution (ORS)

- Cleaning the child after defecating

- Waking at night when child is sleepless

- Encouraging you that the child shall be alright

APPENDIX V

DRUG USE IN HOME MANAGEMENT OF MALARIA

The questions are asked so that the drugs you used are known, the source of the drugs are known, and the considerations that led to your choice of drug(s), (for example, cost, packaging, previous efficacy, brand and others), of treating malaria in the home can be identified as well.

1) **How often do you give the following drugs to your child in malaria?**

	Drug	***Always***	***Frequently***	***Occasionally***	***Never***	***Don't know***
a)	Artemether - Lumefantrire					
b)	Artesunate - amodiaquine					
c)	Artesunate - mefloquine					
d)	Artesunate- Sulphadoxine- Pyrimethamine					
e)	Artesunate- Piperaquine					
f)	Chloroquine					
g)	Sulphadoxine- Pyrimethamine.					
h)	Halofantrine					
i)	Quinine					
j)	Herbal					
k)	Others					

2. How did you know about these drugs?

	Drug	***Doctor***	***Pharmacist***	***Chemist***	***Herbal practice***	***Others, please specify***
a)	Artemether - Lumefantrire					
b)	Artesunate - amodiaquine					
c)	Artesunate - mefloquine					
d)	Artesunate- Sulphadoxine- Pyrimethamine					
e)	Artesunate- Piperaquine					
f)	Chloroquine					
g)	Sulphadoxine- Pyrimethamine					
h)	Halofantrine					
i)	Quinine					
j)	Herbal					
k)	Others					

3. How often do you obtain antimalarial drugs from the following? Complete the boxes using:

A = Always; F = Frequently; O = Occasionally; N = Never; D = Don't Know.

Drug	***Pharmacy (community and Hospital)***	***Doctor***	***Health center***	***Chemist***	***Traditional Practitioner***	***Others***
Artemether-Lumefantrire						
Artesunate amodiaquine						
Artesunate mefloquine						
Artesunate-Sulphadoxine-Pyrimethamine						
Artesunate-Piperaquine						
Chloroquine						
Sulphadoxine-Pyrimethamine						
Halofantrine						
Quinine						
Herbal						
Others, please specify						

4. What is your first choice of treatment when you notice malaria?

a) Paracetamol b) Antimalaria drug c) Tepid sponge

d) Fanning e) Hospital f) Herbal g) Oral Rehydrate Solution (ORS) h) Don't Know
i)Others please specify …….

5) What determine(s) your choice of antimalarial drugs? Rank them in order of importance : 1 = Most important; 2 , then 3, 4, 5 & 6 is least important.

Drug	***Cost***	***Availability***	***Previous Efficacy***	***Brand***	***Packaging***	***Others***
Artemether - Lumefantrine						
Artesunate - amodiaquine						
Artesunate - mefloquine						
Artesunate-Sulphadoxine-Pyrimethamine						
Artesunate-Piperaquine						
Chloroquine						
Sulphadoxine-Pyrimethamine						
Halofantrine						
Quinine						
Herbal						
Others						

5) How often are the drugs available when they are needed?

Drug	***Always***	***Frequently***	***Occasionally***	***Never***	***Don't Know***
Artemether-Lumefantrine					
Artesunate-amodiaquine					
Artesunate mefloquine					
Artesunate-Sulphadoxine-Pyrimethamine					
Artesunate-Piperaquine					
Chloroquine					
Sulphadoxine-Pyrimathamine					
Halofantrine					
Quinine					
Herbal					
Others					

Thank you very much for participating in this study. Your effort and time are highly appreciated. The results will be communicated to you in due course.

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