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COLLEGE OF HEALTH SCIENCES

SCHOOL OF BIOMEDICAL SCIENCES

PERCEIVED TREATMENT FAILURE OF ARTEMISININ COMBINATION THERAPY AMONG HEALTHCARE PROVIDERS IN KAMPALA DISTRICT AND ASSOCIATED FACTORS

By

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DECLARATION

I **NABIRYE LEAH**, hereby declare that the work in this dissertation is entirely my own and that it has not been admitted to any other academic institution for any other academic award.

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DEDICATION

I dedicate this work to my father, Eng. Mwegombi William and my mother, Mrs. Mwegombi Harriet.

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LIST OF ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
API	Active Pharmaceutical Ingredient
AL	Artemether-Lumefantrine
NDR	National Drug Register
R&D	Research and Development
LMIC	Low- and Middle-Income Countries
ADR	Adverse Drug Reaction
OOS	Out of Specification
CDC	Centre for Disease Control and Prevention
GMS	Greater Mekong Sub-region
KEAP1	Kelch Like Erythroid cell-derived Associated Protein 1
K13	Kelch 13
MAKCHS	Makerere University College of Health Sciences
PfPI3k	*P. Falciparum* phosphatidylinositol-3- kinase
USP	United States Pharmacopeia
WHO	World Health Organisation
MOH	Ministry of Health
ODK	Open Data Kit
CQ	Chloroquine
SP	Sulphadoxine/pyrimethamine
UBOS	Uganda Beaural Of Statistics

OPERATIONAL DEFINITIONS

Treatment failure: Failure to clear malaria parasitemia (parasitological treatment failure) or resolve clinical disease (clinical treatment failure) following treatment with an antimalarial drug (WHO, 2018). This study investigated perceived ACT clinical treatment failure.

Healthcare providers: Individuals who provide preventive, curative, promotional or rehabilitative healthcare services in a systematic way to people, families or communities for example medical doctors, pharmacists, nurses and allied health professionals like clinical officers and pharmacy technicians

Perception: The way in which something is regarded, understood, or interpreted.

Healthcare provider perceived ACT treatment failure: Failure of patients to recover from malaria after administration of ACT as judged by healthcare providers (Efunshile, Oduyemi, Igwe, Igwenyi, & Adenugba, 2016).

Suspected treatment failure: when treatment failure is suspected due to observation of slow clearance of malaria parasitemia (parasitological) or slow resolution of clinical disease (clinical) following treatment with ana antimalarial. In this study, suspected clinical treatment failure was implied

Healthcare facility: Healthcare facilities are places that provide health care. They include hospitals, primary healthcare centers, isolation camps, burn patient units, feeding centers and others.

Brand name: Name given to a pharmaceutical product by the manufacturer, e.g., Coartem is the originator brand name (also called trade name) for artemether-lumefantrine. The use of this name is reserved exclusively to its owner as opposed to the generic name (artemether-lumefantrine). Brand names may also be used for generic products; they are then often called ‘branded generics.’ These brand names are different from innovator brand names (Alfonso-Cristancho, Andia, Barbosa, & Watanabe, 2015).

Proprietary brand: This is the registered trade name/brand name; this registered name may be legally protected as long as it is used. A generically equivalent product, unless specially licensed, cannot be sold under the proprietary brand name (Hilal-Dandan & Brunton, 2013).

Innovator names: Refers to the product that was first authorized worldwide for marketing, normally as a patented product, on the basis of the documentation of its efficacy, safety and quality, according to requirements at the time of authorization, e.g., Coartem. The originator product always has a brand name; this name may, however, vary between countries (Alfonso-Cristancho et al., 2015).

Physician: these are specialist medical doctors that diagnose, treat and prevent illness, disease, injury and other physical and mental impairments using specialized testing, diagnostic, medical, surgical, physical and psychiatric techniques (WHO, 2010a).

ABSTRACT

Background: The integrity of artemisinin-based combination therapies (ACTs) is critical in successfully combating malaria in endemic countries. However, ACT use has been linked to treatment failure which can be heightened by overuse, non-compliance by patients to treatment and dosage regimes and proliferation of substandard and falsified medicines among others. This results in high rates of re-infection and changes in artemisinin sensitivity patterns. Perceived ACT treatment failure among healthcare providers may influence their decision-making during health service delivery, and also provide clues on what happens to the health system when there is a failing drug.

Objective: To determine the healthcare provider-perceived ACT treatment failure and associated factors in Kampala district.

Methods: A cross-sectional study among 297 eligible healthcare providers in Kampala, recruited using a multistage sampling. Data was collected using self-administered questionnaires and then entered into EPIDATA 3.1 and analyzed using STATA V 13 with logistic regression analysis. Responses to the open-ended questions were coded and analyzed.

Results: Between June 2018 and July 2018, 297 healthcare providers were recruited. Of these, 165(56) were males and 132(44) were females with ages ranging between 21 and 51 years. Those that reported having ever encountered treatment failure were 62%. The factors that were associated with health worker perceived ACT treatment failure include Age (P<0.001), Professional experience (P<0.001), Health facility type (P=0.003), Health facility status (P<0.001), color of ACT tablets (P=0.001) and previous patient complaints about ACTs (P<0.001).

Conclusion: Six in every ten healthcare providers had ever perceived ACT treatment failure of healthcare providers during treatment of uncomplicated malaria. This was high when compared to a similar study done among nurses in Nigeria, where about four in every ten nurses had ever perceived

ACT treatment failure. The perception of most of the healthcare providers interviewed in this study was that risk of ACT failure has been associated with overuse. In addition, factors which could lead to perceived treatment failure identified included poor patient adherence. Healthcare providers reported patient concerns on color, size, and number of tablets prescribed. Since healthcare providers, during patient care, always interact with medicines, their perceptions about ACTs will influence their decision-making during service delivery. It is important for the MOH to empower healthcare providers with information to make more informed decisions at the point of care

CHAPTER ONE: INTRODUCTION

1.1 Background

Malaria caused approximately 409,000 deaths in 2019, ninety five percent of which occurred in sub-Saharan Africa (World Health Organization, 2016). Uganda ranked third in total number of malaria cases within Africa with 90–95 % of the population at risk and malaria is estimated to contribute 13 % of under-five mortality (UBOS, 2017). The use of efficacious and effective antimalarial medicines is one of the key strategies for malaria control (WHO, 2018). Current WHO recommendations require malaria-endemic countries to switch from the production of monotherapies to combined therapies which include artemisinin-based combination treatment (ACT) for example artemether/lumefantrine (AL) (WHO Antimalarial Drug Combination, 2001). Artemisinin-based combinations are easily available in several malaria-endemic countries and are manufactured in varying quality and packaged differently.

In 2004, Uganda adopted Artemether/Lumefantrine (AL) as the first-line treatment for uncomplicated malaria, with Artesunate-Amodiaquine (AS/AQ) as an alternative first-line (Ambrose, Jane, Albert, Adoke, & Fred, 2014). The recommended second line treatment for uncomplicated malaria is Dihydroartemisinin/Piperaquine (Ambrose et al., 2014; Nabyonga-Orem, Ssengooba, Macq, & Criel, 2014).

The use of ACTs has previously been associated with successful treatment of malaria, however, ACT treatment failure has been on the rise (Achol, Ochaya, Malinga, Edema, & Echodu, 2019; Conrad, Bigira, et al., 2014; Mbogo et al., 2014), with changes in artemisinin sensitivity patterns of commonly used ACTs observed in Southeast-Asia (Takala-Harrison et al., 2014; Zwang et al., 2014). Indeed, the emergence of artemisinin-resistant parasites has, to-date, been reported in Southeast Asia (Arjen Dondorp et al., 2009; Miotto et al., 2013; Noedl et al., 2008).

In Sub-Saharan Africa, drug resistance is a major obstacle to malaria control, accounting for most of the previous increases in the incidence of malaria-specific morbidity and mortality (Menard & Dondorp, 2017; Trape et al., 1998). For example; There was a twofold and fourfold increase in mortality and morbidity respectively in the 1990s observed with chloroquine (CQ) resistance in Uganda (Gething et al., 2016; O'Meara, Mangeni, Steketee, & Greenwood, 2010). Despite increase in the incidence of malaria-specific morbidity and mortality in sub-Saharan Africa, the resources available to national control programs are inadequate. In Uganda, Studies have shown a 17.3% risk of Artemether Lumefantrine treatment failure and 63.3% unadjusted treatment failure in children but no drug resistance (Byakika-Kibwika et al., 2017; Rasmussen et al., 2017).

Several studies show that the ACT treatment failure can be heightened by overuse, non-compliance of patients to treatment regimens and proliferation of substandard and falsified medicines; and is commonly associated with high rates of re-infection/recrudescence (Arjen Dondorp et al., 2009; Muvunyi et al., 2011; Newton et al., 2011; WHO, 2018). Furthermore, the quality of the different ACT brands could contribute to the alarming rise in treatment failures (Onwujekwe et al., 2009). In Nigeria for instance, there was a high failure rate of commonly used antimalarials mentioned by the providers where 37% (60/225) anti-malarial drug brands did not meet the tolerance limits set by United States Pharmacopeia (USP): 78% (47/60) of the drugs that did not meet the tolerance limits set by USP were found in private facilities, mostly in patent medicine stores (drug shops). Some ACT brands had low active pharmaceutical ingredient (API) while others had excessive API. Packaging and labelling of some ACT brands failed to pass the analyses done (Onwujekwe et al., 2009).

ACT treatment failure could compromise the use of artemisinin for the treatment of severe malaria and the development of total artemisinin resistance; which could cause more parasites to be exposed to the long-acting partner drug once the artemisinin component has been rapidly eliminated following the

3-day treatment course. Although recommendations from the national strategy against malaria suggest involving all stakeholders (Shewchuk et al., 2011), the healthcare providers, who have first-hand experience with the different ACT brands as taken by the patients under their care, are key informants (Lwin, Sudhinaraset, San, & Aung, 2014). The perception of healthcare providers is important in decision making; and is key to improving healthcare delivery and treatment outcomes (Manirakiza, Njuimo, Le Faou, Malvy, & Millet, 2010). Thus, the assessment of their perceptions on the failure rates of commonly used ACTs is invaluable. This study therefore sought to assess healthcare provider-perceived ACT treatment failure in selected health facilities in Kampala District.

1.2 Problem statement

Based on WHO standards, Uganda is still at the first stage of controlling malaria but challenges have been posed by decreased effectiveness of recommended ACTs. Studies have shown increased ACT treatment failure in Uganda, which is a major obstacle to the goals of reducing malaria morbidity and mortality levels to near zero by the Ministry of Health National Malaria Control program. In Nigeria, perceived ACT treatment failure among nurses was reported at 40.7%, among whom 68% still had confidence in efficacy of chloroquine. The continued use of the seventy-two ACT brands approved on the National Drug Register (NDR) for Uganda is dependent on the adherence of healthcare providers to the guidelines which can be influenced by their perception of ACT treatment failure.

An increased ACT treatment failure has been reported in Uganda, which may cause perception of treatment failure among Healthcare providers. A rise in the perceived treatment failure rates of commonly used ACT brands might cause healthcare providers to have diminished confidence and be tempted to fall back on the older drugs since there are no newer alternatives to the artemisinin derivatives. Therefore, this may lead to a reduced prescription of ACT and thus increased number of malaria cases and deaths due to inability to control the use of the first line drugs. Despite the

consequences of perceived ACT treatment failure, there is inadequate literature documented among healthcare providers in Uganda. Furthermore, pharmacovigilance of antimalarial drugs in Uganda through strategies like voluntary reporting relies on active participation of health workers. In attempt to ease reporting treatment failure and monitoring clinician perception on decreased efficacy or treatment failure of artemisinin combination therapy, this study sought to assess the perceived ACT treatment failure and the associated factors among healthcare providers in Kampala district.

1.3 Significance of the study

The study assessed the healthcare provider-perceived treatment failure of commonly used ACT brands on the market and the factors associated with the perceived treatment failure. This information provides grounds for National Drug Authority to look out for those brands that are implicated in treatment failure and also in establishing strategies to protect the identity of efficacious ACT brands on the market. Assessing the perceived ACT treatment failure aids in guiding policies concerning malaria treatment hence optimizing and promoting good therapeutic outcomes. This will eventually improve confidence of patients in the health-care system.

1.4 Justification of the study

One of the goals of the MOH National Malaria Control program is to reduce malaria morbidity and mortality to levels near zero using artemisinin combination therapies. However, the use of ACTs is dependent on the adherence of healthcare providers to the guidelines which can be influenced by their perception of ACT treatment failure. Perceived ACT treatment failure among clinicians could because of patient factors, drug factors or parasite factors. Despite the need to protect the new regimen, situations where ACT treatments fail consistently cause healthcare providers to lose confidence and fall back to the older, less efficacious antimalarial drugs. This in turn could lead to a vicious cycle of treatment failure, increase the number of malaria cases and deaths, and, ultimately increase the risk for

drug resistance. There is however inadequate literature documented about the ACT treatment failure perceptions among healthcare providers in Uganda. It was therefore expedient to explore the perception of healthcare provider ACT treatment failure in Kampala district.

1.5 Research questions

1. What is the prevalence of perceived ACT treatment failure among healthcare providers in Kampala District?
2. What factors are associated with the perceived ACT treatment failure among healthcare providers in Kampala District?

1.6 General objective

To determine the prevalence and factors associated with perceived ACT treatment failure among healthcare providers in Kampala district.

1.6.1 Specific objectives

1. To determine the prevalence of perceived ACT treatment failure among healthcare providers in Kampala District
2. To determine factors associated with perceived ACT treatment failure among healthcare providers in Kampala District

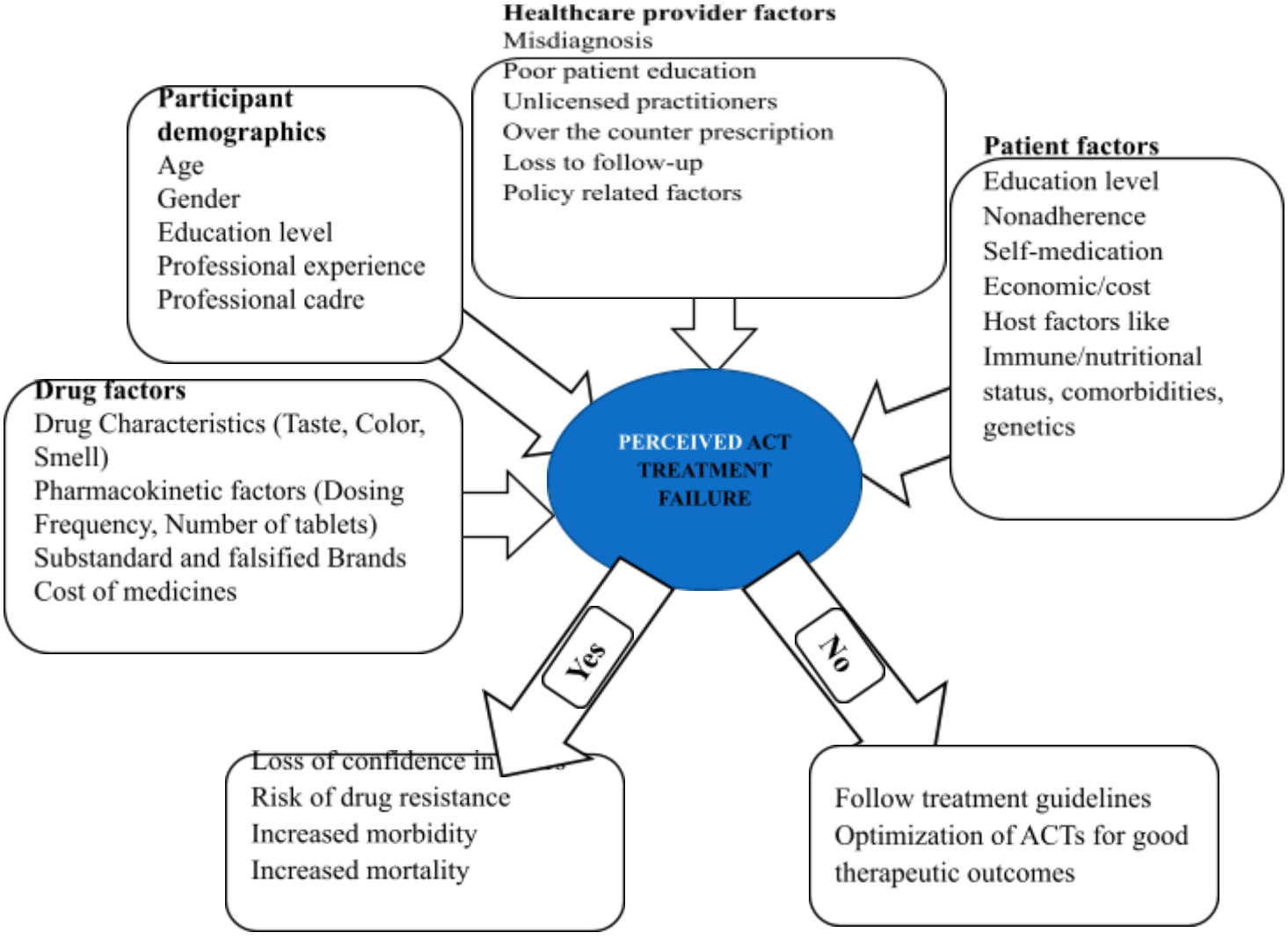
1.6 Conceptual framework

Scope of the study

There are various factors influencing perceived ACT treatment failure. These include participant demographics, patient factors, Healthcare provider factors, policy related factors, community factors, drug factors, to mention a few. This perceived ACT treatment failure results in loss of confidence of

Figure 1. Factors influencing perceived ACTs treatment failure

healthcare providers in ACTs causing reliance on older less efficacious antimalarials, which increases the risk of drug resistance and ultimately results in increased malaria morbidity and mortality. However, the scope of this study focused on the factors influencing perceived ACT treatment failure



CHAPTER TWO: LITERATURE REVIEW

2.1 The burden of malaria

The plasmodium falciparum malaria occupies a unique place in the annals of history. In the 20th century alone, it claimed between 150 million and 300 million lives, accounting for 2 to 5 percent of all deaths (Carter & Mendis, 2002). Its chief sufferers today are the poor of sub-Saharan Africa, Asia, the Amazon basin, and other tropical regions. Malaria is considered to be one of the main global health problems, causing approximately 438,000 deaths in 2015, ninety percent of which occurred in sub-Saharan Africa. Seventy percent (70%) of these deaths occurred among children under 5 who have yet to acquire sufficient immunity to protect them from heavy malaria infections (World Health Organization, 2016).

Uganda ranked third in the total number of malaria cases in sub-Saharan Africa. It experiences weather conditions that often allow transmission to occur all year round with only a few areas that experience low or unstable transmission. Malaria is the leading cause of morbidity in Uganda with 90–95 % of the population at risk and it contributes to approximately 13 % of under-five mortality (UBOS, 2017). Malaria is not simply a matter of episodes of illness and deaths, as enormous as those burdens are. There are less obvious, but equally serious, consequences of the chronic infections and repeated reinfections that characterize life in high-transmission areas, including most of sub- Saharan Africa. Chronic, subclinical infections can cause anemia and predispose to under-nutrition (Yeka et al., 2012).

These processes may further increase the chances of severe malaria with subsequent infection, and severe outcomes of infections with other pathogens. Unlike other adults in endemic areas, pregnant women are themselves more susceptible to malaria's most severe effects including death and asymptomatic infection of the placenta significantly reduces the weight of newborn children, reducing their chances of surviving infancy (Gelband, Panosian, & Arrow, 2004).

Some proportion of those who survive severe malaria—with or without effective treatment—are left with permanent, serious effects, including epilepsy and spasticity. More subtle consequences described include behavioral disturbances and cognitive impairment (Ambrose et al., 2014). The use of efficacious and effective antimalarial medicines is one of the key strategies for malaria control.

2.2 Antimalarial drugs

Currently available antimalarials fall into three broad categories according to their chemical structure and mode of action:

1. Aryl aminoalcohol compounds: quinine, quinidine, chloroquine, amodiaquine, mefloquine, halofantrine, lumefantrine, piperaquine, tafenoquine
2. Antifolate compounds ("antifols"): pyrimethamine, proguanil, chlorproguanil, trimethoprim
3. Artemisinin compounds (artemisinin, dihydroartemisinin, artemether, artesunate)

Atovaquone is an antimalarial in its own class with a unique mode of action; combined with proguanil it is sold under the trade name Malarone®. Several antibacterial drugs (e.g., tetracycline, clindamycin) also have antiplasmodial activity, although in general their action is slow for malaria treatment (as opposed to prophylaxis); they are recommended only in combination with other antimalarial drugs (Gelband et al., 2004; Hilal-Dandan & Brunton, 2013).

Figure 2; Antimalarial drug summary table

Subclass	Mechanism of Action	Effects	Clinical Applications & Pharmacokinetics	Toxicities
Antimalarials				
Chloroquine	Prevents heme→hemozoin	Blood schizonticide	Oral • All nonresistant malarias • Autoimmune diseases	GI upset, rash, headache
Artemisinins	Metabolism to toxic free radicals in protozoa	Blood schizonticides	Oral, IV • Combined with lumefantrine for prophylaxis and treatment of falciparum malaria, including resistant forms	GI upset
Mefloquine	Unknown	Blood schizonticide	Oral • Weekly for prophylaxis, daily for infection	GI upset, rash, cardiac abnormalities, psychiatric disturbance, sizures
Primaquine	Unknown	Active against liver forms of *P vivax* and *P ovale* • *P jiroveci* pneumonia (PCP)	Oral	Blood cytopenias, hemolysis in G6PD deficiency
Atovaquone	Disrupts mitochondrial metabolism	As Malarone (with proguanil) for falciparum • alternative for PCP	Oral	Fever, rash, GI upset
Antifolates Pyrimethamine, proguanil, Fansidar (pyrimethamine + sulfadoxine)	Inhibits folate synthesis	Mostly blood schizonticides	Oral	GI upset, rashes (sometimes severe), cytopenias

Extracted from Katzung & Trevor's Pharmacology Examination and Review, 11th Edition

Chloroquine (CQ) was an efficacious, safe, and affordable antimalarial agent that formed the cornerstone of malaria treatment globally in the 1950s and 1960s (Frosch, Venkatesan, & Laufer, 2011). However, its use was compromised by the development and worldwide spread of resistance.

2.3.Malaria treatment policy in Uganda

In Uganda, national policy for treatment of uncomplicated malaria was first changed from chloroquine (CQ) monotherapy to CQ plus sulfadoxine-pyrimethamine (SP) (CQ + SP) combination therapy in 2000. Parasitological resistance to antimalarial drugs and related treatment failures (clinical failure rate of ≥25% between 2001 and 2004), led to antimalarial drug policy change from chloroquine to alternative treatments such as artemisinin combination therapies (ACTs). Specifically, in 2004, Uganda adopted Artemether-Lumefantrine (AL) as the first-line treatment for uncomplicated malaria, with IV artesunate as first line for severe malaria as shown below (table 1) (Ambrose et al., 2014; Nabyonga-Orem et al., 2014).

Table 1 shows the current treatment protocols for uncomplicated and severe malaria in Uganda. Uganda adopted Artemether-Lumefantrine (AL) as the first-line treatment for uncomplicated malaria, with Artesunate-Amodiaquine as the alternative first line. IV artesunate is first line for severe malaria, with IV Quinine or Artemether injection as the alternative first line. Quinine tablets are indicated for pregnant women during the first trimester, with them adhering to the above treatment guidelines for uncomplicated malaria during second and third trimester. Over all the use of ACTs has been associated with successful treatment of malaria (Muhindo et al., 2014)

Table 1: Current WHO treatment protocols for uncomplicated malaria and severe malaria

NATIONAL MALARIA TREATMENT POLICY (2015)	
Uncomplicated Malaria	
All patients: including children <4 months of age and pregnant women in 2nd and 3rd trimesters	***First line medicine*** ▶ **Artemether/Lumefantrine** ***First line alternative*** ▶ **Artesunate/Amodiaquine** ***Second line medicine*** ▶ **Dihydroartemisin/ Piperaquine** ▶ If not available: quinine tablets
Pregnant women 1st trimester	▶ **Quinine** tablets ▶ ACT may be used if quinine not available

Extracted from Ministry of Health Uganda Clinical guidelines, 2016

Severe Malaria	
All age groups or patient categories	***First line*** ▶ IV **Artesunate** ***First line alternative*** ▶ IV **Quinine** ▶ Or **Artemether** injection ***Pre-referral treatment*** ▶ Rectal artesunate
Intermittent preventive treatment in pregnancy	
▶ **Sulfadoxine/Pyrimethamine (SP)** for IPT. Start at 13 weeks and give monthly till delivery	

Extracted from Ministry of Health Uganda Clinical guidelines, 2016

2.3 Use of Artemisinin in treatment of malaria

Artemisinin was first isolated from the stems, leaves, and flowers of *Artemisia annua* by Chinese scientists (Chang, 2016; Klayman et al., 1984). Of the available antimalarials, the artemisinins are effective at killing the broadest range of asexual stages of the parasite, ranging from medium sized rings to early schizonts; they also produce the most rapid therapeutic responses by accelerating clearance of circulating ring-stage parasites (Terkuile, White, Holloway, Pasvol, & Krishna, 1993).

Qinghaosu, or artemisinin, is a sesquiterpene lactone peroxide extracted from the leaves of the shrub *Artemisia annua* (qinghao). Three derivatives are widely used: the oil-soluble methyl ether, artemether (artemotil [arteether] is a closely related compound); the water-soluble hemi-succinate derivative, artesunate; and dihydroartemisinin (DHA). Artesunate, artemether, and arteether are all synthesized from DHA, and they are converted back to it within the body.

However, the use of ACTs for malaria control has been followed by decreased effectiveness of recommended regimen. Studies have shown increased ACT treatment failure in Uganda (Byakika-Kibwika et al., 2017; Conrad, LeClair, et al., 2014) which is a major obstacle to the goals of reducing malaria morbidity and mortality levels to near zero by the Ministry of Health; National Malaria Control program (MOH, 2019).

2.4 ACT treatment failure

WHO defines ACT treatment failure as the inability to clear parasites from a patient's blood or to prevent their recrudescence after administration of an antimalarial (World Health Organization, 2018). Over the past decade, increased malaria control efforts and the introduction of artemisinin derivatives has led to substantial reductions in malaria transmission, morbidity, and mortality (World Health Organization, 2016). However, this powerful anti-malarial when given alone results in a high frequency of recrudescence (Arjen Dondorp et al., 2009). This high rate of recrudescence has prompted WHO to recommend that uncomplicated P. falciparum malaria be treated with artemisinin or its derivatives in combination with another effective blood schizontocide to delay the selection of resistant strains (Menard et al., 2005). Even with ACT, there are still issues with treatment failure and recrudescence of infections (Rogers et al., 2009).

A systematic review conducted by the Worldwide Antimalarial Resistance Network (WWARN) to search for the individual patient level data from 25 clinical efficacy studies reported no evidence suggesting artemisinin resistance (delayed parasite clearance) at any of the Ugandan sites. No site and no treatment regimen (AL, Amodiaquine –Artesunate-ASAQ or Dihydro Artemisinin- Piperaquine-DHAPQP) had a point estimate of the proportion with persistent parasitemia at day 3 exceeding 3% (Ambrose et al., 2014). Nevertheless, ACT treatment failure has been on the rise in Africa (Gething et al., 2016). In 2006, three polymorphisms in the *pmfdr* gene following administration of AL were identified but were not associated with clinical

treatment failure (Dokomajilar, Nsobya, Greenhouse, Rosenthal, & Dorsey, 2006). These however were evidence for the ability of this drug combination to drive selection of parasites toward resistant phenotypes that may result in treatment failure (Dokomajilar et al., 2006).

Studies in East Africa, including Uganda have reported high rates of disease recurrence in patients treated with ACTs. A study in Tororo, a high transmission area reported a 17.3% risk of treatment failure after treatment with Artemether Lumefantrine, the first-line regimen for uncomplicated malaria in Uganda (Conrad, LeClair, et al., 2014). Healthcare providers have first-hand experience with the different ACTs, as taken by the patients under their care, and are therefore key informants in decision making to improving healthcare delivery and treatment outcomes (Lwin et al., 2014). Research shows that adherence of healthcare providers to the treatment guidelines can be influenced by their perception of ACT treatment failure (Bhattacharyya et al., 2014).

2.5 Previous healthcare provider-perception of antimalarial treatment failure

While resistance is the ability of parasite strain to survive despite administration of drug in recommended or higher doses and appears to occur due to mutation, healthcare provider perceived treatment failure is failure of patients to recover from malaria after administration of ACTs as judged by the health care providers (Efunshile et al., 2016). Among the key activities that support prompt and effective malarial treatment is the provision of effective malaria case management services by health workers. In the past, perceived treatment failure of antimalarials by healthcare providers has had an impact on their prescription patterns of those particular antimalarials (Masanja, Lutambi, & Khatib, 2012).

A study in Tanzania showed that sulphadoxine-pyrimethamine (SP) was not well received by the healthcare workers several years after it substituted CQ, thus they continued prescribing CQ in the height of its resistance (Nsimba, 2006). When healthcare providers realize that their

experience contributed to a decision that led to a change in treatment policy, they are more like to adhere to such a joint decision, compared to when they perceive the policy emanated from a group of sponsored researchers alone (Efunshile et al., 2016). Healthcare providers also tend to withdraw from prescribing antimalarials they perceive to be failing. In a study done in Nigeria (Efunshile et al., 2016), 40.7% nurses had experienced ACT treatment failures with their patients during the course of their practice, which were eventually treated with another antimalarial. Majority of those who still had confidence in the efficacy of CQ were those that had experienced treatment failure with ACTs (68.3%) (Efunshile et al., 2016). Studies on perception of failing antimalarial by healthcare providers therefore promotes effective malaria case management and therefore reduces morbidity and mortality. Many factors can contribute to ACT treatment failure including incorrect dosing, non-compliance with duration of dosing regimen, poor drug quality, drug interactions, poor or erratic absorption, and misdiagnosis (Bloland & Organization, 2001)

2.6 Factors and predictors of ACT treatment failure

2.6.1 Inadequate dosing

Studies by Nakazawa et al suggested that treatment failure may be due to blood levels of the drug that are insufficient to further suppress the parasite. The recommended dosage for artemether lumefantrine is 80mg A/480 mg L, while dihydroartemisinin piperaquine is 40mg D/320 mg P (Ashley & White, 2005) Previous studies suggested that a small percentage of the parasites may be in a dormant state and are unaffected by drug treatment. When such treatment is discontinued, these parasites resume normal development, resulting in a detectable parasitemia (LaCrue, Scheel, Kennedy, Kumar, & Kyle, 2011; Nakazawa, Kanbara, & Aikawa, 1995)

Lumefantrine absorption is greatly increased when taken with food, especially fatty foods. Plasma concentrations of the drug are low after initial doses, when patients are typically anorexic; levels increase in parallel with improved appetite (Ezzet, Van Vugt, Nosten,

Looareesuwan, & White, 2000). The day-7 plasma concentration of lumefantrine is a predictor of therapeutic response. This concentration is judged to be the in-vivo minimum inhibitory concentration for multidrug-resistant falciparum parasites. Concentrations of less than 280 µg/L were associated with an increased risk of treatment failure in Thailand (Brockman et al., 2000).

2.6.2 Non-compliance with duration of dosing regimen

One major drawback of the combination remains its cost. Many African countries are not able to afford artemether lumefantrine for public-sector use without external support, such as from the Global Fund. This factor could also compromise adherence, since African patients and caregivers often use incomplete doses, keeping the remaining tablets for the next attack of malaria (Williams & Jones, 2004). Adherence to the complicated regimen then becomes suboptimum. To increase AL absorption, all doses should be correctly spaced and taken with food. The manufacturer recommends an interval of 8 h between the first and the second dose, 24 h between the first and the third dose, and 12 hourly intervals between doses thereafter.

2.6.3 ACT drug resistance

Artemisinin resistance is defined as delayed parasite clearance; this represents a partial resistance that so far affects only ring-stage parasites. Most patients who have delayed parasite clearance following treatment with an artemisinin-based combination therapy (ACT) clear their infections. However, in partner drug resistance there is resistance to the partner drugs such as mefloquine and piperaquine. ACT drug resistance therefore represents concomitant resistance to both the artemisinin derivative and the partner drug (WHO, 2018).

Artemisinin resistance alone rarely leads to treatment failure, resistance to ACT partner drugs can lead to treatment failure (regardless of the presence of artemisinin partial resistance). Artemisinin resistance is potentially a more pressing concern than partner drug resistance due to the lack of viable alternatives. It is predicted that a failing partner drug will result in greater

increases in malaria cases and morbidity than would be observed from artemisinin resistance only as is the case in Africa where, despite reports of no artemisinin resistance, several ACTs are failing, probably due to partner drug resistance (Slater, Griffin, Ghani, & Okell, 2016). Nevertheless, the proportion of treatment failures increase when both resistance to artemisinin and to ACT partner drugs are present, compared to resistance to the partner drug alone. There is no confirmed artemisinin resistance in Uganda(Asua et al., 2020)

2.6.4 Falsified drugs

The counterfeit/substandard antimalarial medicines may contain inappropriate concentrations of active ingredients, contamination with other drugs or toxic impurities, poor quality ingredients, poor stability and poor packaging which fail for chemical analysis, packaging analysis or are falsified (Karunamoorthi, 2014). Antimalarials are among the most counterfeited drugs globally and there is a diversity of counterfeit packaging types (Newton et al., 2011; Tadeg & Berhane, 2012; WHO, 2010b). This problem is not new; counterfeit antimalarials were a severe problem in the 17th century when counterfeits of the first potent antimalarial drug, cinchona bark (the source of quinine), were widely marketed in Europe (Newton et al., 2006). The illicit trade in counterfeit antimalarial drugs is a great threat to lives of patients and the fight against malaria due to the fact that such patients treated with counterfeit drugs are at a high risk of developing severe malaria and occurrence of death (Cordina, 2010).

Studies done in South East Asia showed high proportion of counterfeit antimalarials in the market, where 38–53% of artesunate tablets did not contain active ingredient (AM Dondorp et al., 2004).

Falsified drugs remain a concern with WHO receiving regular reports i.e. 126 of suspected falsified artemether/lumefantrine (innovator and generic versions), from 14 sub-Saharan African countries have been filed since July 2013 (Kaur et al., 2016). On investigation by the WHO, they

were found to have less than 10 genuine medicines. A database logging reports of substandard drugs has been created and with relevance to falsified anti-malarials, 57 % of those reported so far have been artemisinin-based (World Health Organization, 2011). Consequently, antimalarials are the most used drugs in African tropical countries like Uganda which have a high burden of malaria (Bjorkman Nyqvist, Svensson, & Yanagizawa-Drott, 2012)

2.6.5 Pharmacokinetics and pharmacodynamics of antimalarial drug

The short half-life of artemisinin and its derivatives may contribute to the development of treatment failure, as not all parasites would necessarily be eliminated after the initial rapid effect of a short treatment with oral artemisinin–based monotherapy. Therefore, monotherapy is usually not effective unless it is administered over an extended time. In the same way that parasites that are consistently exposed to a suboptimal dose of treatment develop resistance, an incomplete or short treatment with oral artemisinin-based monotherapy could also facilitate the development of resistance, although the short half-life of these drugs reduces the time window in which resistant parasites can be selected. If treatment fails, the drug concentration in the patient is likely to be less than the minimum inhibitory concentration for proliferating parasites. High treatment failure rates were observed in 2001 (26.1%) and 2002 (28.9%); however, in 2003, when treatment was given with fatty foods, the failure rate decreased to 13.5% (Denis et al., 2006).

Additional analyses showed that the mean plasma concentration of partner drugs may affect the treatment outcome, for example lumefantrine on day 7 was higher among patients with an adequate clinical and parasitological response (860 ng/ml) than among those who failed treatment (510 ng/ml) (Hietala et al., 2010). The investigators concluded that some of the treatment failures were due to low blood levels of the partner drug, lumefantrine.

2.6.6 Malaria specific host immunity

Important host factors like immunity contribute to therapeutic outcome of ACT treatment. Epidemiological studies have implicated low-transmission settings as the primary origin of treatment failure that may result in resistance (Anderson & Roper, 2005). This is probably due to the fact that in low-transmission areas, most malaria infections are symptomatic, and therefore proportionally more people receive treatment, providing more opportunities for selection.

In areas of high transmission, most malaria infections are asymptomatic and infections are acquired repeatedly throughout life. Malaria-experienced individuals gradually acquire partial immunity ('premunition'), and the infection is controlled, usually at levels below those that cause symptoms. Adults are therefore relatively immune and tend to self-cure irrespective of the effectiveness of the drug or indeed whether an antimalarial drug is taken at all. Everyone has malaria parasites in their blood all the time, but usually at densities below that causing illness.

Immunity can also considerably reduce the emergence and spread of resistance (Menard et al., 2005). Host defense has a major anti-parasitic effect, and any spontaneously generated drug-resistant mutant malaria parasite must contend not only with the antimalarial drug concentrations but also with host immunity, which kills parasites regardless of their antimalarial resistance and reduces the probability of parasite survival (independently of drugs) at all stages of the transmission cycle. Immunity acts by non-selectively eliminating blood-stage parasites, including the rare de novo resistant mutants, and also improves cure rates, even with failing drugs, thereby reducing the relative transmission advantage of resistant parasites. Even if a resistant mutant survives the initial drug treatment and multiplies, the likelihood that this will result in sufficient gametocytes for transmission is reduced as a result of immunity to the asexual stage (which reduces the multiplication rate and lowers the density at which the infection is controlled) and to the sexual stage (Barrete & Ringwald, 2010).

The sensitivity of the parasite to the drug therefore affects the clinical outcome more noticeably where the hosts are non-immune and unable to control the infection themselves (i.e., patients of all ages in low transmission areas or young children in high transmission areas). In these circumstances, taking an ineffective drug can result in severe or protracted disease and even death.

2.6.7 Brand defining manufacturing processes

The quality of the different ACT brands may differ due to the manufacturing processes and may contribute to the alarming rise in treatment failures. In Nigeria for instance, there was a high failure rate of commonly used antimalarials mentioned by the providers where 37% (60/225) anti-malarials did not meet the tolerance limits set by USP: 78% (47/60) of the drugs that did not meet the tolerance limits set by USP were found in private facilities, mostly in patent medicine stores. Some ACT brands had low API while others had excessive API. Packaging and labelling of some ACT brands failed to pass the analyses done (Onwujekwe et al., 2009).

2.7 Impact of ACT treatment failure.

2.7.1 Increased morbidity

Ineffective treatment causes anemia and low birth weight and renders the health of children and adults infected with *P. falciparum* or *P. vivax* more fragile (Björkman, 2002; Tjitra et al., 2008). Although there is no ACT resistance across Africa, simulation studies estimated that artemisinin and partner drug resistance at levels similar to those observed in Cambodia could result in an additional 78 million cases over a 5 year period, a 7 % increase in cases compared to a scenario with no resistance. A scenario with high levels of slow clearance but no recrudescence resulted in an additional 10 million additional cases over the same period (Slater et al., 2016).

2.7.2 Increased expenditure on malaria treatment

The burden of ACT treatment failure in terms of increased costs includes the direct and indirect costs (Chima, Goodman, & Mills, 2003). Therapeutic failure requires consultation at a health facility for further diagnosis and treatment (more expensive second- or third- line treatments and hospital admissions), resulting in loss of working days for adults, absence from school for children and increased cost to the health system (Talisuna, Bloland, & d'Alessandro, 2004). In addition, there are broader costs at the household and macroeconomic levels as well as intangible costs such as psychological stress and loss of confidence in a health system that fails to deliver a cure (Sachs & Malaney, 2002). Much of this burden falls on the poor, exacerbating already existing inequities, since the more expensive, effective antimalarials are accessible only to patients affluent enough to obtain them, and remain out of reach to the majority of the rural poor who carry the largest burden of disease.

Antimalarial treatment failure has increased the global cost of controlling malaria, including the cost of new drug development (Phillips & Phillips-Howard, 1996). There is currently no good alternative to ACT suitable for large-scale implementation. New drugs could be developed but the lag time between development, registration, change of national treatment policy, training, and large-scale production imply an inevitable and costly delay until affordable substitutes to ACT are widely available. In a simulated study, if malaria incidence remained similar to current levels, the model estimated the excess number of treatment failures in the scenario of widespread artemisinin resistance to approximate 22 million annually, until an effective alternative anti-malarial is deployed. These would lead to 230,000 additional severe malaria cases (surviving) and 116,000 excess deaths per year. The predicted medical costs for retreatment of clinical failures exceeded US$32 million per year. Productivity losses resulting from excess

morbidity and mortality were estimated at US$385 million for each year during which failing ACT remained in use as first-line treatment (Lubell et al., 2014).

2.7.3 ACT drug resistance

Treatment failure provides a greater chance of the resistant sub-population surviving "therapeutic concentrations" than in the original infection. This means that retreatment is likely and provides a second round of selection, so that if the new resistant parasites are still in a minority (and contribute less than 10% of the gametocytes at this stage), they now have a second opportunity for selection, and have considerable parasite numbers present. Multiple treatment failures, therefore, provide a means of enrichment of resistant phenotypes (Nicholas J et al, 2009).

Widespread resistance is a very serious problem with malaria. In the 1980s and 1990s antimalarial drugs such as chloroquine and sulphadoxine / pyrimethamine were used inappropriately so that parasites became resistant to them (Wongsrichanalai, Pickard, Wernsdorfer, & Meshnick, 2002). Those drugs were superseded by artemisinin, which is now used widely, usually in 'combination therapies' (ACTs) designed to prevent resistance. Also, while antimalaria drug resistance is not the only cause of treatment failure, the main consequence of antimalarial drug resistance is treatment failure (WHO Antimalarial Drug Combination, 2001).

2.7.4 Loss of confidence in malaria treatment

In much of Africa, easy access to public sector healthcare is limited and when it is accessible, health care staff are often inadequately trained, insufficiently supplied and supported, ineffectively supervised and/or poorly motivated (Bloland & Organization, 2001). Ineffective treatment in the public sector due to treatment failure could lead to greater reliance of patients on the unregulated private sector, which in turn could increase the use of monotherapies or substandard and falsified medicines and increase the risk for drug resistance.

The routes through which people can obtain antimalarials vary from place to place, but overall in Africa, upwards of 70 percent of these drugs reach consumers through the private sector, particularly small pharmacies, street side drug peddlers, and general store kiosks (Gelband et al., 2004). Access to drugs is widely available for the urban population through private drugstores and an illicit market. In a study in Bangui, defection of health facilities by the community, according to the health workers, was due to the costs of consultation and treatment as they considered that fever is always associated with malaria. Thus self-medication or drugstore counseling was favored (Manirakiza et al., 2010). The price of drugs found in such market is attractive (these drugs are often of poor quality and of a dubious origin).

CHAPTER THREE: MATERIALS AND METHODS

3.1 Study design

This was a nested cross-sectional study which aimed at assessing the healthcare provider perceived ACT treatment failure in Kampala district. This study was part of another bigger study titled "**Pharmacovigilance of Antimicrobial Agents in Uganda: Emphasis on Artemisinin Combination Therapies for Malaria Treatment**" The main study sought to perform prescription event monitoring and investigate local perceptions of health workers on the therapeutic failure rates and drug related predictors for commonly used ACTs in Uganda. The study also mapped and predicted ACT resistance trends as well as evaluated the safety profiles and efficacy of 5-day and 7-day ACT regimens against the standard 3-day regimen in treatment of uncomplicated malaria. Study coordination was done at department of pharmacology and therapeutic, Makerere University while study participant recruitment was done at six randomly selected regional referral hospitals.

3.2 Study site

The study was conducted in selected health facilities in Kampala District. Kampala is the capital and largest city of Uganda. The city's five divisions are Kampala central division, Kawempe division, Lubaga division, Makindye division and Nakawa division. The city is estimated to have a population of 1,680,800 people. It has the highest number of health facilities in Uganda which include both private and public health facilities, as well as the highest number of healthcare providers (UBOS, 2017). The continuum of health services in the public sector begins with a village level community health extension worker, a parish level outpatient Health Centre II, a sub-county based 8-bed in-patient Health Centre III to a 12-bed Health Centre IV facility with a theatre manned by a medical doctor. This network of facilities is complemented by a

general hospital and regional referral hospitals are at the top of this continuum. The lowest level of care in the public health system is given by the community health workers who are volunteers in villages facilitating health promotion, service delivery, community participation, and empowerment. The private health sector in Uganda is diverse, comprising both public-not-for-profit organizations (faith-based, non-governmental, or community-based) and private-for-profit organizations (commercial, self-sustaining). The private sector players contribute to about 50% of the health service delivery. Our study was representative of all these levels of healthcare. Healthcare providers (clinicians, physicians, nurses, pharmacists) were therefore accessed from Hospitals (private, private not for profit and government), HCIVs, HCIIIs, HCIIs, private clinics, pharmacies and drug shops.

3.3 Study participants

3.3.1 Target population

All healthcare providers involved in management of malaria patients in Uganda. These included physicians/medical doctors, pharmacists, Nurses and allied health workers like clinical officers and pharmacy technicians.

3.3.2 Accessible population

All healthcare providers involved in management of malaria patients within public, private-for-profit and private not-for-profit health facilities in Kampala district.

3.3.3 Study population

The study was comprised of healthcare providers involved in management of malaria patients within various health facilities in Kampala district that met the eligibility criteria.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

Healthcare providers on duty in the health facilities that gave a written informed consent and available to answer the questionnaire.

Healthcare providers that had, by self-declaration, ever managed a malaria patient. These made up the study unit.

3.4.2 Exclusion criteria

Healthcare providers that were unable to withstand the study procedures but were on duty.

3.4.3 Sample size

The minimum sample size required for this study was determined using the formula by Kish Leslie for cross-sectional studies is as below;

$$\frac{N = Z\alpha^2 P (1-P)}{\delta^2}$$

Where by: N = Sample size estimate of health-care providers in infectious disease clinics in Kampala district.

P = percentage of health care providers that encountered ACT treatment failure (60.6%) according to the main study preliminary results at the time. (ACT treatment failure was defined as the percentage of as the proportion of healthcare providers who reported treatment failure encounter out of total healthcare provider participants interviewed.)

(1-P) = probability of no health-care professional perceived treatment failures, so 1-P = 39.4%

Zα = Standard normal deviation at 95% confidence corresponding to 1.96

δ = Absolute error between the estimated true population prevalence of healthcare provider perceived ACT treatment failure of 5%.

Therefore, the sample size required will be;

$$N = \frac{1.96^2 \times 0.606\ (0.394)}{(0.05)^2}$$

N = 367 healthcare providers

3.5 Sampling procedure

Multistage sampling was used to select healthcare providers. In the first stage, Kampala district was purposively divided into five strata basing on the division. Using purposive sampling again, the hospital with the highest bed capacity in each division was selected and using convenient sampling, health facilities around the selected hospital were selected. Due to complex nature of the environment, pharmacies, drug shops, hospitals and health centers/clinics around selected health facilities were included, by distance to the selected hospital, with the facilities nearer to the selected hospital being considered. Two hundred and ninety-seven healthcare providers were enrolled from 93 health facilities (19 in Central, Nakawa and Makindye division each, and 18 each in Rubaga and Kawempe division). A table representative of this stratification has been included in the appendices (Appendix 4). This stratification brought on board all kinds of facilities, that is to say, government facilities, private not for profit facilities and pharmacies from every division. This was also representative of the healthcare stratification in Uganda.

In the last stage, the healthcare providers on duty and available to answer the questionnaire in the selected health facility were recruited to assess their perceived ACT treatment failure.

3.6 Study variables.

3.6.1 Independent variables

Healthcare provider factors; Gender, Age, Education level, professional Cadre, Professional experience, instructions on ACT provided to patient

Health system related factors; Health facility status, Health facility type, ACT brand used.

Patient-related factors; patient perceptions on ACT color, size, taste, smell, Number of ACT tablets, dosing frequency of ACT and ACT failure complaints from patients,

3.6.2 Dependent variable

Healthcare provider-perceived ACT treatment failure. This was being measured as the proportion of healthcare providers who reported treatment failure encounter out of total healthcare provider participants interviewed.

3.7 Data collection

3.7.1 Data collection tools

A self-administered pre-formulated questionnaire (Appendix 1) was completed in by the participants (healthcare providers – prescribers), to find out (by brand, source and other relevant predictors) the healthcare provider perceived ACT treatment failure. It was modified from the questionnaire used by the main study. The tool included both closed and open-ended questions to explore participant demographics, perceived ACT treatment failure and factors related to perceived ACT treatment failure.

The questionnaire was divided into three sections. Section A explored participant demographics. Section B captured perceptions of healthcare providers on ACT treatment failure. Perceived ACT treatment failure was measured subjectively based on a healthcare provider having ever entered an ACT treatment failure. This section also captured information on the commonly used

ACT brands at the health facility, those that resulted in satisfactory patient outcomes, those implicated in treatment failure and information on ACT resistance. Section C captured factors related to ACT failure, which included the drug related factors, factors in the practice of patients that were responsible for poor response of patients to ACTs as well as healthcare provider related factors that caused treatment failure. Some open-ended questions helped to collect the qualitative data.

3.7.2 Data collection procedure.

The study employed two field officers (Pharmacy interns) to carry out the data collection. They were trained on how to use the data collection tool and how to carry out data entry using an open data kit (ODK) collection mobile application. The android mobile phone of each field officer was configured and uploaded with the questionnaire in the ODK collect tool. The tool worked well with limited internet connectivity. Healthcare providers in the selected health facilities completed the self-administered questionnaire. At the end of each day, each research assistant transferred the data from the paper questionnaire into the ODK too and then submitted the data to the central database server.

During data collection, healthcare providers on duty at selected health facilities were recruited using consecutive sampling, screened against inclusion procedure to obtain the eligible study participants. The healthcare providers were then consented and administered to the questionnaire. Administration of the tool took approximately 15 minutes per participant.

3.8 Data management

At the end of each data collection session, data was checked for completeness and accuracy and entered into the ODK collection application. Data obtained was exported to an excel file and then cleaned and analyzed in SPSS version 23. The data cleaning included labelling values and variables, coding and recoding. Open ended questions were coded using Excel and through open

coding, and analyzed for major themes. Inductive grounded theory for analysis was applied. All codes were then reviewed with a research assistant, first separately and then together and major themes were identified. The dataset was be stored on a computer hard drive that is password protected and backed up on a separate external hard drive that had limited access to ensure confidentiality.

3.9 Data analysis

Data was be analyzed in SPSS version 23 and STATA version 13.0. This analysis was done at various levels including univariate, bivariate and multivariable analysis level.

3.9.1 Univariate analysis (descriptive analysis)

It was performed for various variables; continuous variables like age and professional experience were reported in terms of mean and standard deviation for normally distributed data, median and interquartile range for skewed numerical data. Categorical variables like gender and healthcare cadre were reported in terms of frequencies and percentages. These results were reported in tables, cross-tabulations and text.

For objective one, the healthcare provider perceived ACT treatment failure was defined as the proportion of healthcare providers who reported treatment failure encounter out of total healthcare provider participants interviewed. For objective two, open ended questions were coded using Excel and through open coding, and analyzed for major themes. Inductive grounded theory for analysis was applied. All codes were then reviewed with a research assistant, first separately and then together. The specific categories were then discussed, and finally categorized, described and agreed upon major themes. The themes were coded into numeric variables and then reported as frequencies and percentages.

3.9.2 Bivariate analysis

For the bi-variate analysis, associations between independent variables and the outcome variable (Healthcare provider perceived ACT treatment failure) were assessed. Continuous independent variables were categorized and their association with the outcome variable was established using Chi-square tests. The measure of association for categorical variables was the odds ratios (OR) with 95% confidence intervals and P values less than 0.05 considered significant.

Since the outcome variable was binary, we used logistic regression to assess relationship between predictors and the outcome. Variables with p-value less than 0.2 were considered for further multivariable analysis.

3.9.3 Multivariable analysis

This was done using multiple logistic regression for all the variables that had p-value less than 0.2. Testing for interaction and confounding was done to develop the final model in order to determine the significant associated factors with Healthcare provider perceived ACT treatment failure at the level of significance of 0.05. In order to test for interaction, a stepwise model was ran to obtain significant variables at the level of 0.05. Interaction terms among the significant variables was formed and then a stepwise model was ran to determine if there were any significant interaction terms at the level of 0.05.

Confounding effect was assessed for any variables dropped from the model (that has p-value greater than 0.05) by putting them back in the model one by one and calculating the percentage difference in the coefficients in the crude models and adjusted models (variables that caused a greater than 10% difference in the coefficients were considered confounders)

3.10 Quality control

The data was reviewed for completeness and erroneous entries such as typos, missing data, inconsistency and out of range entries. Where necessary, the participants were contacted to correct any errors, otherwise data with errors was treated as missing data during analysis

3.11 Ethical considerations

The protocol was presented before the Journal club at the department of Pharmacology and Therapeutics, Makerere University and then to the institutional review board of the school of biomedical sciences (IRB-SBS), Makerere University. Ethical approval of the main study was already sought from the IRB-SBS as well as the Uganda National Council for Science and Technology. A waiver from the IRB-SBS was therefore sought because the main study was already approved.

Participants were absolutely free to decline or withdraw their participation in the study. The risks of taking part in the study were minimal and ranged from minor discomfort during the consent and some information concerning participant identity being known by the study team. It was a minimal risk study without any anticipated problems. Written informed consent was obtained from all the study participants and all information concerning their identities were kept anonymous, with the questionnaires and consent forms kept under lock and key with access only to the study team.

CHAPTER FOUR: RESULTS

4.1 Characteristics of study participants and health facilities

A total of 297 healthcare providers (Coverage = 81%) were interviewed on their perceived ACT treatment failure and the associated factors. The participants ages ranged between 21 and 51 years with median age of 28 years (IQR; 25, 32) and mean age of 29.2 (SD = 5.1). Males were 56% (165/297) of the healthcare providers and the biggest proportion of the healthcare providers were nurses 38% (113/297). Sixty percent of the healthcare providers were in private-for-profit facilities, 29% (87/297) in public facilities while 10% (31/297) were in private-not-for-profit health facilities. The rest of the characteristics are shown in Table 2 below.

Table 2: Sociodemographic and professional characteristics of health workers within various health facilities in Kampala District

Variable	Frequency (N=297)	Percentage (%)
Age in years		
Mean (SD); Median (IQR)	29.2 (5.1); 28 (25,32)	
Gender		
Male	165	56
Female	132	44
Education level		
Certificate/Diploma	170	57
Bachelors/Masters	127	43
Cadre of health professional		
Nurse	113	38
Physician/Medical Officer/Clinical Officer	103	35
Pharmacist/ Pharmacy Technician	70	24
Other	11	3
Health facility type		
Hospital/HC IV	147	50
Pharmacy/Drug shop	80	27
Private Clinic	58	20
HC III. HC II	12	4
Health facility status		
Private-for-profit	179	60
Public	87	29
Private-not-for-profit	31	11
Professional experience in years		
Mean (SD); Median (IQR)	4.1 (3,4); 3,0 (2,5)	

Number of malaria patients seen by each facility type per day	
Mean (SD); Median (IQR)	
Hospital/HC IV	9.3 (7.2); 8.0 (4,13)
HC III/ HCII	9.8 (5.1); 10.0 (6, 13.5)
Private clinic	6.0 (5.2); 4.0 (3,7)
Pharmacy/Drug shop	7.1 (5.0); 5.0 (4,8)

A high percentage of healthcare providers aged 31 and above and those with 6 years and above professional experience, according to this study, had certificate/diploma as their highest education level as shown in table 3 below.

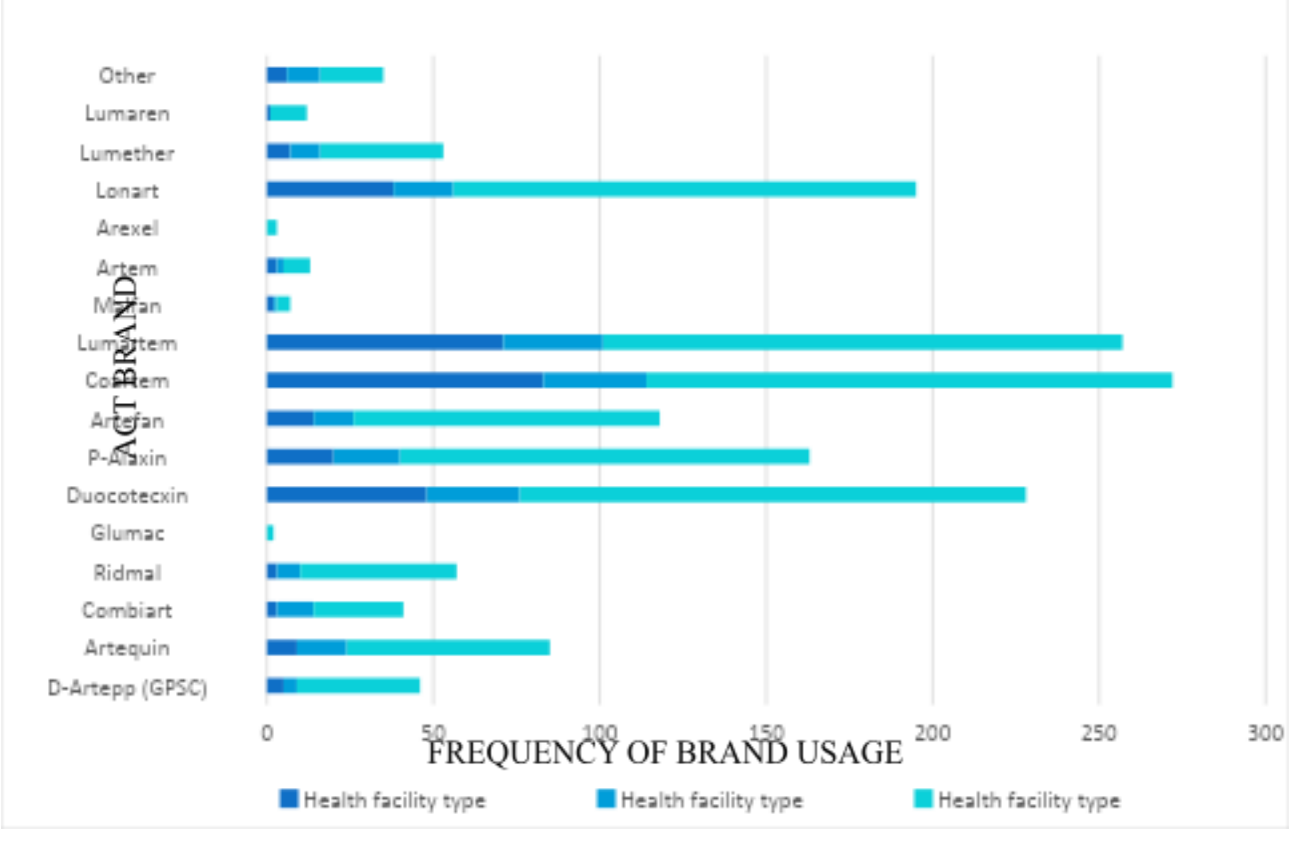
Table 3: Association between healthcare provider-Education Level and their Age and Professional Experience

Variable	**Total**	**Education level**		**Chi-square p-value**
	Frequency	**Certificate/Diploma**	**Bachelors/Masters**	
Age				
21 to 25 years	77	37(48.1)	40(51.9)	0.013
26 to 30 years	131	71(54.2)	60(45.8)	
31 and above	89	62(69.7)	27(30.3)	
Professional experience				
less than 2 years	121	38(31.4)	83(68.6)	<0.001
3 to 5 years	108	79(73.1)	29(26.9)	
6 years and above	68	53(77.9)	15(22.1)	

4.2 Commonly used ACTs in health facilities

The order of the four most selected as commonly used ACTs was similar in the health facility types, with the commonest being Coartem (273/297, 92%), followed by Lumartem (257/297, 87%), Duocotecxin (228/297, 77%) and, finally Lonart (195/297, 66%) as shown in figure 2 below. A number of private facilities complained about coartem (158/179; 88%).

Figure 3. Relative frequencies comparing the brand usage in various health facility types



4.3 Healthcare provider perceived ACT treatment failure.

The healthcare providers were asked if they had ever encountered an ACT treatment failure while treating uncomplicated malaria and 62% (185/297) reported that they had ever encountered an ACT treatment failure. There were 53% (95/179) healthcare providers that perceived ACT treatment failure in private-for-profit health sector, 69% (60/87) in public health sector and 96% (30/31) in private not for profit health sector. There was a significant difference between the healthcare

providers that reported having ever encountered ACT treatment failure and those that had never for the following variables; education level of respondents, age, professional experience, and professional cadre, the health sector of practice. Previous patient-complaints about ACT treatment failure also significantly influenced healthcare provider perceived ACT treatment failure, as illustrated in the table 4 below. Furthermore, more than a quarter healthcare providers (81/297, 27%) reported having suspected an ACT treatment failure in the past 4 weeks.

Table 4: Comparison of characteristics of healthcare providers that had ever encountered versus those that had never encountered ACT treatment failure

Variable	Ever encountered ACT treatment failure		Chi-square	p-value
	Yes %(N)	No %(N)		
Overall	**62.3(185)**	**37.7 (112)**		
Professional Cadre				
Nurse	68.1(77)	31.9(36)	12.8	**0.005**
Physician/Medical officer/ clinical officer	67.0(69)	33.0(34)		
Pharmacist/ Pharmacy technician	44.3(31)	55.7(39)		
Other (interns and medical students)	72.7(8)	27.3(3)		
Gender				
Male	60.6(100)	39.4(65)	0.5	0.503
Female	64.4(85)	35.6(47)		
Age categorized				
<25 years	34.2(27)	65.8(52)	43.4	**0.000**
25-34 years	67.7(113)	32.3(54)		
35 - 44 years	89.1(41)	10.9(5)		
45 years and above	80(4)	20(1)		
Education level				
Certificate/ Diploma	71.2(121)	28.8(49)	13.4	**0.000**
Bachelors/ Masters	50.4(64)	49.6(63)		
Professional experience				
0-5 years	55.0(126)	45.0(103)	22.8	**0.000**
6 - 10 years	88.5(46)	11.5(6)		
10 years and above	81.3(13)	18.7(3)		
Health sector of practice				
Public	69.0(60)	31.0(27)	23.8	**0.000**
Private not for profit	96.8(30)	3.2(1)		
Private for profit	53.1(95)	46.9(84)		
Received patient complaints of treatment failure				
No	94.5(120)	5.5(7)	97.9	**0.000**
Yes	38.2(65)	61.8(105)		

The brands with the highest perceived treatment failure included Coartem (150/297, 51%) and Lumartem (122/297, 41%) while the brand that resulted into most satisfactory outcome was Duocotecxin (176/297, 59%) as shown in the table 5 below. The percentage treatment failure for Artemether-Lumefantrine was 357/497 (71.8%)

Table 5: Percentage use and perceived treatment failure of various ACT brands on the market in Kampala district

Brand	Active Ingredient	%use n=297 (95%CI)	Perceived treat failure% (95%CI)	Satisfactory outcome%(95%CI)
Coartem	Artemether-lumefantrine	92 (88.4±94.8)	51 (44.8±56.2)	34 (30.5±41.5)
Lumertam	Artemether-lumefantrine	87 (82.6±90.)	41 (35. 0±46.7)	33 (27.3±38.0)
Lonart	Artemether-lumefantrine	66 (60.2±71.1)	14 (10.5±18.5)	36 (30.5±41.5)
Duocotecxin	Dihydroartemisinin –piperaquine	77 (71.9±81.5)	10 (6.7±13.5)	59 (53.6±64.9)
Artefan	Artemether-lumefantrine	40 (34.1±45.3)	8 (5.0±11.2)	17 (13.2±21.9)
Lumether	Artemether-lumefantrine	18 (13.4±22.2)	3 (0.8±0.5)	7 (4.1±10.0)
Combiart	Artemether-lumefantrine	14 (9.9±17.7)	3 (0.8±4.5)	7 (4.4±10.4)
P-Alaxin	Dihydroartemisinin –piperaquine	55 (49.2±60.6)	2 (0.4±3.6)	42 (36.8±48.0)
Artekin	Dihydroartemisinin –piperaquine	29 (23.4±33.7)	1 (0.1±2.2)	18 (13.8±22.6)
Ridmal	Dihydroartemisinin –piperaquine	19 (14.7±23.7)	1 (0.1±2.2)	11 (7.8±15.0)
D-Artepp (GPSC)	Dihydroartemisinin –piperaquine	16 (11.3±19.6)	1 (0.2±2.2)	12 (8.3±15.9)
Artem	Artemether	4 (2.0±6.7)	0 (0)	1 (0.0±2.6)
Other		12 (8.1±15.5)	32 (26.7±37.3)	29 (24.1-34.5)

4.4 Factors associated with the healthcare provider perceived ACT treatment failure

4.4.1 Bivariate analysis

At Bivariate level, Older HCPs (those 26-30 and those 31 and above) in this study were more likely to perceive treatment failure compared to those who were 21-26 years. Those with certificate/diploma were more likely to perceive treatment failure. Clinicians who had been practice for over 6 years were more likely to perceive ACT treatment failure. The following variables had p-values less than 0.2 and were therefore considered for multivariable analysis; Gender, Age, Education Level, Professional Cadre and Professional Experience as shown in table 6 below.

Table 6: Bivariate analysis of factors associated with Healthcare provider perceived ACT treatment failure

Variable	No %(N)	Yes %(N)	Crude OR	95% CI	p-value
Gender					
Male	39.4(65)	60.6(100)	1		
Female	35.6(47)	64.4(85)	1.18	0.92±1.50	**0.188***
Age					
21 to 25 years	66.2(51)	33.8(26)	1		
26 to 30 years	35.9(47)	64.1(84)	3.51	1.69±7.26	**0.001***
31 and above	15.7(14)	84.3(75)	10.51	1.81±60.94	**0.009***
Education level					
Certificate/diploma	28.8(49)	71.2(121)	1		
Bachelor/masters	49.6(63)	50.4(64)	0.41	0.16±1.06	**0.065***
Professional cadre					
Nurse	31.9(36)	68.1(77)	1		
Physician/Medical Officer/Clinical officer	33(34)	67(69)	0.95	0.38±2.35	0.910
Pharmacist/Pharmacy technician/other	51.9(42)	48.1(39)	0.43	0.21±0.89	**0.022***
Professional experience					
less than 2 years	60.3(73)	39.7(48)	1		
3 to 5 years	27.8(30)	72.2(78)	3.95	1.70±9.19	**0.001***
6 years and above	13.2(9)	86.8(59)	9.97	1.20±82.5	**0.033***
Health facility type					
Public	31(27)	69(60)	1	-	-
Private not-for-profit	3.2(1)	96.8(30)	13.5	0.83±220.06	0.613
Private for-profit	46.9(84)	53.1(95)	0.51	0.27±0.95	0.747
Health facility status					
Hospital/HCIV	25.2(37)	74.8(110)	1		

HCIII/HCII/Private clinic	40(28)	60(42)	0.50	-	**<0.001***
Pharmacy/Drug shop	58.8(47)	41.3(33)	0.24	-	**<0.001***
Patient complaints about ACTs					
No	61.8(105)	38.2(65)	1		
Yes	5.5(7)	94.5(120)	27.69	9.27±82.76	**<0.001***
Color of ACT tablets					
No	40.3(85)	59.7(126)	1		
Yes	31.4(27)	68.6(59)	1.47	1.45±1.49	**<0.001***
Size of ACT tablets					
No	28(40)	72(103)	1		
Yes	46.8(72)	53.2(82)	0.44	0.18±1.12	**0.084***
Number of ACT tablets					
No	48.4(15)	51.6(16)	1		
Yes	36.5(97)	63.5(169)	1.63	0.61±4.35	0.327
Lack of information about ACTs					
No	29.7(11)	70.3(26)	1		
Yes	38.8(101)	61.2(159)	0.67	0.47±0.95	**0.023***

4.4.2 Multivariable analysis

In the adjusted model, factors independently associated with healthcare provider perceived ACT treatment failure were Age and Professional experience. The health facility type and health facility status of the healthcare providers were also independently associated with perceived ACT treatment failure. Patient related factors like complaints about ACTs and color of ACT tablets were also independently associated with healthcare provider perceived treatment failure. These are shown in the multivariable table 7 below.

Healthcare providers aged 31 and above were 10.5 times more likely to perceive treatment failure compared to those 25 and below (aOR=1.38; 95% CI=1.16 - 1.65; p=0.001); and, those with 6 years and above professional experience were also 9.97 times more likely to perceive treatment failure

compared to those with experience of less than two years (aOR=2.48; 95% CI= 2.20 - 2.79; p=0.001 and aOR=2.84; 95% CI= 1.10 - 7.29; p=0.030 respectively).

Healthcare providers in private-not-for-profit health facilities were more likely to perceive treatment failure than those in public facilities (aOR=6.49; 95% CI=1.89 - 22.26; p=0.003); Health system related themes that were perceived to result in treatment failure circled around poor health service delivery (170/297, 57%) like misdiagnosis, patient negligence and poor prescription practices like polypharmacy. Healthcare providers also noted that sometimes patients are given unclear instructions (121/297, 41%) probably through unclear prescriptions, bad handwriting or because of language barrier. Other factors like high patient load (22/297, 7%), dispensing of over the counter drugs (19/297, 6%), Poor patient follow up (10/297, 3%) and poor clinician-patient relationships were all reported to result in poor response of patients to ACTs. The following statements describe some of the experiences;

'*Clinicians who dispense ACTs over be counter without first testing the patients for mps sometimes end up giving wrong medicine to patients who don't have malaria. Later when the patients actually have the malaria they may fail to respond to the ACTs (40 years, Physician)*

'Not giving attention to patient history. Little time with patients because patients are many so patients don't get adequate information' (28 years, Nurse).

For the health facility status, healthcare providers in Hospital/HCIV were more likely to perceive treatment failure than those in HCIII/HCII/Private clinic and those in Pharmacy/Drug shop (aOR=0.42; 95% CI= 0.34 - 0.53; p=0.001 and aOR=0.26; 95% CI= 0.14 - 0.49; p=001 respectively); This is expected since hospital and HCIV settings usually admit their malaria patients and so easily follow-up patient outcome. Also, they tend to receive referral patients with severe malaria, who will more likely have failed on ACTs for treating uncomplicated malaria. In these other

health facilities like pharmacies and drug shops, there is usually lack of follow up and possibility of financial gain influencing the judgement of the healthcare providers cannot be ruled out, as stipulated in some of their responses.

'Clinicians sometimes over charge patients for drugs. Selling free government drugs to patients there by limiting those that can't afford (40 years, Physician)

Health care providers who had received complaints from patients about ACTs were more likely to perceive treatment failure than those that had not (aOR=30.00, 95% CI=13.36 - 67.37; p=0.001). They explained that patients because they had fewer tablets. Other patient complaints they reported include; Burdensome dosing frequency especially with the "24s" (111/297, 37%) so patients generally preferred single dose regimen to twice daily dosing (71/297, 23%). Healthcare providers reported that some drugs, like the Duocotecxin tablets, were too big (137/297, 46%) difficult to swallow easily (26/297, 9%). These factors however were not significant

'Yes, patients prefer the double strengthened tablets that are fewer. They say they don't like the 24s. They are many' (26 years, Nurse)

They also highlighted that when patients don't receive adequate information regarding ACT treatment (150/297, 50%) especially when they resort to self-medication or purchase the ACT drug over the counter without testing (130/297, 44%), most of these patients will not complete the ACT dose (30/297, 10%) either because of improvement (19/297, 6%) or side effects (10/297, 3%).

'Patients are misinformed about these medicines do if they buy them over the counter without proper instructions they can misuse the drugs' (38 years, Pharmacist)

On further probing, healthcare providers reported that most patients complain about the unpleasant taste (141/297, 47%) and smell 60/297, 20%) of Coartem that causes nausea (n=22, 7%).

'The taste of the first lines for uncomplicated malaria ie the coartem and lumartem is not sour but their smell gives them a funny taste that is nauseating to some patients hence the poor compliance' (27 years, Pharmacist)

The color of ACTs was reported to affect patient compliance, according to clinicians (aOR=011.41; 95% CI= 1.15 - 1.73; p=0.001), and could result in treatment failure among patients. Some Healthcare providers (46/297, 15%) reported that patients linked the color of ACTs to bad smell and taste.

'*Clients tend to have color preferences, they associate the yellow color of Coartem and lumartem with bitterness so they tend to prefer Duocotecxin' (40 years, Pharmacy Technician)*

ACT size was a confounder for the relationship between the outcome and the following predictors: professional experience, Health facility type (specifically the level of private not for profit) and color of the ACT tablets. Professional cadre was a confounder for the relationship between the outcome and the following predictors: Health facility status (specifically the level of pharmacy/drug shop) and patient complaints about ACTs. Gender was a confounder for the relationship between the outcome and health facility type (specifically the level of private not for profit).

Table 7: Multivariable analysis of factors associated with perceived ACT treatment failure among healthcare providers in Kampala district

Variable	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Gender				
Male	1		1	
Female	1.18(0.92±1.50)	0.188	1.36 (0.49±3.72)	0.555
Age				
21 to 25 years	1		1	
26 to 30 years	3.51(1.69±7.26)	0.001	1.84 (0.95±3.56)	0.070
31 and above	10.51(1.81±60.94)	0.009	1.38 (1.16±1.65)	**<0.001***
Professional cadre				
Nurse	1		1	
Physician/Medical Officer/Clinical officer	0.95(0.38±2.35)	0.910	0.68 (0.15±2.99)	0.606
Pharmacist/Pharmacy technician/other	0.43(0.21±0.89)	0.022	1.62 (0.80±3.30)	0.179
Professional experience				
Less than 2 years	1		1	
3 to 5 years	3.95(1.70±9.19)	0.001	2.48 (2.20±2.79)	**<0.001***
6 years and above	9.97(1.20±82.5)	0.033	2.84 (1.10±7.29)	**0.030***
Health facility type				
Public	1		1	
Private not-for-profit	13.5(0.83±220.06)	0.068	6.49 (1.89±22.26)	**0.003***
Private for-profit	0.51(0.27±0.95)	0.034	0.58 (0.14±2.32)	0.438
Health facility status (Cluster variable)				
Hospital/HCIV	1		1	
HCIII/HCII/Private clinic	0.5	<0.001	0.42 (0.34±0.53)	**<0.001***
Pharmacy/Drug shop	0.24	<0.001	0.26 (0.14±0.49)	**<0.001***
Patient complaints about ACTs				
No	1		1	
Yes	27.69(9.27±82.76)	<0.001	30.00 (13.36±67.37)	**<0.001***
Color of ACT tablets				
No	1		1	
Yes	1.47(1.45±1.49)	<0.001	1.41 (1.15±1.73)	**0.001***
Size of ACT tablets				
No	1		1	
Yes	0.44(0.18±1.12)	0.084	0.60 (0.21±1.66)	0.322

CHAPTER FIVE: DISCUSSION

5.1 Healthcare provider perceived ACT treatment failure

The WHO recommends regular antimalarial clinical efficacy trials with standardized protocol so as to keep an eye on impending Plasmodium resistance. However, the potential contribution of healthcare provider perceived ACT treatment failure has not received much attention in most Sub-Saharan African countries. In this study, a healthcare provider-focused approach was used to assess perceived ACT treatment failure as well as the factors associated with the perceived ACT treatment failure and has provided seminal and important information to guide pharmacovigilance of ACTs.

A study in Tanzania found that perceptions of healthcare providers about antimalarial drugs influenced their decision-making during health service delivery (Masanja et al., 2012), hence, governments and decision makers need to look out for those brands implicated in treatment failure and also work towards establishing strategies to protect identity of efficacious ACT brands on the market for the benefit of the Ugandan population. The perceived ACT treatment failure by healthcare providers in this study was rather high, considering 185/297, 62% healthcare providers reported having ever encountered ACT treatment failure while treating uncomplicated malaria. The literature review suggested that very few studies on healthcare provider-perceived treatment failure of artemisinin combination therapy had been done. Moreover, perceived ACT treatment failure among nurses in this study (68. 1%) was rather high in comparison to a similar study done in Nigeria among nurses (40.7%) (Efunshile et al., 2016). Perceived treatment failure among nurses in this study done in Nigeria was attributed to previous encounter with ACT treatment failure and fake and substandard ACT drugs as has been reported in other studies(Kaur et al., 2016; Malimbo, Mugisha, Kato, Karamagi, & Talisuna, 2006). Higher perceived treatment failure among nurses in Uganda

could also be because most malaria cases in Uganda are still being treated without laboratory evidence(Diggle et al., 2014).

More than a quarter healthcare providers (81/297, 27%) reported having suspected an ACT treatment failure in the past 4 weeks. Elsewhere, studies show that if healthcare providers suspect treatment failure or serious adverse effects with a particular ACT, they may not prescribe it to their patients (Masanja et al., 2012). In Ghana for example, healthcare providers who perceived artesunate/amodiaquine (AS-AQ) as a drug with some serious side-effects either refused to prescribe AS-AQ to their patients or sometimes reduced the dosage of the drug for their clients as a way of preventing or minimizing its side-effects (Asante et al., 2010). This practice among healthcare providers may lead to misdiagnosis and therefore increased perceived treatment failure as there is no algorithm for malaria treatment based solely on clinical examination (Chandramohan, Jaffar, & Greenwood, 2002; Manirakiza et al., 2010). Moreover, in this study, healthcare providers reported a possibility of prescribing ACTs for the wrong diagnosis due to various reasons like lack of or unavailability of appropriate diagnostic tools (170/297, 57%).

5.2 Factors associated with the healthcare provider perceived ACT treatment failure

In this study, perceived ACT treatment failure was associated with age, with the older healthcare providers more likely to perceive treatment failure when compared with those less than 25 years. This is similar to a study done among nurses in Nigeria (Efunshile et al., 2016). High healthcare provider perceived ACT treatment failure among older healthcare providers calls for concern because the impression can be readily transmitted to the younger ones who they are expected to instruct and mentor (Malimbo et al., 2006). Perceived ACT treatment failure was also associated with years of professional experience. Clinicians who had been in practice for over 6 years, when compared with those less than 2 years, were two times more likely to perceive ACT treatment failure. A similar study in Nigeria found that the more experienced health workers were more likely

to perceive ACT treatment failure (Efunshile et al., 2016). Studies have reported a declining response of patients to ACTs over the years (Jagannathan et al., 2012), therefore healthcare providers who have been in practice for over 6 years may rightly perceive more treatment failures.

In this study, 62/89 (69.7) healthcare providers aged 31 and above and 53/68 (77.9) of those with 6 years and above professional experience, according to this study, had certificate/diploma as their highest education level. Moreover, healthcare providers with master/bachelors were 0.4 times less likely to perceive treatment failure. Studies have shown better adherence to guidelines among higher cadres of healthcare providers and have recommended continuous medical education sessions for health workers (Bawate, Callender-Carter, Nsajju, & Bwayo, 2016). Healthcare providers demonstrated a good understanding of the importance of correct dosing but there was some confusion over specific details of the dosing schedule. Therefore, it is important to organize proper training of healthcare providers in contents that seem not well understood, and avail them with job aids will better their understanding about ACTs.

Perceived ACT treatment failure was also associated with health facility type. Healthcare providers in HCIII/HCII/Private clinic and those in Pharmacy/Drug shop were less likely to perceive treatment failure than those in Hospital/HCIV. This is to suggest that drug shops, private clinics and pharmacies, which are a major source of health care for more than 50% of patients (Chuma, Okungu, & Molyneux, 2010; Rutebemberwa, Pariyo, Peterson, Tomson, & Kallander, 2009) have better treatment outcomes compared to public sources since they receive patients with uncomplicated malaria that is easily managed. This is expected since severe cases of malaria are usually referred to the hospitals or HC IV therefore, they are more likely to have healthcare providers who have perceived ACT treatment failure. Furthermore, healthcare providers in pharmacies and drug shops usually don't admit and/or follow up on their patients.

The perceived ACT treatment failure among healthcare providers was associated with private-not-for-profit sources of healthcare. Fortunately, in Uganda, public and private-for-profit sources are the major sources of healthcare(Orem, Mugisha, Okui, Musango, & Kirigia, 2013). Private-for-profit sources had the least healthcare provider ACT treatment failures, which is expected since they probably sell better ACT brands than public and private not for profit sources. The order of the four most selected commonly used ACTs brands, however, was similar across the health facility types, including the proprietor brand, coartem. In Uganda, coartem brand is available in three types; the government subsidized brand, low cost market brand and the original innovator brand (Buregyeya et al., 2017; Kassam, Collins, Liow, & Rasool, 2015). While the healthcare providers did not differentiate them in their responses, it is expected that drugs provided free by the government were implicated in public and private not for profit health facilities and not used at all in private health facilities, while the original innovator and low-cost market brands were implicated in private facilities since a number of private facilities also complained about coartem (158/179; 88%). It could be also, that since most healthcare providers tend to hold more than one job across the different health facility types, they gave their overall percentage use of the different brands without regard to the health facility type. Also, it could mean that the healthcare providers are not familiar with the different ACT brands on the market and therefore mentioned the commonly known ACT brands.

Healthcare providers in some public health facilities mentioned that some patients could not afford medication especially if they were required to buy a drug that was not available at the public health-facility. This resulted in poor compliance patients purchase only half the dose. Cost however should not be a challenge since AL is available free of charge in most public hospitals unless there are stock outs (Kaula, Buyungo, & Opigo, 2017). Previous studies in Uganda, unlike this study, have

reported higher prevalence of treatment failure in private for profit sources (private clinics and drug shops) compared to government health facilities (Malimbo et al., 2006).

Clinicians reported that health facility related factors like high patient load, over the counter prescriptions without laboratory testing, poor patient follow up and poor clinician-patient relationships that were found to result in poor response of patients to ACTs have also been cited in previous studies (Diggle et al., 2014; Wasunna, Zurovac, Goodman, & Snow, 2008). Clinicians that had ever received a complaint from a patient about ACT treatment failure were 30 times more likely to perceive treatment failure. These clinicians most likely presumptively identified treatment failure basing on the previous failure encountered. In this study, healthcare providers reported that most patients' complaints arose due to a number of factors including the unpleasant taste, and smell of Coartem that causes nausea and many of the patients preferred coated tablets. Healthcare providers reported greater patients' preference to once daily dosing ACT regimen like dihydroartemisinin (DHA-PPQ), despite the improved taste and solubility of dispersible AL. This has been seen with other studies and that previous experience with AL may have influenced adherence and widespread use (Ewing et al., 2015).The bitter taste of medications was said to be a general problem in administering medication to children. Respondents suggested that there were some benefits of the improved dispersible flavored formulation with administering medications to children and this has been seen in similar studies (Asante et al., 2010).

At the same time, other studies also report patient expectations of healthcare providers; the role of the provider to educate the patient, and reported good outcomes from taking the time to speak with patients and explain to them how malaria is transmitted, how testing works and the possibility of further illness following nonadherence (Diggle et al., 2014). More than half the healthcare providers mentioned poor health service delivery like misdiagnosis, negligence and poor prescription practices like polypharmacy and also noted that sometimes patients are given unclear instructions probably

through unclear prescriptions, bad writing or because of language barrier. Studies in other countries have found that few healthcare providers receive training after changes in treatment policy and this has an impact on prescription practices (Ahmed & Yousif, 2004; Kalilani-Phiri, Lungu, & Coghlan, 2011).

In this study, clinicians mentioned that patient practices like over-dosing through taking all doses over a shorter period than intended, taking a reduced dose over a longer period of time and failing to complete the entire treatment course; could potentially lead to treatment failure. These have all been previously reported (Bruxvoort, Goodman, Kachur, & Schellenberg, 2014). Since the introduction of ACT, there has been increasing concern about adherence to anti-malarials since the dosing schedules are more complex than the previous first-line therapy (Achan et al., 2009; Chatio et al., 2015; Checchi et al., 2006). Under-dosing potentially leads to treatment failure and may contribute to the spread of antimalarial drug resistance. Pharmacologically, artemisinin clears malaria symptoms quickly so that patients feel better soon after starting the medication and may end up stopping the dosage (Checchi et al., 2006). Overdosing may lead to drug toxicity and contribute to poor perceptions of available anti-malarials and discourage appropriate treatment seeking. The lack of adherence to the treatment regimen and sub-optimal dosing of AL have been implicated in the increase in artemisinin treatment failure, which have been shown to be dependent upon the healthcare providers' instructions on how to take AL and the patient's attitude towards completing the prescribed regimen (Banek, Lalani, Staedke, & Chandramohan, 2014).

When healthcare providers are made aware of patient experiences, they are encouraged to target these knowledge gaps when providing instructions at the health facility (Ewing et al., 2015). Healthcare providers actually highlighted that when patients do not receive adequate information regarding ACT treatment especially when they resort to self-medication or purchase the ACT drug over the counter without testing, most of these patients will not complete the ACT dose either

because of improvement or side effects. Studies have reported that adherence is generally better when “interventions focusing on provider knowledge and behaviour, packaging and provision of correct dosage” were implemented (Yakasai et al., 2015; Yeung & White, 2005). The color of ACTs was perceived by healthcare providers to result in treatment failure among patients. One of the suggested reasons for linking color to poor treatment adherence is that patients had poor attitude toward the color of ACTs, and some attributed the color to bad smell and taste. Others thought that the patients found the color unattractive and nauseating. Some of these factors have also been cited in other previous studies(Asante et al., 2010; Kalilani-Phiri et al., 2011). Better understanding of these factors should guide further interventional studies to improve dispensing and counseling practices as an integral part of appropriate prescribing.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusions

The study results showed that 62.3% of the healthcare providers perceived ACT treatment failure during treatment of uncomplicated malaria which is a high proportion when compared to a similar study done among nurses in Nigeria that reported 40.7%. This may also suggest that there could be declining response of patients to ACTs. Since the outcome measure of the study is rare, there were no recommended perceived ACT treatment failure levels by the MOH or the WHO. A lower proportion of healthcare providers within public and private-for-profit sectors reported perceived ACT treatment failure compared to healthcare providers in private not for profit sources. The perception of most of the healthcare providers interviewed in this study was that risk of ACT failure has been associated with overuse. Since healthcare providers, during patient care, always interact with medicines, their perceptions about ACTs will influence their decision- making during service delivery.

In addition, factors which could lead to perceived treatment failure identified in this study need to be addressed. Of importance is poor patient adherence, which could be improved if patients are properly educated in medicine use at the point of care. Healthcare provider perspectives made on basis of observing the ways in which patients respond to medicines included their concerns on color, size, and number of tablets prescribed. Findings from this study have implications in public health as it emphasizes healthcare provider perspectives on ACT treatment failure, which influences their decision-making during service delivery.

6.2 Recommendations

From the results of this study, it is recommended that standard methods should be developed to evaluate and document personal experience of healthcare providers regarding ACT treatment failure. Records from such data can help create an algorithm that could help clinicians predict treatment failure. Such information can also serve as an adjunct to the standard clinical efficacy trial. When healthcare providers realize that their experience and perceptions contribute to decisions that guide post-marketing surveillance of ACTs, they are more likely to work towards stewardship of the efficacious antimalarials than when they perceive stewardship emanated from other stakeholders like the drug regulatory bodies or a group of sponsored researchers alone.

Governments and decision makers need to look out for those brands implicated in treatment failure and also work towards establishing strategies to protect identity of efficacious ACT brands on the market for the benefit of the Ugandan population. Furthermore, it is important for the MOH to empower healthcare providers with information to make more informed decisions at the point of care. Further studies can search into patients' perspectives on ACT treatment failure. Bioequivalence analysis of the four brands with the highest perceived treatment failure is recommended to verify this outcome

6.3 Limitations

The response rate of the study was 81% due to insufficient funds. These findings are not generalizable since the study was done in health facilities located in the urban area. Health workers in the rural areas may have a different experience due to the difference in societal and contextual factors. However, despite this limitation, important information was obtained on the Healthcare provider-perceived treatment failure of ACTs in Kampala district

Furthermore, since what is perceived cannot be confirmed, it is possible that some healthcare providers reported what was considered appropriate rather than what is actually happening, leading

to courtesy bias. This study, however, provided additional information on predictors of preferences and practices among health care providers toward ACTs, which complimented previous anecdotal reports of poor healthcare provider-perceptions towards ACTs in Uganda; as well, it provides a clue on what happens to the health system when there is a failing drug.

Also, recalling what happened in terms of treating malaria in the past may have been difficult for some participants, introducing a recall bias. These biases could have affected measures of effect estimated. In this respect, the recall was limited for up to the past three weeks. Some healthcare providers on duty were not available/did not respond to the questionnaire. Some however requested that the questionnaire be left behind so that they can fill them in at their convenience and picked later in the day or the following day by the study team.

REFERENCES

Achan, J., Tibenderana, J. K., Kyabayinze, D., Mangen, F. W., Kamya, M. R., Dorsey, G., . . . Talisuna, A. O. (2009). Effectiveness of quinine versus artemether-lumefantrine for treating uncomplicated falciparum malaria in Ugandan children: randomised trial. *Bmj, 339*, b2763.

Achol, E., Ochaya, S., Malinga, G. M., Edema, H., & Echodu, R. (2019). High prevalence of Pfmdr-1 N86 and D1246 genotypes detected among febrile malaria outpatients attending Lira Regional Referral Hospital, Northern Uganda. *BMC research notes, 12*(1), 1-4.

Ahmed, M., & Yousif, M. (2004). Impact of the national protocol for malaria treatment on prescribing patterns in Gezira state, Sudan.

Alfonso-Cristancho, R., Andia, T., Barbosa, T., & Watanabe, J. H. (2015). Definition and classification of generic drugs across the world. *Applied health economics and health policy, 13*(1), 5-11.

Ambrose, O., Jane, A., Albert, P., Adoke, Y., & Fred, K. (2014). The Changing Landscape of Malaria Case Management in Uganda: Decades of Struggle with Evolving Malaria Case Management Strategies and Drug Policies. *Malar Chemoth Cont, 3*(117), 2.

Anderson, T. J., & Roper, C. (2005). The origins and spread of antimalarial drug resistance: lessons for policy makers. *Acta tropica, 94*(3), 269-280.

Asante, K. P., Abokyi, L., Zandoh, C., Owusu, R., Awini, E., Sulemana, A., . . . Segbaya, S. (2010). Community perceptions of malaria and malaria treatment behaviour in a rural district of Ghana: implications for artemisinin combination therapy. *BMC Public Health, 10*(1), 409.

Ashley, E. A., & White, N. J. (2005). Artemisinin-based combinations. *Current opinion in infectious diseases, 18*(6), 531-536.

Asua, V., Conrad, M. D., Aydemir, O., Duvalsaint, M., Legac, J., Duarte, E., . . . Yeka, A. (2020). Changing Prevalence of Potential Mediators of Aminoquinoline, Antifolate, and Artemisinin Resistance Across Uganda. *The Journal of Infectious Diseases*.

Banek, K., Lalani, M., Staedke, S. G., & Chandramohan, D. (2014). Adherence to artemisinin-based combination therapy for the treatment of malaria: a systematic review of the evidence. *Malaria journal, 13*(1), 7.

Barrete, A., & Ringwald, P. (2010). Global report on antimalarial drug efficacy and drug resistance: 2000–2010. *Geneva: WHO*.

Bawate, C., Callender-Carter, S. T., Nsajju, B., & Bwayo, D. (2016). Factors affecting adherence to national malaria treatment guidelines in management of malaria among public healthcare workers in Kamuli District, Uganda. *Malaria journal, 15*(1), 1-10.

Bhattacharyya, N., Mukherjee, H., Bose, D., Roy, S., Das, S., Tripathy, S., & Hati, A. (2014). Clinical case of artesunate resistant Plasmodium falciparum malaria in Kolkata: A first report. *J Trop Dis, 2*(128), 2.

Björkman, A. (2002). Malaria associated anaemia, drug resistance and antimalarial combination therapy. *International journal for parasitology, 32*(13), 1637-1643.

Bjorkman Nyqvist, M., Svensson, J., & Yanagizawa-Drott, D. (2012). Can Good Products Drive Out Bad? Evidence from Local Markets for (Fake?) Antimalarial Medicine in Uganda.

Bloland, P. B., & Organization, W. H. (2001). Drug resistance in malaria.

Brockman, A., Price, R., Van Vugt, M., Heppner, D., Walsh, D., Sookto, P., . . . Nosten, F. (2000). Plasmodium falciparum antimalarial drug susceptibility on the north-western border of Thailand during five years of extensive use of artesunate-mefloquine. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 94*(5), 537-544.

Bruxvoort, K., Goodman, C., Kachur, S. P., & Schellenberg, D. (2014). How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs. *PloS one, 9*(1), e84555.

Buregyeya, E., Rutebemberwa, E., LaRussa, P., Lal, S., Clarke, S. E., Hansen, K. S., . . . Mbonye, A. K. (2017). Comparison of the capacity between public and private health facilities to manage under-five children with febrile illnesses in Uganda. *Malaria journal, 16*(1), 1-7.

Byakika-Kibwika, P., Achan, J., Lamorde, M., Karera-Gonahasa, C., Kiragga, A. N., Mayanja-Kizza, H., . . . Merry, C. (2017). Intravenous artesunate plus Artemisnin based Combination Therapy (ACT) or intravenous quinine plus ACT for treatment of severe malaria in Ugandan children: a randomized controlled clinical trial. *BMC infectious diseases, 17*(1), 794.

Carter, R., & Mendis, K. N. (2002). Evolutionary and historical aspects of the burden of malaria. *Clinical microbiology reviews, 15*(4), 564-594.

Chandramohan, D., Jaffar, S., & Greenwood, B. (2002). Use of clinical algorithms for diagnosing malaria 1. *Tropical Medicine & International Health, 7*(1), 45-52.

Chang, Z. (2016). The discovery of qinghaosu (artemisinin) as an effective anti-malaria drug: a unique China story. *Science China. Life Sciences, 59*(1), 81.

Chatio, S., Aborigo, R., Adongo, P. B., Anyorigiya, T., Akweongo, P., & Oduro, A. (2015). Adherence and uptake of artemisinin-based combination treatments for uncomplicated malaria: a qualitative study in northern Ghana. *PloS one, 10*(2), e0116856.

Checchi, F., Piola, P., Fogg, C., Bajunirwe, F., Biraro, S., Grandesso, F., . . . Kiguli, J. (2006). Supervised versus unsupervised antimalarial treatment with six-dose artemether-lumefantrine: pharmacokinetic and dosage-related findings from a clinical trial in Uganda. *Malaria journal, 5*(1), 59.

Chima, R. I., Goodman, C. A., & Mills, A. (2003). The economic impact of malaria in Africa: a critical review of the evidence. *Health policy, 63*(1), 17-36.

Chuma, J., Okungu, V., & Molyneux, C. (2010). Barriers to prompt and effective malaria treatment among the poorest population in Kenya. *Malaria journal, 9*(1), 144.

Conrad, M. D., Bigira, V., Kapisi, J., Muhindo, M., Kamya, M. R., Havlir, D. V., . . . Rosenthal, P. J. (2014). Polymorphisms in K13 and falcipain-2 associated with artemisinin resistance are not prevalent in Plasmodium falciparum isolated from Ugandan children. *PloS one, 9*(8), e105690.

Conrad, M. D., LeClair, N., Arinaitwe, E., Wanzira, H., Kakuru, A., Bigira, V., . . . Greenhouse, B. (2014). Comparative impacts over 5 years of artemisinin-based combination therapies on Plasmodium falciparum polymorphisms that modulate drug sensitivity in Ugandan children. *The Journal of infectious diseases, 210*(3), 344-353.

Cordina, M. (2010). Counterfeit medicines. *Journal of the Malta College of Pharmacy Practice, 16*, 4-6.

Denis, M. B., Tsuyuoka, R., Lim, P., Lindegardh, N., Yi, P., Top, S. N., . . . Christophel, E. M. (2006). Efficacy of artemether–lumefantrine for the treatment of uncomplicated falciparum malaria in northwest Cambodia. *Tropical Medicine & International Health, 11*(12), 1800-1807.

Diggle, E., Asgary, R., Gore-Langton, G., Nahashon, E., Mungai, J., Harrison, R., . . . Soti, D. (2014). Perceptions of malaria and acceptance of rapid diagnostic tests and related treatment practises among community members and health care providers in Greater Garissa, North Eastern Province, Kenya. *Malaria journal, 13*(1), 502.

Dokomajilar, C., Nsobya, S. L., Greenhouse, B., Rosenthal, P. J., & Dorsey, G. (2006). Selection of Plasmodium falciparum pfmdr1 alleles following therapy with artemether-lumefantrine in an area of Uganda where malaria is highly endemic. *Antimicrobial agents and chemotherapy, 50*(5), 1893-1895.

Dondorp, A., Newton, P., Mayxay, M., Van Damme, W., Smithuis, F., Yeung, S., . . . Hien, T. (2004). Fake antimalarials in Southeast Asia are a major impediment to malaria control: Multinational cross-sectional survey on the prevalence of fake antimalarials. *Tropical Medicine & International Health, 9*(12), 1241-1246.

Dondorp, A., Nosten, F., Yi, P., Das, D., Phyo, A. P., Tarning, J., . . . Lee, S. J. (2009). Artemisinin resistance in Plasmodium falciparum malaria. *New England Journal of Medicine, 361*(5), 455-467.

Efunshile, A., Oduyemi, R., Igwe, D., Igwenyi, C., & Adenugba, V. (2016). Perception of the efficacy of artemisinin-based combination therapy (ACT) and chloroquine prescription pattern and among nurses in South-West Nigeria. *African Journal of Clinical and Experimental Microbiology, 17*(2), 76-82.

Ewing, V. L., Terlouw, D. J., Kapinda, A., Pace, C., Richards, E., Tolhurst, R., & Lalloo, D. G. (2015). Perceptions and utilization of the anti-malarials artemether-lumefantrine and dihydroartemisinin-piperaquine in young children in the Chikhwawa District of Malawi: a mixed methods study. *Malaria journal, 14*(1), 13.

Ezzet, F., Van Vugt, M., Nosten, F., Looareesuwan, S., & White, N. (2000). Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrobial agents and chemotherapy, 44*(3), 697-704.

Frosch, A. E., Venkatesan, M., & Laufer, M. K. (2011). Patterns of chloroquine use and resistance in sub-Saharan Africa: a systematic review of household survey and molecular data. *Malaria journal, 10*(1), 116.

Gelband, H., Panosian, C. B., & Arrow, K. J. (2004). *Saving lives, buying time: economics of malaria drugs in an age of resistance*: National Academies Press.

Gething, P. W., Casey, D. C., Weiss, D. J., Bisanzio, D., Bhatt, S., Cameron, E., . . . Rao, P. C. (2016). Mapping Plasmodium falciparum mortality in Africa between 1990 and 2015. *New England Journal of Medicine, 375*(25), 2435-2445.

Hietala, S. F., Mårtensson, A., Ngasala, B., Dahlström, S., Lindegårdh, N., Annerberg, A., . . . Björkman, A. (2010). Population pharmacokinetics and pharmacodynamics of artemether and lumefantrine during combination treatment in children with uncomplicated falciparum malaria in Tanzania. *Antimicrobial agents and chemotherapy, 54*(11), 4780-4788.

Hilal-Dandan, R., & Brunton, L. (2013). *Goodman and Gilman manual of pharmacology and therapeutics*: McGraw Hill Professional.

Jagannathan, P., Muhindo, M. K., Kakuru, A., Arinaitwe, E., Greenhouse, B., Tappero, J., . . . Dorsey, G. (2012). Increasing incidence of malaria in children despite insecticide-treated bed nets and prompt anti-malarial therapy in Tororo, Uganda. *Malaria Journal, 11*(1), 435.

Kalilani-Phiri, L. V., Lungu, D., & Coghlan, R. (2011). Knowledge and malaria treatment practices using artemisinin combination therapy (ACT) in Malawi: survey of health professionals. *Malaria journal, 10*(1), 279.

Karunamoorthi, K. (2014). The counterfeit anti-malarial is a crime against humanity: a systematic review of the scientific evidence. *Malaria Journal, 13*(1), 209.

Kassam, R., Collins, J. B., Liow, E., & Rasool, N. (2015). Narrative review of current context of malaria and management strategies in Uganda (Part I). *Acta tropica, 152*, 252-268.

Kaula, H., Buyungo, P., & Opigo, J. (2017). Private sector role, readiness and performance for malaria case management in Uganda, 2015. *Malaria journal, 16*(1), 219.

Kaur, H., Clarke, S., Lalani, M., Phanouvong, S., Guérin, P., McLoughlin, A., . . . Hopkins, H. (2016). Fake anti-malarials: start with the facts: BioMed Central.

Klayman, D. L., Lin, A. J., Acton, N., Scovill, J. P., Hoch, J. M., Milhous, W. K., . . . Dobek, A. S. (1984). Isolation of artemisinin (qinghaosu) from Artemisia annua growing in the United States. *Journal of natural products, 47*(4), 715-717.

LaCrue, A. N., Scheel, M., Kennedy, K., Kumar, N., & Kyle, D. E. (2011). Effects of artesunate on parasite recrudescence and dormancy in the rodent malaria model Plasmodium vinckei. *PLoS one, 6*(10), e26689.

Lubell, Y., Dondorp, A., Guérin, P. J., Drake, T., Meek, S., Ashley, E., . . . White, L. J. (2014). Artemisinin resistance–modelling the potential human and economic costs. *Malaria journal, 13*(1), 452.

Lwin, M. M., Sudhinaraset, M., San, A. K., & Aung, T. (2014). Improving malaria knowledge and practices in rural Myanmar through a village health worker intervention: a cross-sectional study. *Malaria Journal, 13*(1), 5.

Malimbo, M., Mugisha, E., Kato, F., Karamagi, C., & Talisuna, A. O. (2006). Caregivers' perceived treatment failure in home-based management of fever among Ugandan children aged less than five years. *Malaria journal, 5*(1), 124.

Manirakiza, A., Njuimo, S. P., Le Faou, A., Malvy, D., & Millet, P. (2010). Availability of antimalarial drugs and evaluation of the attitude and practices for the treatment of uncomplicated malaria in Bangui, Central African Republic. *Journal of tropical medicine, 2010*.

Masanja, I. M., Lutambi, A. M., & Khatib, R. A. (2012). Do health workers' preferences influence their practices? Assessment of providers' attitude and personal use of new treatment recommendations for management of uncomplicated malaria, Tanzania. *BMC Public Health, 12*(1), 956.

Mbogo, G. W., Nankoberanyi, S., Tukwasibwe, S., Baliraine, F. N., Nsobya, S. L., Conrad, M. D., . . . Staedke, S. G. (2014). Temporal changes in prevalence of molecular markers mediating antimalarial drug resistance in a high malaria transmission setting in Uganda. *The American journal of tropical medicine and hygiene, 91*(1), 54-61.

Menard, D., & Dondorp, A. (2017). Antimalarial drug resistance: a threat to malaria elimination. *Cold Spring Harbor perspectives in medicine, 7*(7), a025619.

Menard, D., Matsika-Claquin, M. D., Djalle, D., Yapou, F., Manirakiza, A., Dolmazon, V., . . . Talarmin, A. (2005). Association of failures of seven-day courses of artesunate in a non-immune population in Bangui, Central African Republic with decreased sensitivity of Plasmodium falciparum. *The American journal of tropical medicine and hygiene, 73*(3), 616-621.

Miotto, O., Almagro-Garcia, J., Manske, M., MacInnis, B., Campino, S., Rockett, K. A., . . . Sreng, S. (2013). Multiple populations of artemisinin-resistant Plasmodium falciparum in Cambodia. *Nature genetics, 45*(6), 648.

MOH. (2019). National Control Programme. Retrieved from https://health.go.ug/programs/national-malaria-control-program

Muhindo, M. K., Kakuru, A., Jagannathan, P., Talisuna, A., Osilo, E., Orukan, F., . . . Kamya, M. R. (2014). Early parasite clearance following artemisinin-based combination therapy among Ugandan children with uncomplicated Plasmodium falciparum malaria. *Malaria journal, 13*(1), 32.

Muvunyi, C. M., Masaisa, F., Bayingana, C., Mutesa, L., Musemakweri, A., & Muhirwa, G. (2011). Decreased susceptibility to commonly used antimicrobial agents in bacterial pathogens isolated from urinary tract infections in Rwanda: need for new antimicrobial guidelines. *The American journal of tropical medicine and hygiene, 84*(6), 923-928.

Nabyonga-Orem, J., Ssengooba, F., Macq, J., & Criel, B. (2014). Malaria treatment policy change in Uganda: what role did evidence play? *Malaria journal, 13*(1), 345.

Nakazawa, S., Kanbara, H., & Aikawa, M. (1995). Plasmodium falciparum: recrudescence of parasites in culture. *Experimental parasitology, 81*(4), 556-563.

Newton, P. N., Green, M. D., Mildenhall, D. C., Plançon, A., Nettey, H., Nyadong, L., . . . Powell, K. (2011). Poor quality vital anti-malarials in Africa-an urgent neglected public health priority. *Malaria journal, 10*(1), 352.

Newton, P. N., Ward, S., Angus, B. J., Chierakul, W., Dondorp, A., Ruangveerayuth, R., . . . Looareesuwan, S. (2006). Early treatment failure in severe malaria resulting from abnormally low plasma quinine concentrations. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 100*(2), 184-186.

Noedl, H., Se, Y., Schaecher, K., Smith, B. L., Socheat, D., & Fukuda, M. M. (2008). Evidence of artemisinin-resistant malaria in western Cambodia. *New England Journal of Medicine, 359*(24), 2619-2620.

Nsimba, S. E. (2006). How sulfadoxine-pyrimethamine (SP) was perceived in some rural communities after phasing out chloroquine (CQ) as a first-line drug for uncomplicated malaria in Tanzania: lessons to learn towards moving from monotherapy to fixed combination therapy. *Journal of ethnobiology and ethnomedicine, 2*(1), 5.

O'Meara, W. P., Mangeni, J. N., Steketee, R., & Greenwood, B. (2010). Changes in the burden of malaria in sub-Saharan Africa. *The Lancet infectious diseases, 10*(8), 545-555.
Onwujekwe, O., Kaur, H., Dike, N., Shu, E., Uzochukwu, B., Hanson, K., . . . Okonkwo, P. (2009). Quality of anti-malarial drugs provided by public and private healthcare providers in south-east Nigeria. *Malaria Journal, 8*(1), 22.
Orem, J. N., Mugisha, F., Okui, A. P., Musango, L., & Kirigia, J. M. (2013). Health care seeking patterns and determinants of out-of-pocket expenditure for malaria for the children under-five in Uganda. *Malaria journal, 12*(1), 175.
Phillips, M., & Phillips-Howard, P. A. (1996). Economic implications of resistance to antimalarial drugs. *Pharmacoeconomics, 10*(3), 225-238.
Rasmussen, S. A., Ceja, F. G., Conrad, M. D., Tumwebaze, P. K., Byaruhanga, O., Katairo, T., . . . Cooper, R. A. (2017). Changing antimalarial drug sensitivities in Uganda. *Antimicrobial agents and chemotherapy, 61*(12).
Rogers, W. O., Sem, R., Tero, T., Chim, P., Lim, P., Muth, S., . . . Wongsrichanalai, C. (2009). Failure of artesunate-mefloquine combination therapy for uncomplicated Plasmodium falciparum malaria in southern Cambodia. *Malaria Journal, 8*(1), 10.
Rutebemberwa, E., Pariyo, G., Peterson, S., Tomson, G., & Kallander, K. (2009). Utilization of public or private health care providers by febrile children after user fee removal in Uganda. *Malaria journal, 8*(1), 45.
Sachs, J., & Malaney, P. (2002). The economic and social burden of malaria. *Nature, 415*(6872), 680.
Shewchuk, T., O'Connell, K. A., Goodman, C., Hanson, K., Chapman, S., & Chavasse, D. (2011). The ACTwatch project: methods to describe anti-malarial markets in seven countries. *Malaria Journal, 10*(1), 325.
Slater, H. C., Griffin, J. T., Ghani, A. C., & Okell, L. C. (2016). Assessing the potential impact of artemisinin and partner drug resistance in sub-Saharan Africa. *Malaria Journal, 15*(1), 10.
Tadeg, H., & Berhane, Y. (2012). Substandard and counterfeit antimicrobials: recent trends and implications to key public health interventions in developing countries. *East African journal of public health, 9*(2), 85-89.
Takala-Harrison, S., Jacob, C. G., Arze, C., Cummings, M. P., Silva, J. C., Dondorp, A. M., . . . Noedl, H. (2014). Independent emergence of artemisinin resistance mutations among Plasmodium falciparum in Southeast Asia. *The Journal of infectious diseases, 211*(5), 670-679.
Talisuna, A. O., Bloland, P., & d'Alessandro, U. (2004). History, dynamics, and public health importance of malaria parasite resistance. *Clinical microbiology reviews, 17*(1), 235-254.
Terkuile, F., White, N., Holloway, P., Pasvol, G., & Krishna, S. (1993). Plasmodium falciparum: in vitro studies of the pharmacodynamic properties of drugs used for the treatment of severe malaria. *Experimental parasitology, 76*(1), 85-95.
Tjitra, E., Anstey, N. M., Sugiarto, P., Warikar, N., Kenangalem, E., Karyana, M., . . . Price, R. N. (2008). Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. *PLoS medicine, 5*(6), e128.
Trape, J.-F., Pison, G., Preziosi, M.-P., Enel, C., du Loû, A. D., Delaunay, V., . . . Simondon, F. (1998). Impact of chloroquine resistance on malaria mortality. *Comptes Rendus de l'Académie des Sciences-Series III-Sciences de la Vie, 321*(8), 689-697.
UBOS, U. B. o. S.-. (2017). *Uganda Demographic and Health Survey 2016* Retrieved from Calverton, Maryland, USA:
Wasunna, B., Zurovac, D., Goodman, C. A., & Snow, R. W. (2008). Why don't health workers prescribe ACT? A qualitative study of factors affecting the prescription of artemether-lumefantrine. *Malaria journal, 7*(1), 29.
WHO. (2010a). *Classification of health workforce statistics*. Retrieved from Geneva:

https://www.who.int/hrh/statistics/Health_workers_classification.pdf

WHO. (2010b). IMPACT! International medical products anti-counterfeiting taskforce. *Agenzia Italiana del Farmaco (AIFI), Roma*.

WHO. (2018). *Artemisinin resistance and artemisinin-based combination therapy efficacy: status report*. Retrieved from

WHO Antimalarial Drug Combination. (2001). Report of a WHO technical consultation. *Geneva: World Health Organization*.

Williams, H. A., & Jones, C. O. (2004). A critical review of behavioral issues related to malaria control in sub-Saharan Africa:: what contributions have social scientists made? *Social science & medicine, 59*(3), 501-523.

Wongsrichanalai, C., Pickard, A. L., Wernsdorfer, W. H., & Meshnick, S. R. (2002). Epidemiology of drug-resistant malaria. *The Lancet infectious diseases, 2*(4), 209-218.

World Health Organization. (2011). Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. *World Health Organization*, 118.

World Health Organization. (2016). *World malaria report 2015*: World Health Organization.

World Health Organization. (2018). *Summary report on the ninth intercountry meeting of national malaria programme managers from HANMAT and PIAM-Net countries Cairo, Egypt, 24–26 October 2017*. Retrieved from

Yakasai, A. M., Hamza, M., Dalhat, M. M., Bello, M., Gadanya, M. A., Yaqub, Z. M., . . . Hassan-Hanga, F. (2015). Adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria: a systematic review and meta-analysis. *Journal of tropical medicine, 2015*.

Yeka, A., Gasasira, A., Mpimbaza, A., Achan, J., Nankabirwa, J., Nsobya, S., . . . Talisuna, A. (2012). Malaria in Uganda: challenges to control on the long road to elimination: I. Epidemiology and current control efforts. *Acta tropica, 121*(3), 184-195.

Yeung, S., & White, N. J. (2005). How do patients use antimalarial drugs? A review of the evidence. *Tropical Medicine & International Health, 10*(2), 121-138.

Zwang, J., Dorsey, G., Mårtensson, A., d'Alessandro, U., Ndiaye, J.-L., Karema, C., . . . Olliaro, P. (2014). Plasmodium falciparum clearance in clinical studies of artesunate-amodiaquine and comparator treatments in sub-Saharan Africa, 1999–2009. *Malaria journal, 13*(1), 114.

APPENDIX 1: QUESTIONNAIRE

A study to evaluate perceived treatment failure of artemisinin combination therapy among healthcare providers in Kampala district.

Interviewer's Name: _____

Region: _____

Health Facility Name: _____

Date of Interview: _____/_____/_____

Healthcare provider-perceived ACT Treatment Failure: *Inadequate clinical improvement after administration of ACT as perceived by Healthcare providers.*

SECTION A: DEMOGRAPHICS

1. Gender: [1] Male [2] Female

2. Age (*in completed years*): …….

3. Education Level:
   [1] Certificate
   [2] Diploma
   [3] Bachelor
   [4] Masters
   [5] Other (*specify*)._____

4. Professional experience (Years):

5. If less than 1 year in **Q4**, state number of completed months ……..……

6. Professional Cadre:
   [1] Physician
   [2] Medical Officer
   [3] Pharmacist
   [4] Nurse
   [5] Clinical Officer
   [6] Pharmacy Technician
   [7] Other (*specify*)._____

7. Health Facility Type:
   [1] Public
   [2] Private Not-for-Profit
   [3] Private for-Profit

8. Health Facility Status: ☐
   [1] Hospital
   [2] Health Centre IV
   [3] Health Centre III
   [4] Health Centre II
   [5] Private Clinic
   [6] Pharmacy
   [7] Drug Shop
   [8] Other, (*specify*)._____

SECTION B: HEALTHCARE PROVIDER-PERCEIVED ACT FAILURE

Please, complete the questionnaire by indicating the appropriate responses.

1. What is the approximate number of malaria-patients you see per day? ……

2. In the use of ACTs in treating uncomplicated malaria, have you ever encountered any treatment failure(s) in your malaria-patients?
   [1] Yes [2] No

3. Have you suspected any ACT treatment failure in the past 4 weeks?
   [1] Yes [2] No

4. If ***YES*** to **Q3**, how many cases of ACT treatment failure? .....

5. Have you received patient-complaints of ACT treatment failure in the past 4 weeks?
   [1] Yes [2] No

6. If ***YES*** to **Q5**, how many patient-complaints of ACT treatment failure? ……..……

7. What are the commonly used ACTs at your health facility? (***Please tick all appropriate***)

Brand			Coartem	
D-Artepp (GPSC)			Lumartem	
Artequin			Malfan	
Combiart			Artem	
Ridmal			Arexel	
Glumac			Lonart	
Duocotecxin			Lumether	
P-Alaxin			Lumaren	
Artefan			Other, (*specify*)……..	

8. Which ACT brand(s) have you observed to result in treatment failure? (***Please tick all appropriate***)

Brand			Coartem	
D-Artepp (GPSC)			Lumartem	
Artequin			Malfan	
Combiart			Artem	
Ridmal			Arexel	
Glumac			Lonart	
Duocotecxin			Lumether	
P-Alaxin			Lumaren	
Artefan			Other, (*specify*) ……..	

9. Which ACT brand(s) have given satisfactory patient outcomes? (***Please tick all appropriate***)

Brand			Coartem	
D-Artepp (GPSC)			Lumertam	
Artekin			Malfan	
Combiart			Artem	
Ridmal			Arexel	
Glumac			Lonart	
Duocotecxin			Lumether	
P-Alaxin			Lumaren	
Artefan			Other, (Specify)	

10. Do you think ACT resistance is a growing concern nationally?
    [1] Yes [2] No [9] Don't Know

11. If yes to **Q19,** briefly describe why?

_____
_____
_____

12. Do you think ACT resistance is a growing concern in your institution?
    [1] Yes [2] No [9] Don't Know

13. If yes to **Q21**, briefly describe why?

_____
_____
_____

SECTION C: DRUG FACTORS RELATED TO ACT FAILURE

14. Do you think the **color** of an ACT could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

15. Briefly describe why giving examples?

_____
_____
_____

16. Do you think the **taste** of an ACT could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

17. Briefly describe why giving examples?

_____
_____
_____

18. Do you think the **size** of an ACT tablets could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

19. Briefly describe why giving examples?

_____
_____
_____

20. Do you think the number of tablets swallowed could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

21. Briefly describe why giving examples?

_____
_____
_____

22. Do you think that inadequate information about an ACT could lead to patient misuse of the drug hence treatment failure? [1] Yes [2] No

23. Briefly describe why giving examples?

_____
_____
_____

24. Do you think the dosing frequency of an ACT could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

25. Briefly describe why giving examples?

_____
_____
_____

26. What other factors in the practice of <u>patients</u> are responsible for the poor response of patients to ACT? (***Please briefly outline***)

_____
_____
_____
_____

27. What other factors in the practice of <u>healthcare providers</u> are responsible for the poor response of patients to ACT? (***Please briefly outline***)

_____
_____
_____
_____

We appreciate your time taken to respond to this questionnaire. Thank you

APPENDIX 2: INFORMATION SHEET AND CONSENT FORM

Information Sheet

Study Title: Perceived Treatment Failure of Artemisinin Combination Therapy Among Healthcare Providers in Kampala District

Principal Investigator: Ms. Nabirye Leah, MSc Pharmacology, MakCHS

Introduction
Artemisinin combination therapies have over the years been associated with the global and national reduction in the prevalence of malaria. Currently in Uganda, they are considered a first line medicine for the management of uncomplicated malaria (UCG 2016). However, reports from South-east Asia indicate the development of artemisinin resistant malaria parasites, which is attributed to ACT overuse. There is no data to ascertain the status of ACT sensitivity patterns in Uganda. Therefore, this study seeks to establish the healthcare provider-perceived treatment failure rates of commonly used ACTs and the factors related to the perceived treatment failure.

Why have you been invited to participate?
You have been asked to participate in the study because of your role as a prescribing healthcare provider who also does follow-up on treatment outcomes of the prescriptions.

What will happen to you during the study?
You will be expected to complete a pre-formulated self-administered questionnaire intended to capture the above information.

What are the risks of taking part in this study?
None at all!, since all respondent's individual identities will be kept anonymous

What are the possible benefits of taking part in the study?
There are no direct benefits for participating in the study, although based on findings from the study both policy and malaria treatment guidelines may be improved resulting into better care for malaria patients in Uganda and rest of sub-Saharan Africa.

Costs/Payments
The study will not offer financial benefits but compensations for time: UGX 10,000 will be made

What if I have questions about the study or my participation during the study period?
If you a question, concern or complaint about the study, you should speak to any member of the study team who will do their best to address your concerns. You can also call Nabirye Leah, the principal investigator of the study on 0701405133.

If for any reason you do not want to discuss your concern or complaint with the study team and the principal investigator, you may contact Dr. Erisa Mwaka (0752575050), the Chairman of Makerere University School of Biomedical Sciences Research and Ethics Committee.

What will happen if I do not participate in the study?

Nothing at all!

Do I have a right to withdraw consent of participation?

Yes, if for any reason, you wish to withdraw your participation from the study at any time you are absolutely free to do it. To or not to disclose the reasons for the withdrawal will be at your discretion.

Will information about me be kept anonymous?

Yes, all information concerning your identity will be kept anonymous.

Thank you for reading this and considering taking part in this study.

Consent form

I confirm that I have read and understood the information sheet for the above study and have had enough time to think about my participation in it.

- I am satisfied with the answers given to all my questions
- I voluntarily agree to participate in the study, to follow the procedures and to provide the information requested for by the research team
- I understand that I am free to withdraw my participation from the study without obligation to justify my decision and that this will not affect the routine care in any way.
- I have received a copy of the study information sheet and a copy of the signed consent for my record.
- I understand I may also be contacted at a later date(s) in connection with this study or any other related study.
- By signing this document, I agree to take part in this study as set out in the information sheet and this consent form

.....
Name of participant (In Print)
.

.....
Signature or finger print of participant Date / time

.....
Name (In Print) and signature of Study Staff administering the consent Date / time

APPENDIX 3: STUDY SITES

NO	HEALTH UNIT	FACILITY TYPE

	KAMPALA CENTRAL DIVISION	
1	NAKASERO HOSPITAL	PRIVATE FOR PROFIT, HOSPITAL
2	MARANATHA PHARMACY	PRIVATE FOR PROFIT, PHARMACY
3	PINE PHARMACY	PRIVATE FOR PROFIT, PHARMACY
4	MELAIN PHARMACY	PRIVATE FOR PROFIT, PHARMACY
5	SPRING PHARMACY	PRIVATE FOR PROFIT, PHARMACY
6	CEDAR PHARMACY	PRIVATE FOR PROFIT, PHARMACY
7	ABACUS PHARMACY	PRIVATE FOR PROFIT, PHARMACY
8	SURU PHARMACY	PRIVATE FOR PROFIT, PHARMACY
9	MOKAS PHARMACY	PRIVATE FOR PROFIT, PHARMACY
10	ZAM ZAM CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
11	KOLOLO HOSPITAL KAMPALA	PRIVATE FOR PROFIT, HOSPITAL
12	CHURCH ROAD CLINIC	PRIVATE FOR PROFIT, DRUG SHOP
13	ST CATHERINE'S HOSPITAL	PRIVATE FOR PROFIT, HOSPITAL
14	KAMPALA HOSPITAL	PRIVATE FOR PROFIT, HOSPITAL
15	NORVICK HOSPITAL	PRIVATE FOR PROFIT, HOSPITAL
16	CASE HOSPITAL	PRIVATE FOR PROFIT, HOSPITAL
17	KAMPALA MEDICAL CHAMBERS	PRIVATE FOR PROFIT, HOSPITAL
18	OLD KAMPALA HOSPITAL	GOVERNMENT, HOSPITAL
19	**AGA KHAN UNIVERSITY HOSPITAL (SELECTED HOSPITAL, BED CAPACITY = 150)**	**PRIVATE FOR PROFIT, HOSPITAL**
	KAWEMPE DIVISION	
1	**MULAGO REFERRAL HOSPITAL (SELECTED HOSPITAL, BED CAPACITY >1000)**	**GOVERNMENT, HOSPITAL**
2	AKRAM PHARMACY	PRIVATE FOR PROFIT, PHARMACY
3	JOSH PHARMACY	PRIVATE FOR PROFIT, PHARMACY
4	TRINITY PHARMACY	PRIVATE FOR PROFIT, PHARMACY
5	FIRST PHARMACY	PRIVATE FOR PROFIT, PHARMACY
6	GERNASSA PHARMACY	PRIVATE FOR PROFIT, PHARMACY
7	NUMACK PHARMACY	PRIVATE FOR PROFIT, PHARMACY
8	MULAGO HOSPITAL, KAWEMPE	GOVERNMENT, HOSPITAL
9	FRIECCA PHARMACY	PRIVATE FOR PROFIT, PHARMACY
10	MM PHARMACY	PRIVATE FOR PROFIT, PHARMACY
11	DISCHEM PHARMACY	PRIVATE FOR PROFIT, PHARMACY
12	DESIRE PHARMACY	PRIVATE FOR PROFIT, PHARMACY
13	PRIME CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
14	DEVINE CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
15	ABII CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
16	PLUS MEDIC PHARMACY	PRIVATE FOR PROFIT, PHARMACY
17	JICCA CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
18	LIFELINE MEDICAL CENTER	PRIVATE FOR PROFIT, PRIVATE CLINIC
	MAKINDYE DIVISION	
1	GENESIS HEALTH MEDICAL CENTRE	PRIVATE FOR PROFIT, HEALTH CENTRE II
2	CARE MEDICAL CENTRE	PRIVATE FOR PROFIT, HEALTH CENTRE II
3	**NSAMBYA HOSPITAL (SELECTED HOSPITAL, BED CAPACITY > 540)**	**PRIVATE NOT-FOR-PROFIT, HOSPITAL**
4	KIBULI MOSLEM HOSPITAL	PRIVATE NOT-FOR-PROFIT, HOSPITAL
5	KAMPALA FAMILY CLINIC	PRIVATE FOR PROFIT, HOSPITAL

6	ALIVE MEDICAL SERVICES	PRIVATE FOR PROFIT, PRIVATE CLINIC
7	MOTHER MARY CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
8	ALL SAINTS D/S	PRIVATE FOR PROFIT, DRUG SHOP
9	GILEAD PHARMACY	PRIVATE FOR PROFIT, PHARMACY
10	PARAM PHARMACY	PRIVATE FOR PROFIT, PHARMACY
11	CORNERSTONE MEDICAL CENTRE	PRIVATE FOR PROFIT, PRIVATE CLINIC
12	ROPHE AMADEO PHARMACY	PRIVATE FOR PROFIT, PHARMACY
13	ROKANA PHARMACY	PRIVATE FOR PROFIT, PHARMACY
14	KINGS MEDICAL SERVICES	PRIVATE FOR PROFIT, HEALTH CENTRE II
15	MALCOLM PHARMACY	PRIVATE FOR PROFIT, PHARMACY
16	PATIENCE DOMICILIARY CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
17	ST LUKE MEDICAL CENTER	GOVERNMENT, HEALTH CENTRE
18	JOVAN MEDICAL CENTER	PRIVATE FOR PROFIT, PRIVATE CLINIC
19	INTERNATIONAL HOSPITAL KAMPALA	PRIVATE FOR PROFIT, HOSPITAL
	RUBAGA DIVISION	
1	RUBAGA HOSPITAL	PRIVATE NOT-FOR-PROFIT, HOSPITAL
2	RUBAGA ROAD PHARMACY	PRIVATE FOR PROFIT, PHARMACY
3	LIFE CARE CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
4	**MENGO HOSPITAL (SELECTED HOSPITAL, BED CAPACITY = 300)**	**PRIVATE NOT-FOR-PROFIT, HOSPITAL**
5	JK MEDICAL CENTRE	PRIVATE FOR PROFIT, PRIVATE CLINIC
6	ZEBRAWOOD PHARMACY	PRIVATE FOR PROFIT, PHARMACY
7	UMOJA PHARMACY	PRIVATE FOR PROFIT, PHARMACY
8	ALPHA MEDICAL CENTER	PRIVATE FOR PROFIT, PRIVATE CLINIC
9	CEDAR PHARMACY	PRIVATE FOR PROFIT, PHARMACY
10	LITE HEALTH CENTER II	PRIVATE FOR PROFIT, PRIVATE CLINIC
11	SUUBI MEDICAL CENTER	PRIVATE FOR PROFIT, PRIVATE CLINIC
12	ROYAL MEDICAL CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
13	VISION MEDICAL CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC
14	A&A MEDICOR PHARMACY	PRIVATE FOR PROFIT, PHARMACY
15	DAKA MEDICAL CENTRE	PRIVATE NOT-FOR-PROFIT, PRIVATE CLINIC
16	VICTORY HEALTH CARE	PRIVATE FOR PROFIT, PRIVATE CLINIC
17	AISHA DRUG SHOP	PRIVATE FOR PROFIT, DRUG SHOP
18	ECOPHARM PHARMACY	PRIVATE FOR PROFIT, PHARMACY
	NAKAWA DIVISION	
1	KISWA HEALTH CENTRE	GOVERNMENT, HEALTH CENTRE III
2	**NAGURU HOSPITAL (SELECTED HOSPITAL, BED CAPACITY = 100)**	**GOVERNMENT, HOSPITAL**
3	MEDEXPRESS MEDICAL CENTRE	PRIVATE FOR PROFIT, PRIVATE CLINIC
4	NIM MEDICINE CENTRE	PRIVATE FOR PROFIT, PRIVATE CLINIC
5	NIM PHARMACY	PRIVATE FOR PROFIT, PHARMACY
6	PHERRY MEDIC PHARMACY	PRIVATE FOR PROFIT, PHARMACY
7	C AND A PHARMACY	PRIVATE FOR PROFIT, PHARMACY
8	VANGUARD PHARMACY	PRIVATE FOR PROFIT, PHARMACY
9	GUARDIAN HEALTH PHARMACY	PRIVATE FOR PROFIT, PHARMACY
10	GENERAL MEDICAL CARE	PRIVATE FOR PROFIT, PRIVATE CLINIC
11	DAWA PHARMACY	PRIVATE FOR PROFIT, PHARMACY
12	GITTOES	PRIVATE FOR PROFIT, PHARMACY
13	BANDA HEALTH CARE	PRIVATE FOR PROFIT, PRIVATE CLINIC
14	MAMA ZAM CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC

15	BANDA HEALTH CENTER	PRIVATE FOR PROFIT, HEALTH CENTRE II
16	KIREKA HEALTH CENTER II	GOVERNMENT, HEALTH CENTRE II
17	KIREKA MEDICAL CENTER	PRIVATE FOR PROFIT, PRIVATE CLINIC
18	NAKAWA MEDICAL CLINIC	PRIVATE FOR PROFIT, DRUG SHOP
19	PULSE MEDICAL CLINIC	PRIVATE FOR PROFIT, PRIVATE CLINIC