ACEPTABILITY, ADHERENCE, AND CLINICAL OUTCOMES, OF AMOXICILLIN DISPERSIBLE TABLETS VERSUS ORAL SUSPENSION IN CHILDREN AGED 2-59 MONTHS WITH PNEUMONIA, KENYA.

BY

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A THESIS SUBMITTED IN PARTIAL FULFILMENT FOR THE REQUIREMENTS OF THE DEGREE OF MASTER OF PUBLIC HEALTH (HEALTH PROMOTION)

SCHOOL OF PUBLIC HEALTH AND COMMUNITY DEVELOPMENT

MASENO UNIVERSITY

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DECLARATIONS

I declare that this thesis is my original work and has not been previously presented for a Masters' degree in Maseno University or in any other University. The work herein has all sources of information supported by relevant references.

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ACKNOWLEDGEMENT

I would like to thank the persons mentioned below in a special way:

My supervisors: Prof. Collins Ouma and Dr. Maricianah Onono, thank you for your insightful suggestions and critical reviews on the proposal and thesis. Thank you for all the support that you have given me throughout my graduate studies. Your great support throughout the period of writing the thesis and in making the final preparation is highly appreciated.

KEMRI/RCTP for funding the research. This study would not have been possible without their support.

The study participants and research assistants for the study: caregivers, children, community health workers, quality assurance nurses who generously shared their experience and KEMRI/RCTP staff for their time and support.

Faculty at Department of Public Health Sciences, thank you for all the support you gave me throughout my graduate education.

DEDICATION

This work is dedicated to my father, Mr. Moffat Obutinda who has always loved me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve and my late mother, Mrs. Grace Obutinda who could not see this thesis completed.

ABSTRACT

Amoxicillin dispersible tablet (DT) is now recommended by the World Health Organization as a first line product for treatment of pneumonia in children below 5 years. This formulation, is however, not readily available in most of Africa. The main aim of this study was to compare the acceptability, adherence and clinical outcome of amoxicillin dispersible tablets to that of the conventional Amoxicillin oral suspension (OS) in treatment of children aged 2-59 months with pneumonia in Kenya. The study was conducted to inform national roll out of the amoxicillin DT in Kenya. The study employed a two arm cluster randomized controlled trial and utilized quantitative methods in Homa Bay County, Kenya. The community unit (CU) was the unit of implementation and thus the unit of randomization. Children aged 2-59 months with pneumonia were enrolled into the study and depending on which CU they lived, were treated with either amoxicillin DT or OS. Children were then followed up on day 4 and day 6. Acceptability was measured as the proportion of children to whom treatment was considered acceptable defined by perception of taste of the medication given to the child as same or better compared to other medicines and expression of willingness of caregivers to use DT/OS in future, Adherence was measured as the proportion of children who adhered to treatment based on dose given, treatment duration, frequency of daily administration and tablet preparation/suspension reconstitution, and Clinical outcome was measured as complete resolution of symptoms on day 6 without a change of antibiotic treatment. The sample size was 346 children. Differences in acceptability between children put on DT compared to those on OS were assessed using chi-square test. Multivariate logistic regression accounting for clustering was used to assess the differences in treatment adherence and treatment outcomes between children put on DT compared to those on OS (reporting odds ratios and 95% confidence interval bounds). Statistical analysis was performed using SAS and a p-value of less than 0.05 used to define statistical significance. There were high levels of 'good acceptability' among both the caregivers administering DT and OS (94% vs. 96%, respectively) (p=0.49). The likelihood of objectively measured adherence on the fourth-day and overall objectively measured adherence, were significantly higher among children put on DT compared to children on OS (OR=13.54, 95% CI=7.74-23.69, p<0.01 & OR=10.51, 95% CI=6.28-17.59, p<0.01, respectively). Cure rates were high in both children put on DT and those put on OS (99% vs. 97%, respectively) and the difference was not statistically significant. These results indicate that Amoxicillin dispersible tablets is as acceptable and as effective as the oral suspension in the treatment of pneumonia in children aged 2-59 months, but has better treatment adherence. Given the higher adherence rates and equivalence in effectiveness and acceptability, I recommend that Amoxicillin dispersible tablet be preferentially prescribed over the oral suspension for the treatment of pneumonia in children aged 2-59 months.

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LIST OF ABBREVIATIONS

AIDS	—	Acquired immunodeficiency Syndrome
AL	—	Artemether-Lumefantrine
CCM	—	Community Case Management
CHEW	—	Community Health Extension Worker
CHW	—	Community Health Worker
DP	—	Dihydroartemisinin-piperaquine
DT	—	Dispersible Tablet
EML	—	Essential Medicines List
HIV	—	Human Immunodeficiency Virus
ICCM	—	Integrated Community Case Management
IMCI	—	Integrated Management of Childhood Illness
KEMRI	—	Kenya Medical Research Institute
LCI	—	Lower Chest In-drawing
MOH	—	Ministry of Health
OS	—	Oral Suspension
RCPT	—	Research Care and Training Program
UN	—	United Nations
UNICEF	—	United Nations Children's Fund
WHO	—	World Health Organization

OPERATIONAL DEFINITIONS

Pneumonia: Pneumonia is an infection that inflames the air sacs in one or both lungs. The air sacs may fill with fluid or pus (purulent material), causing cough with phlegm or pus, fever, chills, and difficulty breathing. A variety of organisms, including bacteria, viruses and fungi, can cause pneumonia (Mayo Clinic, 2017).

Appropriate treatment: Receiving the recommended drug, in the recommended dose, and for the recommended frequency, and duration (Nsungwa-Sabiiti *et al*., 2007).

Community Health Workers (CHWs): These are persons selected from the communities in which they live and work; they are selected by and are answerable to the communities, are supported by the health system, and undergo shorter training than professional health workers (Sanders & Lehmann, 2007).

Adherence to medicines: The extent to which a person's behavior in taking medicines corresponds with agreed recommendations from a health care provider (Osterberg & Blaschke, 2005; Sabaté, 2003).

Integrated community case management (iCCM): Integrated Community Case Management (iCCM) is an equity-focused strategy to improve access to essential treatment services for pneumonia malaria and diarrhea in sick children aged 2-59 months (Young *et al*., 2012).

Community Case Management: The community-level provision to children of curative treatments for diarrhoea, pneumonia, malaria and/or neonatal infections by community health workers (CHWs) (Sousa *et al*., 2012).

Dispersible Tablet: Uncoated or coated tablets that can be dispersed in liquid before administration resulting in a homogenous dispersion. Dispersible tablets usually disintegrate within three minutes when put in water or a small amount of breast milk (UNICEF, 2013b).

Oral Suspension: a suspension consisting of undissolved particles of one or more medicinal agents suspended in a liquid vehicle using a suspending agent for oral administration (Merriam-Webster, 2017).

Clinical outcome: Broadly agreed, measurable changes in health or quality of life that result from our care (Great Ormond Street Hospital for Children, 2017).

Conventional: Based on or in accordance with what is generally done or believed (Oxford, 2017).

Palatability: The overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e. feeling in the mouth). It is determined by the characteristics of the active substance, the way the active substance is formulated into a finished medicinal product and by the characteristics of the excipients (EMA, 2013).

Flexible Solid Oral Dosage Forms: These are solid dosage forms that do not have to be swallowed whole such as dispersible tablets, effervescent tablets, chewable tablets, orodispersible tablet and sprinkle capsules (World Health Organization, 2014b: Orubu & Tuleu, 2017).

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CHAPTER ONE

INTRODUCTION

1.1: Background Information

Pneumonia, Malaria, and Diarrhea remain the leading cause of morbidity and mortality in children under 5 years in Sub-Saharan Africa. Although there exist known interventions, lack of prompt access to qualified medical attention and these effective interventions is still a major limitation to achieving a reduction in morbidity and mortality. As such, there has been increasing importance placed on early and appropriate treatment of malaria and pneumonia within the community, and if possible within the child's own home. Integrated Community Case Management (iCCM) an initiative of UNICEF and the Government of Kenya is a blueprint to expand case management of childhood illness beyond health facilities in areas where access to facility-based services is limited so that more children have access to lifesaving treatments. Essential iCCM interventions include oral antibiotics for pneumonia, rapid diagnostic tests and antimalarials (principally artemisinin-based combination therapy) for malaria, and oral rehydration salt (ORS) and zinc for diarrhea. Seventy percent of pneumonia-related mortality in children under-five can be prevented by implementing iCCM of pneumonia (Theodoratou *et al*., 2010). iCCM is implemented through Community Health Workers (CHWs) linked to existing health facilities. These CHWs undertake short courses, normally provided either by the ministry of health staff or Non-Governmental Organizations, to enable them obtain the requisite skills and knowledge to provide appropriate care. Studies have shown that CHWs can successfully diagnose and treat child pneumonia, malaria, and diarrhea using interventions such as ORS and zinc for diarrhea, antibiotics for pneumonia, and antimalarials for malaria.

Pneumonia is the leading cause of under-five child mortality globally, with an estimated 1.2 million deaths annually. About 60% occur in just ten countries: Bangladesh, D.R. Congo, Ethiopia, India, Kenya, Niger, Nigeria, Pakistan, Tanzania and Uganda (Theodoratou *et al.*, 2010). In Kenya, pneumonia is the leading cause of death dislodging malaria as the top killer (Njiru, 2017). In Nyanza, Homa Bay County has the highest percentage of acute respiratory tract infections (12.8%) (Demographic, 2014). Studies have shown that prevention and treatment of pneumonia would prevent one million deaths among children each year. Remarkable achievements have been made that are bringing lifesaving vaccines to the developing world. In addition to vaccines, effective and low cost treatment for the disease e.g. oral amoxicillin are also helping to fight pneumonia. Despite these strides there are several challenges in Africa which include poor nutrition, crowding, poverty, inadequate immunizations and settings with poor access to healthcare (Adegbola, 2012). Many children in developing countries are unable to access health facilities. A recent study has shown that treating children at home with an oral antibiotic is as effective as treatment at a health facility (Global Health Technologies Colition, 2011).

Amoxicillin, a broad-spectrum antibiotic is often prescribed to children for the treatment of pneumonia and several other bacterial illnesses. Studies have demonstrated greater effectiveness in the treatment of children who have severe cases of pneumonia with amoxicillin compared to co-trimoxazole by 4% to 15% (Grant *et al.*, 2009). A five-day course of oral amoxicillin was also found to be as safe and clinically as effective as a referral to a health facility or care provider (Soofi *et al.*, 2012). Amoxicillin is a low cost

(estimated \$0.21-0.42 per treatment course) (Jonathan & Stoltenberg, 2012), highly effective antibiotic treatment which could prevent the death of up to 1.56 million children over five years (UNICEF, 2012). Amoxicillin is available in capsules, tablets, oral suspension powder, syrup, oral drops and dispersible tablets formulations.

Effective drug administration in children requires formulations, which allow for critical weight or age- based dosing. With syrups and suspensions this is often done as full, half, or quarter spoonfuls, which has been shown to be inaccurate (Grießmann, *et al*., 2007). An alternative is to dispense measured syringes alongside medications. For decades, oral liquid dosage forms, such as syrups and suspensions, have been considered as favorable type of dosage form in which to administer medicines to children (Nunn & Williams, 2005) . Although they are considered simple to administer and the dose can easily be changed, they also have major disadvantages such as chemical, physical or microbial instability, taste issues, portability problems or refrigerated storage conditions and lack of controlled release properties (Cohen *et al*., 2009; Walsh *et al*., 2011; Spomer *et al*., 2012). Substances or excipients used to solubilize the active ingredient or ensure microbial stability in oral liquids may be harmful to young children (Fabiano, Mameli & Zuccotti, 2011). Liquid medicines tend to be more expensive than solid medicines and this makes them less accessible to patients who pay for medicines out-of-pocket (Orubu & Tuleu, 2017). Drug cost savings would be considerable if oral liquid formulations were substituted with suitable solid dosage forms (Lajoinie *et al*, 2016).

The purpose of good pediatric formulations is to achieve safe and accurate dose administration, reduce the risks of medication errors and enhance medication compliance (Ernest *et al*., 2007). Many existing formulations are not suitable for children, which often leads to off-label and unlicensed use of adult medicines (Ivanovska *et al*., 2014). The World Health Organization now recommends that where available, dispersible tablets should be chosen above suspensions due to advantages in dosing, stability, storage, cost and transportation (Nunn & Williams, 2005; EMEA, 2006; World Health Organization, 2009; Lajoinie *et al*., 2016).

Studies carried out have reported that dispersible tablets are acceptable to children and do not back the historic approach that medicines should conventionally be given to young children as an oral liquid formulation as other formulation may result in equivalent acceptability (Ahmed *et al*., 2013; van Riet-Nales *et al*., 2013; Ogutu *et al*., 2014) . Many of these studies on acceptability have been conducted in Western populations, and as such, there is a need for acceptability studies to be conducted in areas where the products will be distributed globally (EMA, 2013; Mistry & Batchelor, 2017). These studies have also not identified a defined methodology or standard to support acceptability claims in pediatric products. While the use of amoxicillin dispersible tablet (DT) has been promoted by WHO, its acceptability versus that of oral suspension (OS) remains unknown in children aged 2-59 months. As such, this study was designed to determine the acceptability of amoxicillin dispersible tablets and amoxicillin oral suspension formulation in children aged 2-59 months with pneumonia in Kenya.

One of the essential determinants of clinical success is the extent to which any patient adheres to a medical regimen (Gardiner & Dvorkin, 2006). There is strong evidence that medication non-adherence is prevalent and associated with adverse outcomes and higher costs of care (Dawood *et al*., 2012). DT and Orally Disintegrating Tablets (ODTs) may allow improved patient compliance, in particular with pediatric, geriatric, and institutionalized patients (Velmurugan & Vinushitha, 2010). Different methods have been used to assess adherence in clinical trials but there is no method identified as the 'gold standard' for this purpose. It is important to adopt objective tools in Randomized Controlled Trials to facilitate better interpretation of study outcomes (Abbeddou *et al*.,2015). There has been no direct comparison of the adherence rates to amoxicillin DT compared to those of OS in children aged 2-59 months in Kenya. This study therefore, sought to compare the adherence rates of amoxicillin dispersible tablets and amoxicillin oral suspension formulation in children aged 2-59 months with pneumonia in Kenya.

Dispersible pediatric tablets have many potential advantages over traditional suspensions and are now preferentially recommended by the World Health Organization where available (Afriyie, Danquah, & Buabeng, 2013). The use of DT versus OS is beneficial as it reduces the risk of dosing errors observed when administering OS (Dhaon, 2004; UNICEF, 2013a) and is, therefore, likely to improve the clinical outcome. However, comparative clinical outcomes of amoxicillin dispersible tablet versus the oral suspension in children aged 2-59 months have not been studied in Kenya. As such, this study compared the treatment outcomes for amoxicillin dispersible tablets and amoxicillin oral suspension formulation in children aged 2-59 months with pneumonia in Kenya. In addition, despite

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the comparatively lower costs of amoxicillin dispersible tablets, the Kenya essential medicines list still, does not include amoxicillin dispersible tablets. There is therefore a need to provide evidence for the need to transition from amoxicillin OS to amoxicillin DT. Providing this evidence would directly influence the adherence behavior of caregivers and promote the health of sick children under 5 with pneumonia.

1.2: Problem statement

Under-five mortality in Homa Bay County is 91/1000 compared to the National average of 52/1000. This implies that 1 in every 11 children born in Homa Bay County does not survive to his or her fifth birthday. Among the most critical health conditions for children is pneumonia which accounts for 10% of all morbidity (County Government of Homa Bay., 2013). The most serious barriers to the availability of child health services in Homa Bay are inadequate human resources, poor service integration and lack of quality care. Despite an adequate number of health facilities, Homa Bay County suffers from inequities in health worker distribution with an average of 4 doctors and 51 nurses per 100,000 populations. To address the inequitable provision of services and the high under- five mortality, Homa Bay was selected to receive the iCCM intervention. Apart from the high under-five mortality, the study was done in Homa Bay because it is the only county in Kenya that has been approved to implement integrated community case management of pneumonia with full coverage of community health units including over 2,600 community health workers (CHWs) and 200 community health extension workers (CHEWs) who have been trained in iCCM. Each CHW covers 50-100 households while 10-20 CHWs are supervised by one

CHEW. One of the current challenges in resource-constrained settings is the suitability of existing formulations of amoxicillin for children.

1.3: Objectives

1.3.1: Broad objective

To assess the acceptability, adherence rates, and clinical outcomes of amoxicillin dispersible tablets versus oral suspension in children aged 2-59 months with pneumonia on day 4 and day 6 after initiation of treatment in Homa Bay County, Kenya.

1.3.2: Specific objectives

1. To determine the level of acceptability of amoxicillin dispersible tablets and amoxicillin oral suspension formulations in a population of children aged 2-59 months with pneumonia on day 6 after initiation of treatment in Homa Bay County, Kenya.

2. To compare the adherence rates of amoxicillin dispersible tablets and amoxicillin oral suspension formulations in a population of children aged 2-59 months with pneumonia on day 4 and day 6 after initiation of treatment in Homa Bay County, Kenya.

3. To compare treatment outcomes for amoxicillin dispersible tablets and amoxicillin oral suspension formulations in a population of children aged 2-59 months with pneumonia on day 4 and day 6 after initiation of treatmentin Homa Bay County, Kenya.

1.3.3: Research questions

1. What is the level of acceptability of amoxicillin dispersible tablets and amoxicillin oral suspension formulations in a population of children aged 2-59 months with pneumonia on day 6 after initiation of treatment in Homa Bay County, Kenya?

2. What is the rate of adherence of amoxicillin dispersible tablets and amoxicillin oral suspension formulations in a population of children aged 2-59 months with pneumonia on day 4 and day 6 after initiation of treatment in Homa Bay County, Kenya?

3. What are the treatment outcomes for amoxicillin dispersible tablets and amoxicillin oral suspension formulations in a population of children aged 2-59 months with pneumonia on day 4 and day 6 after initiation of treatment in Homa Bay County, Kenya?

1.4: Significance of the study

It is important that the pediatric formulations offer flexibility for dose adjustment, while at the same time remaining within the effective therapeutic range. This reduces the possible risk of microbial resistance with under-dosing, and of toxicity with over-dosing. Use of oral solid medicines, such as powders or tablets can avoid these disadvantages. This is in line with the World Health Organization recommendation that where available DT should be chosen above suspensions due to advantages in dosing, storage, and transportation (WHO, 2009). The dosage of amoxicillin for treatment of pneumonia has been revised from 45mg/kg/day to 80 - 90mg/kg/day, this means that the children will be required to take larger volumes of the OS which has potential to reduce the adherence rates. Dosing of OS using household spoons and measuring devices provided with the product may constitute a remarkable source of lack of dosing accuracy. Even though UNICEF, independently and through partnership with the UN Commission on Life-Saving Commodities for Women and Children, is supporting the scale-up of limited access and use of amoxicillin DT (UNICEF, 2013a), this has not been included the national guidelines for treatment of pneumonia in Kenya. A study comparing the acceptability, adherence and

clinical outcomes of amoxicillin dispersible tablet and oral suspension was needed to help the Kenyan government in making necessary changes in policies dealing with antibiotic use for the treatment of pneumonia in children, budgeting and supply of appropriate antibiotic formulation to improve adherence to antibiotics hence reducing drug resistance and improving the clinical outcome.

CHAPTER TWO

LITERATURE REVIEW

2.1: Introduction

Pneumonia is one of the world's leading causes of morbidity and mortality in children, which causes approximately 1·6 million child deaths per year (Black *et al*., 2010). Over 150 million cases of pneumonia occur yearly, with most deaths occurring in sub-Saharan Africa and South Asia (Rudan *et al*., 2008; Duthey, 2013). In 2015, 920,000 children under the age of five died of pneumonia globally, which translate to approximately 2,500 young lives per day (UNICEF, 2015). Pneumonia accounts for around 30,000 of the 124,000 under-five child deaths in Kenya each year (Manuel & Kyle, 2011).

The worldwide burden of childhood mortality due to pneumonia in the early 1980s prompted the World Health Organization (WHO) to come up with a pneumonia control strategy appropriate for resource-constrained countries and health systems (WHO, 2014b). The management of pneumonia cases formed the basis of this strategy. The cornerstone of pneumonia control strategies is community-based case management (UNICEF & World Health Organization, 2013). It involves classifying the severity of illness using simple clinical signs such as fast breathing, chest indrawing, and general danger signs (convulsions, lethargy or reduced level of consciousness, inability to drink or vomits everything), and then applying the appropriate treatment. Management includes home care advice, antibiotics for home therapy, or referral to a higher-level health facility. WHO, IMCI recommends 5 days course of amoxicillin for the treatment of pneumonia due to its efficacy and increasing high resistance to co-trimoxazole (World Health Organization,

2014a). Community case management of pneumonia, could reduce the improper use of antibiotics for cough and cold and increase their proper use for algorithm-positive pneumonia provided that supervision reinforces CHW performance (Gouws *et al*., 2004; Marsh *et al*., 2008). Expanding and reinforcing existing facility-based health care and introducing and/or scaling-up CCM of pneumonia are the key challenges to increasing coverage of appropriate treatment for childhood pneumonia (Marsh *et al*., 2008).

Over the years, development of revised guidelines has been prompted by new evidence that has emerged. The changes are a result of new evidence generated from research carried out in the last decade in low and middle-income countries which have the highest burden of pneumonia mortality (World Health Organization, 2014b). A study on clinical efficacy of co-trimoxazole versus amoxicillin twice daily for treatment of pneumonia in Pakistan concluded that the formulations were equally efficacious in non-severe pneumonia (Catchup Study Group, 2002). Another study carried out in India to determine the clinical effectiveness of co-trimoxazole versus amoxicillin in the treatment of non-severe pneumonia in children reported that compliance to amoxicillin was slightly poor and cost of treatment high, but the response to treatment was faster. It further recommended that further studies are required to establish the efficacy of amoxicillin in high dosage over a short duration of time and better counseling needed in order to improve the compliance (Rajesh & Singhal, 2013). A study on clinical effectiveness of 3 days versus 5 days of oral amoxicillin for treatment of pneumonia in children conducted by Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group concluded that 3 days treatment with oral amoxicillin was equally as effective as 5 days treatment in children

with non-severe pneumonia (Pneumonia Study Group, 2002). Amoxicillin formulation used in these studies was not indicated. Integrated Management of Childhood Illness (IMCI) at the level of the health facility has been updated appropriately. Some of the new recommendations include increasing the dose of amoxicillin from 45mg/kg/day to 80-90mg/kg/day in children age 2–59 months with chest indrawing pneumonia and the use of flexible solid dosage forms, such as dispersible tablets (World Health Organization, 2014b). Results from a study on Flexible Solid Oral Dosage (FSOD) forms as the preferred formulations for children suggested that the WHO proposal of FSOD forms as the preferred formulations for children is a viable modality to increase access to age-appropriate medicines for children under the age of 5 years (Orubu, 2016).

Adherence and acceptability influence clinical outcome. The widespread assumption that medicines for children should be liquid by both end-users and clinicians, even in the presence of well-known efficacious alternative formulations is one of the issues affecting adherence and acceptability. One of the current challenges is the suitability of existing formulations of amoxicillin for children in limited-resource settings (Schirm *et al*., 2003). It is generally believed that children prefer the liquid formulation. Although liquid formulations make weight-based dosing much easier, the accurate administration of a liquid medicine is not assured even when the dose is correctly calculated. There is evidence that significant under or over-dosing can occur because of the inaccuracy of measuring spoons and other devices supplied with liquid medicines (Grießmann, *et al*., 2007; Falagas *et al*., 2010). The WHO endorsed 'Flexible Solid Oral Dosage' forms as the ideal oral formulation for children's medicines, as they are less bulky to ship and store and have

better stability and shelf life as compared to liquids (World Health Organizatonema, 2011). Despite this knowledge, liquid formulations continue to be the predominant formulation procured and dispensed. One of the reasons for this might be that, the clinical outcome, adherence, and acceptability of amoxicillin dispersible tablets versus the oral suspension in children aged 2-59 months has not been studied. As such this study determined the clinical outcome, adherence rate and acceptability of the dispersible tablet versus the oral suspension in children aged 2-59 months in Homa Bay County, Kenya.

2.2: Acceptability

Acceptability has been defined as 'the overall ability and willingness' of the patient and their caregiver to administer the medicines as intended (van Riet-Nales *et al*., 2012). There is much evidence to support the need for age-appropriate medicines to treat paediatric patients. The acceptability of a product needs to be clearly defined for paediatric populations and this is currently an area of great interest (Mistry & Batchelor, 2017).

Before the regulatory change in the latest European Paediatric guideline on pharmaceutical development of formulations for paediatric use, there was no requirement for medicines to be demonstrated to be acceptable to children (EMA, 2013). Patient acceptability is likely to have a significant impact on patient adherence and consequently, on the safety and efficacy of a medicinal product (Mistry & Batchelor, 2017). Acceptability therefore, must be an integral part of paediatric formulation developed. Acceptability is determined by both product and user characteristics. The pharmaceutical characteristics of a product include palatability, swallowability; appearance; complexity of the modification to be conducted

by the child or its caregivers prior to administration; the required dose (e.g. the dosing volume, number of tablets, etc.); the required dosing frequency and duration of treatment; the selected administration device; the primary and secondary container closure system; the actual mode of administration to the child and any related pain or discomfort (World Health Organization, 2012; EMA, 2013).

Palatability is one of the main elements of the patient acceptability of an oral pediatric medicinal product (EMA, 2013). The palatability of flexible solid oral dosage forms needs to be considered early on in product development. This can be achieved with the use of sweetening and flavouring agents (EMA, 2013: Orubu & Tuleu, 2017). When a company manufactures a product for different regions it may be necessary to adapt flavours to different regional preferences (Orubu & Tuleu, 2017). The palatability of a pediatric preparation should be satisfactory on its own merit, i.e. without mixing with food or drinks (EMA, 2013). Access to safe water remains a concern in many low-resource countries (Ivanovska et al., 2014; Orubu & Tuleu, 2017). The use of milk or food to administer dispersible tablets – to improve palatability or when safe water is unavailable – is little studied. The compatibility of administered medicines with these different media is also not known. One option is for manufacturers to consider including plastic vials of drinking water with dispersible medicines in certain countries (Orubu & Tuleu, 2017).

Acceptability of oral medicines in children has been studied for many years (Cloyd *et al*., 1992; Ameen *et al*., 2006; van Riet-Nales *et al*., 2010) but only few studies have focused

on the acceptability of oral dosage forms (Ansah *et al*., 2001; Spomer *et al*., 2012; van Riet-Nales *et al*., 2013). In addition, only few publications focus on dispersible tablets (Nasrin *et al*., 2005; Ahmed *et al*., 2013; Ogutu *et al*., 2014). It is believed that young children have difficulty swallowing solid dosage forms but prefer sweet liquid drug formulations, however studies have demonstrated that small mini-tablets can be swallowed by most young children and infants. Actually, mini-tablets are at least equally accepted or significantly better accepted than the suspension, syrup and powder (Ansah *et al*., 2001; Spomer *et al*., 2012; van Riet-Nales, *et al*., 2013). Therefore, there is no reason to refuse drug approval for small, dissolvable tablets for young children. One of the limitations in the study of van Riet-Nales *et al.* (2013) was the fact that the evaluation of the child acceptability and preference relied on parental reports. Therefore, recruiters focused heavily on adequate verbal instructions to the method of administration and reporting.

There are no studies done to determine the acceptability of amoxicillin DT, however, studies have been done on other pediatric medications. For example, a study done in Bangladesh reported that there was very high acceptability of zinc dispersible tablets in children (Ahmed *et al*., 2013). This study did not collect information regarding health care providers' instructions on methods of preparation of suspension, what dose of zinc to administer, and how long they should give the treatment and the researchers were also unsure if they properly informed the children's caregivers about possible common side effects, such as vomiting and what to do if the child vomits. The study however had several strengths: it studied a large number of young children over a year-long period that included seasonal differences; health professionals counselled mothers' of children with diarrhea

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and promoted zinc treatment and participants were visited at home 2 - 3 weeks after beginning the zinc treatment; therefore, more accurate and relevant data was collected. A study on acceptability of different oral formulations in infants and preschool children in Netherlands concluded that the mini-tablets were considerably better accepted than the suspension, powder, and syrup (van Riet-Nales *et al*., 2013). In another study done in Kenya, the acceptability of artemether-lumefantrine dispersible regimen was found to be significantly better than dihydroartemisinin-piperaquine pediatric non-dispersible tablet (Ogutu *et al*., 2014). These studies demonstrate that alternative formulations may result in equal acceptability, and thus do not support the historic approach that medicines should conventionally be given to young children as oral liquid formulation only (van Riet-Nales *et al*., 2013).

Although there are many reports on acceptability of medicines for pediatric population, there are no recommended standard methods or criteria that define what is classed as acceptable to children. The choice of the method and the acceptance criteria are left to the applicant. Different methods have been used in these studies, which resulted in different outcomes when testing the same medicine in the same patient population (EMA, 2013). Therefore, there was need to identify a defined methodology or standard to support acceptability claims in pediatric products. Many studies on acceptability have been conducted in Western populations, there is a need for acceptability studies to be conducted in areas where the products will be distributed globally (EMA, 2013; Mistry & Batchelor, 2017).

A better understanding of acceptability of paediatric medicines offers advantages to the patients. Patients benefit by having access to medicines known to be acceptable both during clinical evaluation and for subsequent therapy with a better clinical outcome and improved quality of life. Furthermore, an understanding of acceptable formulations reduces the barrier to the development of new age-appropriate formulations of existing medicines (Mistry & Batchelor, 2017).

2.3: Adherence

Medication non-adherence is a growing concern to clinicians, healthcare systems, and other stakeholders because of mounting evidence that it is prevalent and associated with adverse outcomes and higher costs of care (Dawood *et al*., 2012). The effectiveness of drug regimens may be compromised by non-adherence, thus reducing the desired treatment goal, or may lead to modification in treatment regimens or doses and an increase in toxicity, unwarranted investigations, and treatment costs. Estimates of non-compliance in adults are less than in children and adolescents (Stevenson *et al*, 2004) . Serious consequences in pediatric patients may result from poor adherence to medical regimes in terms of their health outcomes. Partially treated pneumonia will lead to the following complications; Lung abscess, Respiratory Failure, Bacteremia, Pleural Effusions, Empyema, and Lung Collapse. Occasionally, infection may extend to the heart and possibly throughout the entire body. This can cause abscesses in the brain and other organs (University of Maryland Medical Centre, 2017). If left untreated, these complications cause more severe illness and increase the risk of death.

Selecting the most appropriate dosage form, that ensures safe administration and adherence of medications, is a major issue for children. There is a need for more data on drug formulations administered to children to identify unmet needs, and drive future paediatric research. This is because marketed drugs have rarely been tested for their use in children (Lajoinie *et al*., 2016). Children's adherence to therapy is affected by many factors including their cognitive skills, their acceptability or ability to swallow, and their own taste perception, whether or not affected by their disease (Lajoinie *et al*., 2016). Importantly, children need appropriate parental and professional support in taking control of their medication and treatment (Gardiner & Dvorkin, 2006) . There is limited research on the most effective methods for improving adherence to recommended treatment in children (Sabaté, 2003).

The problem of getting caregivers of children to follow a treatment regimen is widespread and is frustrating for physicians. Clinical success is determined by the extent to which a caregiver of a child adheres to a medical regimen. Strategies to improve adherence in children include using simplified drug regimens (e.g., once-daily dosing), pleasant-tasting medicines, liquid or other non-solid formulations, regular phone contact between parents and physicians, reminders, counseling, self-management plans, and other forms of individualized supervision or attention. Adherence can also be increased through physicians providing clearly written explanation or patient information sheets that list, dosage, schedule, duration, and common side effects and practical ways of coping with them. Involving the child in devising the plan improves adherence. Physicians, children,

and parents should, therefore, develop a mutually agreed-upon treatment plan (Gardiner & Dvorkin, 2006) .

The typical volume of medicine administered in a child is expected to be swallowable in one unit; therefore, the maximum volume should equate to the volume of a swallow (Mistry & Batchelor, 2017). However, Larger dose volumes are used in children routinely, yet typical target dose volumes should be <5 ml for children under 5 years and <10 ml for those 5 years and older (EMEA, 2006). For example, Paracetamol suspension is available as 120 mg/5 ml or 250 mg/5 ml products, and the recommended dose for a child of 2–3 years is 180 mg; this is likely to be administered as 7.5 ml of the 120 mg/5 ml product (Joint Formulary Committee, 2016). In addition, oral liquid medicine multiple preparation steps, such as suspension reconstitution and homogenization, dose and volume calculation and precision of volume measurement (Yin *et al*., 2010) as well as misunderstanding of instruction for liquid medicines use by caregivers (Bailey *et al*., 2009; Schillie *et al*., 2009) are risk factors for medicine error in children. Most administration errors result from decimal place errors or confusion between mg and ml (Schillie *et al*.,2009, Dahani *et al*., 2013). Dose volume and frequency of administration can lead to reduced compliance in children receiving multiple drugs in the long run (Yeung & Wong, 2005). The conversion to solid dosage forms for children with HIV may have resulted from the volume of liquid taken (Yeung & Wong, 2005).

ODTs have the potential of improving the treatment of childhood pneumonia and save lives (PATH, 2013). Dispersible and ODTs offer improved patient compliance,

particularly with pediatric, geriatric, and institutionalized patients (Velmurugan &
Vinushitha, 2010). A study on efficacy and safety of artemether-lumefantrine (AL)
dispersible versus dihydroartemisinin-piperaquine (DP) non-dispersible pediatric tablet in
the treatment of uncomplicated *Plasmodium falciparum* malaria in Kenyan children aged
less than five years demonstrated this by concluding that adherence to treatment regimen
was better for children treated with AL dispersible (93.6%) compared to DP non-
dispersible pediatric tablets (85.6%)(Ogutu *et al.*, 2014). A separate study on acceptability
and adherence to zinc dispersible tablet for the treatment of acute childhood diarrhea
reported that adherence was quite good despite the fact that it was a new treatment and
information regarding treatment was not directly communicated to health care providers
and caretakers (Nasrin *et al.*, 2005).

Adherence has been assessed using different methods in clinical trials. The least costly and
most widely used methods, such as participant reporting and product disappearance rate
have important limitations (Kehoe *et al.*, 2009). Participants (or caregivers in the case of
children) may under-report adherence because of lapses in memory or over-report to gain
the approval of study staff (Kehoe *et al.*, 2009). Disappearance rates can also be inaccurate,
for example, if remaining supplements are discarded or given to non-trial participants
(Kehoe *et al.*, 2009). Direct observation of subjects consuming the supplements is a more
objective method to assess adherence, although this may not reflect true adherence during
non-observation days and may lead to a decreased willingness to participate because of the
additional burden on the participants (Huybregts *et al.*, 2009; Kehoe *et al.*, 2009; Abbeddou
et al., 2015). Moreover, consumption may occur outside the observation period. Extended

periods of home observations are also quite costly and logistically difficult. Other options include the measurement of a metabolically inactive tracer (De Roos *et al*., 2001) or a dietary biomarker (Hedrick *et al*., 2012). However, these methods are expensive to implement in large community-based trials and logistically challenging because of the need to collect additional biological specimens. A study by Abbeddou *et al*. (2015), reported that there was no best method that could serve as a 'gold standard' for measuring adherence to small-quantity lipid-based nutrient supplements (SQ-LNS) or dispersible tablets and recommended that objective tools to assess adherence should be adopted in randomized controlled trials to allow for better interpretation of the study outcomes.

2.4: Dispersible tablets and Oral suspension

Amoxicillin is one of the most common antibiotics prescribed for children. Oral amoxicillin is formulated into conventional capsules ("Amoxicillin Caps"), tablets ("Amoxicillin Tab."), Powder for suspension ("Amoxicillin OS"), and dispersible tablets ("Amoxicillin DT"). Other forms available include syrups, sachets, and oral drops. Currently, amoxicillin oral suspension is the most frequently used pediatric formulation. It is available in strengths of 125mg/5ml and 250mg/5ml. Its administration as a liquid facilitates the treatment of children and those with difficulties in swallowing solid dosage forms like tablets or capsules. Amoxicillin dispersible tablet exists in the same strength (UNICEF, 2013a).

WHO EML17 (WHO., 2011b) and Priority Medicines List for Children (World Health Organization, 2011a) recognize amoxicillin 250 mg Scored, DT as a first line product for

treatment of pneumonia in children below 5 years. Market for DT is more developed in Asia, but still most products in the market are suspension and capsules. This is because of limited national focus and action on pneumonia as a main cause of child mortality, limited registration of amoxicillin DT in Africa: the majority of the market (as per number of products registered) is for powder for oral suspension and capsules, many countries still have co-trimoxazole indicated as the first-line pneumonia treatment for children below 5 and so registration and policy revision is necessary. The use of 250 mg DT is rarely mentioned in national treatment guidelines, and is often not included in national EMLs, and amoxicillin and antibiotic distribution is usually limited to a certain trained cadre of health providers (Hamer *et al.*, 2012) limiting access and distribution/administration possibilities at the community level and yet, the evidence base exists to support safety and efficacy of community-level administration (Global Health Technologies Colition, 2011; Hamer *et al.*, 2012).

Dispersible amoxicillin provides significant benefits over suspensions in terms of cost, dose accuracy, stability and ease of transport (Afriyie *et al.*, 2013). UNICEF, independently and through a partnership with the UN Commission on Life-Saving Commodities for women and Children, is supporting the scale-up of and use of amoxicillin DT. The UN Commission is specifically looking to shape global and local delivery markets, quality, regulatory efficiency, supply, demand, awareness and the use of innovative financing to improve the access and availability of amoxicillin DT to resource-poor communities. The availability of amoxicillin in DT form simplifies the administration and dosage of treatment. Amoxicillin 250mg DT can also replace other forms of amoxicillin for the

treatment of infections as demand and its inclusion in EMLs by national Ministries of Health (MoH) increases (UNICEF, 2013a).

There are no studies comparing DT with OS but pilot programs using amoxicillin 250mg DT have demonstrated safe, effective and quality treatment of pneumonia through community case management (Hamer *et al.*, 2012). The dispersible tablets have also been perceived to be easy to use (Orubu, 2016). A study on amoxicillin dispersible tablets in the treatment of acute otitis media found that the formulation retains the efficacy, safety, and tolerability features of conventional amoxicillin formulations while providing the additional potential benefits of improved portability, patient convenience and compliance, and dosing accuracy (Dhaon, 2004). Despite these advantages of solid forms compared with liquids and recent evidence from randomized controlled trials showing their acceptability in infants, they are seldom used in pediatric practice (Lajoinie *et al*., 2016).

In Kenya, amoxicillin DT is not found on the EML and there are no approved local WHO prequalified manufacturers. With the change in pneumonia treatment guideline which increases the dose of amoxicillin from 45mg/kg to 90mg/kg and advocates for use of oral amoxicillin for severe pneumonia, there will be an increase in the amount of oral amoxicillin required. As such there is need to expand formulation choices to include DT.

2.5: Conceptual Framework
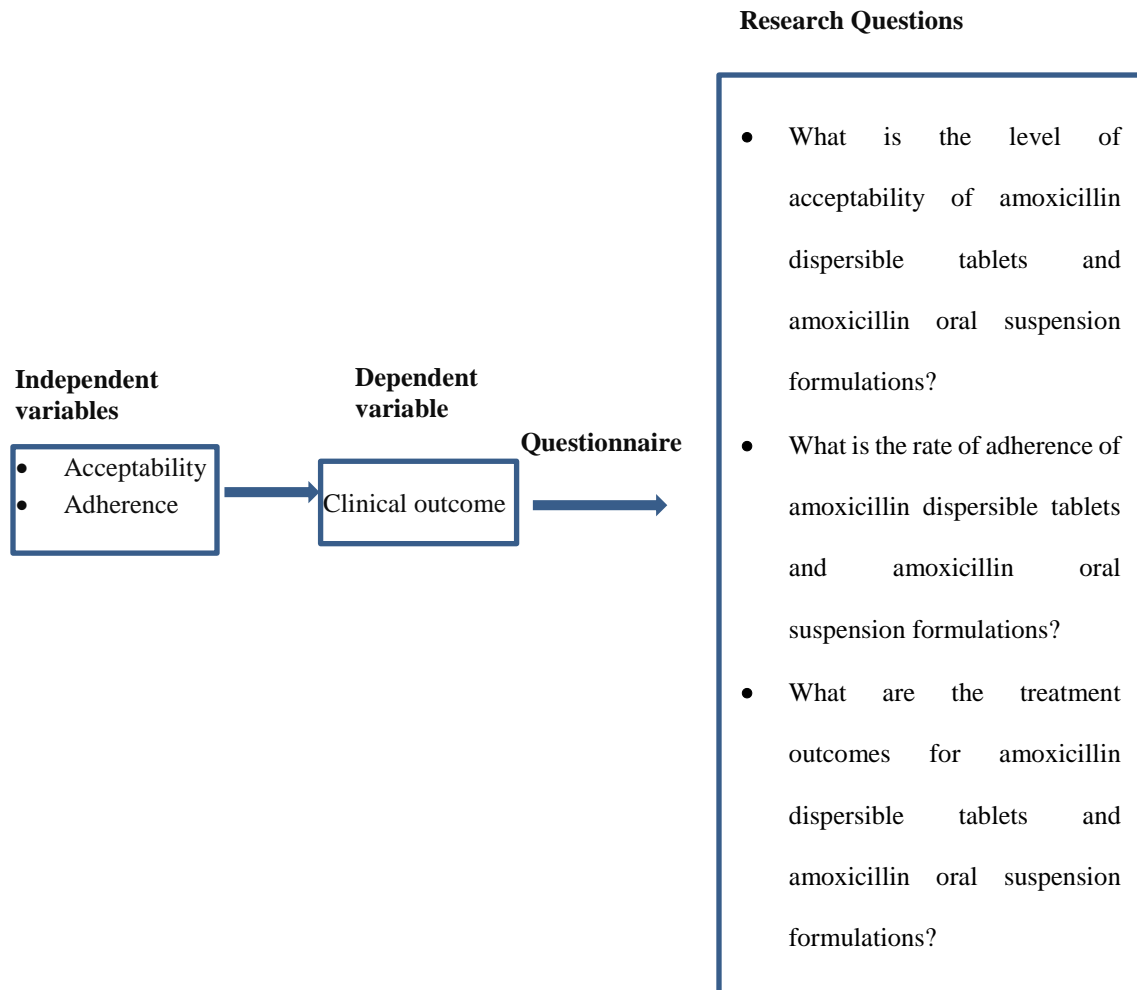
Figure 2.1: Conceptual framework (Modified PRECEDE model (Taylor *et al.*, 1999): It is expected that good acceptability and adherence will result in better clinical outcome. Since dispersible tablet has the advantage of dose accuracy, long shelf-life, ease of transportation and lower cost, it's likely to result in increased acceptability and adherence to treatment leading to better clinical outcomes.

CHAPTER THREE

MATERIALS AND METHODS

3.1: Introduction

This chapter gives an outline of research methods that were followed in the study. It provides information on the participants, that is, the criteria for inclusion and exclusion in the study, who the participants were and how they were sampled. It describes the research design that was chosen for the purpose of this study and the reasons for this choice. The instrument that was used for data collection is also described and the procedures that were followed to carry out this study are included. This chapter also discusses the methods used to analyze the data. Lastly, the ethical issues that were followed in the process are also discussed.

3.2: Study area

The study was conducted in Homa Bay County (Appendix I), which is located in the former Nyanza Province, it borders Lake Victoria to the West and North, and the following counties; Kisumu and Kericho to the North East, Nyamira and Kisii to the East, and Migori to the South. The county has a population of 963,794 of whom 175,738 are children below 5 years of age and 218,557 are women of reproductive age (15-49 years) (See Appendix I). It has an area of 3,154.7 km² and 50.2% of the population lives below the poverty line. Poverty is attributed to: lack of food security; low life expectancy; high prevalence of HIV-AIDS; Increased insecurity; poor infrastructure; dwindling health standards; high under 5 mortality rates and inequitable resource distribution. Major causes of morbidity in Homa Bay County, accounting for more than 70 per cent of all morbidity are malaria (36%),

Upper Respiratory Tract Infection (15%), diarrhea (11%), Pneumonia (10%) and skin diseases (10%). There are 211 health facilities in the County, which include nine tier three hospitals and four mission hospitals. The rest are health centers and dispensaries that are connected to community health units. There is lack of adequate health care personnel evidenced by the high doctor-population ratio of 1:40,000 and the nurse-population ratio of 1:1,500 (County Government of Homa Bay, 2013) when compared to the WHO minimum threshold of 3 nurses and midwives per 1000 population and 1 doctor per 1000 population (World Health Organization, 2017a, 2017b).

Temperatures in Homa Bay County range between 17.1°C and 34.8°C, with rainfall amounts of between 250mm and 700mm per annum. The main economic activities are agriculture and fishing which account for the largest share of household income in the region. Subsistence farming is practiced extensively with crops such as maize, sorghum, groundnut, millet and potatoes being grown.

3.3: Study design

The study employed a two-armed, prospective; cluster randomized controlled trial (RCT) design with the community unit (CU) as the unit of randomization (cluster). The study was nested within a larger quasi-experimental trial looking at the effectiveness of integrated community case management (iCCM) for pneumonia malaria and diarrhea in Homa Bay County. In the parent iCCM study, the delivery of the intervention was at the CU (sub-location) level, therefore, the CU was used as the level of randomization. Randomization

at the CU level avoided contamination, i.e. leaking of the intervention to non-intervention areas. At the time of the trial, it was not known which treatment is best.

3.4: Study population

The study population included all children aged 2-59 months residents of Homa Bay County with pneumonia at the time of the study in the study clusters. The lower cut-off of two months was selected because of the difficulty of assessing very young children (<2months) for pneumonia. Further children in this age bracket are classified as having pneumonia if they have a cough or difficulty in breathing and chest indrawing or fast breathing. This classification is not available for children under 2 months of age. The upper cut-off of 59 months is selected since beyond this age the microorganisms responsible for causing pneumonia may be different and warrant different treatment and further evaluation. The common causes of community acquired pneumonia in children under the age of 5 are *Streptococcus pneumoniae* and *Haemophilus influenza type B* while *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* often are the etiologic agents in children older than five years (Ostapchuk, Roberts, & Haddy, 2004).

3.4.1: Inclusion criteria

Study participants were;

   i.   Children aged 2 to 59 months.

  ii.   Residents of Homa Bay County.

 iii.   Diagnosed with pneumonia.

  iv.   Those whose parents or caregivers agreed to give informed consent.

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3.4.2: Exclusion criteria

Participants were excluded from the study if:

i. They were away during the time of the study.

ii. They were diagnosed with very severe disease, severe pneumonia or chronic illness according to the Integrated Management of Childhood Illness algorithm.

iii. They had taken either of the study antibiotics in appropriate dose during the previous 48 hours.

3.5: Sample Size Calculation

Sample size requirements for clinical trials are designed to show equivalence. To verify that a dose of amoxicillin tablets is non-inferior than that of amoxicillin syrup at 0.10 significance level and power of 80% a randomized clinical trial sample size determination formula by Allan Donner and Neil Klar (Donner & Klar, 2000) was adopted. The formula is as follows:

$(H_o: P_C \geq P_E + \Theta$ vs. $H_1: P_C < P_E + \Theta)$

$n = \{Z_\alpha \sqrt{[2 \dot{P} (1 - \dot{P})]} + Z_\beta \sqrt{[P_E(1 - P_E) + P_C(1 - P_C)]}\}^2 / (P_E - P_C - \Theta)^2 = 145$ per group/arm

Where $P_C < P_E + \Theta$ and $\Theta > 0$

It was anticipated that there will be about 80% efficacy for both administrations.

n = size per group; P_C = the response rate of drug 1 treatment group (amoxicillin syrup, 80% (0.80)); P_E = the response rate of drug 2 treatment group (amoxicillin tablet, 80% (0.80)), Θ = 10% (0.10) a clinically acceptable margin determined by a clinical expert to have

clinical significance, average proportion is $\dot{P} = (P_C + P_E)/2$. The level of significance was

set at 10% ($\alpha = 0.10$, $Z_\alpha = 1.282$) and power at 80% (0.20, $Z_\beta = 0.84$).

The required sample size per arm, a Design Effect (DEFF) of 1.19 (based on an Intra

Cluster Correlation coefficient (ICC=0.01) and average of 20 children per cluster.)

$n = \{1.282\sqrt{[2*0.80(1-0.80)]} + 0.84\sqrt{[0.80(1-0.80) + 0.80(1-0.80)]}\}^2 / (0.080 - 0.080 - 0.10)^2$

$n = \{1.282\sqrt{[0.32]} + 0.84\sqrt{[0.32]}\}^2 / (-0.10)^2 = 144.09$.

$n_{CRCT} = n*DEFF = 145 *1.19 = 173$ children per arm (Total of 346)

3.6: Sampling procedure

Community units were allocated numbers randomly between 1 and 241 (corresponding to

the number of community units within the study sites). A total of 52 CUs were randomly

selected using computer generated simple random sampling and assigned to receive

amoxicillin OS or DT. (https://www.randomizer.org/). 26 of the selected community units

were entered into the control arm and the other 26 into the intervention arm. The children

in each eligible community unit were selected purposively. All the study participants within

the sub-location were allocated to start the intervention concurrently.

Children aged 2-59 months presenting with a cough, difficult breathing, or fast breathing

were screened. They were then classified into the following categories using the WHO

classification: (1) Severe pneumonia or very severe disease- cough or difficulty in

breathing with any general danger sign (convulsions, lethargy or reduced level of

consciousness, inability to drink or vomits everything) or stridor in a calm child. (2)

Pneumonia- a cough or difficulty in breathing with chest indrawing or fast breathing (respiratory rate ≥ 50 breaths per minute for children aged 2-11 months; ≥ 40 breaths per minute for children aged 12-59months). (3) A cough or cold- a cough or difficulty in breathing with no sign of pneumonia or very severe disease. Children with pneumonia constituted the study population.

The CHWs were provided with a secure hotline number (*Utoto salama* iCCM hotline). Once a case of pneumonia had been identified by the CHW using the WHO algorithm, the CHW administered the first dose of oral amoxicillin to the child and sent a please call me text message to the hotline number. The hotline operator then called the CHW to get details of the child (name, age, sex, presenting symptoms, community unit, and household number). These details were sent to the Sub-County coordinator as a text message. The text message was then forwarded by Sub-County coordinator to the Quality Assurance Nurse who supervises the CHW from that community unit. The Quality Assurance Nurse made a follow-up visit on day 0 to verify the child's details, classification, and correctness of dosing.

Caregivers of children in the control arm were given amoxicillin OS and advised to administer 10ml to children aged 2 months up to 12 months and 20ml to children aged 12 months up to 5 years twice daily for 5 consecutive days while caregivers of children in the intervention arm were given amoxicillin DT and advised to administer 1 tablet to children aged 2 months up to 12 months and 2 tablets to children aged 12 months up to 5 years twice daily for 5 consecutive days. This dose is safe and efficacious for treatment of even severe

pneumonia in community settings. The caregivers received counseling on how to prepare amoxicillin DT in 5 to10ml of water and on how to reconstitute the amoxicillin OS to the mark on the bottle. They were informed that a follow-up visit will be made and advised to keep the remaining "pills" and used blister pack at home and not discard any suspension left after treatment. A second follow-up visit was done on day 4 (after 3 completed days of treatment) at the CHW's house or in the patient's home to assess for adherence and clinical outcomes, and the last follow-up visit on day 6 (after 5 days of completed treatment) to assess for acceptability, adherence, and clinical outcomes. Clinical assessment was done at each follow-up visit. During the last visit, spoons used by the caregivers to administer the OS were collected and measured for volume appropriateness.

A register of patients seen as part of standard care was kept by the CHWs. The CHWs extracted information to complete identification and baseline form for every child with pneumonia from this register. This form was used by research quality assurance assistants (Kenya Registered Nurses) to locate patients for follow-up visits and also to measure accuracy of classification and appropriateness of treatment according to the WHO Integrated Management of Childhood Illness (IMCI).

The child was considered lost to follow-up if contact was not made after the fourth day. Referral was made as per standard of care for children with severe pneumonia or very severe disease or any other classification and children whose caregiver refused home treatment or were already on antibiotics for more than 48hours with no improvement for

management. A random sample of spoons was collected from caregivers to measure volume appropriateness.

3.7: Data collection instruments

3.7.1: Questionnaires

Structured Questionnaires were used to collect data (Appendix II). The questionnaire was administered with the help of the interviewers (Quality Assurance Nurses). Training of interviewers was conducted for two days. Thereafter, pretesting of the data collection tool was done in Kayanja, Kamolo, Kamenya North, Goyo, and Rakwaro community units in Homa Bay County to determine the accuracy and relevance of the tool. To test the reliability of the study questionnaire, a reliability test on the same was conducted. The aim of the test was to ascertain whether the questionnaire is sufficient to meet the objectives of the study. A pilot of the study tools was conducted with 40 respondents who were not part of the study. The data was analyzed using the Cronbach's alpha test through SPSS. The Cronbach's alpha provided an overall reliability coefficient for a set of variables (e.g., questions).

Table 3.1: Reliability Statistics

Cronbach's Alpha	Cronbach's Alpha Based on Standardized Items	N of Items
.734	.904	39

From the results, the Cronbach's alpha is 73.4%, based on 39 questionnaire items (Table 3.1). The rest were removed automatically as they did not contribute to the measurement alpha. The observed Cronbach's Alpha indicates a high level of internal consistency and validity of the questionnaire used to conduct the study.

3.7.2: Outcome variables

Acceptability: Acceptability was assessed based on the caregivers' observation of their children's behavior when they were given the OS/DT formulations. Specifically, the mothers were asked about their perception of the taste of the formulation given to their children compared to other medicines given to the child before (the three options were: better, same, or worse). Good acceptability was defined as the perception of the taste of the formulation as same or better and expression of willingness of caregivers to use amoxicillin tablet in future.

Adherence: Adherence was described in relation to dose, treatment duration, frequency of administration, and tablet preparation/suspension reconstitution. Adherence was measured by comparing self-reported adherence with objectively measured medication adherence using pill count for dispersible tablet and volume measurement for oral suspension using calibrated measuring cups (actual adherence). Good adherence was defined as twice a day (12-hour interval) intake of an accurate dose of DT / twice a day intake of an accurate dose of OS for 5 consecutive days.

Clinical outcome: A child was judged to have been cured if they had complete resolution of symptoms on day 6 without a change of antibiotic treatment. Treatment was considered to have failed if the child had no/partial resolution of symptoms presenting on enrollment (presence of a cough or difficulty in breathing with chest indrawing or fast breathing), had a danger sign, had developed severe pneumonia or very severe disease or did not improve after 48 hours of antibiotics.

3.8: Data management and analysis

After data collection, the questionnaires were checked for consistency and completeness, data entry was performed using Epi Info (version 7.0) and cleaned and corrected for the outliers. Frequencies presented as proportions were used to summarize categorical variables. Means and medians reporting the respective standard deviations (SD) and interquartile ranges (IQR) were used to summarize continuous variables. The baseline characteristics included child's age, child's sex, caregiver's relationship to the child, caregiver's age, and caregiver's education level. These baseline characteristics of the study

participants were summarized using descriptive statistics, wherever appropriate. Acceptability of DT and OS was assessed based on the perceived taste of the caregiver and willingness of the caregiver to use the drug in the near future. Chi-square test was used to determine the differences in acceptability (reporting p values at the 95% confidence interval level). Treatment adherence to DT and OS was assessed based on the self-reported adherence, actual pill count/volume measurement verified by the research officers, frequency of treatment administration within a day and duration of treatment at the fourth and sixth day. Multivariate logistic regression accounting for clustering was used to assess the differences in treatment adherence between children put on DT compared to those on OS at the fourth day, sixth day and overall while adjusting for age, sex, and respiratory rate (reporting odds ratios and 95% confidence interval bounds). Similarly, logistic regression accounting for clustering was used to assess the differences in treatment outcomes between children put on DT compared to those on OS at the fourth day and sixth day while adjusting for age, sex, and respiratory rate. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and a p-value of less than 0.05 used to define statistical significance with 95% confidence interval bounds.

3.9: Ethical considerations

The proposal was submitted to the School of Graduate Studies for academic approval (Appendix III) while ethical approval was obtained from Maseno University Ethics Review Committee (See Appendix IV). No study procedures took place without prior approval from the Ethical Review Board.

The human subjects who were involved in the study were mothers or caregivers of children aged 2-59 months in 52 community units in Homa Bay County, Kenya. Data on mothers and their children aged 2-59 months was included in this study as they were the main beneficiaries. The risk to these vulnerable populations was minimal because the data collected was only data abstracted from survey instruments without any personal identifiers. In addition, all of the care and treatment provided at the study community units followed the accepted World Health Organization standards of care. The formulations that were used have all been tested in preclinical studies and clinical studies and are indeed utilized for the same indications. Therefore, the risk to the children under the age of five is not greater than minimal and the purpose of the research was to develop important policy informing knowledge, which cannot be obtained by any other means.

Written informed consent was sought from the parents/caregivers on the child's behalf prior to enrolling the child in the study (Appendix V). A research assistant who speaks the local language was responsible for conducting the consent process. Parents/caregivers were given information about the study, the rights to refuse participation in the study, contact persons in case of any questions about the study after the completion of the interview and made aware that they were free to withdraw their informed consent, without giving explanations. Parents/caregivers were also reassured that the withdrawal would not affect treatment, would not result in any harm and would not prejudice the child. In addition, there would be no liability or discrimination against any person who refused to give consent or withdrew consent to participate in research. If they agreed to participate, they would be asked to sign the consent form.

The women/caregivers were also given a copy of the consent form to keep. This page included names and phone numbers of contact persons in case of any questions regarding the study. Follow-up questions were also asked by the research assistants to ensure that the potential participant had understood the informed consent process.

Participation was brief, voluntary, and anonymous. Participants were informed during the consent process that they may refuse to participate or may refuse to answer any question, which they do not want to answer, and no harm would occur to them or anyone in their family regardless of their participation decisions. Interviews were done in private.

CHAPTER FOUR

RESULTS

4.1 Introduction

Results of the study are presented in this chapter according to the objectives of the study. The first section has the baseline characteristics of the participants; the second section has the acceptability of DT and OS among the caregivers; the third section compares treatment adherence to DT and OS, and the fourth section compares the clinical outcome among children on DT and those on OS.

4.2: Baseline characteristics

A total of 428 children diagnosed with pneumonia were interviewed, of which 215 were assigned to DT while 213 were assigned to OS for treatment of pneumonia. Among those assigned to DT; 76% were aged 12-59 months, 56% were female, a majority were accompanied by the mothers (91%), slightly more than half of the caregivers were aged <30 years (56%), and 48% had attained post-primary education. Among those assigned to OS; three-quarters were aged 12-59 months, about half were female (48%), majority were accompanied by the mothers (90%), about half of the caregivers were aged <30 years (49%), and half had attained post-primary education. In summary, there were no statistically significant differences in the baseline characteristics of children treated with DT and those treated with OS (Table 4.1).

Table 4.1: Baseline characteristics of children aged 2-59 months with pneumonia and their caregivers, Homa Bay County, Kenya

Characteristics	Dispersible tablet (N=215)	Oral suspension (N=213)	P-value
Age(months)			
2 up to 12	51 (24%)	54(25%)	0.70
12 up to 59	164 (76%)	159 (75%)	
Sex			
Female	121 (56%)	102 (48%)	0.08
Male	94 (44%)	111 (52%)	
Relationship of caregiver to child			
Mother	195 (91%)	191 (90%)	
Father	16 (7%)	19 (9%)	0.78
Other	4 (2%)	3 (1%)	
Caregiver age (Years)			
<30	120 (56%)	105 (49%)	0.18
≥30	95 (44%)	108 (51%)	
Caregiver highest level of education			
Primary or less	110 (51%)	104 (49%)	
Post-primary	104 (48%)	106 (50%)	0.60
Declined	1 (0.5%)	3 (1%)	

DT and OS are the two treatments to almost equal number of children
Most children are between 12 and 59 months of age. Data analyzed using SAS version 9.3
There is no statistically significant difference in gender across the two treatment groups

4.3: Acceptability of DT and OS among the caregivers

The results show statistically significant differences in perceived taste of the amoxicillin DT and OS when compared to other medicines (p=0.03). Specifically, caregivers administering DT perceived the taste to be better than other medicines when compared to those in the OS arm (51% vs. 39%, respectively), while more caregivers administering OS to the children believed that the drug tasted the same as other medicine compared to those who administered DT to the children (60% vs. 48%, respectively). The willingness of caregivers to use DT or OS in the future did not differ significantly between the two

treatment arms (p=0.30). The proportions of 'good acceptability' among both the caregivers administering DT and OS were high (94% vs. 96%, respectively) (p=0.49) (Table 4.2).

Table 4.2: Acceptability of DT and OS among caregivers of children aged 2-59 months with pneumonia, Homa Bay County, Kenya

	Dispersible tablet (N=215)	Oral suspension (N=213)	P-value
Taste perceived by caregivers			
Same as other medicines	99 (48%)	124(60%)	
Better than other medicines	105 (51%)	80 (39%)	0.03[*]
Worse than other medicines	2 (1%)	2 (1%)	
Willingness of caregivers to use the drug in future[ǂ]			
Willing	197 (95%)	203 (97%)	0.30
Not willing/depends	10 (5%)	6 (3%)	
Good acceptability	195 (94%)	200 (96%)	0.49

Data are n (%) or p-values. Data analyzed using SAS version 9.3
ǂ Numbers are only for those who have an answer to the questions
* Statistically significant result at α=0.05

4.4: Treatment adherence to DT and OS

Children who received DT were 20 times more likely to have an accurate pill count compared to volume measurement for children on OS (OR=20.02; 95% CI=10.73-37.34; p<0.01) even after adjusting for age, sex and respiratory rate, on the fourth day of treatment. The mean volume of spoons collected was 9.54ml. Children on DT were 13 times more likely to adhere to treatment on the fourth-day and 10 more likely to adhere to treatment on the sixth-day when adherence was objectively measured (OR=13.54, 95% CI=7.74-23.69, <0.01 &OR=10.51, 95% CI=6.28-17.59, P<0.01 respectively) (Table 4.3).

Table 4.3: Treatment adherence to DT and OS among children aged 2-59 months with pneumonia, Homa Bay County, Kenya

Day	Characteristics	Dispersible tablet (N=215)	Oral suspension (N=213)	Adjusted Odds Ratio§ (95% CI)	P-value
Day 4	**Dose**				
	Self-reported accurate dosage	208 (97%)	207 (97%)	0.80 (0.26-2.47)	0.70
	Pill count/volume measurement accurate dosage	200 (93%)	91 (43%)	20.02 (10.73-37.34)	<0.01*
	Frequency of administration: Administered drugs two times/day	208 (98%)	208 (98%)	1.69 (0.39-7.26)	0.48
	Duration: Administered drugs for 3 days	205 (97%)	202 (95%)	1.42 (0.52-3.89)	0.49
	Self-reported adherence at day 4	193 (92%)	183 (91%)	1.14 (0.56-2.33)	0.71
	Objectively measured adherence at day 4	188 (90%)	84 (42%)	13.54 (7.74-23.69)	<0.01*
Day 6	**Dose**				
	Self-reported accurate dosage	205 (96%)	205 (96%)	0.78 (0.29-2.11)	0.63
	Finished tablet/syrup at day 6	198 (96%)	185 (93%)	1.93 (0.80-4.70)	0.14
	Frequency of administration: Administered drugs two times/day	212 (99%)	205 (97%)	4.90 (0.57-42.41)	0.15
	Duration: Administered drugs for 5 days	202 (95%)	193 (91%)	1.83 (0.85-3.95)	0.12
	Self-reported adherence at day 6	190 (91%)	176 (88%)	1.34 (0.71-2.54)	0.37
	Objectively measured adherence at day 6	193 (92%)	174 (87%)	1.76 (0.91-3.40)	0.09
Overall	Overall self-reported adherence	182 (87%)	169 (84%)	1.24 (0.71-2.17)	0.45
	Overall actual-adherence	181 (87%)	80 (40%)	10.51 (6.28-17.59)	<0.01*

Data are n (%) or odds ratio (95%CI) or P-values. Data analyzed using SAS version 9.3

§Adjusted for age, sex and respiratory rate in the model

* Significant at α=0.05

4.5: Clinical outcome among children on DT compared to those on OS

There were no significant differences in the odds of 'appearances of danger signs' or 'fast breathing' or 'receipt of additional antibiotics' on the fourth-day following treatment among children put on DT compared to children on OS (Table 4.4) after adjusting for age, sex and respiratory rate. Similarly, there were no significant differences in the odds of 'appearances of danger signs' or 'fast breathing' or 'receipt of additional antibiotics' on the sixth-day following treatment among children put on DT compared to children on OS. The proportions of children who got cured after treatment were high for both children put on DT and children put on OS (99% vs. 97%, respectively) and there was no significant difference in the odds of cure between the two treatment arms. None of the children in both arms of treatment died while on treatment (Table 4.5).

Table 4.4: Clinical outcome on day 4 among children aged 2-59 months with pneumonia, Homa Bay County, Kenya

Clinical Outcome	Dispersible tablet (N=215)	Oral suspension (N=213)	Adjusted Odds Ratio§ (95% CI)	P-value
Appearance of danger signs on day 4	4 (2%)	3 (1%)	2.31 (0.46-11.59)	0.31
Fast breathing on day 4	2 (1%)	2 (1%)	1.78 (0.22-14.00)	0.59
Additional antibiotics on day 4	1 (0.5%)	4 (2%)	0.24 (0.03-2.21)	0.21

§ Adjusted for age, sex and respiratory rate in the model. Data analyzed using SA version 9.3

Table 4.5: Clinical outcome on day 6 among children aged 2-59 months with

pneumonia, Homa Bay County, Kenya

Clinical Outcome	Dispersible tablet (N=215)	Oral suspension (N=213)	Adjusted Odds Ratio[§] (95% CI)	P-value
Appearance of danger signs on day 6	0 (0%)	2(1%)	0.578 (0.0-7.88)	0.69
Fast breathing on day 6	0 (0%)	0 (0%)	-	-
Additional antibiotics on day 6	1 (0.5%)	5 (2%)	0.22 (0.02-1.91)	0.17
Cured	214 (99%)	207 (97%)	5.77 (0.68-49.14)	0.11
Deaths	0 (0%)	0 (0%)	-	-

§ Adjusted for age, sex and respiratory rate in the model. Data analyzed using SAS version 9.3

CHAPTER FIVE

DISCUSSION

5.1: Introduction

To date, there are no trials directly comparing amoxicillin DT with amoxicillin OS in sub-Saharan Africa. The overall aim of this study was to assess the acceptability, adherence and clinical outcome of amoxicillin DT versus the OS in children aged 2-59 months with pneumonia. Amoxicillin has been recognized as a "priority essential" medicine by WHO and UNICEF World Health Organization & UNICEF, 2010a). It is critical that the pediatric formulations have flexibility for dose adjustment, while at the same time remaining within the effective therapeutic range because there is a possible risk of toxicity with over-dosing, and of microbial resistance with under-dosing (WHO, 2014b). The use and storage of liquid formulations in some areas can be difficult, thus rendering their use unsuitable in these areas (World Health Organization & UNICEF, 2010a) . Suitability of existing formulations of amoxicillin for children in resource-constrained situations still remains a challenge, and for this reason 'Flexible Solid Oral Dosage' forms have been recommended by the WHO as the optimum oral formulation for children's medicines, as they are less bulky to ship and store and have better stability and shelf life as compared to liquids (World Health Organization, 2011).

The proportions of 'good acceptability' among both the caregivers administering DT and OS were high (94% vs. 96%, respectively) and did not differ significantly (p=0.49), however the study showed that more caregivers administering DT to the children believed that the drug tasted better than other medicine compared to those who administered OS to

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the children (51% vs. 39%, respectively). Overall objectively measured adherence was over ten times much higher in children on DT when compared to actual adherence in children on OS (OR=10.5, 95% CI=6.3-17.6, p=0.001). There was no difference in proportions of children who got cured after treatment with DT when compared to children on OS (OR=5.8, 95% CI=0.7-49.1, p=0.11).

5.2: Acceptability

This study has indicated that in a population with little experience and no knowledge of DTs, the formulation was acceptable and did not differ significantly among the caregivers whose children received amoxicillin OS. Caregivers administering DTs to the children believed that the drug tasted better than other medicine compared to those who administered OS to the children (51% vs. 39%, respectively). A total of 48% of caregivers administering DTs and 60% of caregivers administering oral suspension believed that the drug was same as other medicines. 'Good acceptability' among both the caregivers administering dispersible tablets and oral suspension were high (94% vs. 96%, respectively) and did not differ significantly.

The results on good acceptability are similar to those done for other indications. For example, a study on acceptability of and adherence to dispersible zinc tablet done in Dhaka division, Bangladesh showed that dispersible zinc tablets were equally or even more acceptable to their children than other medicines as reported by caretakers of 282 (93.1%) of the treated children. In this study, 66.7% of caretakers perceived the formulation to be same as other medicines while 26.4% perceived the formulation to be better than other

medicines. 83.5% of the caretakers were willing to use dispersible zinc to treat their children's diarrhea in future. The study demonstrated that, dispersible zinc formulation was acceptable in a population with no knowledge of zinc as a treatment and little experience with dispersible tablets (Nasrin *et al*, 2005). In a similar study in the rural community of Mirzapur, 77% of the mothers/caretakers perceived the taste of the zinc tablets as same or better than that of other medicines given to their children and expressed willingness to use zinc in the future (good acceptability)(Ahmed *et al*, 2013).

A report on acceptability and adherence of zinc tablets in young children in Bangladesh found that the formulation is well acceptable among young children. In the report, almost all of the parents/caregivers (99%) showed positive intention to use zinc tablet in future during their child's diarrhea. More than two-thirds of the respondents perceived the zinc tablet has good taste (67%) as their children took the medicine easily and 14% opined that the tablet seemed bitter to them. Parents/caregivers also found the procedure of administering the zinc tablets to be easy to remember (ACNielsen, 2006). A similar study on the acceptability of different oral formulations in infants and preschool children concluded that all formulations were well accepted but mini-tablets were the best-accepted formulation (van Riet-Nales *et al.*, 2013). In Kenya, a study evaluating efficacy and safety of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) in the treatment of uncomplicated falciparum malaria in children below 5 years of age, found that acceptability of AL dispersible regimen was significantly better than DP non-dispersible pediatric tablets (Ogutu *et al.*, 2014). In summary, the results of this study are consistent

with studies in other settings which have proven that dispersible tablets are acceptable in children under five years.

5.3: Adherence

The current study demonstrated a 10 fold higher odds of adherence with DT when compared to OS when adherence was measured objectively per protocol. The study also found that when adherence was measured by self-report, adherence was high in both arms and had no statistically significant difference. The discrepancies between self-reported and objectively measured adherence are consistent with findings of a previous study on the accuracy of children's self-reported adherence to treatment (Burkhart, Dunbar-Jacob & Rohay, 2001). Two possible explanations may underlie the difference between self-reported and objectively measured adherence. First, the caregivers were using spoons to measure amoxicillin OS. There is evidence that significant under or over-dosing can occur since the accuracy of measuring spoons and other devices supplied with liquid medicines is not guaranteed (Grießmann *et al*., 2007; Johnson & Meyers, 2016). A measurement of these spoons was done and showed diversity in measuring spoons with regard to size and depth. On average the spoons were ~0.6ml smaller than required. Secondly, caregivers may not want to admit that they were non-adherent and therefore reported to be adherent to gain the approval of study staff (Kahoe *et al*., 2009).

In one trial that administered amoxicillin as ODTs, mean compliance was 84.9% for a 5-day course (Agarwal *et al*., 2004)*.* In another study that compared the compliance to tablet and syrup forms of antimalarials, there was no disparity between the two forms in terms of

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duration of administration (Ansah *et al*., 2001). However, despite the caregivers being instructed to give medication once a day, there was a significant difference in the frequency of administration in the syrup group. In contrast, a study in Bangladesh on zinc dispersible tablets found that only one-half of the cases fully complied with the 10-day length of treatment and great efforts are required to enhance adherence. In a study of compliance with antimalarial medication, compliance was found to be greater when information is communicated directly by the provider to the caregiver (Agyepong *et al*., 2002). The content of messages regarding amoxicillin treatment communicated to the caregivers by the Quality Assurance Nurses was not observed in this study. The main reasons cited for non-adherence including being away from home, forgetfulness, too busy and improvement of the child have also been reported in other studies (Kolaczinski et al., 2006; Beer *et al*., 2009; Kalyango, 2013).

The primary determinant of treatment success is adherence to therapies. Poor adherence is known to attenuate optimum clinical benefits and therefore reduces the overall effectiveness of health systems. Poor adherence to medical treatment, its consequences of poor health outcomes and increased healthcare costs are widespread and well recognized (Sabaté, 2003; Atreja, Bellam, & Levy, 2005). Overall, about 20% to 50% of patients are non-adherent to medical therapy (Kripalani, Yao & Haynes, 2007). Reduced treatment benefits can occur as a consequence of poor adherence to prescribed medication. Poor adherence can also obscure the clinician's assessment of therapeutic effectiveness. Non-adherence accounts for 30% to 50% of treatment failures and leads to unacceptable medical treatment outcomes, higher avoidable hospitalization rates; increased institutionalization

and increased healthcare costs (DiMatteo *et al.*, 2002; Sokol *et al.*, 2005; Wroth & Pathman, 2006). Non-adherence to medications accounts for 10% to 25% of hospital and nursing home admissions and is estimated to cause 125,000 deaths annually (Atreja *et al.*, 2005; ASCP Foundation, 2006). New evidence indicates that medication non-adherence results in 2.5 times increased risk of hospitalization for patients with diabetes , 5.4 times increased risk of hospitalization, re-hospitalization, or premature death for patients with high blood pressure, and more than 40 percent of nursing home admissions (Lau & Nau, 2004; Gwadry-Sridhar *et al.*, 2009).

Overall health care costs and health care service utilization is increased by poor outcomes. A study on the economic burden of inpatient pediatric care in Kenya: household and provider costs for treatment of pneumonia, malaria, and meningitis showed that an average of 1 hour and 49 minutes was spent by caretakers in traveling to seek health care services for their sick children. As a result, an average round trip would last approximately 0.5 working days, or 3 hours and 38 min. On average, caretakers spent 6.5 days in caring for an admitted child regardless of diagnosis. The mean total costs for pneumonia treatment were US$ 197.54, US$ 135.26 and US$ 74.64 at the national, mission and public district hospitals, respectively. Within these facilities, pre-admission costs, transport costs and the opportunity costs of caretaker time amounted to US$ 27.28 representing 14% of total costs in National hospitals, and on average US$ 18.82 and US$ 12.54 for mission and district hospitals, respectively (Ayieko *et al.*, 2009). The time spent taking care of the sick reduces productivity, causes absenteeism and increases disability on employers and society while

the cost of care uses up savings and leads to the sale of assets. The benefits of improved medication adherence, therefore, may be even greater when considered at a societal level.

5.4: Clinical outcomes

This study shows that the DT formulation of amoxicillin was equivalent in effectiveness to the OS in children aged 2-59 months with pneumonia at day 5 and day 3. The proportions of children who got cured after treatment were high for both children put on DT and children put on OS (99% vs. 97%, respectively). The high cure rates among children on amoxicillin OS despite low objectively measured adherence can be attributed to the fact that the administered dose of 80mg/kg/day is more effective than the standard dose of 45mg/kg/day (WHO, 2014b). It is also likely that some patients with fast breathing enrolled in the study did not have pneumonia, as the sensitivity and specificity of fast breathing (as defined by the WHO to categorize non-severe pneumonia), is around 80% (Mulholland *et al*., 1992). Previous research shows that a three-day course of antibiotics is as efficacious as a five-day course in treating children with fast breathing pneumonia (Pneumonia Study Group, 2002; Agarwal *et al*., 2004). While holding the antibiotic constant, these studies compared the duration of two courses of treatment, one lasting three days and the other five days. The primary outcome was treatment failure at the end of the treatment. The studies recommended a shorter course of antibiotic therapy since they found no significant difference in either the treatment failure or relapse rates between groups (Pneumonia Study Group, 2002; Agarwal *et al*., 2004) . In the study reported here, there was no significant difference in clinical outcomes after 3 days and 5 days of completed treatment.

These findings are similar to a study in African infants and children that indicated the dispersible formulation of artemether-lumefantrine was not inferior in efficacy to crushed tablets in children with acute uncomplicated Plasmodium falciparum malaria, and had a similar safety profile (Abdulla *et al*., 2008). This study did not assess the risk factors for treatment failure because it was not an objective of the study.

CHAPTER SIX

SUMMARY OF FINDINGS, CONCLUSION AND RECOMMENDATIONS

6.1: Summary of Findings

This study is one of the very first studies to compare amoxicillin OS and DT for home treatment of pneumonia in sub-Saharan Africa. The results of this study show no significant difference between acceptability and clinical efficacy of the OS and DT for the treatment of non-severe pneumonia in children aged 2-59 months. However, the objectively measured adherence rate to OS is significantly lower than objectively measured adherence to the DT.

6.2: Conclusion

1. Acceptability among caregivers who administered amoxicillin DT is equivalent to acceptability among caregivers who administered amoxicillin OS to their children despite the fact that they had no knowledge of and little experience with DT.

2. Adherence to amoxicillin DT is superior when compared to OS mainly due to better accurate dose administration. The accurate administration of a liquid medicine is not assured even if the dose is correctly calculated.

3. The clinical outcomes of Amoxicillin DT and OS are equivalent, therefore, Amoxicillin DT is equal in effectiveness to OS in children aged 2-59 months with pneumonia in Homa Bay County.

6.3: Clinical and Policy recommendations from current study

Amoxicillin DT should be chosen preferentially over the OS because of the following;

1. The DT is equivalent to OS in terms of acceptability and there is potential benefit of improving acceptability of the formulation once it is in the market.

2. The DT is more superior in terms of adherence due to ease of dose administration, in addition, cost savings will be possible once DT is in the market. The prices quoted for dispersible amoxicillin suggest that DT could represent a significant cost saving over OS if a reliable supplier can be found: cost per treatment course; $ 0.22 dispersible tablets versus $ 0.8 suspension (World Health Organization & UNICEF, 2010b).

3. The DT is equivalent to OS in terms of clinical outcomes and can therefore be used without increasing the risk of treatment failure.

6.4: Recommendation for future research

1. A longitudinal study to establish the rate and risk of recurrence of pneumonia in children aged 2-59 months who have used amoxicillin OS versus DT.

2. A longitudinal study to establish the rates of drug resistance pneumonia in children aged 2-59 months who have used amoxicillin OS versus DT.

3. Costing and cost-effective analysis of the large-scale use of amoxicillin DT versus OS.

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APPENDICES

APPENDIX I: Map showing the study site (Homa Bay County), Kenya.

MAP OF HOMA BAY COUNTY

ACCEPTABILITY, ADHERENCE, AND CLINICAL OUTCOMES, OF AMOXICILLIN DISPERSIBLE TABLETS VERSUS ORAL SUSPENSION IN CHILDREN AGED 2-59 MONTHS WITH PNEUMONIA, KENYA.

INSTRUCTIONS TO INTERVIEWER: Have the caregiver answer each of the questions below. For each question, tick the option that corresponds to the caregiver's answer choice.

INSTRUCTIONS TO CAREGIVER: I will ask you some general questions about you and your child. Your answers are totally confidential.

QUESTIONNAIRE IDENTIFIERS

Date of interview_____/_____/ 2014

Sub- County Name: _____

Community Unit: _____

Child Study ID: _____

Interviewer's Name_____

1. DEMOGRAPHIC INFORMATION

1.1 Age in months: _____

1.2 Sex:

1. Male ………….   [ ]

2. Female ……….   [ ]

1.3 Relationship of caregiver to child:

1. Mother…………..   [ ]

2. Father……………   [ ]

3. Other…………….   [ ]

1.4 Caregiver's age

1. Below 18………………………………..[ ]

2. 18-29……………………………………[ ]

3. 30-49……………………………………[ ]

4. 50-64……………………………………[ ]

5. 65 and above……………………………[ ]

1.5 Caregiver's sex

1. Male………………..   [ ]

2. Female……………..   [ ]

1.6 Caregiver's highest educational level :

1. Never attended school……………………………...   [ ]

2. Incomplete Primary Education……………..…………   [ ]

3. Complete Primary Education…………………………   [ ]

4. Incomplete Secondary Education ……………………. [ ]

5. Complete Secondary Education ……………………… [ ]

6. Tertiary Education………………………………….. [ ]

7. Declined to answer……………………………………. [ ]

1.7 Type of intervention:

Dispersible Tablet (DT)………………….….……….. [ ]

Oral Suspension (OS)…………………….…………. [ ]

DAY FOUR (4) QUESTIONNAIRE

1. **ASSESSMENT OF CLINICAL OUTCOME**

INSTRUCTIONS TO INTERVIEWER: Examine the child and tick where appropriate then have the caregiver answer 1.3 and 1.4 of the questions below. For each question, tick the option that corresponds to the caregiver's answer choice.

INSTRUCTIONS TO CAREGIVER: I will examine your child to find out how he/she is responding to treatment and thereafter ask you questions about the medication and the general status of your child.

1.1 What is the respiratory rate [   ] (breaths per minute)

1.2 Does the child have any of the following signs today? (***Tick all that apply***)

a. Inability to breastfeed or drink………………………………...…. [ ]

b. Vomiting everything……………………………………….…….…. [ ]

c. Convulsions…………………………………..……………….……. [ ]

d. Lethargy or unconsciousness…………...………………….…………. [ ]

e. Severe respiratory distress e.g. head nodding…….…………….….. [ ]

f. Lower chest in drawing…………………………………….….. [ ]

g. Fast breathing…………………………...………………….…...… [ ]

(Respiratory rate ≥ 50 breaths per minute for children aged 2-11 months;

≥ 40 breaths per minute for children aged 12-59months)

1.3 Has there been a change of antibiotic treatment or use of additional antibiotics

or medicines beyond those prescribed and dispensed by the CHW?

1. Yes ……………. [ ]

2. No……………… [ ]

If Yes, kindly probe and tick all changes that are mentioned

a. Stopped medication…………………………………………..….. [ ]

b. Increased the dosage more than prescribed……………….….. [ ]

c. Reduced the dosage…………………………………………….….. [ ]

d. Gave additional antibiotics…………………………………….….. [ ]

e. Altered treatment ………..……………………………….…. [ ]

f. Other (specify)_____[ ]

1.4 What is the baby's current general condition?

a. Child is better…………….…………..…………….. [ ]

b. Child is not better…………….……..……..…….. [ ]

c. Child has a danger sign………..……….…..….. [ ]

d. Child is dead…………………….…………..….... [ ]

2. ADHERENCE ASSESSMENT

INSTRUCTIONS TO CAREGIVER: I will now ask you some questions on how you are administering the medication to the child. Please remember that your answers are totally confidential.

DT (Only for children on dispersible tablets);

2.1. Which liquid did you use to dissolve the tablet?

    a. Milk…………………………………………. [ ]

    b. Water……………………………………… [ ]

    c. Porridge……………………………………. [ ]

    d. Soup………………………………………….. [ ]

    e. None…………………………………………. [ ]

2.2. What volume of the liquid was used to dissolve the tablet?

    a. 0ml.. [ ]

    b. <5ml……………………………………………….. [ ]

    c. 5ml-10ml……………………………………………. [ ]

    d. > 10ml…………………………………………………….[ ]

2.3. How often did the child take the total amount of dissolved solution?

    a. Always…………………………………………………… [ ]

    b. Sometimes………………………………………….. [ ]

    c. Rarely…………………………………………………… [ ]

    d. Never……………………………………………………….. [ ]

2.4.How many tablets are remaining on day 4? (Do a pill count to confirm)

2.4.1. Age 2 months up to 12 months

a) 4 or 3 tablets if one dose has been given………....……………. [ ]

b) More than 4 or 3 tablets if one dose has been given……………[ ]

c) Less than 4 or 3 tablets if one dose has been given…………… [ ]

2.4.2. Age 12 months up to 5 years

a) 8 or 6 tablets if one dose has been given………………………. [ ]

b) More than 8 or 6 tablets if one dose has been given……………[ ]

c) Less than 8 or 6 tablets if one dose has been given…………… [ ]

OS;

2.5.To what level did you reconstitute the suspension? (Ask the caregiver to show you the mark on the bottle for verification)

a) At the mark on the bottle ………………………………………… [ ]

b) Above the mark on the bottle…………………………………………[ ]

c) Below the mark on the bottle……………………………………….. [ ]

2.6.What volume of syrup is remaining on day 4? (Measure the volume using a measuring cup)

2.6.1. Age 2 months up to 12 months

a. 40ml or 30ml if one dose has been given………………………   [ ]

b. More than 40mlor 30ml if one dose has been given ……………. [ ]

c. Less than 40ml or 30ml if one dose has been given…………… [ ]

2.6.2. Age 12 months up to 5 years

    a. 80ml or 60ml if one dose has been given……………………….… [ ]

    b. More than 80ml or 60ml if one dose has been given…………… [ ]

    c. Less than 80ml or 60ml if one dose has been given …………… [ ]

The following questions apply to all children

2.7. How many days did you administer the medication to the child?

    a. 0 days …………………………………… [ ]

    b. 1 day………………………………….….... [ ]

    c. 2 days…………………………………. [ ]

    d. 3 days…………………………………. [ ]

2.8. How many times per day did you administer the medication to the child?

    a. 0 times per day……………………… [ ]

    b. Once per day……………………………….. [ ]

    c. 2 times per day……………………… [ ]

    d. 3 times per day……………………… [ ]

    e. > 3times per day…………………….... [ ]

2.9. How much did you administer each time?

DT;

    a. 0 pills…………………………….... [ ]

    b. 1 pill each time…………………………… [ ]

    c. 2 pills each time……………………..... [ ]

    d. 3 pills each time…………………….... [ ]

(2 months up to 12 months-1 tablet, 12 months up to 5 years-2 tablets)

OS;

a. 0ml each time……………………………… [ ]

b. 2.5ml each time …………………………. [ ]

c. 5ml each time …………………………..... [ ]

d. 7.5ml each time …………………………… [ ]

e. 10ml each time …………………………... [ ]

f. 20ml each time………………………….. [ ]

(2 months up to 12 months-10ml, 12 months up to 5 years-20ml)

2.10. Did the child vomit any of the doses within 30 minutes of taking the
medicines?

    1. Yes………………………………………. [ ]

    2. No……………………………………….. [ ]

If yes,

2.11. Did you administer replacement medicines for the vomited doses?

    1. Yes……………………………………..…… [ ]

    2. No……………………………………….. [ ]

2.12. How many days did the child miss taking the medication as prescribed?

a. 0 days…………………………………… [ ]

b. 1 day……………………………………. [ ]

c. 2 days…………………………………………… [ ]

d. 3 days…………………………………………… [ ]

2.13.   What were the reasons for NOT administering the medication

(**Do not read out answers. Multiple responses are possible. Tick all that**

apply)

    a. Were away from home…………………………..……… [ ]

    b. Simply forgot……………………………………..……….. [ ]

    c. Too many doses…………………………………..……….. [ ]

    d. Too busy to give…………………………………………… [ ]

    e. Child was more ill………………………..………….... [ ]

    f. Felt like the drug was toxic/harmful………..…………… [ ]

    g. Run out of drugs………………………………………… [ ]

    h. Did not want to give……………………………..………… [ ]

    i. Child got better…………………………………..………… [ ]

    j. Others……………………………………………………… [ ]

Specify_____

DAY SIX (6) QUESTIONNAIRE

INSTRUCTIONS TO INTERVIEWER: Examine the child tick where appropriate then have the caregiver answer each of the questions below. For each question, tick the option that corresponds to the caregiver's answer choice.

INSTRUCTIONS TO CAREGIVER: I will examine your child to find out how he/she is responding to treatment and thereafter ask you questions about the medication and the general status of your child.

1. **ASSESSMENT OF CLINICAL OUTCOME**

    1.1 What is the respiratory rate [   ] (breaths per minute)

    1.2 Does the child have any of the following signs today? (***Tick all that apply***)

    a. Inability to breastfeed or drink…………………………….....… [ ]

    b. Vomiting everything……………………………………….…….. [ ]

    c. Convulsions………………………………..……………….….. [ ]

    d. Lethargy or unconsciousness…………...………….………..… [ ]

    e. Severe respiratory distress e.g. head nodding……..………….….. [ ]

    f. Lower chest in drawing………………………………….…….. [ ]

    g. Fast breathing…………………………...…………………..….… [ ]

    (Respiratory rate ≥ 50 breaths per minute for children aged 2-11 months; ≥ 40 breaths per minute for children aged 12-59months)

1.3 Has there been a change of antibiotic treatment or use of additional antibiotics

or medicines beyond those prescribed and dispensed by the CHW?

1. Yes …………….   [ ]

2. No………………   [ ]

If Yes, kindly probe and tick all changes that are mentioned

a. Stopped medication………………………………………….….. [ ]

b. Increased the dosage more than prescribed……………………..….. [ ]

c. Reduced the dosage…………………………………………….….. [ ]

d. Gave additional antibiotics………………………………….….. [ ]

e. Altered treatment ………..…………………………………….…… [ ]

f. Other (specify)_____   [ ]

1.4 What is the baby's current general condition?

a. Child is better…………….………….…………… [ ]

b. Child is not better……………..……..…………… [ ]

c. Child has a danger sign………..………………….. [ ]

d. Child is dead…………………….………..…......... [ ]

2. ADHERENCE ASSESSMENT

INSTRUCTIONS TO INTERVIEWER: Confirm by checking the medicines' packet to determine if there are any pills and the number of pills that are left on the day of evaluation (pill counts for the DT and the level of suspension remaining for the oral suspension).

INSTRUCTIONS TO CAREGIVER: I will now ask you some questions on how you administering the medication to the child. Please remember that your answers are totally confidential.

DT (Only for children on dispersible tablets);

a. Is there any tablet left on day 6?

      1. Yes…….………………………………………………... [ ]

      2. No.. [ ]

OS;

b. Is there any amount of syrup left on day 6?

      1. Yes…………….……………..………………………… [ ]

      2. No………………….………….…..…………………….. [ ]

The following questions apply to all children

c. How many days did you administer the medication to the child?

      a. 0 days ……………………………………………………   [ ]

      b. 1 day…………………………………………….......   [ ]

      c. 2 days………………………………………………….   [ ]

      d. 3 days………………………………………………….   [ ]

e. 4 days…………………………………………………. [ ]

f. 5 days…………………………………………………. [ ]

g. >5 days……………………………………………….. [ ]

d. How many times per day did you administer the medication to the child?

    a. 0 times per day…………………………… [ ]

    b. Once per day…………………………….. [ ]

    c. 2 times per day……………………………. [ ]

    d. 3 times per day……………………………. [ ]

    e. > 3times per day………………………….. [ ]

e. How much did you administer each time?

DT;

    a. 0 pills………………………………………... [ ]

    b. 1 pill each time…………………………… [ ]

    c. 2 pills each time…………………………... [ ]

    d. 3 pills each time…………………………... [ ]

(2 months up to 12 months-1 tablet, 12 months up to 5 years-2 tablets)

OS;

    a. 0ml each time……………………………. [ ]

    b. 2.5ml each time …………………………. [ ]

    c. 5ml each time …………………………….... [ ]

    d. 7.5ml each time …………………………. [ ]

  e. 10ml each time ……………………….... [ ]

  f. 20ml each time………………………….. [ ]

(2 months up to 12 months-10ms, 12 months up to 5 years-20ml)

 f. Did the child vomit any of the doses within 30 minutes of taking the medicines?

  1. Yes……………………………………….. [ ]

  2. No……………………………………….. [ ]

  If yes,

 g. Did you administer replacement medicines for the vomited doses?

  1. Yes………………………………….…… [ ]

  2. No……………………………………….….. [ ]

2.7. How many days did the child miss taking the medication as prescribed?

  a. 0 days……………………………………… [ ]

  b. 1 day………………………………………. [ ]

  c. 2 days………………………………………. [ ]

  d. 3 days……………………………………… [ ]

  e. 4 days……………………………………… [ ]

  f. 5 days …………………………………….. [ ]

2.8. What were the reasons for NOT administering the medication

(Do not read out answers. Multiple responses are possible. Tick all that apply)

    a. Were away from home………………………..……… [ ]

    b. Simply forgot…………………………………..……….. [ ]

    c. Too many doses………………………………..……….. [ ]

    d. Too busy to give…………………………………………… [ ]

    e. Child was more ill…………………..…………….... [ ]

    f. Felt like the drug was toxic/harmful………..…………… [ ]

    g. Run out of drugs…………………………………………… [ ]

    h. Did not want to give………………………..………… [ ]

    i. Child got better………………………………..………… [ ]

    j. Others………………………………………………… [ ]

Specify_____

3. ASSESSMENT OF ACCEPTABILITY

INSTRUCTIONS TO INTERVIEWER: Have the caregiver answer each of the questions below. For each question, tick the option that corresponds to the caregiver's answer choice.

INSTRUCTIONS TO CAREGIVER: I will now ask you some questions about your perception of taste of the medication and your willingness to use it in future. Please remember that your answers are totally confidential.

3.1. What is your perception of taste of the amoxicillin suspension/dispersible tablet given to your child compared to other medication?

        a. Same as other medicines……………………………..   [ ]

        b. Better than other medicines………………………….   [ ]

        c. Worse than other medicines…………………………   [ ]

        d. Don't know………………………………………….   [ ]

3.2. Would you be willing to use this medication in future?

        a. Willing…………………………………………………   [ ]

        b. Not willing/depends…………………………….......   [ ]

        c. Don't know…………………………………………   [ ]

APPENDIX III: School of Graduate Studies Approval

MASENO UNIVERSITY

SCHOOL OF GRADUATE STUDIES

Office of the Dean

Our Ref: PG/MPH/06005/2013

Private Bag, MASENO, KENYA
Tel:(057)351 22/351008/351011
FAX: 254-057-351153/351221
Email: sgs@maseno.ac.ke

Date: 16th September, 2015

TO WHOM IT MAY CONCERN

RE: PROPOSAL APPROVAL FOR LINET ANGWA MUSUNGU — PG/MPH/06005/2013

The above named is registered in the Master of Public Health programme in the School of Public Health and Community Development, Maseno University. This is to confirm that her research proposal titled "Acceptability, Adherence, and Clinical Outcomes, of Amoxicillin Dispersible Tablets Versus Oral Suspension in Children Aged 2-59 Months with Pneumonia, Homabay County, Kenya" has been approved for conduct of research subject to obtaining all other permissions/clearances that may be required beforehand.

16 SEP 2015

Prof. P.O. Owuor
DEAN, SCHOOL OF GRADUATE STUDIES

Maseno University　　　　ISO 9001:2008 Certified

MASENO UNIVERSITY ETHICS REVIEW COMMITTEE

Tel: +254 057 351 622   Ext: 3050   Private Bag – 40105, Maseno, Kenya
Fax: +254 057 351 221   Email: muerc-secretariate@maseno.ac.ke

FROM: Secretary - MUERC   DATE: 21st January, 2016

TO: Linet Musungu Angwa   REF: MSU/DRPI/MUERC/00252/15
      PG/MPH/06005/2013
      Department of Public Health
      School of Public Health and Community Development
      Maseno University
      P.O. Private Bag, Maseno, Kenya

RE: Acceptability, Adherence and Clinical Outcomes of Amoxicillin Dispersible Tablets Versus Oral Suspension in Children aged 2-59 Months with Pneumonia, Homabay County, Kenya. Proposal Reference Number MSU/DRPI/MUERC/00252/15

This is to inform you that the Maseno University Ethics Review Committee (MUERC) determined that the ethics issues raised at the initial review were adequately addressed in the revised proposal. Consequently, the study is granted approval for implementation effective this 21st day of January, 2016 for a period of one (1) year.

Please note that authorization to conduct this study will automatically expire on 20th January, 2017. If you plan to continue with the study beyond this date, please submit an application for continuation approval to the MUERC Secretariat by 21st December, 2016.

Approval for continuation of the study will be subject to successful submission of an annual progress report that is to reach the MUERC Secretariat by 21st December, 2016.

Please note that any unanticipated problems resulting from the conduct of this study must be reported to MUERC. You are required to submit any proposed changes to this study to MUERC for review and approval prior to initiation. Please advice MUERC when the study is completed or discontinued.

Thank you.

Yours faithfully,

Dr. Bonuke Anyona,
Secretary,
Maseno University Ethics Review Committee.

Cc: Chairman,
Maseno University Ethics Review Committee.

MASENO UNIVERSITY IS ISO   9001:2008 CERTIFIED

CONSENT FOR A RESEARCH SUBJECT.

TITLE OF THE STUDY: Acceptability, adherence, and clinical outcomes of amoxicillin dispersible tablets versus oral suspension in children aged 2-59 months, Homa Bay County, Kenya.

INSTITUTIONS:

Kenya Medical research Institute, Kisumu Kenya.

School of Public Health and Community Development, Maseno University.

STUDENT:

Linet Musungu Angwa

PG/MPH/ 06005/ 2013

School of Public Health and Community Development.

SUPERVISORS:

1. Prof. Collins Ouma

School of Public Health and Community Development.

2. Dr. Maricianah Onono

Kenya Medical Research Institute/ Fogarty Global Health.

Information for a Research Participant

You are being requested to take part in a medical research performed by Kenya Medical Research institute and Maseno University. This consent form gives you information to enable you decide whether to be in the study or not. Feel free to ask questions regarding the following; the purpose of the research, what happens if you participate, the possible benefits and risks, your rights as a volunteer, and any other clarification that you require. When all your questions have been answered, you can choose to be in the study or not. This process is called 'informed consent.' We will give you a copy of this form to keep.

Introduction

This study is about amoxicillin formulations. Amoxicillin, a broad-spectrum antibiotic is the first line treatment for pneumonia. Pneumonia is an infection of the lungs, which can be caused by a variety of microorganisms, including viruses, bacteria, fungi, and parasites (commonly bacteria) and is one of the world's leading causes of disease and death in children. It is most serious in infants and young children, old age and people with a weakened immune system. Common symptoms are cough, difficulty in breathing and fever. If not treated, it can lead to serious complications and death.

Purpose of the study

The researcher is collecting information about the use of amoxicillin dispersible tablet and oral suspension in children aged 2-59 months who are managed by Community Health

Workers at home in Homa Bay County. The purpose of this study is to compare treatment outcomes, adherence rates, and acceptability of amoxicillin dispersible tablets and oral suspension in children aged 2-59 months with pneumonia. You are being invited to participate in this study because you are the mother or primary caregiver of a child under aged 2-59 months who has been diagnosed with pneumonia by a community health worker.

What is important for you to know

You are considered to be eligible to participate in the study because your child is 2-59 months and has been diagnosed with pneumonia by a community health worker. If you give your permission, a trained research assistant will follow you up on day 4 and day 6 to check on how the child is responding to treatment in a private location of your choice. The interview will last approximately 15-30 minutes. Information that will be collected during this visit will include, treatment given, counseling or advice given on how to prepare and administer medication, self-reported adherence to the medication, alternative treatment after the visit and where such alternative treatment was obtained, current general condition and results of respiratory rate taken. After the interview, the research assistant can answer your questions and provide you with correct information about the interview topics. In addition, we would like to examine your child if possible and write down information about their current medical condition and health outcomes after treatment on day 4 and day 6 from when they were first diagnosed and managed. No samples will be collected. You will continue to receive your regular health services from the community health worker.

Risks involved

There is minimal risk to participants, except possibility of creating misunderstanding between the CHWs and the community units since CHWs would know when children from their units are enrolled into the study this will be avoided by maintaining confidentiality of the information given by mothers/caregivers. The interview may take time to complete and may cause some discomfort. You can stop the interview at any time or decline to answer any questions you do not wish to answer. Another risk is loss of privacy. No identifying information will be obtained that can be used to link the individual for future studies and the Interviews will happen in private.

Benefits

There are no monetary benefits from participating in this study. However, your child will be given treatment and followed up during treatment. The information that you give will help researchers to learn more about how best to treat pneumonia in children aged 2-59 months.

Confidentiality

If you accept to participate in this study, you will be assigned a study number that will be used on the questionnaire. No names will be used on any of the study reports and the information collected in the study will be kept private. Only study personnel will have access to the information collected in this study.

Costs

There will be no costs to you as a result of taking part in this study. The government of Kenya provided for free health care for children less than 5 years of age in public health facilities. Treatment provided at the community level as well is provided free of charge.

Reimbursement

No reimbursement will be given for participation in this study.

Your rights as a participant in this study

You have the right to refuse or withdraw your services at any time of this study without any penalty.

Questions about research

This study is approved by the Maseno University Ethics Review Committee (MUERC). Please do not hesitate to contact Ms. Linet Angwa at lynangwa@gmail.com,if you have any further questions during the study and in future. You may also contact the Secretary of the Maseno University Ethical Review Committee, P. O. Box, Private Bag, Maseno, Kenya. Telephone Numbers: + 254 57 351 622 EXT. 3050.You have the right to ask, and have answered, any questions you may have about this research.

I have read the above information, or it has been read to me. I have been given the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study.

Name of Parent or Guardian _____

Signature of Parent of Guardian _____

Date _____

       Day/month/year

BY: _____

_____

       NAME OF RESEARCH ASSISTANT   SIGNATURE
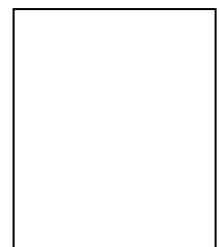
If illiterate

I have observed the accurate reading of the consent form to the mother/ primary caretaker of the child and the individual has had the opportunity to ask questions. I confirm that the individual has given consent voluntarily**.**

Name of witness _____   AND Thumb print of participant

Signature of witness _____

Date _____

       Day/month/year

BY: _____ _____

       NAME OF RESEARCH ASSISTANT   SIGNATURE