Evaluation of Adherence to Artemisinin-based Combination Therapy for the Treatment of Uncomplicated Malaria in Sierra Leone

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DECLARATION BY CANDIDATE

I, Kristin Banek, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Signed: ……  ..

ABSTRACT

Background: Artemisinin-based combination therapies (ACTs) are most effective for the treatment of malaria if patients adhere to their prescribed treatment regimen. Most adherence studies have focused on artemether-lumefantrine (AL), with limited research on adherence to the fixed-dose co-formulation of amodiaquine-artesunate (AQAS). To address this gap in evidence, this thesis aimed to: 1) measure and compare the level of adherence to ACTs at the population and to AL and AQAS at the health facility level in Sierra Leone; and 2) identify factors associated with adherence to these ACTs.

Methods: A mixed-methods approach was taken to address four specific objectives. First, data from a nationwide cross-sectional household survey were used to estimate adherence and factors associated with adherence to ACTs at the population level. Second, a randomised controlled trial (RCT) was conducted to compare the level of adherence to AL and AQAS in children aged < 5 years at two public health facilities in Freetown, Sierra Leone. Third, factors associated with non-adherence to ACTs were identified using data from the RCT. Finally, in-depth interviews with caregivers enrolled in the RCT were conducted to explore the barriers, facilitators, and contextual factors that may influence adherence.

Results: In the nationwide survey, 1,641 children under-five with fever were identified. Of these, only 467 received treatment with an ACT; 220 (47.2%) received the recommended 3-day treatment. In contrast, adherence to ACTs was much higher in the RCT. Of the 784 children enrolled and randomised into the trial, 660 (85.6%) were included in the per protocol analysis (340 AL, 340 AQAS). Definite adherence (self-reported adherence plus empty package) was higher for AL than AQAS at both sites (Site 1: 79.4% AL vs 63.4% AQAS, OR 2.16, 95% CI 1.34–3.49, p=0.001; Site 2: 52.1% AL vs 37.5% AQAS, OR 1.53, 95% CI 1.00–2.33, p=0.049). Self-reported adherence (ignoring drug package inspection) was higher for both regimens at both sites and there was no strong evidence of variation by treatment (Site 1: 96.6% AL vs 95.9% AQAS, OR 1.19, 95% CI 0.39–3.63, p=0.753; Site 2: 91.5% AL vs 96.4% AQAS, OR 0.40, 95% CI 0.15–1.07, p=0.067). AL was less likely to be taken correctly at one site, but was better tolerated than AQAS at both sites. In an adjusted multinomial regression analysis of the RCT data, the relative risk ratio (RRR) of non-adherence compared to definite

adherence was significantly higher if the caregiver reported their child disliked the drug (RRR=8.04; 95% CI 2.69–23.98; p<0.001) or experienced adverse events/side effects (RRR=4.48; 95%CI 1.78–11.24; p=0.001) versus caregivers who did not. Logistic regression models assessing factors associated with self-reported non-adherence and incorrect treatment revealed strong associations with receiving AL, disliking the medication, and experiencing an adverse event. Interviews with 49 caregivers highlighted three key factors that influenced access to medications and adherence to treatment: (1) characteristics of the medications; (2) health system-related factors; and (3) caregivers' previous experience with malaria treatment.

Conclusions: Although adherence to ACTs in the national survey was low, adherence to both AL and AQAS in the RCT was much higher, but was influenced by the criteria used to define adherence. Higher number of tablets or daily doses (such as those required for AL), dislike of the medication (including bitter taste), and perceived side effects may contribute to poor adherence. Child-friendly formulations and patient-centred services may positively impact adherence to ACTs as may prior caregiver experience with ACTs. The responsibility to maximize adherence to ACTs lies not only with the patient and caregiver, but also more broadly with the health workers and the health system. This thesis contributes to the knowledge base on adherence by providing a population estimate for ACT adherence in Sierra Leone, comparative estimates of two co-formulated ACTs, explores factors associated with non-adherence, as well as expands on the methodological challenges highlighting the need to standardize the methodology for defining and measuring adherence.

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To the children and caregivers thank you for your participation. I tell papa god tenki and wish you and your pikin welbodi.

DEDICATION

To little David that would not give up his fight to live even after weeks in the hospital; it is for children like you and those that could no longer fight that we do this type of work in the hope that one day none of you will have to worry about getting sick with malaria.

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ACRONYMS & ABBREVIATIONS

95% CI	95% confidence interval
ACT	Artemisinin-based combination therapy
AL	Artemether-lumefantrine
AMFm	Affordable Medicines Facility – malaria
AQ	Amodiaquine
ANC	Antenatal Clinic
AQ+AS	Amodiaquine plus artesunate co-packaged
AQAS	Amodiaquine-artesunate co-formulated (fixed-dose)
AQ+SP	Amodiaquine + Sulfadoxine-pyrimethamine
AS	Artesunate
AS+MQ	Artesunate plus mefloquine co-packaged
ASMQ	Artesunate-mefloquine co-formulated
AS+SP	Artesunate plus sulfadoxine-pymetheramine
BMQ	Brief medical questionnaire
CASP	Critical Appraisal Skills Programme
CHC	Community Health Centre
CHO	Community Health Officer
CHP	Community Health Post
CONSORT	Consolidated Standards for Reporting Trials
CPD	Chlorproguanil-dapsone (Lapdap®)
CQ	Chloroquine
CQ+SP	Chloroquine + Sulfadoxine-pyrimethamine
CRS	Catholic Relief Service
DHAPQ	Dihydroartemisinin-piperaquine
DHMT	District Health Management Team
DHS	Demographic and Health Survey
DNDi	Drugs for Neglected Diseases Initiative
DOT	Directly observed therapy
DPPI	Department for Policy, Planning & Information
DRC	The Democratic Republic of Congo
FDC	Fixed-Dose Combination
FGD	Focus Group Discussion
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
GoSL	Government of Sierra Leone
GPS	Global Positioning System

IDI	In-depth Interview
ITT	intention-to-treat
KAP	Knowledge, Attitudes & Practices
LACT	Long-lasting Artemisinin-based Combination Therapy
LLIN	Long-Lasting Insecticidal Net
MCH	Maternal and Child Health
MCHaide	Maternal and Child Health Aide
MCHP	Maternal and Child Health Post
MDA	mass drug administration
MDG	Millennium Development Goals
MEMS	Medication Event Monitoring System
MICS	Multiple Indicator Cluster Survey
MIS	Malaria indicator survey
MoHS	Ministry of Health & Sanitation
MSF	Médecins Sans Frontières
NDOT	Non-directly Observed treatment
NMCP	National Malaria Control Programme
OIC	Officer in Charge
OR	Odds Ratio
PHU	Peripheral Health Unit
PMI	The President's Malaria Initiative
PP	Per-Protocol
PQ	Primaquine
QNN	Quinine
RBM	Roll Back Malaria
RCT	Randomized Controlled Trial
RDT	Rapid Diagnostic Test
RR	Relative Risk
RRR	Relative Risk Ratio
SP	Sulfadoxine-pyrimethamine
SSL	Statistics Sierra Leone
STROBE	The strengthening the reporting of observational studies in epidemiology
UNICEF	United Nations Children's Fund
WHO	World Health Organization

PREFACE

This thesis includes a collection of research papers and unpublished results chapters. Although presented or published independently they are all related and as such some of the background and methods is repeated in both the introduction and methods chapters as well as within the same sections of the results chapters.

CHAPTER 1: INTRODUCTION

1.1 Antimalarial Treatment Policy

Despite increased support for malaria control, the burden of malaria remains high, particularly in sub-Saharan Africa [1]. Prompt treatment with effective antimalarial drugs is a key malaria control strategy [2, 3]. The cornerstone of this strategy is artemisinin-based combination therapy (ACT). To further improve malaria case management, the World Health Organization (WHO) updated the malaria treatment guidelines in 2010, recommending that ACT treatment should be targeted to only parasitologically confirmed malaria cases (either using rapid diagnostic tests (RDT) or microscopy) [2, 3].

In 2003, less than twenty countries had adopted ACT as the first line treatment for uncomplicated malaria [4, 5]; by 2007 that number had increased to 67 countries [4]. With the support of donors, specifically, the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM), more countries have deployed ACT making the treatment more widely available [5]. By 2010, 84 countries had adopted ACTs with the number remaining over 80 since then (Figure 1.1). In 2010, over 60 countries provided ACTs free of charge to all ages in the public sector, and a further eight have piloted the provision of subsidised ACT through the private sector [2, 6, 7].

Changing antimalarial treatment policy to ACTs is not enough to ensure proper treatment of malaria; addressing access to and targeting of these efficacious treatments is necessary [8]. The delivery of effective treatment for malaria is often challenged by limited health-care infrastructure and skilled human resources, particularly in Africa [9, 10]. To improve access to lifesaving treatment, malaria treatment delivery systems have expanded to include the community level [11, 12] as well as the private sector [13, 14].

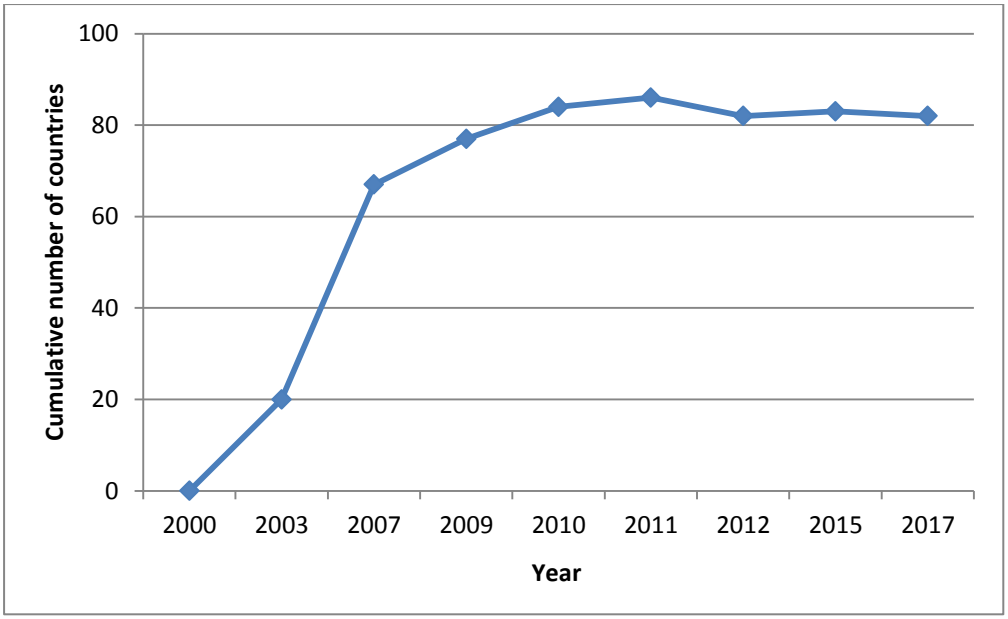

Figure 1.1 Cumulative number of countries adopting ACTs as first-line treatment of malaria from 2000 to 2017. Data from World Malaria Reports[1, 12, 15-17] and Bosman et al. [4]

1.2 Recommended ACTs

In 2013, the WHO recommended five ACTs for the treatment of uncomplicated *P. falciparum* malaria: 1) artemether-lumefantrine (AL); 2) amodiaquine plus artesunate (co-packaged (AQ+AS) or co-formulated (AQAS); 3) artesunate plus mefloquine (co-packaged (AS+MQ) or co-formulated (AQMQ); 4) Dihydroartemisinin-piperaquine (DHAPQ); 5) artesunate + sulfadoxine-pyrimethamine (AS+SP) [18]. Another ACT, pyronaridine-artesunate, has also been prequalified for use for uncomplicated malaria, specifically for use in areas where other ACTs are failing [19-21].

The two ACT regimens primarily adopted as first or second line therapy over the past ten years in sub-Saharan Africa are artemether-lumefantrine (AL) and amodiaquine plus artesunate (AQ+AS) [22]. Decision-making for antimalarial treatment policy in individual countries is based on efficacy, availability and cost, with the requirement that the formulation is prequalified by the WHO. AL was chosen for much of East and Southern Africa where resistance to amodiaquine has emerged [22].

However, in the West African region, AQ has retained a relatively high efficacy (median treatment failure rate of 12%; minimum <5%, maximum ~65%), and thus it is assumed that

the combination AQ+AS remains effective [22]. As AQ+AS was initially substantially cheaper than AL, as well as effacatious, 23 countries in Africa, including Sierra Leone, had chosen AQ+AS as the first- or second-line treatment for uncomplicated malaria by 2010 (Figure 1.2).

However, the choice of AQ+AS does not come without concerns. As amodiaquine is cross-resistant with chloroquine, the overall efficacy of the combination is at risk if resistance to amodiaquine increases [22]. Moreover, some studies have suggested that repeated exposure to amodiaquine may cause toxicity, such as instances where amodiaquine has been used for chemoprophylaxis [23]. However, amodiaquine appears to be much safer when used for a shorter duration [24]. Adherence to the amodiaquine + artesunate regimen has been a concern due to the multiple tablets per dose as well as patient tolerability to amodiaquine, particularly in adults [23, 25-28].

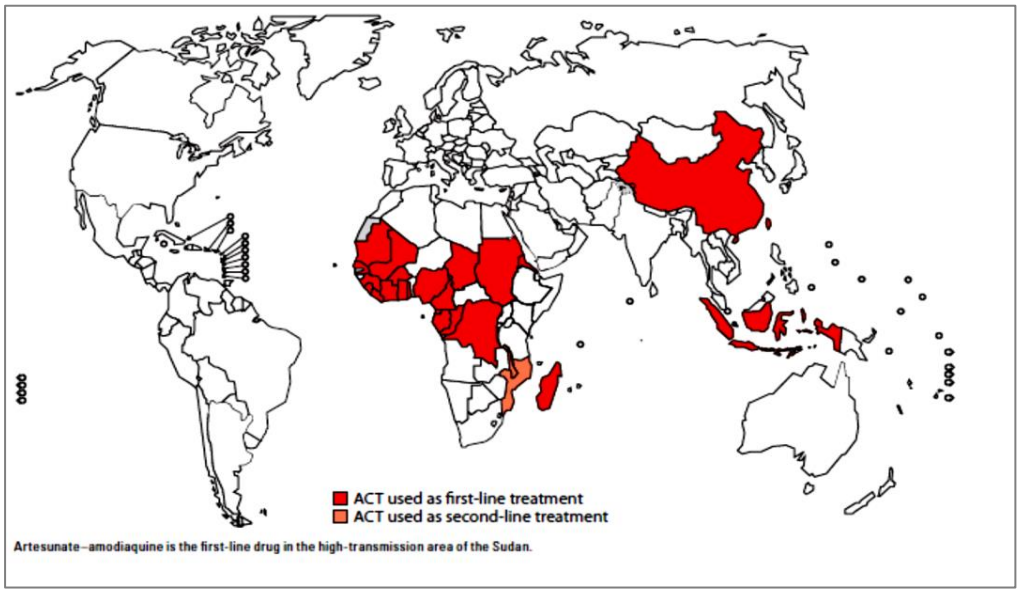

Figure 1.2 Countries in which artesunate–amodiaquine was recommended for the treatment of uncomplicated malaria [22]

1.3 The importance of adherence for effectiveness

The effectiveness of an antimalarial treatment regimen is dependent on multiple factors. The pathway to effectiveness illustrates how each of the five factors contributes to the overall effectiveness of an intervention, in this case, antimalarial treatment effectiveness (Figure

1.3). For example, even if the best antimalarial (efficacy 99%) is used, with high access or coverage (80%), and targeting and provider compliance reach the minimum targets of 80% [29], if patient adherence to the regimen is only 50%, the overall effectiveness will be just 25%. Therefore, all steps within the effectiveness pathway should be considered critical to the successful treatment of malaria.

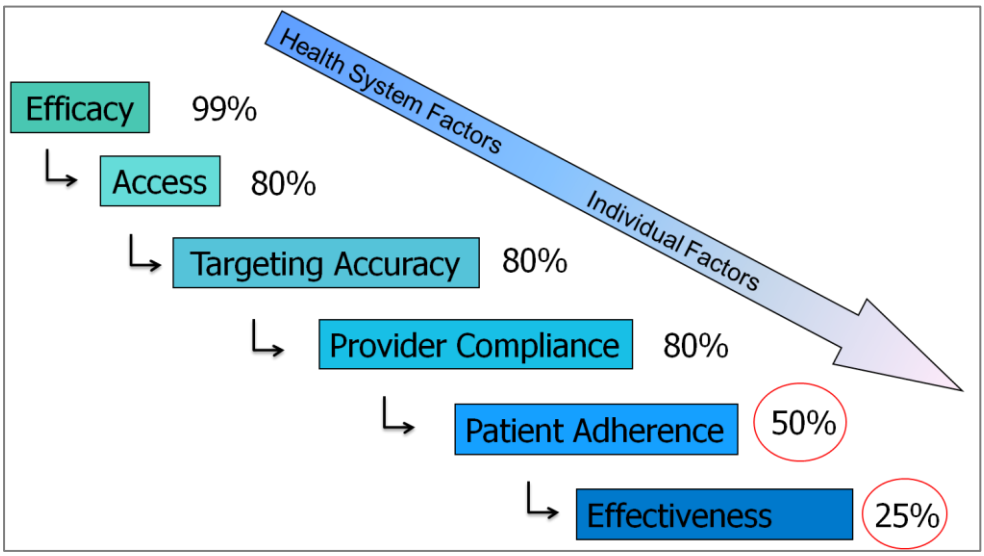

Figure 1.3 Pathway to treatment effectiveness (Original figure courtesy of Marcel Tanner, personal communication 2012 & [30])

Increasing access to effective drugs does not guarantee patient acceptability and ultimately adherence to the medications [31]. Focusing on the health system challenges, (i.e. access and targeting) without consideration for other factors that may influence adherence, will ultimately lead to suboptimal outcomes for malaria treatment. However, there is some evidence that strategies that address 'therapy-related' factors [32], such as co-packing antimalarials into blister packs, improve adherence to antimalarials, and stop the practice of using mono-therapies (thus preserving efficacy) [31, 33, 34].

1.4 Approaches to Improve Antimalarial Adherence

While co-packaging antimalarial combinations assists both provider and patient in ensuring the correct treatment dose, it does not reduce the number of tablets nor the frequency at which the medications need to be taken. Furthermore, co-packaging does not necessarily

change perceptions the patient may already have about individual drugs, and patients may choose not to take all of the tablets or choose to take only one of the co-packaged medications.

In an effort to overcome the limitations of co-packed antimalarial drugs and to improve adherence, several antimalarials have been produced to be co-formulated; the most common of these are artemether–lumefantrine (AL), dihydroartemisinin-piperaquine (DHA-PQ), and the co-formulated versions of amodiaquine-artesunate (AQAS) and artesunate-mefloquine (ASMQ).

AL (branded Coartem® Novartis, Basel, Switzerland) was the first co-formulated antimalarial that contained an artemisinin derivative [35]. Children weighing 5-14 kg (roughly under 12 months of age) take one tablet twice a day for three days (Figure 1.4). Children 12-59 months (15-24 kg) take two tablets, twice a day for three days (total of 12 tablets). However, AL should be taken with food to be the most effective [36].

Figure 1.4 Coartem® (artemether-lumefantrine) dosing for children 5-25kgs [37]

Co-formulated AQAS (branded Winthrop® for the public sector or Coarsucam® for the commercial sector, Sanofi, Paris, France) was developed by the public-private partnership

Drugs for Neglected Diseases Initiative (DNDi) [38, 39] with the objective to create a product that would "improve patient compliance" [40]. The new product has a simple dosing schedule: 1 dose a day for three days. Children under the age of 14 only take one tablet, while patients 14 years and over, take 2 (Figure 1.5). The co-formulation reduces the number of tablets to be taken compared to the co-packaged version of the same combination, thus easing treatment intake and hopefully improving patient adherence. However, the switch to co-formulated AQAS by countries was initially slow due to availability and cost implications.

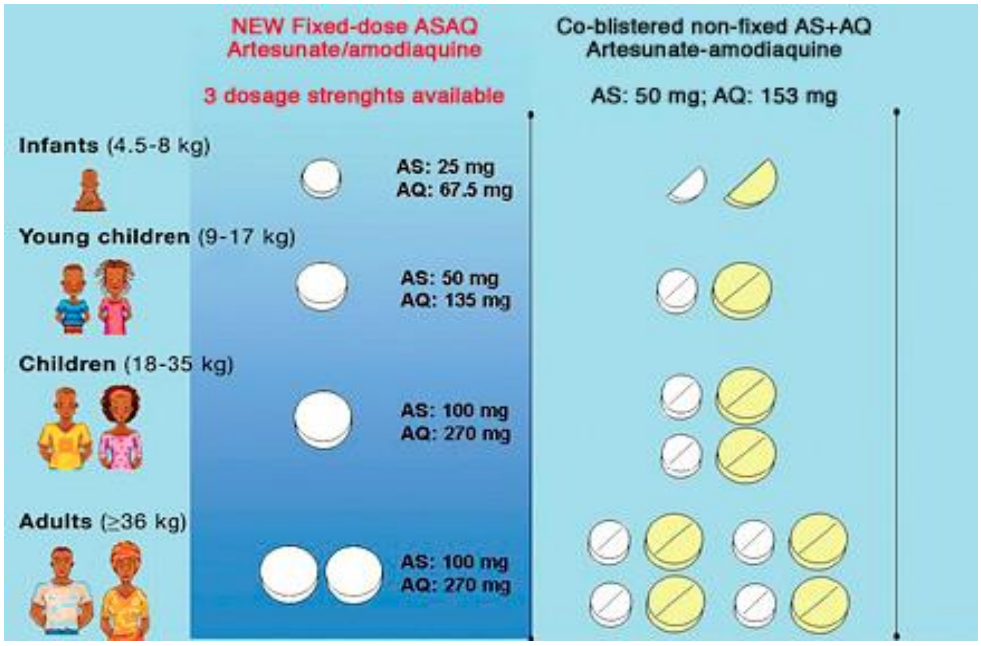

Figure 1.5 Dosing for co-formulated AQAS versus co-packaged AQ+AS [40]

1.5 Thesis Rationale

Better treatment, targeting and improved access may improve the coverage of malaria treatment. However, these aspects only address health system factors, and do not adequately address individual factors that improve the overall effectiveness of malaria treatment. Specifically, factors which negatively influence patient acceptance and adherence not only threaten individual outcomes (recovery), but may lead to higher treatment costs (retreatment) and even resistance [41]. In an era of malaria elimination strategies and developing resistance to artemisinin compounds in South East Asia [42], provider compliance

with malaria treatment guidelines and patient and/or caregiver adherence to treatment are vital.

It is often assumed that co-formulated antimalarials will facilitate adherence in the same way that co-packaged treatments have previously. It is also expected that the co-formulated version, would not only improve dispensing, but would also improve patient adherence. However, factors other than treatment packaging may influence patient/caregiver adherence to treatment. Furthermore, despite the assumption that the co-formulated versions of ACTs will yield higher adherence and hence better treatment outcomes, information on specific factors affecting adherence to ACTs remain unclear.

Both AQAS and AL are available and recommended for the treatment of uncomplicated malaria in Sierra Leone, however, in 2013 AL was only found in the private sector. In 2015, the National Malaria Control Programme (NMCP) switched the first line ACT to AL with AQAS as the alternate [43] even though it has yet to be established if one formulation is better tolerated by patients in Sierra Leone. Although a co-formulated antimalarial, AL still has a dosing schedule that requires multiple administrations each day and it is recommended to be taken with fatty food, both of which may impact on optimal patient adherence. AQAS, although currently available and efficacious, may lose efficacy in the coming years. Furthermore, patient tolerance to AQAS formulations is problematic (e.g. bitter taste and complaint of side effects). Only one study in Benin [44] has compared the adherence to these two co-formulated ACTs, and there is no study to date that has rigorously evaluated, either individually or in comparison, the adherence of these two co-formulated ACTs in Sierra Leone.

This thesis addresses this gap in knowledge by measuring the level of patient adherence to co-formulated AQAS compared to AL at two government health facilities in Freetown, Sierra Leone. Additionally, this thesis explores the key factors that influence adherence to antimalarial treatment.

1.6 Research Questions

Specifically, this thesis aimed to answer the following questions:

- *What is the level of adherence to ACTs in Sierra Leone?*
- *What are the key factors associated with adherence to ACTs in Sierra Leone?*

Specific Objectives:

I. To calculate population level adherence and the factors associated with adherence/non-adherence to antimalarial treatment in Sierra Leone.

II. To evaluate and compare the level of adherence to co-formulated amodiaquine-artesunate compared to artemether-lumefantrine for the treatment of malaria in children aged 6 to 59 months seeking care at government health facilities in Sierra Leone.

III. To identify factors associated with patient adherence to these two ACT formulations.

IV. To explore barriers and facilitators of adherence to ACTs in Sierra Leone using qualitative methods.

1.7 Thesis structure

Part I

Part I introduces the thesis rationale, objectives, research context and methodology. Specifically, Chapter 2 begins by providing a thematic background on the subject of adherence. This review of the literature is then carried further in Chapter 3, which presents a systematic literature review paper entitled, "Adherence to Artemisinin-based Combination Therapy: a review of the evidence," published in Malaria Journal in January 2014. Finally, Chapter 4 provides an overview of the study context, study design and a summary of the research methods used for data collection and analysis.

Part II

Chapters 5-8 present the results. Chapter 5 identifies factors associated with adherence at the population level in Sierra Leone using national survey data. Chapter 6 presents the results of a randomised trial that measured and compared the level of caregiver adherence to AQAS versus AL for the treatment of uncomplicated malaria in children under five at two government health centres in Freetown, Sierra Leone. Chapter 7 explores factors associated with adherence in the trial population using logistic regression models. Finally, Chapter 8 presents the results of a qualitative research study that explored the barriers and facilitors that influence adherence to AL and AQAS by caregivers from the trial population.

Part III

Finally, Part III discusses the research findings and their implications along with the overall contribution of the thesis and suggestions for further research (Chapter 9).

Table 1.1 on the next page summarises the structure of my thesis, related objectives, chapter short titles and type along with publication status at the time of submission.

Table 1.1 Thesis summary

	Chapter	Research Objective	Short Title	Type	Publication Status
Part I	1	-	Introduction	Background	-
	2	-	Thematic Background	Background	-
	3	-	Systematic Literature Review	Research paper (1)	Published Jan 2014
	4	-	Thesis Context & Methods	Context & Methods	-
Part II	5	I	Measuring adherence at the population level	Research paper (2)	Ready for submission
	6	II	Adherence RCT	Research paper (3)	Published June 2018
	7	III	Exploring factors associated with non-adherence	Results chapter	
	8	IV	Barriers and Facilitators of adherence	Research paper (4)	Ready for submission
Part III	9	-	Discussion	Conclusions	-

1.8 Publications from this thesis

Banek, K., Lalani, M., Staedke, S. G., & Chandramohan, D. (2014). Adherence to artemisinin-based combination therapy for the treatment of malaria: a systematic review of the evidence. [journal article]. Malaria Journal, 13(1), p 7. doi:10.1186/1475-2875-13-7 Retrieved from: https://doi.org/10.1186/1475-2875-13-7

Banek, K., Webb, E. L., Smith, S. J., Chandramohan, D., & Staedke, S. G. (2018). Adherence to treatment with artemether-lumefantrine or amodiaquine–artesunate for uncomplicated malaria in children in Sierra Leone: a randomized trial. [journal article]. Malaria Journal, 17(1), p 222. doi:10.1186/s12936-018-2370-x Retrieved from: https://doi.org/10.1186/s12936-018-2370-x

Banek, K., Webb, E. L., Bostick, E., Smith, S. J., Chandramohan, D., & Staedke, S. G. (To be submitted). Factors associated with access and adherence to artemisinin-based combination therapy (ACTs) for children under five: a secondary analysis of the 2012 Sierra Leone malaria knowledge, attitudes and practices (KAP) survey. American Journal of Tropical Medicine and Hygiene.

Banek, K., DiLiberto, D.D., Chandler, C. I. R., Webb, E.L., Chandramohan, D., & Staedke, S. G. (To be submitted). Exploring barriers and facilitators of access and adherence to paediatric artemisinin-based combination therapies in Freetown, Sierra Leone. Global Public Health.

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CHAPTER 2: THEMATIC BACKGROUND--ADHERENCE

Drugs don't work in patients who don't take them.

--C. Everett Koop, M.C. [42]

2.1 Terminology for Adherence

Different terms are used to describe how patients take their medication. The term adherence is preferred by many over the term compliance [1-4]. "Adherence can be defined as the extent to which patients follow the instructions they are given for prescribed treatments" [4]. Some have argued that compliance implies that the patient is under the control of the health provider, that they 'yield to or obey physicians' instructions" [5]. Compliance implies that one is following specific medical guidelines, whereas adherence suggests that the patient actually has the agency to decide whether or not they will take the treatment [1, 4, 5]. Concordance, a term that is being used more frequently, focuses on the provider and patient relationship not the behaviour of the patient [6].

The purpose of this research is to examine the behaviour of caregivers and patients, not to assess the patient-provider interaction. Therefore, the term 'adherence' will be used when describing the extent to which a patient takes medications as prescribed. The term 'compliance' will be used to describe whether health workers follow the recommended malaria treatment guidelines.

2.2 Methods used to measure adherence

Despite a substantial evidence base on adherence to treatment for both chronic and acute disease, there still remains no clear gold standard regarding the best way to measure patient adherence to medications [1, 7]. In general, there are two types of measurement methods: the first measures adherence directly/objectively (biological assays or directly observing the patient take the medication); and the second type measures adherence indirectly/subjectively (self-reporting, interviews, pill counts, use of monitoring devices (i.e., MEMS), records reviews and patient diaries) [1, 3, 7-9].

Biological Assays

Bio-assays measure the levels of drug or their metabolites in a biological sample (usually blood or urine) obtained from the patient shortly after they have taken their medications. This method allows the researchers to determine whether the patient ingested the drug or not, but does not provide information on when or how often the patient took the treatment (frequency or timing). Bio-assays are time sensitive, so drugs that are metabolised quickly (like artemisinins)[10] or that stay in the system for quite some time may not be ideal candidates for this form of measurement [1]. Furthermore, for assays to be suitable, drug or metabolite level cut-offs need to be established and standardised.

Self- report/interviews

There are many different types of questionnaires to determine adherence: in-depth interviews and shorter questionnaires. In assessing adherence for chronic diseases, short or abbreviated versions rather than in-depth questions have been utilized for both HIV and TB treatment regimens. Examples include the Brief Medical Questionnaire (BMQ) and the Morisky Scale, which uses only four questions to determine adherence to antiretroviral treatments for HIV patients [11-13].

Like all interview tools, these are subject to bias. Patients may overestimate their adherence as they may want to provide the 'correct' response (social desirability bias). Also, the quality of the measurement is dependent on the survey instrument and the interviewer's technique [1]. If the interviewer does not administer the questionnaire in a neutral manner, the respondent may give an answer that they feel would be more favourable to the interviewer. However, as this methodology is relatively simple and low cost, it is has been preferred (often in tandem with pill count/package inspection) for the collection of antimalarial adherence data.

Pill count

Counting remaining medication has been widely used to measure chronic disease treatments [9]. Traditionally pill counts, in the context of chronic diseases, were conducted when patients returned for a follow-up appointment and the health worker 'counted' the number of remaining tablets to determine whether the patient was adherent to the prescribed

treatment. Enumerating the number of remaining tablets is rarely used alone, but usually in combination with patient interviews or self-reports.

This method is subject to limitations as the number of pills remaining may not represent the actual patient behaviour. For example, the patient may have removed the medication, but did not actually ingest them (i.e., pill dumping). Additionally, in the instance of malaria and other acute illnesses, the packaging may not be available as the illness is short and the patient may not have kept the packaging or have remaining tablets.

Medication Event Monitoring System (MEMS)

The principal method for measuring medication adherence (particularly in the case of chronic disease) has been the Medication Event Monitoring System (MEMS) [1, 14]. MEMS™ containers (Aardex Ltd, Switzerland) collect data on the frequency and timing of when the medication container was opened. Despite frequent use for chronic illnesses, MEMS is limited in that it only measures the opening of the container and not whether the patient actually removed the prescribed dose and consumed the medication. For malaria, smart blister packs have been piloted in Tanzania with some success; the technology still requires further development to be more discreet (so patients are not aware) and to improve the accuracy of the timestamp [15]. Although not perfect, both the MEMS containers and smart blister packs can be used to collect data to provide a picture of when the patient took their medication.

2.3 Adherence to Antimalarials

In 2005, Yeung and White wrote a comprehensive review about how antimalarials were used by patients. Although comprehensive, it was conducted in the infancy of the ACT era [16]. At the time of the review, a total of 24 studies assessing adherence to antimalarials were identified, half of which were conducted in Africa and the other half in Asia and South America. Eight of the cited studies looked at artemisinin-based treatments, two of which looked only at artemisinin monotherapies [17, 18]. The remaining six studies looked at artemisinin-based combination therapies; four in Asia [19-22] and two in Africa [23, 24]. Only the study carried out in Uganda looked at a co-formulated ACT (artemether-lumefantrine).

Results for adherence varied, but were generally better when "interventions focusing on provider knowledge and behaviour, packaging and provision of correct dosage" were implemented.

Since the Yeung and White review was published, ACTs, and in particular co-formulated versions of ACTs, have been scaled up across Africa [25]. As part of this thesis, I conducted a systematic review to compile and summarise the current evidence base on antimalarial adherence, with a specific focus on adherence to ACTs. Secondary objectives included: how adherence is measured, definitions of adherence, and factors affecting adherence to ACTs. The results of the review were presented in a manuscript published in Malaria Journal in January 2014. In summary, our review highlights the weak evidence base available for ACT adherence and suggests that the considerable variability in findings is a result of lack of standardisation of methods. The complete manuscript is presented in Chapter 3, followed by a section which provides a summary of additional manuscripts available after the publication of the systematic review.

2.4 Conclusions

The direct and indirect methodologies to measure adherence described in this chapter presents both advantages and disadvantages regarding their accuracy and utility. Furthermore, the majority of research on medication adherence using these methods has been conducted for chronic disease medications. Despite the abundance of research and literature available to measure adherence to medications for chronic disease, there lacks a clear standard for acute illnesses, such as malaria.

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CHAPTER 3: SYSTEMATIC LITERATURE REVIEW

3.1 Introduction

This chapter contains a systematic literature review entitled, "Adherence to artemisinin-based combination therapies: a review of the evidence" which was published in the Malaria Journal in January 2014. Section 3.2 presents the published paper and along with the additional files published with it. Updates to the literature are presented in Section 3.3 followed by conclusions in 3.4.

3.2 Systematic Review Paper

The cover sheet is on the next page followed by the manuscript and additional files.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Kristin Banek
Principal Supervisor	Sarah Staedke & Daniel Chandramohan
Thesis Title	Evaluation of Adherence to Artemisinin-based Combination Therapy for the Treatment of Uncomplicated Malaria in Sierra Leone

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Malaria Journal		
When was the work published?	January 2014		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not Applicable		
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study, collected the data, conducted the analysis and wrote the first draft of the manuscript.

Student Signature: [redacted] **Date:** 27 June 2018

Supervisor Signature: [redacted] **Date:** 11 July 2019

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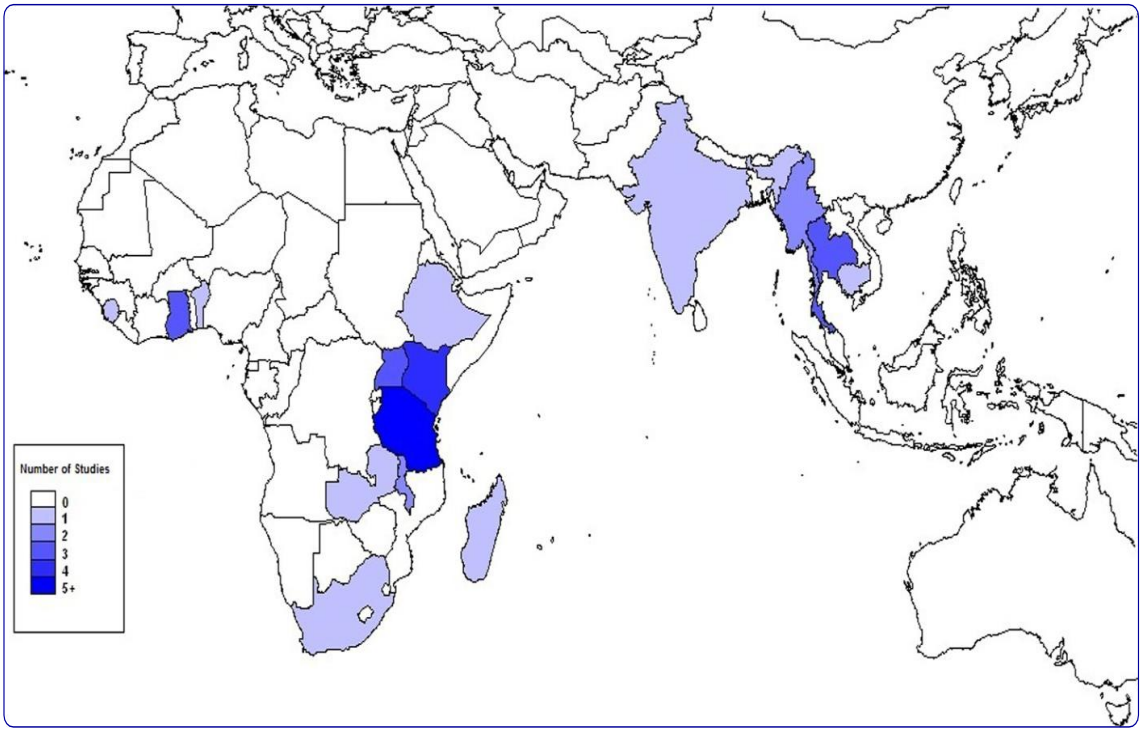

Adherence to artemisinin-based combination therapyforthetreatmentofmalaria: asystematic review of the evidence

Banek *et al.*

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RESEARCH Open Access

Adherence to artemisinin-based combination therapy for the treatment of malaria: a systematic review of the evidence

Kristin Banek[1*], Mirza Lalani[1], Sarah G Staedke[1] and Daniel Chandramohan[2]

Abstract

Background: Increasing access to and targeting of artemisinin-based combination therapy (ACT) is a key component of malaria control programmes. To maximize efficacy of ACT and ensure adequate treatment outcomes, patient and caregiver adherence to treatment guidelines is essential. This review summarizes the current evidence base on ACT adherence, including definitions, measurement methods, and associated factors.

Methods: A systematic search of the published literature was undertaken in November 2012 and updated in April 2013. Bibliographies of manuscripts were also searched and additional references identified. Studies were included if they involved at least one form of ACT and reported an adherence measurement.

Results: The search yielded 1,412 records, 37 of which were found to measure adherence to ACT. Methods to measure adherence focused on self-report, pill counts and bioassays with varying definitions for adherence. Most studies only reported whether medication regimens were completed, but did not assess how the treatment was taken by the patient (i.e. timing, frequency and dose). Adherence data were available for four different ACT formulations: artemether-lumefantrine (AL) (range 39-100%), amodiaquine plus artesunate (AQ+AS) (range 48-94%), artesunate plus sulphadoxine-pyrimethamine (AS+SP) (range 39-75%) and artesunate plus mefloquine (AS+MQ) (range 77-95%). Association between

demographic factors, such as age, gender, education and socio-economic status and adherence to ACT regimens was not consistent. Some evidence of positive association between adherence and patient age, caregiver education levels, drug preferences, health worker instructions, patient/caregiver knowledge and drug packaging were also observed.

Conclusions: This review highlights the weak evidence base on ACT adherence. Results suggest that ACT adherence levels varied substantially between study populations, but comparison between studies was challenging due to differences in study design, definitions, and methods used to measure adherence. Standardising methodologies for both self-report and bioassays used for evaluating adherence of different formulations across diverse contexts would improve the evidence base on ACT adherence and effectiveness; namely, specific and measurable definitions for adherence are needed for both methodologies. Additionally, further studies of the individual factors and barriers associated with non-adherence to ACT are needed in order to make informed policy choices and to improve the delivery of effective malaria treatment.

Keywords: Malaria, Artemisinin-based combination therapy, ACT, Adherence, Compliance

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Background

Despite increased support for malaria control over the past decade, the malaria burden remains high in many endemic countries, particularly in sub-Saharan Africa [1]. Prompt treatment with artemisinin-based combination therapy (ACT) targeted towards those confirmed to have malaria is a key malaria control strategy [2,3].

In 2003, less than twenty countries had adopted ACT as the first-line treatment for uncomplicated malaria [4,5]. With the support of donors, specifically the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM) and the President's Malaria Initiative (PMI), the number of countries that have deployed ACT has increased dramatically, allowing for treatment to be more widely available [5]. By 2010, 84 countries had adopted ACT, with 60 countries providing ACT free-of-charge to all ages in the public sector and eight have piloted the provision of subsidized ACT in the private sector through the Affordable Medicines Facility-malaria (AMFm) [2,6,7]. Changing anti-malarial treatment policy to ACT is not enough to ensure proper treatment of malaria. Addressing access and targeting of these efficacious treatments is necessary [8], recognizing that improving access to effective drugs does not guarantee patient acceptability and ultimately adherence to the medications [9].

The pathway to treatment effectiveness includes a number of factors, each of which contributes to the overall success of an intervention (Figure 1). Each step can independently and collectively impact the overall effectiveness of an anti-malarial treatment regimen. Factors related to poor patient acceptance and adherence not only threatens individual outcomes (recovery), but may lead to higher treatment costs (retreatment) and even resistance [10].

Focusing on the health system challenges to improving access and targeting without addressing factors determining adherence, may ultimately lead to suboptimal health outcomes. Given that resistance to artemisinin compounds has been reported in Southeast Asia [11], and the growing concerns about the spread of resistance and how to contain it, ensuring provider compliance and patient/caregiver adherence to treatment guidelines is even more important.

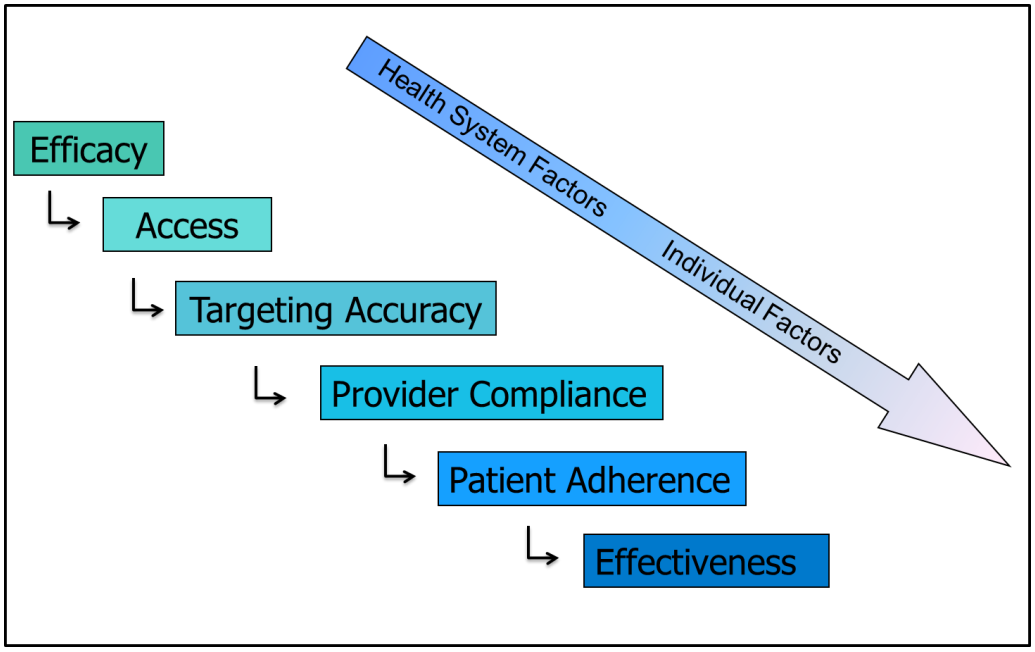

Figure 1 Treatment effectiveness pathway. This figure depicts each step along the pathway to malaria treatment effectiveness. At the top of the pathway are the health system factors such as choosing efficacious treatments such as ACT, improving access to those treatments and targeting treatments to those that need it most. The second half of the pathway depicts individual factors that can enhance or disrupt the effectiveness pathway such as provider compliance to treatment guidelines and patient/caregiver adherence to treatment regimens. Source: Original figure courtesy of Marcel Tanner, personal communication 2012 and manuscript published by, The malERA Consultative Group on Health Systems and Operational Research, A Research Agenda for Malaria Eradication: Health Systems and Operational Research. PLoS Med, 2011. 8(1): p. E1000397.

Strategies that address 'therapy-related' factors [12], such as co-packaging anti-malarials into blister packs, have been shown to improve adherence, and reduce the practice of using mono-therapies [9,13,14]. While co-packaging anti-malarial combinations ensures dispensing the correct combination of drugs, it does not reduce the total number of tablets or the frequency the drugs need to be taken. In addition, co-packaging does not necessarily change patient perception or tolerability of individual drugs, and patients may choose to take only one of the medications or not all of the tablets [15-17].

In an effort to overcome the limitations of co-packaged anti-malarial drugs and to improve adherence, several artemisinin-based combinations have been co-formulated; the most

common of these are artemether–lumefantrine(AL) and the new co-formulated versions of amodiaquine-artesunate (AQAS) and artesunate-mefloquine (ASMQ).

Measuring adherence to medications

Despite the large evidence base on adherence to treatment for both chronic and acute disease, no gold standard has been clearly established for measuring patient adherence to medications [18,19]. Adherence can be measured both directly and indirectly. The four most common methods for measuring adherence are: (i) electronic monitoring devices such as the medical event monitoring system (MEMS), (ii) pill counts, (iii) self- report through interviews; and (iv) biological assays [18-22]. Additionally, adherence to medications can be measured by reviewing medical records, patient diaries or by directly observing drug intake (as is often the case for drug efficacy studies).

The default gold standard for measuring medication adherence has been MEMS [18,23]. MEMS containers collect data on the frequency and timing of when the medication container was opened. Traditionally pill counts in the context of chronic disease occurred when patients came back to the health worker and the health worker 'counted' the number of remaining tablets thus determining whether the patient was adherent to the treatment protocol [22]. Enumerating the quantity of remaining tablets is rarely used alone, but usually in combination with patient interviews or self-reports. Although MEMS has been adopted as the gold standard for adherence to medications administered for chronic disease, it is not optimal for monitoring adherence to anti-malarial medications.

Bio-assays look at the levels of drug or their metabolites in a biological sample (usually blood or urine) taken from the patient shortly after they have taken their medications. Although this can provide a direct method of measuring whether a medication was ingested, such assays can be costly and are dependent on the availability of laboratory testing and thus are impractical in resource limited settings.

Thus, although a variety of methods have been applied to measure medication adherence, each method has both advantages and disadvantages. Therefore, no clear gold standard exists for measuring adherence for treatment of acute diseases (like malaria).

Adherence to anti-malarial drugs

In 2005, Yeung and White produced a comprehensive review of 24 studies on how antimalarials were used by patients [10]. As this review was undertaken in the infancy of the ACT era, two studies looked at artemisinin monotherapy treatments [24,25] and six studies looked at ACT; four in Asia [26-29] and two in Africa [30,31]. Only one study carried out in Uganda looked at a co-formulated ACT (AL) [31]. Results for adherence varied for ACT, ranging from 78% for a three-day regimen of AS + SP in Zambia [30] to a maximum of 93% for AL in Uganda [31]. Adherence was found to be generally better when "interventions focusing on provider knowledge and behaviour, packaging and provision of correct dosage" were implemented [10].

Since 2005, ACT, and in particular co-formulated versions of ACT have been scaled up across Africa. However, despite the key role adherence plays in treatment effectiveness, the evidence on adherence to ACT in operational settings is limited. In order to summarize the current evidence base on ACT adherence, a systematic review of current peer-reviewed literature was undertaken. In addition, the methods to measure adherence, definitions of adherence, and factors affecting adherence to ACT were also examined.

Methods

Search strategy

A systematic search of the published literature was undertaken in November 2012 and updated in April 2013. Three databases (Medline, Embase and Global Health) were searched using predefined search terms (see Additional file 1: Literature Review Search Strategy). References were imported into the electronic reference manager Endnote and duplicates removed. Bibliographies of manuscripts were searched and additional relevant references identified and, where appropriate, included in the review.

Titles and abstracts were screened for relevance based on the inclusion/exclusion criteria. Studies that reported adherence to malaria treatment were retained for further review. The full texts of the remaining studies were read by two different reviewers to ensure they met

the inclusion criteria and to improve the quality of the data extracted. Studies were included if they involved at least one ACT, had primary or secondary data on adherence, were found in a peer-reviewed journal, written in English, and published after 1990 and up to April 2013. We included any study that reported measuring adherence and/or levels of adherence to ACT, including effectiveness trials that had measured adherence as a secondary outcome.

Data extraction and presentation

An electronic matrix was developed in Microsoft Excel prior to the full-text review with predetermined characteristics. Studies were evaluated using quality measures adapted from the Critical Appraisal Skills Programme (CASP) [32], STROBE [33,34] and the CONSORT guidelines [35] to facilitate a comparison of quality across studies (see Additional file 2: Quality Assessment of Studies). Studies were independently assessed and information extracted by two reviewers and the findings were compared and compiled. A third reviewer settled any discordance between the initial two reviewers. Due to a lack of homogeneity among the studies a meta-analysis of the adherence data was not possible. This review provides a description of the study characteristics, methods and their findings presented by drug combination and study design.

Results

The search yielded 1,412 records, 424 of which were duplicate records and were subsequently removed (Figure 2). The titles and abstracts of the remaining records (988) were screened and 42 articles were found to be eligible for a full-text review. An additional nine studies were identified from the reference lists and were also included in the review. From the review of the full-text versions of the 51 articles, 14 studies were found to not meet the inclusion criteria. The search yielded 37 articles that evaluated patient adherence to ACT, which were subsequently reviewed and summarized.

Definitions used for ACT adherence

The definition of patient adherence was not standardized across studies, however the majority used a variation of the same definitions first used by Depoortere and Fogg [30,31],

and defined adherent patients/caregivers as those who reported to have taken the treatment as recommended (in terms of timing and dosage) with no tablets remaining. In the instance where the packaging was not available, the patients were classified as probably adherent.

Twenty-nine studies reported whether patients/caregivers took/administered all of the prescribed medication (using pill count, self-report or both methods), but did not report exactly how the medication was taken (i.e. timing, frequency and dose). Twelve of those studies expanded this definition of adherence and also investigated both the duration and timing of each dose in order to determine whether the drug was taken as recommended, but these were limited to studies investigating AL [36-47]. Some therapeutic effectiveness studies measured drug metabolites to determine if a treatment had been taken, thus the definition of adherence was only based on the presence or levels of drug metabolites in the blood [27,48].

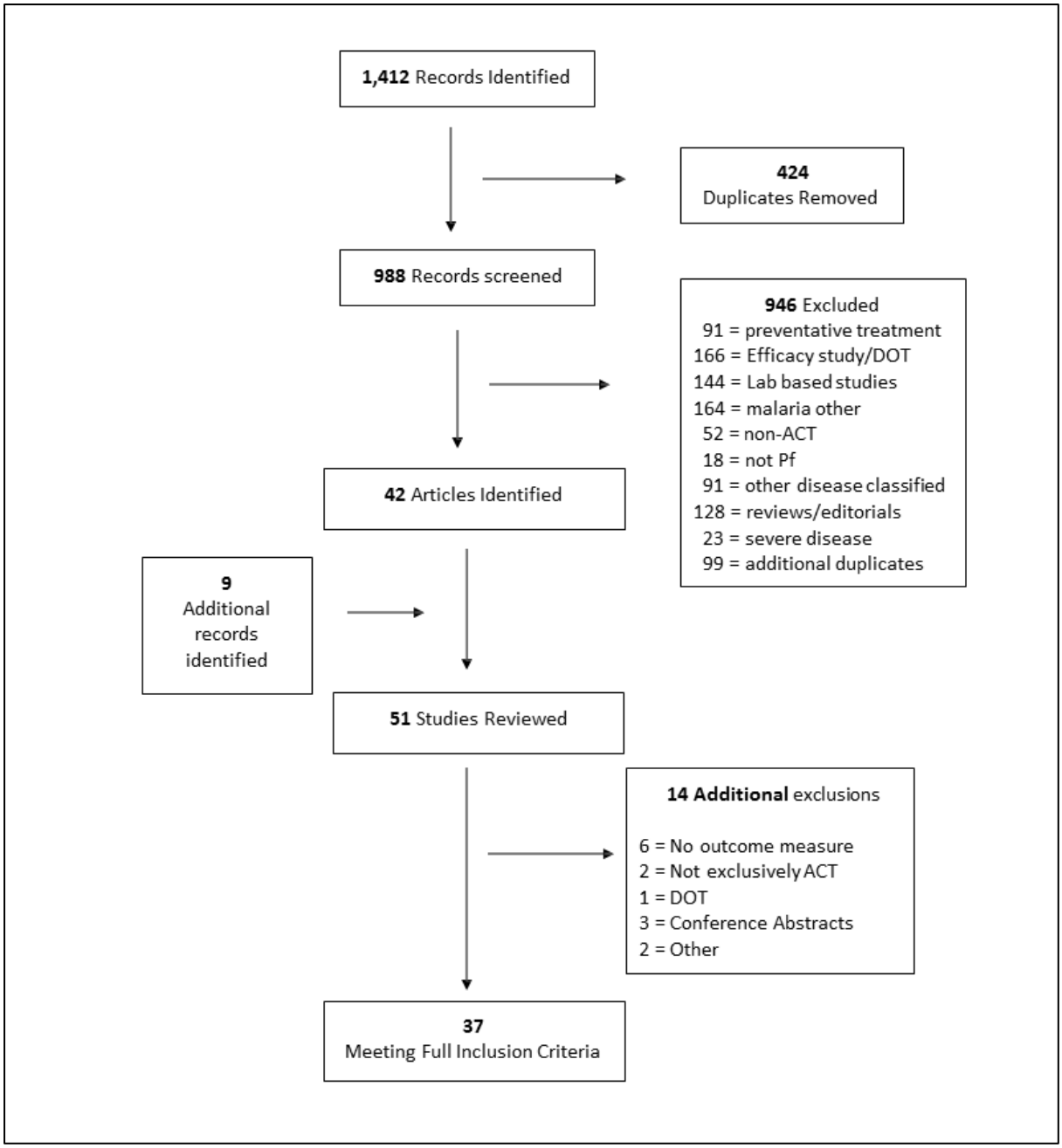

Figure 2 Systematic review process Flow diagram (adapted from PRISMA) describing the systematic review of the literature on ACT adherence

Methods of measuring ACT adherence

All four methods commonly used to measure adherence to medications were used to measure ACT adherence. Self- report from patients/caregivers alone [39-41,46,49-54] or in combination with pill counts was found to be the primary method of assessing adherence to ACT treatment [30,31,36-38,42-45,47,48,55-65]. Only one study in Ghana reported using self-report alone [66].

A single study in Malawi reported using MEMS to measure ACT adherence [67]. The use of MEMS was limited to a subset of patients and was subject to availability of the bottles. This measurement was used in combination with patient questionnaires and biological assays. Patients self-reported 100% adherence to AL, but with the MEMS only 92% were found to be adherent, suggesting that self- report might overestimate adherence.

Eight studies reported using biological assay methods, including five that evaluated lumefantrine blood concentrations [31,45,46,67,68] and three in which bio-assays were used for studies involving AS + MQ and comparator drugs [26,27,50]. Five of the studies used bioassay in combination with self-report [31,46,50,67,68].

Adherence to ACT

Artemether-lumefantrine

Almost half of the studies (17) looked at patient adherence to AL (Table 1), fourteen of which were conducted in East or Southern Africa [30,31,36-38,43,44,46,49,51,57,63,64, 68]. Only one study was conducted in West Africa (Ghana) within a study looking at the feasibility of Home Management of Malaria [42]. Two studies were conducted in Asia, one in Myanmar [47] and the other in Bangladesh [45].

Levels of adherence for AL ranged from as low as 38.7% in Ethiopia [43] to 96.0% in South Africa [49]. Of the 17 studies evaluating AL, two used cross-sectional household surveys [49,69], three were randomized controlled trials [45,57,64], two were pre-post intervention designs [42,51] and 10 used a prospective observational design [31,36-38,43,44,47,58,63,68]. The two cross-sectional studies, one conducted in South Africa and another in Tanzania found adherence rates to be 96.0% and 88.3% respectively [49,69]. A

RCT in Tanzania and another RCT in Bangladesh, both found adherence levels for AL to be greater than 90% [45,64]. In a third RCT in Uganda, patients were blinded to potential follow- up, and adherence was found to be only 65.8% [57]. Pre- post-intervention designs were used in Ghana and Kenya with varying adherence rates post-intervention (92.5% vs. 67.0% respectively) [42,51].

Despite similarities in measurement methods and contexts for the ten prospective observational studies, adherence measurements were inconsistent [31,36-38,43, 44,47,58,63,68]. Ngasala et al. found adherence to be as low 37% in Tanzania using blood lumefantrine levels [68] and Lemma et al. in Ethiopia found similar results (38.7%) using self-report and pill counts [43]. On the upper end of the spectrum adherence levels measured as high as 98.5% in Uganda and 89.5% in Myanmar both of which used self-report and pill counts [47,63].

Two studies presented day-7 lumefantrine levels to validate AL intake and correlate with treatment outcomes [67, 68]. Bell et al. found the median day-7 lumefantrine level to be 214 ng/ml, higher than their reference value (<175 ng/ml) for adequate treatment [67]. However, 4/167 samples were found to have below the lower limit of quantification for the assay and were excluded, but this was not linked by the authors to non-adherence. Ngasala et al. also reported median day-7 lumefantrine levels (205 ng/ml), but used a <280 ng/ml as the reference cut-off level and did not correlate lumefantrine levels with adherence [68].

Two additional studies compared lumefantrine blood levels between patients that had adhered to treatment and those that were considered non-adherent. In Uganda, day-3 lumefantrine levels in patients were 3.19 μg/ml in adherent compared 2.76 μg/ml in non-adherent patients, but the difference was not found to be statistically significant ($p = 0.46$) due to the limited sample size for the non-adherent group [31]. Simba et al. also found no significant difference (p-value not reported) in median blood lumefantrine concentrations on day-7 in patients that adhered (286 nmol/l) compared to those that did not adhere (261 nmol/l) [46].

A study in Bangladesh assessed day-7 lumefantrine levels for both validating AL intake and to compare adherence to non-adherence. Lumefantrine concentrations were not found to be different between patients receiving directly observed treatment (DOT) (860 ng/ml) versus patients with non-directly observed treatment (NDOT) (671 ng/ml) (p = 0.56) [45]. Furthermore, blood concentrations were also not significantly lower on day 7 in patients that did not adhere to treatment (680 ng/ml) compared to those that had adhered (626 ng/ml) (p = 0.31), as a result of the small number in the non- adherent group.

Amodiaquine plus artesunate

The combination amodiaquine plus artesunate (AQ+AS) was investigated in seven studies (Tables 2 and 3) [39,40,56,60,61,65,66]. Reported adherence varied, with a minimum of 48% in Sierra Leone [61] to a maximum of 93% in Ghana [40]. Only two studies (one in Benin and one in Madagascar) have evaluated co-formulated AQAS and the reported adherence was 91% and 83%, respectively [60,65].

Table 1 Studies that measure adherence to AL

Study design	Study author	Country	Study year	Population	Sample size	Measurement method	Adherence
Cross-sectional	Barnes [49]	South Africa	2002	All ages	239	Self-report	96.0%
	Simba [46]	Tanzania	2008	3-59mo	467	Bioassay (blood levels) plus self-report	88.3%
Prospective observational	Depoortere [58]	South Sudan	2002	6-59mo	107	Pill counts & self -report (questionnaire)	59.1%
	Fogg [31]	Uganda	2002	<5 yrs 5-14 yrs 15 + yrs	210	Pill counts & self-report (questionnaire) & bioassay	90.0%
	Ngasala [68]	Tanzania	2007	3-59mo	177	Bioassay (D7 lumefantrine levels)	37%
	Kabanywanyi [36]	Tanzania	2008	<13 yrs 13 + yrs	552	Pill counts & self -report (questionnaire)	89.2%
	Lemma [43]	Ethiopia	2008	>2mo	180	Pill counts & self -report (questionnaire)	38.7%
	Mace [38]	Malawi	2009	6-59mo 5-17 yrs 18 + yrs	868	Pill counts & self -report (questionnaire)	65.0%
	Ogolla [44]	Kenya	2009	12-59mo	73	Pill counts & self -report (questionnaire)	75.8%
	Lawford [37]	Kenya	2009	<15 yrs 15 + yrs	918	Pill counts & self -report (questionnaire)	64.1%
	Kalyango [63]	Uganda	2011	4-59mo	1256	Pill counts & self -report (questionnaire)	99.2% (I)[iii] 98.5% (C)
	Zaw Win [47]	Myanmar	2012[iv]	All ages	248	Pill counts & self -report (questionnaire)	89.5%
Pre-post intervention study	Chinbuah [42]	Ghana	2004/2005	6-59mo	363	Pill counts & self –report (questionnaire)	92.5%[v]
	Kangwana [51]	Kenya	2008/2009	3-59mo	3,288b; 3,182a	Self-report	53.1% Before 67.0% After[v]
RCT	Mubi [64]	Tanzania	2006	All ages	2156	Pill counts & self –report (questionnaire)	99.3% CD[vii] 97.4% RDT
	Rahman [45]	Bangladesh	2006/2007	>2 yrs	320	Pill counts & self –report (questionnaire) & bioassay	93.1%[viii]
	Cohen [57]	Uganda	2009	All ages	395	Pill count or Self-report	65.8%

[i]Self-report only. The lumefantrine levels were not found to be significantly different between those that adhered vs. those that did not adhere.

[ii]Based on a cut-off of 280 ng/ml. Only 37% had > 280 ng/ml.

[iii](I) = intervention and (C) = combination.

[iv]Year published.

[v]Although described as a pre-post intervention study, adherence data was only provided for the post-intervention phase.

[vi]Numbers presented are for the Intervention group. The control group was 40.5% before/49.4% after. There was no significant difference found between the two groups during the post survey.

[vii]CD = Clinical Diagnosis Group; RDT = Rapid Diagnostic Test Group.

[viii]Non-Directly Observed Treatment.

Table 2 Studies that measure adherence to AQ + AS

Study design	Study author	Country	Study year	Population	Sample size	Measurement method	Adherence
Cross-sectional	Beer [56]	Zanzibar	2006/2007	<5	210	Pill counts & self-report (questionnaire)	77.0%*
Prospective observational	Gerstl [61]	Sierra Leone	2008	All patients ≥ 1 year	118	Pill counts & self-report (questionnaire)	48.3%
	Ratsimbasoa [65]	Madagascar	2008/2009	<5	543	self-report	90.0%**
RCT	Asante [66]	Ghana	2009	15+	401	Pill counts	95.7% (S)*** 92.6% (U)

*Range 29-100%.
**Amodiaquine-artesunate co-formulated/fixed-dose combination.
***(S) = supervised; (U) = unsupervised.

Table 3 Studies that measure adherence as comparative studies

Study design	Study author	Country	Study year	Population	Sample size	Measurement method	Drugs	Adherence
RCT	Bell [67]	Malawi	2004-2006	>6 mo	841	Bioassay; self-report (questionnaire); MEMS*	AL	100% SR 92.0% MEMS
							CPD	99.2% SR 90.6% MEMS
							SP	100% DOT
	Dunyo [59]	Gambia	2004	6mo-10 yrs	1238	Pill Counts & self-report (questionnaire	AL	67.0%
							CPD	94.0%
	Faucher [60]	Benin	2007	<5 yrs	240	Recovery of drug blisters (pill-count)	AL	83.0%
							AQAS	91.0%
							SP	100%*
	Achan [55]	Uganda	2007/2008	6-59 mo	175	Pill Counts & care giver self-report (questionnaire)	AL	94.5%
							QNN	85.4%
Cross-sectional	Ajayi [39]	Ghana Uganda Nigeria	2008**	6-59 mo	244	Self-report: (timing, # doses, # of days)	AL AQ + AS	Composite 94%
	Ajayi [40]	Ghana Uganda Nigeria	2008**	6-59 mo	1096	Self-report: (timing, # doses, # of days)	AL AQ + AS	Composite 85%
	Alba [41]	Tanzania	2004-2008	All ages	32***	Self-report: (timing, # doses, # of days):	AL	69.0%
							SP	84.0%
							QNN	0%
							Composite	51.0%

*SR = Self-report; MEMS = Medical Event Monitoring System.

**In Ghana and Nigeria treatments were given at home unsupervised. In Uganda the first dose was administered as DOT.

***Information for AL was only available in the third survey conducted in 2008, so results presented are only from that survey.

Other combinations studied

The remaining formulations of ACT, including AS+SP, AS+MQ, dihydroartemisinin-piperaquine (DHA-PQ) and dispersible AL, have been investigated infrequently. Two studies looked at the combination AS+SP (Table 4); one study found adherence to be only 34% [30], while the other study found adherence to be twice as high at 75% [57]. In Asia, five studies reported on adherence to co-packaged AS+MQ (Table 5), with adherence reported to be >90% in four of them [26,27,50,52], while the fifth study conducted in Cambodia found adherence levels to be only 77% [27]. Two additional studies looked at adherence to ACT in general (Table 6) and found adherence rates to be less than 50% [48, 53]. There were no studies found that presented adherence data on the recently released co-formulated version of ASMQ or DHA-PQ.

Comparative studies/multiple combinations

Seven studies compared AL to at least one other ACT or anti-malarial combination (Table 3) [39-41,55,59,60,67]. In Uganda, mean adherence to AL was 10% higher than the mean found for quinine (95% vs. 85%; p = 0.0008) [55]. In the Gambia, adherence to AL was lower than that of chlorproguanil-dapsone (CPD) (67% versus 94%; p=<0.001), however, no association was found between adherence and treatment outcome for either drug [59]. In Malawi, adherence to AL was similarly compared to SP; self-reported adherence to AL or SP were both ≥ 99% and adherence, as measured by MEMS, was 92% vs. 90% [67]. Three studies compared AL to AQ + AS [39,40,60]. Faucher et al. directly compared the two combinations in Benin, and found adherence levels for co-formulated AQAS were higher (91%) than those of AL (83%), but the difference was not found to be significant (p=0.16) [60].

Reasons for non-adherence

Although reasons for non-adherence were not reported for all studies, there were similar trends found across the 8 studies that did report reasons for non-adherence. Four studies reported that one reason for non-adherence was that the mother/caregiver forgot to give

the medication [43,58,59,63]. Three studies found that the caregiver did not understand the instructions [58, 59] or gave the wrong dose of medication by giving two doses at once [44]. The limited availability of food/drink or a fatty meal/food was cited for both AL and AQ+AS as reasons for non-adherence [58,61,63]. In two studies, care- givers reported that their child was still sick after the first dose or did not improve, so the medication (AL or AQ + AS) was discontinued [43,61]. In contrast, two other studies found that the reason for non-adherence was due to the fact that the patient improved and medication was discontinued [44,63].

Furthermore, sharing or saving medications was found to be a reason for non-adherence in Ethiopia and Kenya [43,44]. In Ethiopia, Lemma et al. reported that patients were non-adherent to AL due to characteristics of the medication such as too many tablets, tablets were too big or bitter or that children refused to take the medication [43]. In Kenya, Ogolloa et al. cited that children did not like AL and were thus non- adherent [44] and Lawford et al. reported dislike for the medication as the reason for non-adherence [37]. Two other studies found similar findings and cited vomiting as the reason for non-adherence in children who took AQ + AS in Sierra Leone [61] and those who took AL in Uganda [63].

Table 4 Studies that measure adherence to AS + SP

Study design	Study author	Country	Study year	Population	Sample size	Measurement method	Adherence
Prospective observational	Depoortere [30]	Zambia	2002	6-59 mo	142	Pill counts & self-report (questionnaire)	39.4%
RCT	Kachur [62]	Tanzania	2003	<5	128	Pill counts & self-report (questionnaire) composite	75.0%

Table 5 Studies that measure adherence to AS + MQ

Study design	Study author	Country	Study year	Population	Sample size	Measurement method	Adherence
Cross-sectional	Yeung [54]	Cambodia	2002	All ages	44	Self-report	77.0%
Prospective observational	Congpuong [50]	Thailand	2008/2009	All ages	240	Self-report & bioassay	96.3%
	Meankaew [52]	Thailand	2009	All ages	534 total; 285*Pf*	Self-report	94.0%
	Na-Bangchang [26]	Thailand	1994/1995	All ages	126	Bioassay	98.1%*
	Shwe [27]	Myanmar	1996	All ages	380	Bioassay	99.5%**

*Full adherence reported; the majority of patients were adults.
**For both groups

Table 6 Studies that measure adherence to unspecified ACT combinations

Study design	Study author	Country	Study year	Population	Sample size	Measurement method	Adherence
Cross-sectional	Onyango [48]	Kenya	2012*	<13	297	Self-report	47.0%
	Watsierah [53]	Kenya	2011*	<13	297	Self-report	29.4% dose 33.0% duration

*Publication year used as year of study unknown.

Factors associated with adherence to ACT

Demographic factors, such as sex, socio-economic status or age were not significantly or consistently associated with adherence [30,31,37,38,43,45-48,54,56,57,61-63]. However, two studies did report a significant association between age of the patient and the level of adherence [37,38]. Lawford et al. found both the age of the respondent (caregiver) and the age of the patient were significant factors associated with adherence in Kenya. Older caregivers (between 25–50 years of age) had 1.65 (95% CI=1.10-1.85) the odds of being fully adherent, compared to younger caregivers (<25 years) [37]. The study also found that older patients (15+ years) were more likely to be adherent compared to those <15 years (OR=1.37; 95%CI=1.02-1.85). Mace et al. also found that younger patients (<5 years of age) in Malawi were less likely to be adherent to AL (OR=0.05; 95%CI=0.3-0.8; p=0.05) compared to older patients (18+ years) [38].

Education levels and literacy were both found to be significantly associated with ACT adherence in five studies, with higher levels of education and/or literacy positively associated with adherence [30,31,48,56,57]. In Zanzibar, Beer et al. reported that caretaker education (7+ years) was a significant predictor of adherence (OR=5.08; p=0.008) [56]. In Zambia, patients whose caretakers had some education had a significantly lower risk of non-adherence (RR=0.46; 95%CI=0.22-0.95) [30]. Similarly, in Uganda patients and/or caregivers that had attended at least some secondary school were 22% more likely to be adherent (p=0.024) in one study [57] and in Uganda a lack of caregiver formal education had a significant association with non-adherence (OR=3.1; p=<0.05) [31]. Another study in Kenya found that higher education level (OR=0.074; p=<0.01) and the ability to read (OR=0.285; p=<0.01) were both positively associated with adherence to ACT [48].

Language was also found to impact adherence. Caregivers in Uganda that could read English were found to have 0.47 fewer doses left compared to those that could not read English (p=0.024) [57]. Depoortere et al. found that giving instructions on administration of treatment to caregivers in their mother tongue lowered the risk of non-adherence (RR=0.46; 95%CI=0.28 to 0.77). In addition, patients given the first dose as directly observed treatment (DOT) at the health centre were 2.4 times more likely to be adherent (p=0.009) [30].

Patient/caregiver knowledge or understanding of treatment dose was found to be a significant predictor of adherence in two studies [37,63]. Patient preference or dislike for a specific drug or ACT was found to be associated with adherence in Kenya and Malawi [37, 38]. And Kalyango et al. found that some signs and symptoms of patients such as no reported fever (OR=3.3), caregivers' perception that disease was not severe (OR=2.0) and vomiting (OR=2.6) were all found to be associated with non-adherence [63]. Achan also found that vomiting was a predictor of non-adherence (p=0.02) [55].

Mace et al. found that caregivers receiving instructions for treatment administration with a visual aide or medication package were slightly more likely to adhere to AL in Malawi (OR=2.5; p=0.02) [38]. Other aspects that have to do with taking or administering ACT, which have been thought to improve adherence, such as packaging doses together, providing pictorial instructions, simplicity of dosage instructions and number of pills were not prominent factors investigated. One study did report that giving the exact number of tablets for the prescribed dose was associated with adherence [56], suggesting that pre-packaged doses should improve adherence. Almost all of the patients in a Tanzanian study reported that the pictogram printed on the packages and the blister packaging depicting the correct treatment doses were helpful, but the impact of this on adherence was not assessed [36].

Discussion

Over the past decade, substantial efforts have been made to increase access and targeting of ACT for the effective management of malaria. In order to ensure that efficacious drugs are also effective in routine heath care systems, patient/caregiver adherence is important. This review summarizes the current evidence base on ACT adherence levels, adherence definitions and measurement as well as factors associated with adherence to ACT.

Adherence levels

ACT adherence levels varied, from less than <30% for ACT in general in Kenya [53] and up to 100% adherence to AL in Malawi [67]. The lack of homogeneity in findings and the large range in adherence levels can be attributed not only to the variability between study settings, study designs and ACT formulations, but also as a result of differences in study implementation such as questionnaire/interviewing methods, blinding patients/caregivers to follow-up and study design features (e.g. RCT vs. observational).

For example, the questionnaire used by Kabanywanyi et al. to assess AL adherence in Kenya was semi- structured with open-ended questions embedded within the questionnaire [36]. Whereas the questionnaire used by Lawford et al. (also looking at AL adherence in Kenya) was more structured and resembled a malaria indicator survey and thus collected a different type of data [37]. Despite similar contexts and drug regimens, the findings were different with one study finding adherence to be only 64.1%, while the other found adherence to be as high as 89.2%.

Ideally, standardized, comprehensive definitions and measuring tools would be used to assess adherence, including a definition which incorporates duration, timing and frequency of dose. However, we found that this comprehensive definition was only utilized for observational studies that looked at AL, a regimen requiring multiple doses per day. In contrast, randomized controlled trials (RCTs) looked primarily at whether the drug was taken and not necessarily as to when or how it was taken.

For certain ACT formulations, such as AL, timing is important to the overall effectiveness of the regimen and should, therefore, be taken into account when determining adherence levels. From a public health perspective, a more synchronized evidence base on how and when patients take ACT can lead to more patient friendly packaging and dosing instructions. Therefore, a standardized definition of adherence would be useful to enable comparison between ACT regimens as well as to help identify contextual trends.

Factors associated with adherence

Little is known with regard to the determinants of adherence to ACT. Findings and trends were not consistent across studies. Demographic factors, such as sex, socio-economic status or age do not seem to be factors strongly or consistently associated with adherence [30,31,37,38,43,45-48,54,56,57,61-63]. However, it is important to note that some studies were not actually representative and/or powered to look at age groups. Two studies did find a significant association between age of the patient and the level of adherence, both suggesting that younger patients were less likely to be adherent. In Malawi, children less than five were less adherent than older children [38]; while in Kenya patients less than 15 years of age were less adherent than older patients [37].

Previously, age has been reported as a risk factor for poor adherence to non-ACT regimens [16], suggesting that age related factors should be considered when developing anti-malarial regimens and communication campaigns. Vomiting has also been found to be negatively associated with adherence to both AQ + AS and AL [61, 63], however, it was also considered as exclusion criteria for some studies or not accounted for when defining adherence in others. As vomiting can be influenced by severity of disease as well as treatment regimen and patient/caregiver behaviour after vomiting is influenced by knowledge provided by health workers, care should be taken when attributing non-adherence to vomiting. Further investigations surrounding vomiting and related factors and the impact on adherence is warranted.

Study designs

As adherence is difficult to measure accurately retrospectively, the majority of studies (17) were found to be prospective observational studies. Although many of these were similar in

design, differences in context and study regimes made direct comparisons challenging and precluded data synthesis.

Cross-sectional household surveys [40,70] and effectiveness studies [45,55,59,60,67], reported higher levels of adherence, however this can be attributed to the study design. In the cross-sectional surveys, adherence questions are asked retrospectively; patients or caregivers were asked to recall how they took or gave the ACT. Cross-sectional surveys are vulnerable to recall bias, particularly as the time frame for recall is often two or more weeks after receiving treatment, and thus may over- or underestimate adherence levels.

Furthermore, cross-sectional household surveys, which are often influenced by the Roll Back Malaria (RBM), Malaria Indicator Survey (MIS), focus primarily on the treatment seeking process and not on how one particular regimen was taken (dose & timing), thus offering an indication of adherence, but not an exact measurement. Additionally, patient knowledge or recognition of the drugs may not be sufficient through these types of surveys. Likewise, differences in nomenclature may play a large role in understanding the survey questions, whereby the study researchers may use the actual drug names; respondents may use local names to describe the same medication. To address this, one study carried out in Kenya made treatment charts with examples of drugs to assist respondents with their recall [48], however, this was not the norm.

Prospective observational studies that interviewed patients or caregivers the day following the last treatment, should have better recall, however, the accuracy of the measurement is dependent on how patients/caregivers were recruited and whether they knew they would be followed up at a later date. In studies like that of Cohen et al. and Gerstl et al. where patients were blinded to potential follow-up, adherence levels were lower than other studies [57,61]. Souares et al. found similar results in Senegal, where patients were also blinded to follow-up visits after receiving treatment for amodiaquine plus sulphadoxine-pyrimethamine (AQ + SP), and reported an adherence rate of 64.7% [16]. Therefore, one could consider that participants that were aware of future follow-up visits at the time of recruitment may adhere better than those that do not.

Effectiveness study designs (RCT and pre-post designs) have similar challenges, as patients are enrolled and consent to participation prior to taking part in the study. In the majority of studies, patients/caregivers knew that they were enrolled in a study and therefore may have altered their behaviour to be more favourable (i.e. Hawthorn effect).

Methods of measuring ACT adherence

Although studies on adherence to antimalarials have been conducted for over a decade, methodologies and definitions of adherence still lack standardization. In a number of studies the definition for adherence was categorized as; probably adherent, probably non-adherent and non-adherent. This approach to defining adherence is crude and imprecise and may lead to an individual's adherence status being misclassified resulting in an over- or underestimation of adherence.

Most of the methods used to measure adherence to anti-malarials were developed measuring non-ACT formulations [10], yet they are still widely used to measure adherence to ACT today. However, many of the current measurement methods used are suboptimal as malaria is typically found in countries with limited resources where patients often live in remote or hard to reach areas, which makes follow-up difficult and biological assays impractical.

Currently, questionnaires for ACT adherence are not standardized and follow more complex household survey structures similar to the RBM malaria indicator survey and demographic and health surveys. For both HIV and TB treatment regimens standardized questionnaires have been used to assess treatment adherence. Some questionnaires are long and detailed (e.g. AIDS Clinical Trials Group adherence questionnaire), while others are short or abbreviated versions, which can be used during patient consultations and still provide a relatively accurate adherence measurement (e.g. the Brief Medical Questionnaire (BMQ) and Morisky Scale) [71-73]. Al- though questionnaires utilized for chronic disease medication adherence are not directly translatable to acute illnesses such as malaria, the idea of a short and standardized questionnaire that can be easily implemented in low resource settings would make it easier to routinely assess adherence to ACT.

Although measuring adherence through self-report is operationally less expensive and easier to implement, it is subject to social desirability bias, which may overestimate adherence. Study designs should take this into account by blinding patients/caregivers to potential follow-up visits as well as asking about medication intake in different ways during the interviews. MEMS and biological assays are more objective methods to measure adherence and may offer more precise adherence measurements, however, they can both be costly and biological assays may not be possible for all ACT combinations. Furthermore, MEMS strategies may alter packaging, which may impact the way in which patients consume medications [9,13,14].

Further consensus is needed with regard to translating bio- assay data into a measurement of adherence/non-adherence. Studies in this review found that biological assays were primarily incorporated into effectiveness studies looking at supervised versus unsupervised administration AL treatment with the purpose of validating whether the patient had ingested the medication. Although this method is itself objective in terms of measuring drug metabolites in the blood, interpretation of the results can be problematic. Absorption levels for lumefantrine are known to be variable due to sub- optimal absorption with low fat intake [68,74,75]. None of the studies collected information on fat intake at the time of assessing adherence, thus this method may underestimate adherence levels.

Only three studies compared day-7 lumefantrine blood levels between adherent and non-adherent patients, but no study found a significant difference between the two groups [31,45,46]. Furthermore, all three studies had limited numbers of patients that were non-adherent, thus limiting their power to detect differences. For bioassays to be a viable method for measuring adherence to AL, additional studies with larger samples may be needed in order to determine if there is a correlation between blood lumefantrine levels and adherence status

Limitations of the review

This review has several limitations. First, information on adherence to ACT is often a secondary outcome embedded into larger studies, and details on the measurement of

adherence outcomes are often missing or not re- ported. As a result, studies with limited information on adherence may have been missed or excluded. Second, this review was limited to peer-reviewed publications. As adherence can be considered an operational issue, much of the data collected on ACT in developing countries may be unpublished. Third, the majority of studies regarding ACT adherence (~60%) have been conducted in East or Southern Africa and the range of ACT formulations studied was narrow, with over half of the studies looking primarily at adherence to AL. Only seven studies compared adherences levels between ACT formulations, thus lacking critical information that may improve access and targeting ACT and inform policy decision- making. Fourth, as the studies were conducted in a variety of countries with different ACT combinations, amongst different age groups and populations, in different settings with different methods and sample sizes, direct comparisons of ACT adherence levels should be reviewed with caution. However, trends in adherence levels and associated factors can be noted and further explored. Finally, as adherence may be influenced by cultural and contextual factors, this review pro- vides only a narrow picture of how ACT is taken and further qualitative investigations should be considered.

Conclusions

This review highlights the weak evidence base on ACT adherence. Results suggest that ACT adherence levels varied substantially between study populations and comparison between studies was challenging due to differences in study design, definitions, and methods used to measure adherence. Standardising methodologies for both self-report and bioassays used for evaluating adherence of different formulations across diverse contexts would improve the evidence base on ACT adherence and effectiveness; namely, specific and measurable definitions for adherence are needed for both methodologies. Additionally, further studies of the individual factors and barriers associated with non-adherence to ACT are needed in order to make informed policy choices and to improve the delivery of effective malaria treatment.

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Additional files

Additional file 1: Literature review search strategy. Table with details about the databases, key terms, limits, as well as the inclusion/exclusion criteria used for this review.

Additional file 2: Quality assessment of studies. This file contains three tables which showing how the quality studies were assessed. Table 1 shows the quality assessment criteria and results for Pre-/Post-Intervention and RCTs. Overall study quality was assessed to be good; however there were very few studies that incorporated blinding into the studies. Table 2 shows quality assessment criteria and results for prospective observational studies. Although the outcome definition and measurement were well defined, there were weaknesses in reporting participant selection, limited range of co-factors assessed and details about the statistical analysis, with few providing power calculations, confidence intervals or p-values. Table 4 shows quality assessment criteria and results for household cross-sectional surveys. Overall quality was assessed to be good; however information participant selection was limited particularly with regards to generalizability. Additionally, statistical details such as power calculations and refusal rates were not always reported.

Abbreviations

ACT: Artemisinin-based combination therapy; AL: Artemether-lumefantrine; AMFm: Affordable Medicines Facility – malaria; AQAS: Amodiaquine-artesunate co-formulated; AQ + AS: Amodiaquine plus artesunate co-packaged; ASMQ: Artesunate-mefloquine co-formulated; AS + AS: Artesunate plus mefloquine co-packaged; AS + SP: Artesunate plus sulfadoxine-pymetheramine; BMQ: Brief medical questionnaire; CASP: Critical Appraisal Skills Programme; CONSORT: Consolidated Standards for Reporting Trials; CPD: Chlorproguanil-dapsone; DHA-PQ: Dihydroartemisinin-piperaquine; DOT: Directly observed therapy; GFATM: The global fund to fight AIDS, tuberculosis and malaria; MEMS: Medical event monitory services; MIS: Malaria indicator survey; NDOT: Non-directly observed treatment; PMI: The President's Malaria Initiative; OR: Odds ratio; RBM: Roll Back Malaria; RR: Relative risk; RCT: Randomized Controlled Trial; STROBE: The strengthening the reporting of observational studies in epidemiology; WHO: World Health Organization.

Competing interests

The author's declare that they have no competing interests.

Authors' contributions

KB and DC conceived and designed the review. KB and ML conducted the review and synthesized the findings. KB conducted the analysis and wrote the first draft of the manuscript. KB, DC, ML and SS revised and edited the manuscript. All authors read and approved the final version of the manuscript.

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Additional File 1 Literature Review Search Strategy

Databases	1. Medline 2. Embase 3. Global Health
Key/Search Terms	malaria or antimalarial* or anti-malarial* combination adj1(therap* or treat* or drug* or medic*) Sulfadoxine-pyrimethamine or Sulfadoxine/pyrimethamine or SP or fansidar or Sulfadoxine-pyrimethamine plus Chloroquine or Sulfadoxine-pyrimethamine/Chloroquine or CQ+SP or Sulfadoxine-pyrimethamine plus amodiaquine or Sulfadoxine-pyrimethamine/amodiaquine or AQ+SP Sulfadoxine-pyrimethamine plus mefloquine or Sulfadoxine-pyrimethamine/mefloquine or SP+MQ or Fansimef Quinine and tetracycline or quinine/doxycycline or quinine/clindamycin Azithromycin-Chloroquine or azithromycin+Chloroquine or Azithromycin and Chloroquine or AZ+CQ artemisinin or artemisinin-based adj3(therap* or treat* or medic* or drug*) amodiaquine-artesunate or amodiaquine+Artesunate or ASAQ or AQAS or Winthrop or coarsucam Artesunate-mefloquine or artesunate/mefloquine or ASMQ or Artequin AL or artemether-lumefantrine or artemether/lumefantrine or coartem or artemether or lumefantrine Sulfadoxine-pyrimethamine plus artesunate or Sulfadoxine-pyrimethamine/artesunate or AS+MQ or Sulfadoxine-pyrimethamine and artesunate dihydroartemisinin-piperaquine or DHAPQ or dihydroartemisinin/piperaquine or *Duo-Cotecxin* or *Artekin* chlorproguanil-dapsone-artesunate or CDA or CD+A or

	lapdap or Artesunate/SP or artesunate-pyronaridine azithromycin-artesunate or azithromycin + Artesunate or AZ+AS or azithromycin and Artesunate or azithromycin/artesunate adherence or compliance or use* or effectiveness adj2(treat* or medic* or patient or therap* or drug*)
Limits	
Date	1990-
Language	English
Types of People/population	Humans of all ages
Location	All regions
Type of publication	Peer reviewed article
Inclusion/Exclusion Criteria	
Types of Studies	Not specified
Types of intervention	1) Treatment of malaria with ACTs
Exclusion Criteria	1) No severe disease 2) Preventative/Chemoprophylaxis 3) Efficacy study 4) Pharm kinetics or other laboratory studies 5) Non *falciparum* malaria 6) Non-ACT studies 7) Other diseases 8) Reviews/commentaries 9) Other malaria related interventions
Type of outcome measures	• Proportion that are adherent/non-adherent
Secondary Information	• Definitions of adherence • Measurement of adherence • Factors/Determinants of adherence
Other areas of interest	• Impact of non-adherence • Reasons for non-adherence
When search conducted	November 2012 Updated April 2013

Additional File 2: Quality Assessment of Studies

Table 1: Quality assessment – Pre-/Post-Intervention & RCT Studies

	Authors (Year)	Groups			Blinding			Follow- up		Analysis				
		Arms	*Random*[1]	*Balance*[2]	*Subjects*	*Investigator*	*Analysis*	*Objective*[3]	*LTFU*[4]	*Power*[7]	*Stat Methods*	*Effect size*[8]	*CI*[9]	*P-Value*[10]
Intervention Studies	Chinbah [1]	1	N	N	N	N	N	Y	n/a	N	N	N	N	N
	Kangwana [2]	2	Y	Y	Y	N	N	Y	n/a	Y	Y	N	Y	Y
RCT	Achan [3]	2	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
	Asante [4]	2	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
	Bell [5]	3	Y	Y	N	N	N	Y	Y	Y	Y	N	N	Y
	Cohen [6]	1	N	Y	Y	N	N	Y	Y	N	Y	N	Y	Y
	Dunyo [7]	2	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y
	Faucher [8]	3	Y	Y	N	N	N	Y	Y	Y	Y	N	N	Y
	Kachur [9]	3	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y
	Mubi [10]	2	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	N
	Rahman [11]	2	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y

[1] *Allocation / sampling process described and truly random ;* [2] *Comparison group characteristics* provided and balanced; [3]Objective measures of outcome used; [4]Numbers of subject lost to follow up provided and analysed; [5]Intention to Treat analysis used; [6]Identical follow-up in each arm; [7] Power calculation provided; [8] Measure of effect provided (e.g. OR / RR); [9] Confidence Intervals provided; [10] P-Value provided

Table 2: Quality assessment – Prospective Observational Studies

Author (Year)	Selection			Outcome		Co-factors			Analysis			
	Represent.[1]	*Refusals*[2]	*Power*[3]	*Definition*[4]	*Measured*[5]	*Range*[6]	*Definition*[4]	*Measured*[7]	*LTF*[8]	*Effect size*[9]	*CI*[10]	*P-Value*[11]
Congpuong [12]	N	N	N	Y	Y	N	N	N	N	N	N	N
Depoortere [13]	N	N/A	N	Y	Y	N	N	Y	Y	N	Y	N
Depoortere [14]	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N
Fogg [15]	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gerstl [16]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kabanywanyi [17]	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N
Kalyango [18]	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Lawford [19]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lemma [20]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N
Mace [21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Meankaew [22]	N	N	N	N	Y	N	N	Y	N	N	N	N
Na-Bangchang [23]	N	N	N	Y	Y	N	N	N	Y	N	N	N
Ngasala [24]	Y	Y	N	Y	Y	N	N	N	Y	N	N	N
Ogolla [25]	N	N	N	Y	Y	N	N	N	Y	N	N	Y
Ratsimbasoa [26]	N	N	N	Y	Y	N	N	N	Y	N	Y	Y
Shwe [27]	N	N	N	Y	Y	N	N	N	N	N	Y	Y
Zaw Win [28]	N	N	N	Y	Y	Y	Y	N	N	N	Y	Y

[1] *Sample representative of wider population of interest (selection bias);* [2] *Response rate provided and* explained; [3] Power calculation provided; [4] Outcome / co-factor(s) clearly defined; [5]Outcome collected appropriately (misclassification bias); [6] Suitable range of variables collected; [7] Clear methods explained for collection (misclassification bias); [8] Loss to follow-up reported [9] Measure of effect provided (e.g. OR / RR); [10] Confidence Intervals provided; [11] p-values provided

Table 3: Quality assessment – Household Cross-sectional Surveys

Author (Year)	Selection				Outcome		Co-factors			Analysis			
	Sampling[1]	*Refusals*[2]	*Power*[3]	*Represent.*[4]	*Definition*[5]	*Measured*[6]	*Range*[7]	*Definition*[5]	*Measured*[8]	*Adjustment*	*Effect size*[9]	*CI*[10]	*P-Value*[11]
Ajayi [29]	N	N	N	N	Y	N	N	N	N	N	N	Y	N
Ajayi [30]	N	N	N	Y	Y	Y	N	N	N	Y	N	N	Y
Alba [31]	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y
Barnes [32]	N	Y	N	N	Y	Y	N	N	N	Y	N	N	N
Beer [33]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Onyango [34]	y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Simba [35]	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N
Watsierah [36]	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y
Yeung [37]	Y	Y	N	N	Y	Y	N/A	N/A	N/A	Y	Y	Y	N

[1] *Simple random sampling (SRS) or reasonable alternative where SRS not possible;* [2] *Response rate* provided and explained; [3] Power calculation provided; [4] Sample representative of wider population of interest (selection bias); [5]Outcome/co-factor(s) clearly defined; [6] Outcome collected appropriately (misclassification bias); [7] Suitable range of variables collected; [8] Clear methods explained for collection (misclassification bias); [9] Measure of effect provided (e.g. OR / RR); [10] Confidence Intervals provided; [11] p-values provided

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3.3 Updates to the literature

This section presents an update of the literature since the publication of the systematic review. Overall, the main conclusions of the review remain relevant even in light of the additional literature available.

3.3.1 Other reviews on antimalarial adherence

In addition to this systematic review, two other reviews on adherence were published in January 2014. The first review by Fuangchang et al., focused on interventions that improve adherence to antimalarials [1]. The review identified 16 studies that met the inclusion criteria as comparative studies that investigated the effectiveness of interventions for improving antimalarial drug adherence for uncomplicated malaria. The majority of studies involved improving adherence to chloroquine or other non-artemisinin antimalarials. However, five of the 16 studies identified looked at interventions to improve adherence to ACTs [2-6]; all five studies were also included in our review.

The authors identified six intervention types: packaging aids (5 studies) [7-11]; visual media (1 study) [12]; combined visual media and verbal information (2 studies) [12, 13]; community education (3 studies) [5, 14, 15], supervision of medication intake (2 studies)[6, 16]; and convenient administration (2 studies for once daily administration [3, 4] and 2 studies for shorter duration of treatment [2, 17]; however a "most effective" intervention was not identified. The authors do suggest that combinations of these interventions may have the highest potential of effecting change in adherence behaviours. Finally, as with our review, the authors found that the concept of adherence within the identified studies was not well defined and the heterogeneity of study designs prohibited a meta-analysis.

The second review by Bruxvoort et al. [18] updated the Yeung and White review from 2005 [19] and focused on adherence to all antimalarials. The review identified 55 studies with quantitative data on patient adherence to antimalarials for the treatment of malaria (40 from Africa, 11 from Asia and four from Latin America). In contrast to our review which identified 37 studies that assessed adherence to ACTs, the authors of this review only found 26 studies all of which were included in our original review; however, we found 11 additional studies

that measured adherence to ACTs. Similar to our review, the authors reported that the majority (18) of ACT adherence studies were measuring adherence to AL. Likewise, the authors also reported significant variations in study design, definitions and methods of measuring adherence.

Unlike our review which focused on ACTs, the review by Bruxvoort looked at all antimalarials and examined the effects of study participation on adherence measurements. The authors suggest study participation may inflate adherence estimates and propose that future studies remain aware of the impact that study participation may have on medication adherence. Finally, despite suggestions by Yeung and White in 2005 that the methodology for measuring adherence to antimalarial drugs treatment needs improvement [19], both our review and that of Burxvoort et al. conclude that there remains a lack of standardisation for assessing adherence to antimalarial drugs.

Finally, a third review published in 2016 by Anyanwu et al. used a narrative synthesis approach to compile evidence on the socioeconomic determinants of antimalarial drug use behaviours [20]. The review identified 17 quantitative studies (16 in Africa and 1 in Myanmar) that met the inclusion criteria. Sixteen studies reported associations for adherence/non-adherence (16 studies) while five reported on self-medication or presumptive diagnosis behaviours. While the review collected information on drug use for all antimalarials, 12 of the 16 reporting on adherence included ACTs [21-33].

The authors identified six sociodemographic factors associated with antimalarial drug use: education level, wealth/income level, occupation/source of income, literacy, type of settlement (rural vs. urban), and household size, with education level and wealth as the two most cited. Similar to our review, this review found that studies defined adherence as administering the medication as prescribed, and pill counts and self-report were the primary methodologies used to measure adherence.

The authors report that over half (10) of the studies reported on the relationship between higher education level and adherence [21-29, 33]. However, these findings were not consistent across the identified studies, as six studies reported a statistically significant

positive association between higher education level and adherence [21-25, 28], whilst four of the ten studies reporting on education levels found no association between education and adherence [26, 27, 29, 33]. Further to this, two studies, one in Kenya and one conducted in Uganda found a significant positive association between the ability to read and adherence [24, 28].

Six studies reported on the relationship between income level and antimalarial use, all of which took place in Africa. Only three of the studies looked at the relationship between non-adherence and income level [28, 29, 31]. The study from Tanzania did not conduct a statistical analysis for income level [29]. However, the two studies from Kenya found that lower income level was statistically significantly associated with non-adherence [28, 31].

3.3.2 Additional ACT adherence studies

Our published systematic review found 37 studies that reported on adherence to ACTs [34]. Using similar search terms and references lists additional studies published after the review in 2014 were identified. A total of 19 additional studies have been published that measured adherence to ACTs (Table 3.1), raising the total number of ACT adherence studies to 56. New studies measured adherence to artemether-lumefantrine (AL), amodiaquine-artesunate (AQAS) and Dihydroartemisinin-piperaquine (DHAPQ); however, no studies evaluated fixed-dosed artesunate-mefloquine nor the newer WHO-approved combination of pyronaridine-artesunate. Our original review found only three studies that compared two or more ACTs, one conducted in Benin which compared AL with fixed-dose AQAS [4] Additionally, two other publications compared adherence to AL with co-packaged AQ+AS for community based treatment in a multi-site trial conducted in three countries: Ghana, Uganda, and Nigeria [35, 36]. Since our review, three new comparative studies have been carried out, including one comparing adherence of AL to AQAS in Ghana [37, 38] and two studies comparing adherence of AL to DHAPQ in Malawi and Kenya [39, 40].

AL is still the most widely studied ACT, with over half (30/56) of all adherence studies assessing AL (Table 3.2). Two-thirds (6/9) of the new studies that evaluated adherence to AL reported similar levels of adherence, ranging between 60% and 80% using self-report and pill counts [23, 41-46]. Additionally, Talisuna et al. reported on the impact of text-message

reminders on adherence to the paediatric formulation for AL, and found comparable levels of treatment completion between the intervention group (92.3%) and control group (92.4%) [47]. Furthermore, levels of timely completion were also comparable (intervention 69.2% and control 70.8%). Similarly, in 2015 Wassuna *et al*. evaluated the impact a community-level awareness intervention had on treatment-seeking behaviour and use [48]. The authors found no significant difference between pre-intervention (60.2%) and post-intervention (64.5%) adherence to AL (p=0.58).

There were no further studies for co-packaged AQ+AS, as countries switched over to co-formulated AQAS. Three additional prospective observational studies were published for co-formulated AQAS, two in the Democratic Republic of the Congo (DRC) and one in Ivory Coast [49-51]. All three used self-report, and pill counts to assess adherence. The two studies in DRC had comparable levels of adherence with Gerstle *et al.* reporting 75% [50] and Siddiqui *et al.* reporting 62% of participants probably adherent [51]. Assi *et al.* found very high adherence to AQAS in the Ivory Coast (97.2%) [49].

Since our original review, two studies have been published that measured adherence to DHAPQ which produced similar results. The study in Kenya found adherence to DHAPQ to be 87% [40], while in Malawi adherence was 88% [39].

3.3.3 Summary

In summary, this section provides updates to the published systematic review previously presented in this chapter, by summarising new adherence studies, as well as three antimalarial adherence-themed reviews. In contrast to my review, all three of the other reviews chose to look broader than ACTs and include all antimalarials. Fuangchan et al. suggest that multiple interventions should be used to improve adherence to antimalarials [1]. Most of the studies in their review were assessing interventions to improve adherence to chloroquine with only five studies looking at interventions to improve adherence to ACTs, suggesting that further intervention studies to improve ACT adherence are warranted. Finally, although the evidence base is increasing for ACT adherence, the conclusions of our review remain supported as measuring ACT adherence still lacks sufficient standardisation and remains narrowly focused on AL.

Table 3.1 Summary of studies measuring adherence to ACTs

ACT Regimen	Number of studies 2013	Number of studies 2018	Adherence Range
artemether-lumefantrine	21	30	38% in Ethiopia to 96% in South Africa
amodiaquine + artesunate (co-pack) [1]	3	3	48% in Sierra Leone to 93% in Ghana.
amodiaquine-artesunate (fixed-dose)[2]	2	5	62% in DRC to 97% in Ivory Coast
artesunate + sulfadoxine-pymetheramine	2	2	34% in Zambia to 75% in Tanzania.
artesunate + mefloquine	5	5	>90% in all but Cameron (77%)
dihydroartemisinin-piperaquine[3]	0	2	87% in Kenya to 88% in Malawi
pyronaridine-artesunate	0	0	Only recently recommended by WHO
unspecified ACT	2	4	29% to 47% in Kenya
TOTAL	**37**	**56**	

[1] Two of the studies were comparative and also included AL

[2] Three of these studies were comparative and also included AL.

[3] Both studies also measured adherence to AL

Table 3.2 Details for studies measuring adherence to ACTs since 2014

Study Design	Study Author	ACT	Country	Study Year	Measurement Method	Adherence Levels	Comments
Cross-sectional	**Wasunna [48]**	AL	Kenya	2015	Empty package and/or self-report	Pre-intervention 60.2% Post- intervention 64.5%	Intervention Study (community awareness)
	Ajonina [52]	Unspecified	Cameroon	2015	Self-report	57.2% completed treatment 50.9% followed correct dosing interval	
	Afaya [53]	Unspecified	Ghana	2017	Self-report	36.6%	
Prospective Observational	**Minzi [44]**	AL	Tanzania	2014	Self-report + pill count & AL blood concentration	79.9% completed treatment	
	Aung [46]	AL	Myanmar	2015	Self-report + pill count	85.7% probably adherent	
	Bruxvoort [23]	AL	Tanzania	2015	Self-report + pill count	69.8% at Health Facilities 74.5% at private retailers	
	Gore-Langton [43]	AL	Kenya	2015	Self-report + pill count	60% probably adherent	
	Gerstl [50]	AQAS	DRC	2015	Self-report + pill count	75% probably adherent	
	Siddiqui [51]	AQAS	DRC	2015	Self-report + pill count	62% probably adherent	
	Assi [49]	AQAS	Ivory Coast	2017	Self-report + pill count	97.2% completed treatment	
	Liu [54]	Unspecified	Nigeria	2016	Self-report	97% had already or were almost finished with treatment	

Study Design	Study Author	ACT	Country	Study Year	Measurement Method	Adherence Levels	Comments
RCT	**Bruxvoort [42]**	AL	Tanzania	2014	Self-report + pill count	68.3% intervention 69.8% control	Intervention Study (SMS)
	Saran [45]	AL	Uganda	2015	Pill Count	65.8% complete intake	Intervention Study (RDTs)
	Talisuna [47]	AL	Kenya	2017	Self-report + pill count	Completed all doses: 92.4% control 92.3% intervention Completed all doses at correct time: 70.8% control 69.2% intervention	Intervention Study (SMS)
	Raifman [38]	AL & AQAS	Ghana	2014	Self-report + pill count verification	AL 56.5% AQAS 47.9%	Intervention Study (SMS)
	Ogutu [40]	AL & DHAPQ	Kenya	2014	not specified	93.6% AL dispersible 85.6% DHAPQ	Effectiveness Study
Other	**Bruxvoort [41]**	AL	Tanzania	2015	Self-report & smart blister packages	87% self-report (no pack) 66% self-report (with pack) 64% smart blister packs	Nested comparative study
	Ewing [39]	AL & DHAPQ	Malawi	2015	Self-report	79% AL 88% DHAPQ	Mixed-methods

3.4 Chapter References

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CHAPTER 4: THESIS CONTEXT & METHODS OVERVIEW

4.1 Introduction

This chapter provides an overview of the context and study designs utilised to answer the research questions outlined in the introduction. Specifically, section 4.2 presents the context of this thesis research followed by section 4.3, which introduces the two studies used for this thesis. Sections 4.4 & 4.5 provide a summary of each study including a brief overview of the study procedures. This chapter serves as only as an overview, with the specific details on sample size calculations, data collection and analysis provided within each results chapter and associated appendices.

4.2 Research Context

Sierra Leone, located on the West Coast of Africa, is subdivided into 14 administrative districts, two of which (Western Urban and Western Rural) encompass the greater Freetown area. The population at the 2004 Census consisted of 4.9 million people and was projected to be over six million people by 2011 [1]. It was estimated that half (49%) of the population is under 15 years of age [2].

There are two major seasons, a summer rainy season (May to October) with heavy rains in July and August, and a winter dry season (November to April). Malaria is endemic, with stable and perennial transmission in all parts of the country. Malaria accounts for approximately 40% of outpatient morbidity [3]. In 2010, only 46% of children under five who sought care at public health facilities received prompt and effective treatment for malaria with the first line malaria treatment: AQ+AS [3]. Data from the fourth Sierra Leonean Multiple Indicator Cluster Survey (MICS4) conducted by UNICEF in 2010 corroborate this statistic and reported that only half (50.3%) of the children under five receiving treatment with any antimalarial the same or next day from the onset of fever, and only 19.2% receiving an ACT [4]. The first Sierra Leone Malaria Indicator Survey (MIS), conducted in 2013, found that the average combined country prevalence of malaria for children aged 6-59 months was 46.2% (RDT positive) and 42.9% (microscopy positive), with a higher prevalence in the north and western parts of the country and a lower prevalence in the south and around Freetown (Figure4.1)[5].

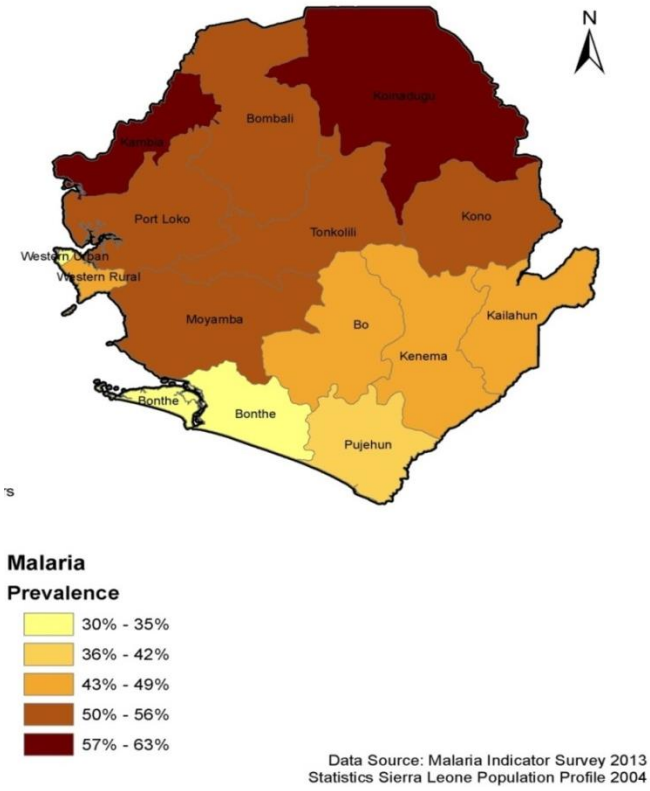

Figure 4.1 Malaria Prevalence map provided by the NMCP-Sierra Leone [5]

4.2.1 Health System Structure

In Sierra Leone, health care is delivered at three levels: (*i)* primary or first point of care through Peripheral Health Units (PHUs); (*ii)* secondary care through district level hospitals; and (*iii)* tertiary or specialised care through regional or national hospitals [6]. However, the system is mainly focused on a primary health care framework with the majority of care delivered through PHUs [7]. There are three types of PHUs (from largest to smallest): 1) Community Health Centres (CHCs); 2) Community Health Posts (CHPs); and 3) Maternal & Child Health Posts (MCHPs). Community health workers attached to PHUs are also being utilised to extend primary health care into the community, particularly those in harder to reach areas.

4.2.2 Antimalarial Medications in Sierra Leone

In 2004, the Government of Sierra Leone (GoSL) changed the national treatment policy for uncomplicated malaria from chloroquine to ACTs [8]. At the time of the study in 2013, the ACTs of choice in Sierra Leone were amodiaquine plus artesunate (AQ+AS) or artemether-lumefantrine (AL) as an alternative if AQ+AS was unavailable. AL was only available in the private sector and was often prescribed when AQ+AS was unavailable. However, the private sector cost of AL was prohibitive to a majority of the population ($8.59 USD for AL compared to $1.56 USD for AQAS) [9], and wide use remained limited. The ACT combination AQ+AS was chosen as the preferred choice for Sierra Leone due to its availability, affordability (costing almost $1 USD less) and efficacy [10, 11]. Since that time, partners, in particular, the Global Fund to Fight AIDs, Tuberculosis and Malaria (GFATM), have supported the procurement and distribution of antimalarial treatments to all levels of the health system in Sierra Leone. The National Malaria Control Program (NMCP) provided this combination in pre-packaged blisters by age group and repeated drug efficacy studies on both co-formulated ASAQ and AL in 2011 at four hospitals in Sierra Leone. The PCR correct efficacy results found that both ACTs were 100% efficacious [12].

To further understand the effectiveness of ACTs in Sierra Leone, Médecins Sans Frontières (MSF) conducted a study in 2008 to measure adherence of patients $\geq$1 year of age to co-packaged AQ+AS at five community health centres in Bo district, Sierra Leone. Patients/caregivers were enrolled in the study if they had confirmed malaria (by rapid diagnostic test), received AQ+AS for treatment, lived within 45 of the clinic, had taken part in the study previously and provided informed consent. The authors concluded that despite efforts to improve access to ACTs in Sierra Leone, patient adherence to AQ+AS was low, with only 48.3% of the 118 participants classified as probably adherent to the treatment regimen [13]. Only the knowledge that mosquito bites can lead to malaria was found to be associated with treatment adherence in this study.

The national policy for antimalarial treatment in Sierra Leone states that cases should be parasitologically confirmed (either by microscopy or by rapid diagnostic test), whenever possible, and treated with an ACT [8]. Clinical diagnosis is acceptable only in the instance that

parasitological confirmation is not possible. In 2012, the National Malaria Control Programme (NMCP) switched from co-packaged AQ+AS to the co-formulated version of amodiaquine-artesunate (AQAS) also termed fixed-dose combination (FDC). The impact of the policy change to confirmatory diagnosis and the switch to AQAS, on provider and patient adherence and the overall effectiveness of malaria treatment, remains unclear. Additionally, at the time of the study, the NMCP was considering if, when and how AL should be introduced into practice in the country. In 2015, the NMCP adopted AL as the first-line treatment, with AQAS as an acceptable alternative [14].

4.3 Overall Design

Two studies provided the data required to answer the research objectives of this thesis. The results presented in chapter 5 were based on a secondary analysis of household survey data collected during the national Sierra Leone Malaria Knowledge Attitudes and Practices (KAP) study conducted in 2012 (Appendix A). The results presented in chapters 6-8 are from a study which measured and explored factors associated with adherence to two different ACTs in Sierra Leone. The adherence study included a randomized controlled trial (RCT) and a concurrent qualitative study (Appendix B).

Ethical Considerations

The main KAP study protocol was approved by the Sierra Leone Ethics and Scientific Review Committee (this is included in an appendix of the secondary analysis protocol). Approval for the secondary analysis of the KAP data was received from the London School of Hygiene and Tropical Medicine Ethics Committee (Appendix C). Approval to use the data from this study for my thesis was obtained from Catholic Relief Services (CRS) and the National Malaria Control Programme (Appendix D).

The Adherence study protocol was reviewed by the LSHTM Clinical Trials Committee and approved by the LSHTM Ethics Committee (Appendix E) and by the Sierra Leone Ethics and Scientific Review committee (Appendix F). Additionally, the trial was registered at www.clinicaltrials.gov (NCT01967472) [15].

4.4 Malaria KAP Study

4.4.1 Implementers & Funding

I was the principal investigator for the KAP study. I designed and oversaw the direct implementation of this study in partnership with the CRS health advisor in the Sierra Leone office. Funding for this study came from the Global Fund to Fight AIDs, Tuberculosis and Malaria (GFATM) Round 10 malaria grant for Sierra Leone.

4.4.2 KAP Study Overview

The Sierra Leone malaria KAP survey was a descriptive study with two components: 1) enumeration of clusters followed by; 2) a two stage cluster randomly selected household survey [16]. The overall goal of the study was to gather information to inform the national malaria communication strategy for Behaviour Change Communication and Information Education and Communication. It also served as a baseline for future evaluations of the malaria communication strategy. Specific objectives of the survey included:

1. To determine the current knowledge, attitudes and practices of households to the recommended malaria prevention and treatment strategies, namely:
   - Knowledge, ownership and utilisation of treated bed nets
   - Knowledge of intermittent preventative treatment (IPTp) among women of childbearing age and uptake of IPTp by pregnant women
   - Early treatment-seeking behaviour
   - Knowledge and uptake of ACT
   - Knowledge of the symptoms of malaria including danger signs

2. To determine to what extent communities are accessing the needed malaria prevention and treatment services and to identify any facilitators and/or barriers to that access.

3. To determine which prevention and treatment practices and/or behaviours communities are already practising and to determine which practices beneficiaries are more inclined to adopt and why.

4. To document the perspectives and perceptions of communities that may positively or negatively impact malaria control efforts.

5. To determine the primary sources of information concerning malaria prevention and treatment practices and behaviours and/or other key channels that might be useful for the rollout of the behaviour change strategy.

6. To ascertain whether certain groups within the population (e.g. disaggregated by gender, socio-economic status, district, etc.) have lower rates of adoption and why.

4.4.3 KAP Study Procedures

The KAP study was a mixed methods study which combined data from a nationally representative household survey with a qualitative study that took place in the four regions of Sierra Leone (North, South, East and West). The secondary analysis presented in this thesis only uses the household survey data. Table 4.1 visually displays the thesis objective, data used and the corresponding thesis chapter.

Table 4.1 Thesis objectives, data and chapter for the mKAP survey

Objective	Data Set	Chapter
Objective I: To calculate population adherence and the factors associated with adherence/non-adherence to antimalarial treatment in Sierra Leone.	KAP Household survey data	**5**

The household survey was a nationally representative two-stage cluster sample with 30 primary sampling units (PSU) per district which were selected using probability proportional to size (PPS) based on estimates from the National Census [17]. This resulted in 5,880 targeted households (14 households per PSU; 420 households per district). The questionnaire was based on the Roll Back Malaria standardised guidelines for core population-level indicators [18]. Households were surveyed (i.e. heads of households and

one woman of Child Bearing Age (WCBA) age 15-49 per household) on basic demographic information, variables for socioeconomic status scores, vital statistics, malaria knowledge, prevention and treatment practices.

Data was collected by trained field staff using Apple iPhones. All electronic data were transferred from the Apple devices into a cloud database regularly while in the field using the local 3G mobile network. Upon completion of the fieldwork, any remaining forms that needed to be transferred were uploaded via wireless internet connections at Statistics Sierra Leone and Catholic Relief Services offices in Freetown. Paper questionnaires were provided to teams to use only as a backup in case of electronic equipment failure. When necessary, data entered onto paper forms were then entered into an iPhone as soon as it was possible. Backup files of the database were stored on two external servers.

4.4.4 Secondary data analysis

The first objective of this secondary analysis study was to quantify the level of access and adherence to ACTs in children less than five in Sierra Leone. The second objective was to assess factors associated with access to ACT for children under-five with fever in the two weeks preceding the survey. Access was defined as receiving an ACT for treatment of the most recent fever. The third objective was to identify factors associated with adherence to ACT in those children that received an ACT for their fever. Adherence was defined as taking the treatment for the recommended three days. Those taking ACT for three days were considered to have completed treatment and were classified as adherent, while those taking ACT for less than three days or more than three days were classified as non-adherent. Further details on the methods and data analysis are presented in Chapter 5.

4.5 Adherence Study (RCT and ancillary studies)

4.5.1 Implementers & Funding

I was the principal investigator for the adherence study. Although I was supported by the national malaria control program with various aspects of the study (clinic selection, ACT and RDT supply chain, health worker training, enlisting the pharmacy board to test the artemether-lumefantrine study medications) the day to day operations (including, staff hiring

and training, trial administration, financial management, logistics & procurement, data collection and entry along with adherence to good clinical practices) were solely carried out by me. Funding for this study came from consultancy work carried out by me in 2012-2013. Digital voice recorders were purchased from funds received from the LSHTM Helena Vrbova scholarship I received in 2012.

4.5.2 Study Sites & Population

The trial was conducted in the capital Freetown, which is located in the Western Area Urban administrative district (Figure 4.2). Two public health facilities and their catchment areas served as the study sites (Ross Road and George Brook CHCs).

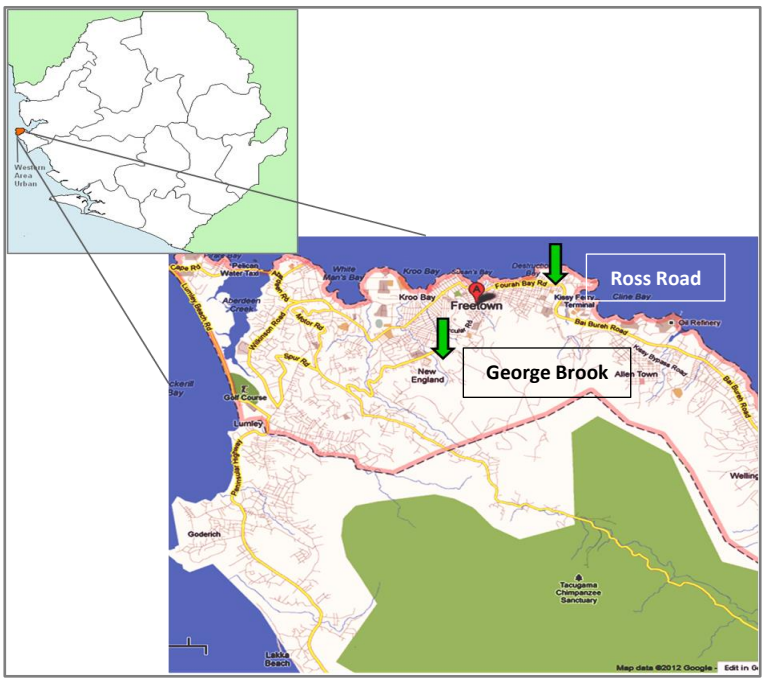

Figure 4.2 Map of the Study Area

The Ross Road clinic is located in a densely populated area in the eastern part of Freetown near the port in an area called Cline Town. In 2012, the clinic had an estimated catchment population of 21,324 people, approximately 10,000 of whom were under 15 years of age. In 2012, the Ross Road Community Health Centre saw approximately 1,000 patients per month, half (50%) of whom are children under five presenting with fever. On average, the Ross Road clinic had 400 children under five with confirmed malaria per month during the year prior to

the study (Table 4.2). This clinic has two Community Health Officers (CHO) who are responsible for the patient consultations and approximately 8-10 other support staff: Maternal and Child Health aides, nurses (state enrolled community health nurses and state registered nurses), midwives and dispensers).

The George Brook Community Health Centre (CHC) is located in the western part of Freetown in a hilly area called Dwarzak Farm. In 2012, this CHC had an estimated catchment population of 27,855 people, approximately 3,000 of whom were under five years of age. Before the study, the George Brook clinic saw approximately 800 patients per month, approximately 60% were children under 5 presenting with fever with an estimated 240 with confirmed malaria each month (Table 4.2). George Brook had around 15 health workers, only one of whom was a CHO.

Table 4.2 Confirmed Malaria Cases for Children Under-5 in 2012

	Ross Road	George Brook
January	169	194
February	200	190
March	288	356
April	310	203
May	437	331
June	622	220
July	300	179
August	202	318
September	615	315
October	411	169
November	609	272
December	613	166
Total	**4,776**	**2,913**
Average	**398**	**243**

*shaded area denotes the rainy season

4.5.4 Trial Overview and Procedures

The open-label randomised controlled study used a mixed methods approach, with the primary objective to measure caregiver adherence to two different ACTs (ASAQ and AL). Additionally, the study design allowed for data to also be collected on health worker compliance to treatment protocols, determinants of caregiver adherence as well as to explore barriers and facilitators of adherence. Table 4.3 provides a summary of the thesis objective, the corresponding data set, and the associated thesis chapter.

Table 4.3 Thesis objectives, data, and thesis chapter for the adherence study

Objective	Data Component(s)	Chapter
Objective II: To evaluate and compare the level of adherence to co-formulated ASAQ compared to AL for treatment of malaria in children aged 6 to 59 months seeking care at government health facilities in Sierra Leone.	**Component 3:** Follow-up Household Survey to assess caregiver Adherence	**6**
Objective III: To identify factors associated with patient adherence to these two ACTs formulations.	**Component 1:** Health Worker Interviews **Component 2:** Observations of Patient/Health Worker consultations **Component 3:** Follow-up Household Survey to assess caregiver Adherence	**7**
Objective IV: To explore barriers and facilitators of adherence to ACTs in Sierra Leone using qualitative methods.	**Component 4:** Caregiver In-depth Interview	**8**

Component 1: Health Worker Interviews

Health workers at the two study sites were interviewed to understand the context of the working environment and their familiarity with malaria treatment guidelines. After agreeing to be interviewed and providing written consent, each health worker was interviewed. Questions covered their knowledge on how to diagnose and treat patients with malaria as well as AQAS or AL prescription practices. Additionally, they were asked about their opinion on patient adherence, potential factors that contribute to non-adherence and the practices they employ to address this issue. Health workers were asked either before or after the interview for their consent to have their patient interactions observed over the subsequent months. Only those providing written informed consent were included in the study.

Component 2: Observations of Patient/Health Worker Consultations

To gather further information on the context of treatment allocation and to better measure health worker compliance with malaria treatment guidelines, patient-provider consultations at both study sites were observed over the course of the study period. Observations were conducted in two phases. Initially, health workers were observed administering AQAS to better understand current malaria diagnosis and treatment practices of the study site health workers. Following this initial observation period, health workers received a brief refresher training on the AQAS co-formulated regimen as well as the newer AL regimen. Additionally, the randomisation scheme was introduced and explained along with the study procedures to administer study medications.

Approximately 6-10 structured observations took place each day, but this was dictated by the number of health workers conducting consultations that day, patient numbers and flow as well as the number of study team members available on that day. Both the health worker and parent/caregiver agreed to be observed before the consultation began. Only consultations for fever were observed and recorded. The study staff who was the observer took notes and completed a structured checklist for each patient observation (Appendix B). Examination procedures (history taking, physical examination, recommended laboratory tests) were noted. Each consulting clinician (primarily the CHOs) at the health facility were observed a minimum of 20 times each where possible [19]. The total number of observations at each site equalled the total number of follow-up adherence surveys.

Component 3: Follow-up Adherence Survey

Parents/caregivers of the patients were visited at their homes four days after their clinic visit; the day after the last prescribed treatment dose should have been taken. If the interview could not be completed on Day-4, the interviewer returned on Day-5. No interviews were intended to be carried out after Day-5. Any interview conducted after Day-5 was excluded from the analysis. The respondents for the adherence survey were the parents/caregivers who gave the treatment to the patient (child). The purpose of the follow-up interview was explained before the assessment of adherence took place [20]. Participation was voluntary,

and the visit proceeded only after additional written informed consent was given. If the clinical condition of the patient required further medical attention at the time of the home visit, she/he was immediately referred to the nearest health centre, and the adherence assessment was conducted later (up to Day-5) if the patient's condition had improved.

A semi-structured questionnaire was administered to assess treatment adherence (Appendix D). The interview began with general questions about the patient, parent/caregiver and the household. Then parents/caregivers were asked to tell the story of how the malaria medication was taken and were also requested to show the original blister packaging if available. If the blister packaging was found, any remaining tablets were tallied and recorded onto the questionnaire. Finally, there were a few additional questions about their experience with the treatment, any side effects (adverse events) experienced, why or why they did not complete the treatment and questions to assess their general malaria knowledge. All parents/caretakers were thanked for participating and encouraged to return to the health facility soon if the child's health condition is of concern. If the treatment was found to be incomplete, the parent/caregiver was encouraged to complete the full treatment course or if that was not possible to return to the health facility.

Component 4: Caregiver In-depth Interviews

In addition to the surveys, in-depth interviews (IDIs) were carried out with a subset of both adherent and non-adherent caregivers to get a more textured picture of the potential factors that affect adherence. Participants were purposefully selected based on the treatment they received and whether they were adherent or non-adherent to the treatment regimen. The interview location was designated by the person being interviewed and was conducted in private in the home of the participant or on occasion at the health facility in a private area. The interviews were one-on-one unless the participant requests to have another person present.

The IDI began by first asking general questions about what the parent/caregiver does when their child has a fever. Next, the interviewer asked the parent/caregiver to identify some common medications used to treat fever. The discussion then turned to inquire about the

parent/caregivers' experience with specific malaria treatments, understandings and expectations of treatment, tolerability, and barriers faced with regard to treatment adherence. See attached draft topic guide for the topics to be covered.

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CHAPTER 5: FACTORS ASSOCIATED WITH ACCESS AND ADHERENCE TO ACTS AT THE POPULATION LEVEL IN SIERRA LEONE: A SECONDARY ANALYSIS

5.1 Chapter Introduction

This chapter addresses Objective I, to calculate population-level adherence and the factors associated with adherence/non-adherence to antimalarial treatment in Sierra Leone. The paper presents the results of a secondary analysis of the nationally representative Sierra Leone Malaria Knowledge, Attitudes and Practices survey (mKAP), whereby the factors associated with receiving and completing treatment for malaria with and ACT was investigated using multivariate logistic regression.

5.2 Research Paper

The cover sheet is on the next page followed by the manuscript, tables and figures.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Kristin Banek
Principal Supervisor	Sarah Staedke & Daniel Chandramohan
Thesis Title	Evaluation of Adherence to Artemisinin-based Combination Therapy for the Treatment of Uncomplicated Malaria in Sierra Leone

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*		Was the work subject to academic peer review?	

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	American Journal of Tropical Medicine and Hygiene
Please list the paper's authors in the intended authorship order:	Kristin Banek, Emily L. Webb, Emily Bostick, Samuel J. Smith, Daniel Chandramohan, Sarah G. Staedke
Stage of publication	Ready for submission

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study, collected the data, conducted the analysis and wrote the first draft of the manuscript.

Student Signature: _____ **Date:** 27 June 2018

Supervisor Signature: _____ **Date:** 11 July 2018

Factors associated with access and adherence to artemisinin-based combination therapy (ACTs) for children under five: a secondary analysis of the 2012 Sierra Leone malaria knowledge, attitudes and practices (KAP) survey

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Keywords: malaria, artemisinin-based combination therapy (ACT), Sierra Leone, prompt treatment, access, adherence, treatment completion

Abstract

Introduction

Prompt access to effective treatment with artemisinin-based combination therapy (ACT) is critical to control malaria. Although ACTs have been the recommended first-line treatment for uncomplicated malaria since 2004, both access and adherence to ACTs remain low in much of Sub-Saharan Africa. This study aimed to quantify access and adherence to ACTs and to determine factors associated with those outcomes in children under-five with fever in Sierra Leone.

Methods

This study was a secondary analysis of data obtained from the 2012 Sierra Leone malaria Knowledge, Attitudes and Practices (mKAP) survey. The analysis used a subset of data to quantify access and adherence to ACTs for children under-five who had a fever in the two weeks preceding the survey. Factors associated with access and adherence to ACTs were assessed using logistic regression.

Results

Only half (47.4%) of fever cases who were treated for malaria received an ACT, most of whom (67.6%) were treated within 24 hours of onset. Adherence was also low, with 47.2% of children taking the ACT for the recommended 3-day duration. In a multivariate analysis, children in the Eastern Region had higher odds of receiving ACT compared to children in other regions. Children had three times the odds of receiving an ACT if they had a caregiver who had knowledge of ACTs (OR: 2.84; 95%CI: 2.07–3.89; p<0.001). Children were more likely to receive an ACT if treatment was sought at a public health facility (OR: 1.85; 95%CI: 1.27–2.71; p=0.002) or if they were aged 24-59 months (OR: 1.46; 95%CI: 1.08–1.98; p=0.014). Children receiving an ACT within 24 hours were 40% less likely to complete treatment, compared to those that received ACT after 24 hours of symptom onset (OR: 0.58; 95%CI: 0.35–0.95; p=0.032).

Conclusions

This study demonstrates that poor access and adherence to ACTs remained key challenges to scaling up malaria treatment in Sierra Leone in 2012. While efforts are being made to improve access to key health services such as malaria treatment, further emphasis on improving adherence is needed to ensure that the last step on the effectivness pathway is achieved. Furthermore, malaria treatment seeking questions used for national surveys could be expanded to also measure adherence providing, the critical information needed to realize optimal malaria treatment effectiveness.

Introduction

Malaria remains a serious health problem in Sub-Saharan Africa and is particularly dangerous for children under-five [1]. Prompt access to effective treatment is critical to control malaria. To this end, World Health Organization malaria treatment guidelines recommend that all confirmed cases should be treated promptly (within 24 hours of onset) using artemisinin-based combination therapy (ACT) [2]. Despite this recommendation, access to prompt and effective treatment remains low across Sub-Saharan Africa; with low access to treatment likely influenced by acceptability, affordability and availability [3]. Furthermore, treatment effectiveness is dependent not only on access, but on multiple factors including efficacious drug regimens (ACTs), targeted testing and treatment, and patient (or caregiver) completion of treatment (adherence) [4, 5].

In Sierra Leone, malaria is the leading cause of morbidity and mortality in children under-five, accounting for 47% of outpatient visits [6]. In the most recent Malaria Indicator Survey (MIS), 40% of children aged 6-59 months tested positive for malaria, with prevalence almost twice as high in rural areas compared to urban (49% vs. 25%) and highest in the northern region (52%) [7]. Although amodiaquine plus artesunate (AQ+AS) has been the recommended first-line treatment for uncomplicated malaria since 2004 [8], access to ACTs has been low, with only 19.2% of children with fever receiving ACT in 2010 [9]. Furthermore, probable adherence to co-packaged AQ+AS in Sierra Leone was reported to be only 48.7% in 2008 [10].

In 2010, the government of Sierra Leone recognized the importance of improving access to essential medications, including antimalarials, to reduce childhood morbidity and mortality. Two initiatives were rolled out to improve access to health care: 1) The Free Health Care Initiative (FHCI), which provides services and medications free of charge to pregnant women, lactating mothers and children under five at government health facilities along with supportive supply-side interventions [11]; and 2) a malaria treatment policy comprising of free malaria testing and treatment with ACTs for all malaria cases [12].

However, these initiatives only address health system factors that impact access and targeting of ACTs, steps at the beginning of the effectiveness pathway [4, 5]. To be truly effective, treatments must also be acceptable, demonstrated by health workers following malaria treatment guidelines and patients and caregivers adhering to the prescribed ACT regimens. If the aims of these last steps of the pathway are not realized, effective treatment and control of malaria cannot be achieved. Therefore it is critical to measure and understand factors associated not only with access, but also adherence to ACTs.

In 2012, a malaria Knowledge, Attitudes and Practices (mKAP) survey was carried out in Sierra Leone [13]. This study is a secondary analysis of data captured in the mKAP survey with the objective to identify factors associated with access and adherence to ACTs for treatment of fever on a national scale.

Methods

The mKAP was conducted in 2012 by Catholic Relief Services (CRS) in partnership with the National Malaria Control Program (NMCP), and supported by Statistics Sierra Leone (SSL). The primary objective of the survey was to gather information to inform and update the national malaria communication strategy. Additionally, data from the survey was used to establish a baseline for malaria control activities that were to be subsequently implemented with support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) [13]. This study is a secondary analysis of a subset of data collected from the mKAP survey.

The mKAP survey was a nationally representative two-stage cluster sample survey conducted in all 14 districts of Sierra Leone. Thirty primary sampling units (PSU) per district were selected using probability proportional to size (PPS) based on estimates from the National Census [14]. This resulted in 5,880 targeted households (14 households per PSU; 420 households per district). The questionnaire was based on the Roll Back Malaria standardized guidelines for core population-level indicators [15]. All respondents answered questions about household demographics and assets, malaria knowledge and prevention practices, recent pregnancy experiences, and if the household contained one or more children aged under-five who had a fever in the previous two weeks, information was collected on the

treatment of up to three children per household. A separate child questionnaire was completed for each child in the household reported to have had a fever.

Data collection

Data were collected by trained field staff using Apple iPhones. The devices were programmed using the iFormBuilder mobile platform (Zerion Software, Inc., Herndon, VA, USA) [16]. All electronic data were transferred from the Apple devices into a cloud database regularly while in the field using the local 3G mobile network. Upon completion of the fieldwork, any remaining forms that needed to be transferred were uploaded via wireless internet connections at Statistics Sierra Leone and Catholic Relief Services offices in Freetown.

Paper questionnaires were provided to teams to use only as a backup in case of electronic equipment failure. When necessary, data entered onto paper forms were then entered into an iPhone as soon as it was possible. Backup files of the database were stored on two external servers (iFormBuilder and a specially created Google email account). Additionally, data were stored on the iPhones until completion of the study. For quality control, validation and built-in skip logic was written into the iFormBuilder program.

Outcome variables and predictors

The first objective of this study was to quantify the level of access and adherence to ACTs in children less than five in Sierra Leone. The second objective was to assess factors associated with access to ACT for children under-five with fever in the two weeks preceding the survey. Access was defined as receiving an ACT for treatment of the most recent fever. The third objective was to identify factors associated with adherence to ACT in those children that received an ACT for their fever. Adherence was defined as taking the treatment for the recommended three days. Those taking ACT for three days were considered to have completed treatment and were classified as adherent, while those taking ACT for less than three days or more than three days were classified as non-adherent.

Using the available variables from the survey dataset along with the factors identified in the ACT adherence literature, a list of *a priori* predictors were identified and evolved into a conceptual framework (Figure 1). Four categories of potential predictors of access and adherence were identified: 1) socio-economic status (i.e. wealth class and education); socio-demographic characteristics (i.e. child age, religion, household size, place of residence); 3) knowledge of malaria (i.e. knowledge of protective measures and treatments); and 4) health practices (i.e. accesses prompt treatment for fever, ITN utilization and source of health care).

Data analysis

Stata Version 12 (StataCorp, College Station, TX USA) and Excel (Microsoft Corp. Redmond, WA, USA) were used for data processing and analysis. In all analyses, the svy commands were used to account for the survey design, including clustering by PSU and stratification by the location of the PSU (urban/rural). Descriptive statistics were used to summarize household and respondent characteristics as well as treatment-seeking behaviour for children with fever. Household socioeconomic status was based on a principal components analysis (PCA) of household assets [17], split into tertiles.

Logistic regression models were used to estimate the crude and adjusted odds ratios and their 95% confidence intervals to assess the strength of the association between the *a priori* predictors and the two outcomes (access and adherence to ACTs). All predictor variables were included in multivariable analyses regardless of p-values, with the exception that for any pair of covariates identified to be strongly correlated (Pearson's correlation r $\geq$0.8) one was removed from the final model. Associations between the predictors and outcomes were considered significant if the p-value was < 0.05.

Ethical considerations

The original study protocol was approved by the Sierra Leone Ethics and Scientific Review Committee prior to the commencement of activities. Ethical clearance to conduct this secondary analysis of the mKAP data set was obtained from the London School of Hygiene & Tropical Medicine. Permission to use this data was obtained from CRS and the NMCP in Sierra Leone.

Results

Survey Profile

This secondary analysis was carried out on a subset of the mKAP survey households (n=1,456) that reported having a child under-five with fever in the last two weeks (Figure 2). Access to ACT was assessed in 1,641 children who had a history of fever and data on treatment received. The factors associated with access to ACTs was estimated in children, whose caregiver sought and received treatment for that fever (n=982). Finally, factors associated with adherence to ACT was determined for children with fever whose caregiver sought and received an ACT (n=467).

Characteristics of households and their under-five children

The households in the subset of those with under-five children with fever showed some differences compared to the larger household sample. Specifically, households were more likely to be located in the north, and were, on average, poorer. Additionally, respondents with children under five with fever were typically less educated (Table 1).

Households with febrile children were primarily located in rural areas (87.6%), practiced the Islamic faith (81.0%) and owned at least one bed net (any type) (87.2%). The average age of the adult caregiver respondents was 39.2 years, and 66.8% reported not having any formal education. Three out of four adult respondents (76.6%) reported sleeping under an insecticide-treated net (ITN) the previous night. Although overall most respondents were knowledgeable about malaria, some gaps in knowledge were identified, specifically regarding the prevention and treatment of malaria. In particular, only 41.8% (95%CI: 38.5% - 45.3%) of respondents were aware that ACTs were the recommended treatment for malaria.

The mean age of children included in this study was 2.3 years (95%CI: 2.3-2.4). Of the 1,641 children under-five who had a fever in the two weeks before the survey, 66.9% were reported to have slept under an ITN the night before the survey.

Treatment for children under-five with fever

Among the 1,641 children under-five with a fever episode in the last two weeks, respondents sought care for 1,038 (63.4%) (Table 2). Of the 1,038 who sought treatment for the fever, 854 (82.2%) took their child to a public health facility. Nearly all (982; 95%) of those who sought treatment received an anti-malarial for treatment of the fever. Despite the fact that ACTs were the recommended first-line treatment for malaria in Sierra Leone, only half (47.4%) of those receiving any treatment, received an ACT, two-thirds of whom (67.6%) were treated within 24 hours of onset. Half (47.2%) of respondents whose child received an ACT reported that their child took ACT for the recommended 3-day duration. Of the 467 children who received an ACT, only 29.5% (135/467) received both prompt treatment (<24hours) and went on to complete the treatment (duration of three days). Using all children whose caregivers sought treatment for the most recent febrile episode as the denominator, the proportion receiving timely ACT treatment that was adhered to was even lower (13.2%; 135/1,038).

Factors associated with Access and Adherence

Five factors were found to be significantly associated with children receiving an ACT (Table 3). Children living in the Eastern Region had higher odds of receiving ACT compared to children in other regions (OR: 2.40; 95%CI: 1.26 – 4.55; p=0.018). Children with caregivers who had any knowledge of ACTs had almost three times the odds of receiving an ACT for treatment of fever, compared to those whose caregivers did not have knowledge about ACTs (OR:2.84; 95%CI: 2.07 – 3.89; p<0.001). Similarly, children living in households where the caregiver knew that ITNs provide protection from malaria had higher odds of receiving an ACT (OR: 1.80; 95%CI: 1.26 – 2.58; p=0.001). Children treated at a public health facility had almost twice to the odds of receiving an ACT compared to those that were not (OR: 1.85; 95%CI: 1.27–2.71; p=0.002), with older children (age 24-59 months) more likely to receive an ACT than younger (0-23 months) (OR: 1.46; 95%CI: 1.08–1.98; p=0.014).

In an analysis restricted to children under five with fever during the last two weeks, who were treated for malaria with an ACT (n=467), only one factor was found to be significantly associated with adherence (Table 4). Children receiving an ACT within 24 hours had 42%

lower odds of completing treatment, compared to those that received ACT after 24 hours of symptom onset (OR: 0.58; 95%CI: 0.35–0.95; p=0.032). Due to collinearity, ITN ownership, knowledge of the term malaria, knowledge of at least one antimalarial, knowledge of at least one sign or symptom of malaria and knowledge of any malaria protective measures were removed from both models.

Discussion

The results from this analysis of the national 2012 mKAP survey from Sierra Leone suggest that the majority of children under-five in Sierra Leone did not receive or complete treatment with ACTs for the most recent febrile episode. The majority (82.2%) of children under-five with fever in the prior two weeks were treated at government health facilities, half of whom sought care within one day of onset of symptoms. Of those who received an antimalarial, only 47.4% received an ACT, although 67.6% of these received the ACT within 24 hours of fever onset. In contrast, only 19.2% of febrile children received an ACT in 2010, and only 50.3% received any antimalarial within 24 hours [9]. The mKAP data also show that among febrile children who received an ACT, adherence to treatment was low (47.2%), and this observation is consistent with the 2008 observational study in Sierra Leone, which also reported that only 48.7% of participants age 1 year or older with a confirmed malaria diagnosis were probably or definitely adherent to co-packaged AQ+AS [10].

Access

The Free Health Care Initiative (FHCI) was founded on improving access to health services by strengthening seven health system pillars (drugs and medical supplies; health workforce; governance; infrastructure for service delivery; communication; monitoring and evaluation; and health financing) [11]. However, implementation success was affected by the weak drug and medical supply chain and the lack of focus on the quality of care [18]. Additionally, environmental factors such as poor road infrastructure and hard to reach health facilities further compound access challenges.

Notwithstanding the challenges to implement the FHCI, there is some evidence to suggest that the prospect of better services and free care may have facilitated increased utilization of

government health facilities as the removal of user fees has been reported to improve access to health services in the public sector in a number of African countries [19]. Seeking care from a public health facility in Sierra Leone doubled the odds of a child receiving an ACT, which was also found in Tanzania, where care-seeking behaviour from governmental health facilities has been shown to improve access to ACTs [20]. A study comparing ACT access across six African countries also found that in five of the study countries, children treated in the public sector were significantly more likely to receive an ACT compared to those treated in the private sector [21]. In the context of Sierra Leone, improved access may be a direct result of increased health financing of programs such as the FHCI [18] coupled with increased funding for malaria diagnostics and treatment provided by the GFATM. However, despite health system improvements, removal of user-fees and increased confidence in the service provision, the present study found that access was still low, with less than 50% of febrile children receiving an ACT. As a result, increased utilization and limited drugs and health supplies may have weakened efforts to provide free health services and malaria treatment [19].

Additionally, this study found that children in the Eastern Region of Sierra Leone were more likely to have access to ACTs than children in other regions, even surprisingly more than in the Western region, which includes the capital, Freetown, which is the location of the port and the national drug store. While this study cannot provide a causal relationship between improved access and the FHCI, the successful implementation of the FHCI in these districts may have contributed to better access to medicines and services [18].

While removing user-fees removes the cost barrier of accessing care for individuals, it can strain weak health systems when demand increases. Higher patient loads require more resources to provide effective service delivery. This study demonstrates a difference in access based on age, with older children more likely to receive an ACT than younger children. Although Sierra Leone has been noted to have relatively high availability of amodiaquine+artesunate (the ACT of choice at the time) compared to other post-conflict countries [22], the number of infant doses has often been insufficient due to improper forecasting and quantification of the estimated need for this age group [23].

Adherence

Adherence to ACT was only associated with not accessing ACT promptly (beyond 24 hours from the onset of symptoms). This result is similar to findings from Ethiopia, which reported that participants that delayed one day before seeking treatment were actually more adherent than those seeking prompt treatment (OR: 5.39; 95% CI: 1.83-15.88) [24]. In contrast, a study in Uganda reported that prompt access to an ACT was associated with higher treatment adherence [26]. Likewise in Kenya, patients seeking treatment greater than one day after the start of fever were 27% less likely to be adherent [25]. Given these mixed results, the association between prompt treatment for fever and lower ACT adherence should be interpreted with caution. Those accessing treatment early may have had a low parasite load which was cleared more quickly, resulting in fewer symptoms and possibly lower treatment adherence. Moreover, as the mKAP survey did not capture information on confirmatory malaria diagnosis the child may have had a non-malaria febrile illness and their symptoms may have resolved despite receiving treatment, thus leading to a discontinuation of treatment.

The present study found that caregivers were more likely to have received an ACT for their child's recent fever if they sought care at a public health facility, but there was no association found between the source of care and adherence. Previous knowledge of malaria treatment and prevention practices has been shown to be associated with increased adherence to ACTs [10, 24, 25]. This study found that a child had three times the odds of receiving an ACT if the caregiver had prior knowledge of ACTs. However, no significant association between knowledge of ACTs and adherence was found, despite suggestions that patient knowledge, attitudes and beliefs may be strong predictors of adherence [27-29].

Bruxvoort et al. reported that age, higher household income, higher education level, malaria knowledge and treatment seeking behaviour are factors facilitating antimalarial adherence [30]. However, in this study, none of the *a priori* socio-economic or demographic factors were shown to be associated with adherence. This is not unexpected as socio-economic and demographic factors have not been consistently associated with adherence to ACTs [4] nor to

other medications [31]. Furthermore, it has been suggested that demographic characteristics are weak predictors of adherence and that adherence should be "measured not inferred" [29], presumably suggesting that it is better to actually measure adherence directly.

Strengths and limitations of measuring access and adherence at the population level

Information about access to ACTs is collected routinely through national cross-sectional household surveys such as the Demographic Health Survey (DHS), Multiple Indicator Cluster Survey (MICS) and the Malaria Indicator Survey (MIS). All three survey questionnaires assess treatment seeking behavior for fever, medications received for that fever and how soon after the onset of symptoms the medication received for treatment of the fever was started. Additionally, all surveys gather information on whether a blood test was received, however this question is not malaria specific ("have you received a blood test for this febrile episode"), nor is information on the test result provided. Additionally, the blood test question is not currently linked to treatment allocation, making it difficult to link a confirmed diagnosis with correct treatment. The methodology used in the mKAP survey to assess adherence was similar to that used in two previous cross-sectional studies in Kenya, which utilized a self-report question to assess whether the duration of treatment with ACT was correct (i.e three days) [32, 33].

The strength of collecting adherence data for ACTs through a cross-sectional survey is that specific questions on ACT treatment duration and completion can be added to routine nationwide surveys (i.e. DHS, MICS and MIS) to quantify population-level data on adherence. Collecting ACT adherence data through national surveys would be simple to implement, sustainable and cost-effective as adherence would be measured using self-report, which, despite its shortcomings, remains the favoured method for collecting antimalarial adherence data.

Using information collected on treatment duration as a proxy for adherence, although crude and lacking the specific insight on other dimensions of adherence (i.e. confirmatory diagnostic testing, quality of care provided by health workers, dose prescribed, information on medication administration provided by the healthcare worker and timing of medication

intake), may be a viable method of estimating ACT adherence. National estimates might serve as a litmus test for further inquiry; much like the questions which assess where and when treatment is sought serve as an indication of prompt access to malaria treatment and services. However, use of national surveys to assess ACT adherence has several limitations: 1) the method assumes that respondents know and recognize which antimalarial or ACT was prescribed for their child; and 2) unless surveys collect information about diagnostic testing for specific for malaria and include testing results, then the utility of adherence data would be limited as it would apply only to children with fever which may or may not be malaria.

In the present study, only 40% of respondents knew ACT was the recommended treatment for malaria. Similarly, almost half of the respondents in this survey reported receiving chloroquine (48.7%). It is not clear whether children actually received chloroquine, whether the drug received looked like chloroquine or whether chloroquine was the name used for all antimalarials. A study in Zambia found that survey questions assessing whether ACT treatment was received in the last two weeks to be relatively sensitive [34], which may also be valid in the Sierra Leonean context, which like Zambia, has also removed fees and has increased international support for free health service delivery and malaria control.

Moreover, this survey followed the MIS convention of other national surveys by asking whether the child received any medication for the recent fever as an open-ended question, without asking the exact name or formulation of the ACT. Unlike the other national surveys, the mKAP did not include a question on whether the child had "*blood taken from his/her finger or heel for testing"* Despite this difference, the other mKAP questions treatment of fever such as medications received for the treatment for this febrile episode and when treatment with that medication commenced are the same as the other surveys. However, all of the survey questionnaires could be improved by specifically asking if the blood test was for malaria, test result and linking that information to subsequent antimalarial treatment. Without this vital specific information, caution should be taken in the interpretation of results from the treatment sections, as these data would represent treatment of fever not confirmed malaria.

At the time of the survey neither co-formulated amodiaquine-artesunate (AQAS) nor artemether-lumefantrine (AL) ACTs were widely available in the country, and if they were,

they were not available in the public sector. So for this study population, it is reasonable to conclude that co-packaged AQ+AS was the ACT received. However, in a context with multiple ACTs in circulation, in particular, ACTs with different treatment duration times or formulations, this methodology may be less precise.

Limitations

Although a strength of this study is that it was a national survey, which allows the generalizability of the findings to the entire country, there were some limitations. First, the initial survey attempted to limit recall bias by only asking about fever episodes in the two weeks preceding the survey, despite this respondents' recollection of the events may not be entirely accurate. Second, the analysis was limited to the variables collected and may not have captured all the factors plausibly associated with receiving or completing treatment with an ACT. In particular, this secondary analysis did not contain health system-related information, such whether the fever was a confirmed malaria case, the quality of care received at the health facility, information provided by the health worker on how to administer the medication or stock-outs of ACTs and malaria rapid diagnostic tests; all of which may have affected patient access and/or adherence. Finally, additional questions on the number of tablets taken or whether treatment was completed were also not included in this survey and would have contributed to a more precise quantification of adherence.

Conclusion

This study demonstrates that poor access and adherence to ACTs remained key challenges to scaling up malaria treatment in Sierra Leone in 2012. While efforts are being made to improve access to key health services such as malaria treatment, further emphasis is needed on improving adherence to ensure that the last step on the effectivness pathway is achieved. Furthermore, malaria treatment seeking questions used for national surveys could be expanded to also measure adherence, providing the critical information needed to realize optimal malaria treatment effectiveness.

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TABLES & Figures

Tables

FIGURE LEGEND

Table 1. Household and individual level characteristics of survey participants, stratified by presence or absence of a child under five with fever in the preceding two weeks

		Under-five Households with fever (N=1,456)		Under-five Households without fever (N=1,199)	
Variable	**Categories**	**n(%)**	**95% CI**	**n(%)**	**95% CI**
Household					
Location	Urban	191 (12.4%)	10.6% – 14.4%	184 (14.8%)	12.8% – 17.0%
	Rural	1,265 (87.6%)	85.6% – 89.4%	1,015 (85.2%)	83.0% – 87.2%
Region of Sierra Leone	North	672 (46.9%)	41.4% – 52.5%	368 (30.6%)	25.8% – 35.9%
	South	371 (25.4%)	21.1% – 30.3%	427 (35.7%)	30.4% – 41.4%
	East	291 (19.5%)	15.7% – 24.1%	236 (19.8%)	15.9% – 24.5%
	West	122 (8.2%)	5.8% – 11.3%	168 (13.9%)	10.6% – 18.0%
Number of household residents	1-5	430 (29.3%)	26.5% – 32.2%	440 (36.6%)	33.6% – 39.8%
	6-10	795 (54.7%)	51.8% – 57.5%	602 (50.4%)	47.3% – 53.5%
	11+	231 (16.1%)	13.9% – 18.5%	157 (12.9%)	11.0% – 15.2%
Religion	Christian	284 (19.0%)	16.2% – 22.2%	261 (21.9%)	18,9% – 25.4%
	Muslim	1,172 (81.0%)	77.8% – 83.8%	938 (78.1%)	74.8% – 81.2%
Socio-economic status	1 (poorest)	508 (35.4%)	31.9% – 39.0%	400 (33.4%)	30.0% – 37.1%
	2	532 (36.2%)	33.3% – 39.1%	410 (34.2%)	31.2% – 37.4%
	3 (least poor)	416 (28.5%)	25.2% – 31.9%	389 (32.3%)	28.6% – 36.3%
Ownership of bed nets	Own any net	1,272 (87.2%)	10.1% – 15.1%	1,045 (86.9%)	84.4% – 89.1%
	Net is an ITN	1,214 (83.1%)	80.5% – 85.5%	989 (82.2%)	79.2% – 84.9%
	Mean ITNs/ household	2.6	2.5 – 2.8	2.5	2.4 – 2.6
Household Adult Respondents					
Mean age (years)		39.2	38.4 – 40.1	38.7	37.8 – 39.6
Gender	Male	684 (47.1%)	44.0% – 50.2%	577 (48.2%)	45.0% – 51.5%
	Female	772 (52.9%)	49.8% – 56.0%	622 (51.8%)	48.5% – 55.0%
Education	None	967 (66.8%)	63.9% – 69.6%	779 (64.7%)	61.4% – 67.9%
	Primary	173 (11.8%)	10.1% – 13.8%	124 (10.7%)	8.9% – 12.7%
	Secondary/ higher[1]	279 (18.7%)	16.4% – 21.2%	277 (23.0%)	20.3% – 25.9%
	Arabic/Other	37 (2.7%)	1.9% – 3.8%	19 (1.7%)	1.0% – 2.8%
ITN use previous night	Adult respondent	1,129 (76.6%)	73.7% – 79.3%	913 (76.2%)	72.9% – 79.2%
Knowledge of malaria-related topics					
—Ever hear of the illness called "Malaria"	Yes	1,492 (98.1%)	97.0% – 98.8%	1,167 (97.4%)	96.1% – 98.3%
—At least one sign or symptom of malaria	Yes	1,374 (94.2%)	92.5% – 95.6%	1,116 (93.0%)	91.1% – 94.6%
—All are susceptible to malaria	Yes	1,065 (73.2%)	70.3% – 75.9%	884 (73.4%)	70.3% – 76.3%
—At least one malaria protective measure	Yes	1,244 (85.2%)	82.6% – 87.5%	1,026 (85.4%)	82.7% – 87.8%
—ITNs can prevent malaria	Yes	865 (59.6%)	56.3% – 62.9%	741 (60.9%)	57.1% – 64.5%
—At least one antimalarial drug	Yes	1,268 (86.9%)	84.7% – 88.8%	1,021 (85.1%)	82.5% – 87.3%
—Recommended treatment with ACTs	Yes	606 (41.8%)	38.5% – 45.3%	527 (43.7%)	40.2% – 47.2%
Children under five with fever in the last two weeks[2]		**(N=1,641)**			
Mean age (years)		2.3	2.26 – 2.42		
Age in months	0-23 mo.	505 (30.1%)	27.8% – 32.6%		
	24-59 mo.	1,136 (69.9%)	67.4% – 72.3%		
Slept under an ITN the previous night		1,103 (66.9%)	63.4% – 70.2%		

[1] *Secondary or higher includes technical and vocational school*

[2] *The denominator is the number of children who had a fever in the last two weeks and who had data included in the section of the survey for child fever*

Table 2. Treatment and treatment seeking behaviours for children under-five with fever (n=1,641)

	Observations			
	n/N	%	Linearized SE	95% CI
Treatment Seeking				
Caregiver sought treatment	1,038/1,641	63.4%	1.67%	60.1% – 66.6%
Caregiver sought prompt treatment (≤ 24 hours)	571/1,038	55.9%	1.87%	52.2% – 59.6%
First treatment source[1]				
Public health facility	854/1,038	82.2%	1.48%	79.1% – 84.9%
Other[2]	184/1,038	17.8%	1.48%	15.1% – 20.9%
Malaria treatment				
Received an antimalarial	982/1,038	94.6%	0.83%	92.7% – 96.1%
Type of malaria treatment				
Artemisinin combination therapy (ACT)	467/982	47.4%	2.10%	43.3% – 51.5%
Chloroquine	472/982	48.7%	2.19%	44.5% – 53.1%
Sulfadoxine-pyrimethamine (SP)	153/982	15.0%	1.37%	12.5% – 17.9%
Panadol	769/982	77.8%	1.67%	74.3% – 80.9%
Herbs	139/982	14.1%	1.36%	11.6% – 17.0%
Other[3]	138/982	13.7%	1.32%	11.3% – 16.5%
ACT Treatment time[4]				
Received ACT same/next day (within 24 hours)	312/467	67.6%	2.34%	62.9% – 72.1%
Received ACT on day 2	93/467	19.5%	2.01%	15.9% – 23.8%
Received ACT 3+ days	29/467	6.0%	2.08%	4.2% – 8.5%
ACT duration				
Took ACT for 3 days (correct duration)	220/467	47.2%	2.56%	42.2% – 52.2%
Mean duration of ACT treatment (days)	n=467	4.17	0.32%	3.55 – 4.80
Prompt and effective treatment with ACT (Received ACT < 24 hours & took for 3 days)				
Children with: fever[5]	135/1,641	8.4%	0.80%	6.9% – 10.1%
Children with: fever + sought treatment	135/1,038	13.2%	1.20%	11.0% – 15.7%
Children with: fever + sought treatment + antimalarial	135/982	14.0%	1.26%	11.7% – 16.6%
Children with: fever + sought treatment + antimalarial+ ACT	135/467	29.5%	2.41%	24.9% – 34.4%

[1] *The denominator is the number seeking treatment for the fever in the last 2weeks (n=1,038)*

[2] *Other Sources of treatment include: Community Health workers [Community Health Worker (CHW), Traditional Birth Attendant (TBA), Blue Flag Volunteer (BFV)] =39; Informal Health workers (drug peddler, traditional healer) =31; Drug shops/Pharmacy=96; private clinics/doctors=9 and self-treatment=9*

[3] *Other drugs received include = ACT mentioned as commercial name (2), other antimalarial--mono-therapy: quinine and amodiaquine (4), antibiotics (34), antidiarrheal/ORS (17), other antipyretic (7), cough medicine (2), deworm (1), vitamins (12), iron (16), unnamed syrup (6), injection (11), routine medication (10), unspecified/unknown (16).*

[4] *The denominator is the number who received ACT (n=467)*

[5] *The denominator is children with a fever that had a fever questionnaire (n=1,641)*

Table 3. Factors associated with receiving an ACT among under-five children with fever (n=982)

Variable	n/N	%	Unadjusted analysis		Adjusted analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Location						
Rural	385/835	46.2%	ref	0.212	ref	0.933
Urban	82/147	54.2%	1.38 (0.83 – 2.27)		1.02 (0.63 – 1.67)	
Region						
West	35/75	46.5%	ref	0.243	ref	0.018
North	203/452	45.0%	0.94 (0.54 – 1.61)		1.23 (0.66 – 2.29)	
South	124/268	45.6%	0.96 (0.53 – 1.74)		1.51 (0.80 – 3.83)	
East	105/187	56.4%	1.48 (0.80 – 2.76)		2.40 (1.26 – 4.55)	
Household Size						
1-5	146/269	52.2%	ref	0.058	ref	0.189
6-10	255/548	47.3%	0.82 (0.59 – 1.15)		0.93 (0.67 – 1. 30)	
11+	66/165	39.9%	0.61 (0.41 – 0.91)		0.69 (0.46 – 1.04)	
Household Religion						
Muslim	374/796	46.7%	ref	0.446	ref	0.548
Christian	93/186	50.2%	1.15 (0.80 – 1.64)		0.89 (0.62 – 1.29)	
Socio-economic status						
1 (poorest)	131/317	41.0%	ref	0.004	ref	0.271
2	175/382	46.1%	1.23 (0.87 – 1.73)		1.00 (0.68 – 1.48)	
3 (least poor)	161/283	56.4%	1.86 (1.28 – 2.69)		1.38 (0.87 – 2.20)	
Respondent Education						
None	290/644	45.1%	ref	0.297	ref	0.911
Primary	63/123	51.2%	1.28 (0.87 – 1.89)		1.04 (0.68 – 1.58)	
Secondary or higher	105/196	52.9%	1.37 (0.95 – 1.96)		0.97 (0.64 – 1.46)	
Arabic school or Other	9/19	47.9%	1.12 (0.44 – 2.87)		1.42 (0.49 – 4.08)	
Everyone is at risk						
—No	119/250	47.0%	ref	0.898	ref	0.414
—Yes	348/732	47.5%	1.02 (0.74 – 1.40)		0.86 (0.60 – 1.23)	
ITNs protect from malaria						
—No	129/370	35.0%	ref	<0.001	ref	0.001
—Yes	338/612	54.9%	2.26 (1.64 – 3.12)		1.80 (1.26 – 2.58)	
Under 5 slept under ITN						
—No	118/287	39.8%	ref	0.008	ref	0.052
—Yes	349/695	50.5%	1.54 (1.12 – 2.12)		1.42 (1.00 – 2.04)	
Knowledge of ACTs						
—No	185/537	34.4%	ref	<0.001	ref	<0.001
—Yes	282/445	63.0%	3.25 (2.39 – 4.42)		2.84 (2.07 – 3.89)	
Child age (months)						
0-23 months	135/321	42.3%	ref	0.042	ref	0.014
24-59 months	332/661	49.7%	1.35 (1.01 – 1.80)		1.46 (1.08 – 1.98)	
Prompt treatment (24hrs)						
—No	259/542	47.7%	ref	0.830	ref	0.842
—Yes	208/440	46.9%	1.03 (0.78 – 1.37)		1.03 (0.76 – 1.39)	
Public Health facility						
—No	57/159	36.4%	ref	0.005	ref	0.002
—Yes	410/823	49.5 %	1.72 (1.18 – 2.50)		1.85 (1.27 – 2.71)	

Table 4. Factors associated with adherence to ACTs among under-five children with fever (n=467)

Variable	n/N	%	Unadjusted analysis		Adjusted analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Location						
Rural	177/385	46.0%	ref	0.197	ref	0.213
Urban	43/82	53.5%	1.47 (0.82 – 2.66)		1.52 (0.79 -2.94)	
Region						
West	10/35	27.4%	ref	0.439	ref	0.164
North	98/203	47.6%	2.15 (0.85 – 5.42)		2.67 (1.05 – 6.78)	
South	59/124	48.6%	2.26 (0.89 – 5.72)		2.97 (1.13 – 7.83)	
East	53/105	50.8%	2.40 (0.93 – 6.17)		2.76 (1.07 – 7.09)	
Household Size						
1-5	63/146	44.7%	ref	0.323	ref	0.714
6-10	120/255	46.7%	1.05 (0.70 – 1.56)		1.05 (0.69 – 1.61)	
11+	37/66	54.2%	1.39 (0.77 – 2.52)		1.29 (0.70 – 2.38)	
Household Religion						
Muslim	171/374	45.6	ref	0.161	ref	0.056
Christian	49/93	53.7	1.41 (0.87 – 2.28)		1.61 (0.99 – 2.63)	
Socio-economic status						
1 (poorest)	62/131	46.5	ref	0.601	ref	0.877
2	83/175	47.0	1.02 (0.64 – 1.63)		1.08 (0.66 – 1.76)	
3 (least poor)	75/161	48.0	1.14 (0.69 – 1.88)		1.18 (0.63 – 2.19)	
Respondent Education						
None	138/290	47.8%	ref	0.661	ref	0.697
Primary	30/63	48.5%	1.01 (0.57 – 1.77)		0.83 (0.44 – 1.56)	
Secondary or higher	45/100	44.4%	0.91 (0.55 – 1.49)		0.73 (0.42 – 1.26)	
Arabic or Other	7/14	47.6%	0.78 (0.18 – 3.46)		0.73 (0.17 – 3.18)	
Know everyone is at risk						
—No	59/119	50.9%	ref	0.460	ref	0.424
—Yes	161/348	45.9%	0.85 (0.54 – 1.32)		0.82 (0.51 -1.33)	
Know ITNs protect						
—No	62/129	48.1%	ref	0.794	ref	0.856
—Yes	158/338	46.8%	0.95 (0.62 – 1.44)		0.96 (0.61 – 1.50)	
U5 slept under ITN						
—No	57/118	48.0%	ref	0.802	ref	0.692
—Yes	163/349	46.9%	0.95 (0.62 – 1.45)		0.91 (0.58 – 1.43)	
Knowledge ACTs						
—No	86/185	46.4%	ref	0.657	ref	0.685
—Yes	134/282	47.8%	1.10 (0.73 – 1.64)		1.09 (0.71 – 1.69)	
Child age (months)						
0-23 months	59/135	43.2%	ref	0.267	ref	0.277
24-59 months	161/332	48.8%	1.24 (0.85 – 1.82)		1.26 (0.83 – 1.90)	
Prompt treatment (24hrs)						
—No	102/208	49.5%	ref	0.453	ref	0.657
—Yes	118/259	45.4%	0.86 (0.58 – 1.28)		1.11 (0.70 – 1.75)	
Public Health facility						
—No	28/58	48.3%	ref	0.938	ref	0.843
—Yes	192/410	47.0%	0.98 (0.55 – 1.74)		0.94 (0.52 – 1.72)	
ACT within 24hrs						
—No	85/155	54.7%	ref	0.040	ref	0.032
—Yes	135/312	43.6%	0.64 (0.42 – 0.98)		0.58 (0.35 – 0.95)	

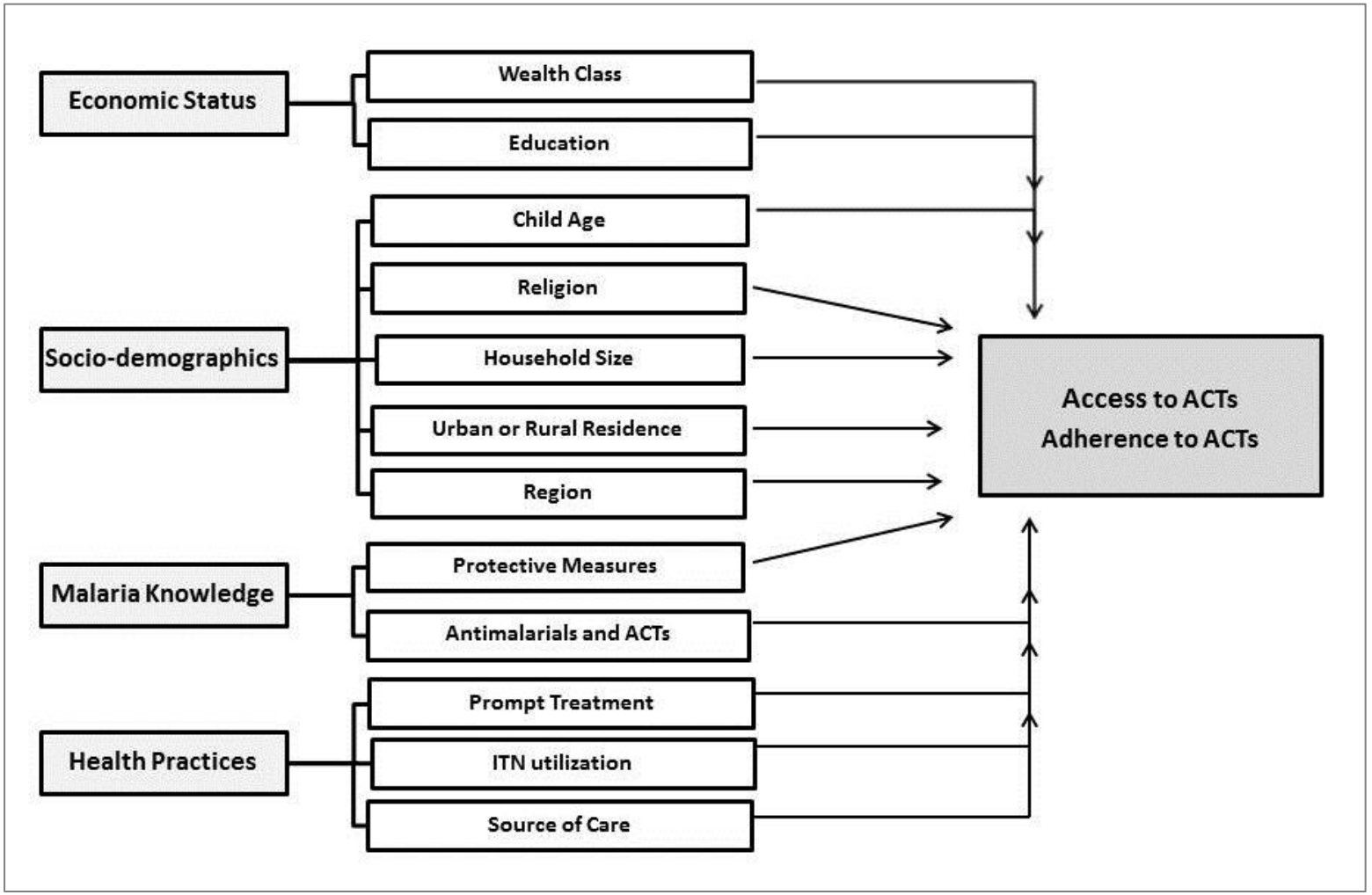

Figure 1. Conceptual Framework. A summary of suspected socio-demographic factors associated with access and adherence to ACTs

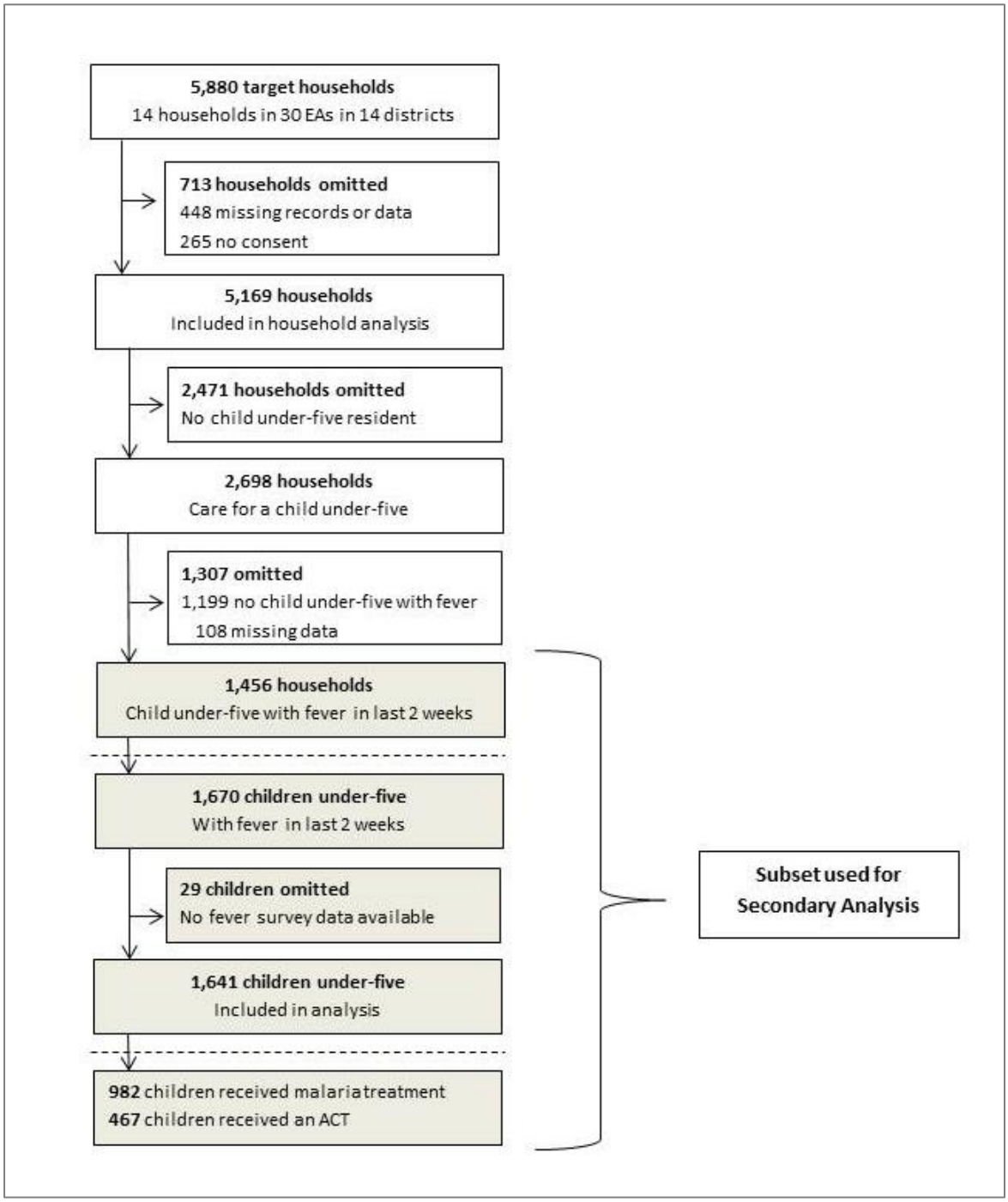

Figure 2. mKAP Survey Profile.

CHAPTER 6: ADHERENCE TO TREATMENT WITH ARTEMETHER-LUMEFANTRINE OR AMODIAQUINE-ARTESUNATE FOR UNCOMPLICATED MALARIA IN CHILDREN IN SIERRA LEONE: A RANDOMIZED TRIAL

6.1 Chapter Introduction

This chapter addresses Objective II, to evaluate and compare the level of adherence to co-formulated amodiaquine-artesunate compared to artemether-lumefantrine for the treatment of malaria in children aged 6 to 59 months seeking care at government health facilities in Sierra Leone. The paper was published by Malaria Journal in June 2018 and presents the results of a randomized control trial conducted in August to December 2013.

6.2 Research Paper

The cover sheet is on the next page followed by the manuscript.

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SECTION A – Student Details

Student	Kristin Banek
Principal Supervisor	Sarah Staedke & Daniel Chandramohan
Thesis Title	Evaluation of Adherence to Artemisinin-based Combination Therapy for the Treatment of Uncomplicated Malaria in Sierra Leone

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Malaria Journal		
When was the work published?	June 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not Applicable		
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study, collected the data, conducted the analysis and wrote the first draft of the manuscript.

Student Signature: _____ **Date:** 27 June 2018

Supervisor Signature: _____ **Date:** 11 July 2019

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Malaria Journal

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Adherence to treatment with artemether–lumefantrine or amodiaquine–artesunate for uncomplicated malaria in children in Sierra Leone: a randomized trial

Kristin Banek[1*], Emily L. Webb[2], Samuel Juana Smith[3], Daniel Chandramohan[4] and Sarah G. Staedke[1]

Abstract

Background: Prompt, effective treatment of confirmed malaria cases with artemisinin-based combination therapy (ACT) is a cornerstone of malaria control. Maximizing adherence to ACT medicines is key to ensuring treatment effectiveness.

Methods: This open-label, randomized trial evaluated caregiver adherence to co-formulated artemether–lumefantrine (AL) and fixed-dose amodiaquine–artesunate (AQAS) in Sierra Leone. Children aged 6–59 months diagnosed with malaria were recruited from two public clinics, randomized to receive AL or AQAS, and visited at home the day after completing treatment. Analyses were stratified by site, due to differences in participant characteristics and outcomes.

Results: Of the 784 randomized children, 680 (85.6%) were included in the final per-protocol analysis (340 AL, 340 AQAS). Definite adherence (self-reported adherence plus empty package) was higher for AL than AQAS at both sites (Site 1: 79.4% AL vs 63.4% AQAS, odds ratio [OR] 2.16, compared to probable adherence plus probable or definite non-adherence, 95% confidence interval [CI] 1.34–3.49; p=0.001; Site 2: 52.1% AL vs 37.5% AQAS, OR 1.53, 95% CI 1.00–2.33, p=0.049). However, self-reported adherence (ignoring drug package inspection) was higher for both regimens at both sites and there was no strong evidence of variation by treatment (Site 1:

96.6% AL vs 95.9% AQAS, OR 1.19, 95% CI 0.39–3.63, p=0.753; Site 2: 91.5% AL vs 96.4% AQAS, OR 0.40, 95% CI 0.15–1.07, p=0.067). In Site 2, correct treatment (correct dose + timing + duration) was lower for AL than AQAS (75.8% vs 88.1%, OR 0.42, 95% CI 0.23–0.76, p = 0.004). In both sites, more caregivers in the AQAS arm reported adverse events (Site 1: 3.4% AL vs 15.7% AQAS, p < 0.001; Site 2: 15.2% AL vs 24.4% AQAS, p=0.039).

Conclusions: Self-reported adherence was high for both AL and AQAS, but varied by site. These results suggest that each regimen has potential disadvantages that might affect adherence; AL was less likely to be taken correctly at one site, but was better tolerated than AQAS at both sites. Measuring adherence to anti-malarials remains challenging, but important. Future research should focus on comparative studies of new drug regimens, and improving the methodology of measuring adherence.

Trial registration: Clinicaltrials.gov, NCT01967472. Retrospectively registered 18 October 2013, https://clinicaltrials.gov/ ct2/show/NCT01967472

Keywords: Malaria, Artemisinin-based combination therapy (ACT), Adherence, Compliance, Artemether–lumefantrine, Amodiaquine, Artesunate, Fixed-dose combination, Co-formulated

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Background

Universal coverage of diagnostic testing and prompt, effective treatment with artemisinin-based combination therapy (ACT) are key malaria control strategies [1, 2]. However, the effectiveness of malaria case management depends on multiple factors, including the availability of (and access to) treatment with ACT, prescriber compliance to guidelines, and importantly, patient (or caregiver) adherence to treatment regimens [3, 4]. Strategies to improve adherence, including co-packaging anti-malarial drugs into blister packs [5, 6], and co-formulating the partner drugs of ACT into a single tablet, have been applied successfully [7, 8]. Although co-formulation may improve the accuracy of prescription and ease of administration of ACT [9], it may not solve all treatment challenges, including complex dosing, bitter taste, and side effects [10–13]. Furthermore, evidence of the impact of co-formulation on adherence to ACT remains limited [3].

Malaria remains a major health problem in Sierra Leone, exacerbated by the Ebola outbreak in 2014, which overwhelmed an already fragile health system [14–18]. In 2004, co-packaged amodiaquine plus artesunate (AQ + AS) was adopted as the first-line recommended treatment of malaria, primarily due to affordability and availability, with artemether–lumefantrine (AL) as an alternative if AQ + AS was not available, or was ineffective [19]. In 2008, a study of adherence to co-packaged AQ + AS in Sierra Leone concluded that only 48.7% of participants were probably or definitely adherent to treatment [20]. In 2013, with support from The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) the fixed-dose combination version of amodiaquine–artesunate (AQAS) replaced the co-packaged AS + AQ regimen, with AL remaining as an alternate. However, in 2015, following the mass drug administration (MDA) campaign during the Ebola outbreak, AL replaced AQAS as the treatment of choice for uncomplicated malaria in Sierra Leone, with AQAS now as the alternate [21]. The impact of these changes in anti-malarial drug policy on patient adherence and the overall effectiveness of malaria treatment in Sierra Leone remains unclear. To date, no studies have evaluated adherence to either AL or AQAS in Sierra Leone.

Only three studies have compared the adherence to multiple ACT regimens in Africa; however, the primary outcome of all three studies was treatment effectiveness; adherence was evaluated as a secondary outcome [22–24]. Only one of these studies, conducted in Benin, compared AL and AQAS [24], finding no significant difference in full adherence to AL compared to AQAS (83.0% vs 91.0%; p = 0.16). To address this gap in evidence, an open-label, randomized trial was conducted in Sierra Leone to compare caregiver adherence to co-formulated AL to that of AQAS for treatment of uncomplicated malaria in children aged 6–59 months.

Methods

Study sites

The study was conducted at two government-run outpatient facilities in Freetown, Sierra Leone (Fig. 1). Both sites were chosen for their high patient loads, similar catchment population and patient numbers as well as the size of staff (10–15 health workers per site). Site 1 is located in a densely populated area in the eastern part of Freetown. The clinic has an estimated catchment population of 21,324 people and manages approximately 1000 patients per month, half of whom are children under 5 years of age presenting with fever. In 2012, the clinic had 400 children under five with confirmed malaria every month (extracted from routine health data). Site 2 is located in the western part of Freetown. This clinic has an estimated catchment population of 27,855 people, with approximately 800 patient visits per month. In 2012, 60% of patients were children under 5 years of age presenting with fever, including an average of 240 confirmed malaria cases each month (routine health data).

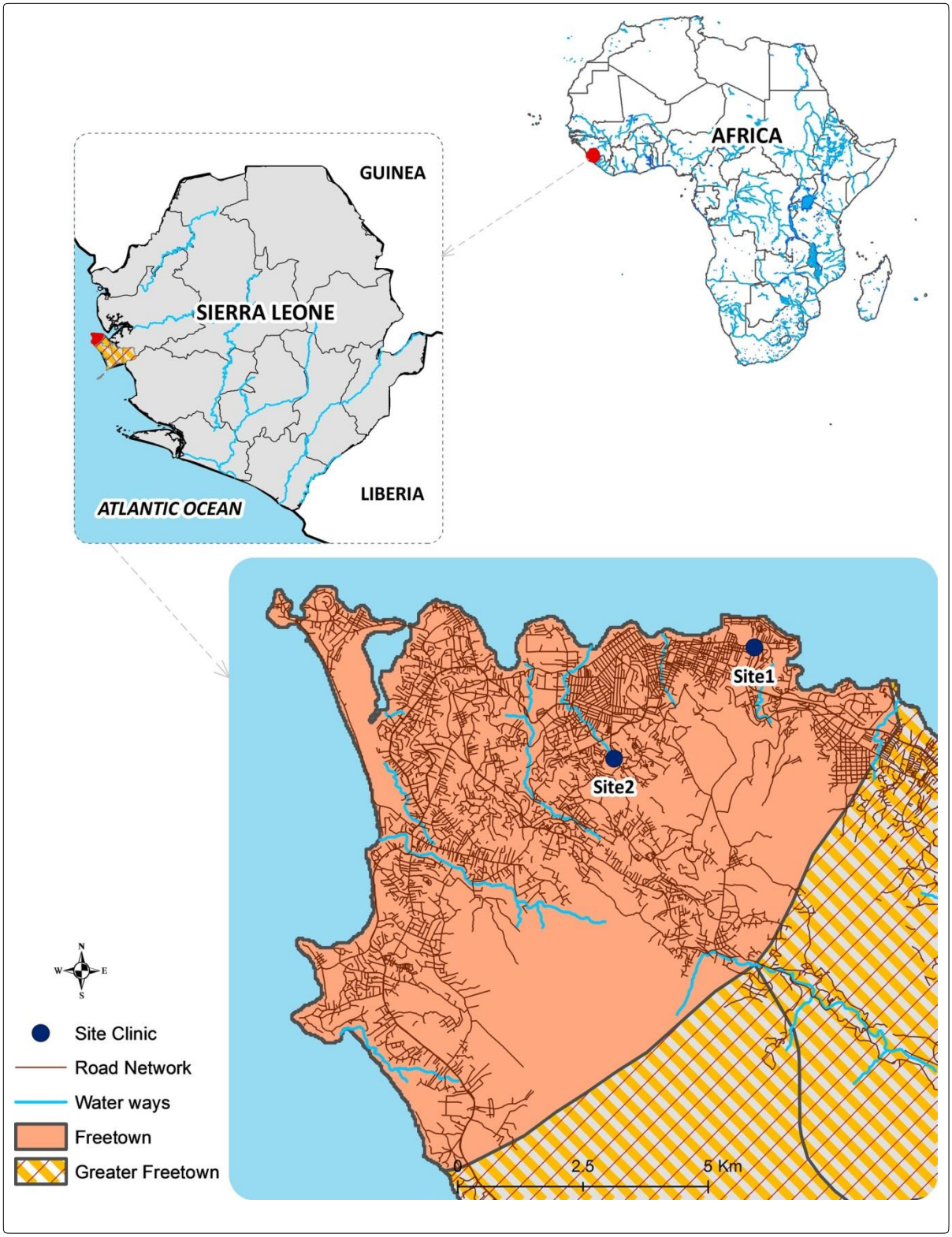

Fig. 1 Map of the study area. Blue dots—Study Sites

Study procedures

Children were enrolled in the study, if they met the following inclusion criteria: (1) age 6–59 months; (2) complaint of fever or history of fever; (3) living within 5 km of health facility; (4) no evidence of severe malaria or danger signs (i.e. inability to eat/drink, extreme lethargy, inability to sit/stand, difficulty breathing, jaundice, severe dehydration, convulsion or persistent vomiting) [2, 21, 25]; (5) not referred to another health facility; (6) not previously enrolled in the study; and (7) written informed consent to participate in the study provided by their parent or guardian. During the consenting process, caregivers were informed about the purpose of the study, but were not told that they would be visited at home or that their adherence to treatment guidelines would be assessed.

Following enrolment, study participants were subject to the standard of care provided at the health centres. All participants first underwent testing for malaria using rapid diagnostic tests (RDTs) at the health centre laboratory, and then saw a consulting health worker for a clinical evaluation. Study staff recorded RDT results onto case record forms, and observed patient-provider consultations for all participants. Children who had a positive RDT and were diagnosed with malaria by the health worker were randomly assigned to receive treatment with either AL or AQAS and were scheduled for a home visit on Day 4. If the RDT was negative for malaria, the child was excluded from the study and was provided standard care by the health worker.

Study medication

Co-formulated AL (Coartem Dispersible®: Novartis) was procured by the research team and provided to both sites for the purpose of this study. Fixed-dose AQAS (Winthrop®: Sanofi-Aventis) was available at both study sites through the standard government supply chain system. All study medications were produced by manufacturers pre-qualified by the World Health Organization (WHO) and approved by the Pharmacy Board of Sierra Leone, and were prescribed according to standard national and WHO treatment guidelines [25, 26].

Participants randomized to treatment with AL received 20/120 mg tablets dosed appropriately, twice a day for 3 days. Health workers prescribed treatment based on weight when possible; if weighing scales were not available, treatment was prescribed by age. Children aged 6–11 months (or weighing 5–15 kg) received 1 tablet per dose (infant-dose), and those aged 12–59 months of age (or weighing > 15 to 20 kg) received 2 tablets per dose (child-dose). Participants randomized to treatment with AQAS received one tablet dosed appropriately for age (or weight) once daily for 3 days. Children aged 6–11 months (or weighing 4.5–8 kg) received the infant dose (67.5 mg AQ/25 mg AS tablets) and children aged 12–59 months (or weighing 9–17 kg) received the child-dose (136 mg AQ/50 mg AS tablets). Caregivers were responsible for administering the treatments to their child as instructed by the health worker.

Randomization and blinding

A computer-generated randomization list (in blocks of 10) was created for each site by a member of the team who was not directly involved in patient recruitment, consultation or follow-up. Prior to study initiation, individual treatment allocation slips were prepared from the randomization list. These were sealed into sequentially- numbered, opaque envelopes containing the treatment group assignments. The consulting health worker opened the envelopes and assigned the treatment number and corresponding treatment at the time of prescription. Health facility nurses were responsible for dispensing the study medications according to the assigned study number. Study medications were not identical in appearance or taste nor were the tablets per dose the same. The participants, health workers, and study team were not blinded to the treatment assignments.

Follow-up

Study participants were visited at home 4 days after their clinic visit; the day after the last treatment dose should have been taken. The purpose of the follow-up visit was explained to the caregivers, and additional written informed consent for the interview was obtained; participation was voluntary [27]. If the participating child required further medical attention at the time of the home visit, s/he was immediately referred to the nearest health centre, and the adherence assessment was conducted the following day, if the participant's condition had improved. No interviews were carried

out more than 5 days after the initial clinic visit.

A semi-structured questionnaire was administered to caregivers to assess adherence to treatment, the characteristics of the child and caregiver, knowledge of malaria, household characteristics, and wealth indicators. Caregivers were asked to describe the treatment, including how the medication was administered and any adverse events, and to show the original medication packaging. If the packaging was available, any remaining tablets were tallied and recorded onto the questionnaire. If treatment had not been completed at the time of the follow-up visit, the caregiver was encouraged to complete the full treatment course or, if that was not possible, to return to the health facility.

Statistical methods

Sample size

In 2010, the prevalence of adherence to co-packaged AQ + AS in Sierra Leone was estimated to be 50% [20]. Based on studies in other countries, it was estimated that fixed-dose AQAS would yield a higher level of adherence (conservatively estimated to be 75%) [24, 28]. At the time of the study, there was no data on adherence levels to AL in Sierra Leone, however, based on the literature it was hypothesized that adherence to AL would be greater than co-packaged AQ + AS, but less than fixed-dose AQAS [3, 29]. In order to determine a 15% or greater absolute difference between the different treatment groups (two-sided test, 5% significance level, 80% power, 20% contingency (i.e. loss to follow-up, missing data etc.), a total of 198 patients were required for each treatment arm. As differences in context, health system and/or socioeconomic factors may influence adherence, the study was powered to detect differences in adherence to the two treatments, separately at each site. Thus, the sample size for each site was 400.

Outcome measures

Using previous ACT adherence studies as a guide, the primary outcome of caregiver adherence was based on self-reports of completion of treatment and, when possible, verified by package inspection [3, 29, 30]. Adherence was classified into four categories:

(1) “definitely adherent”: caregiver reported completion of treatment and verified by an empty package; (2) “probably adherent”: reported completion of treatment but no package available for verification; (3) “probably non-adherent”: reported non-completion of treatment, but no package available for verification; and (4) “definitely non-adherent”: reported non-completion of the treatment verified by a package with remaining tablets.

As the main outcome variable was derived from two different measurements, the variable was recoded to produce two binary variables representing each component. These included: (1) “self-reported adherence”, which does not consider package availability (thus, self-reported adherence =definitely adherent +probably adherent; non-adherence = probably non-adherent + definitely non-adherent); and (2) “package-based adherence”, which does not consider self-reported adherence (thus package-based adherence = definitely adherent; non- adherence = probably adherent + probably non-adherent +definitely non-adherent).

Secondary outcomes were adherence to the prescribed number of doses, time-schedule and duration of treatment. The correct number of doses was defined as receiving the prescribed number of tablets, as indicated. Correct timing was defined as receiving the ACT at the prescribed intervals (twice daily for AL and once daily for AQAS). Correct duration was defined as receiving the ACT for the recommended number of days (3 days for both regimens). Correct treatment was defined as the composite of the three above indicators: correct dose +correct timing +correct duration, in which all three factors were met.

Data management and analysis

Data were recorded on paper forms and entered into a database created in Epi Info ™ 7.1.2.0 (Centers for Disease Control and Prevention (CDC), Atlanta, GA USA). Data were double entered into tablets using the Epi Info Companion for Android mobile application. Statistical analysis was performed using Stata 12 (StataCorp, College Station, TX USA).

Although intention-to-treat analysis is the preferred analytic approach for randomized controlled trials, a per-protocol analysis was favoured for this trial as the primary outcome was adherence. The main objective of this study was to assess the behaviours of caregivers related to the specific ACT received at the health facility. Therefore, the primary analyses were carried out using the per-protocol population, in which only children who received ACT as per the randomization schedule and had outcome data were included. Children who did not receive the correct ACT regimen based on the randomization list were excluded from this analysis. We also conducted and present the intention-to-treat analysis for comparison with the per-protocol findings, to assess whether results from the two analytic approaches were similar. Participant's characteristics and adverse events were tabulated by study site and randomization group in the per- protocol population. The wealth index was created using principal component analysis (PCA) [31].

Chi-squared or Fisher's exact tests were used to compare categorical data, and continuous data were tested using Student's or Welch's *t*-tests. Measures of effect (odds ratios-OR) were calculated using logistic regression for binary outcomes and ordinal logistic regression for multinomial outcomes along with the 95% confidence intervals and associated p-values. For the ordinal logistic regression model, the proportional odds assumption was tested with a likelihood ratio test.

Ethical considerations

The study protocol was approved by the London School of Hygiene and Tropical Medicine (LSHTM) Research Ethics Committee and the Sierra Leone Ethics and Scientific Review Committee. The trial was registered at ClinicalTrials.gov (NCT01967472; https://clinicaltrials.gov/ct2/show/NCT01967472). All participants provided written informed consent at the time of recruitment and again prior to administration of the follow-up survey in their homes.

Results

Enrolment

The study was conducted from September 2013 to January 2014. Of the 1979 children screened (Fig. 2), 834 were excluded at screening, and 361 were excluded after testing negative for malaria. A total of 784 children were randomized to malaria treatment (390 at Site 1; 394 at Site 2); of these, 77 (9.7%) were excluded after randomization (lost to follow-up = 55, missing data = 18, refused 1, serious adverse event = 3; Fig. 2). The total number of children analysed in the intention-to-treat population was 707 (353 at Site 1 and 354 at Site 2). Treatment was misallocated in an additional 27 cases (6 at Site 1; 21 at Site 2); these children were excluded from the per-protocol analysis. Thus, 680 (85.6%) randomized children were included in the final per-protocol analysis (347 at Site 1; 333 at Site 2). Analyses were carried out for both the intention-to-treat and per-protocol populations, but all tables present the results from the per-protocol population. The intention-to-treat analysis is also presented for both the primary and secondary outcomes, but there is little if any difference between the findings.

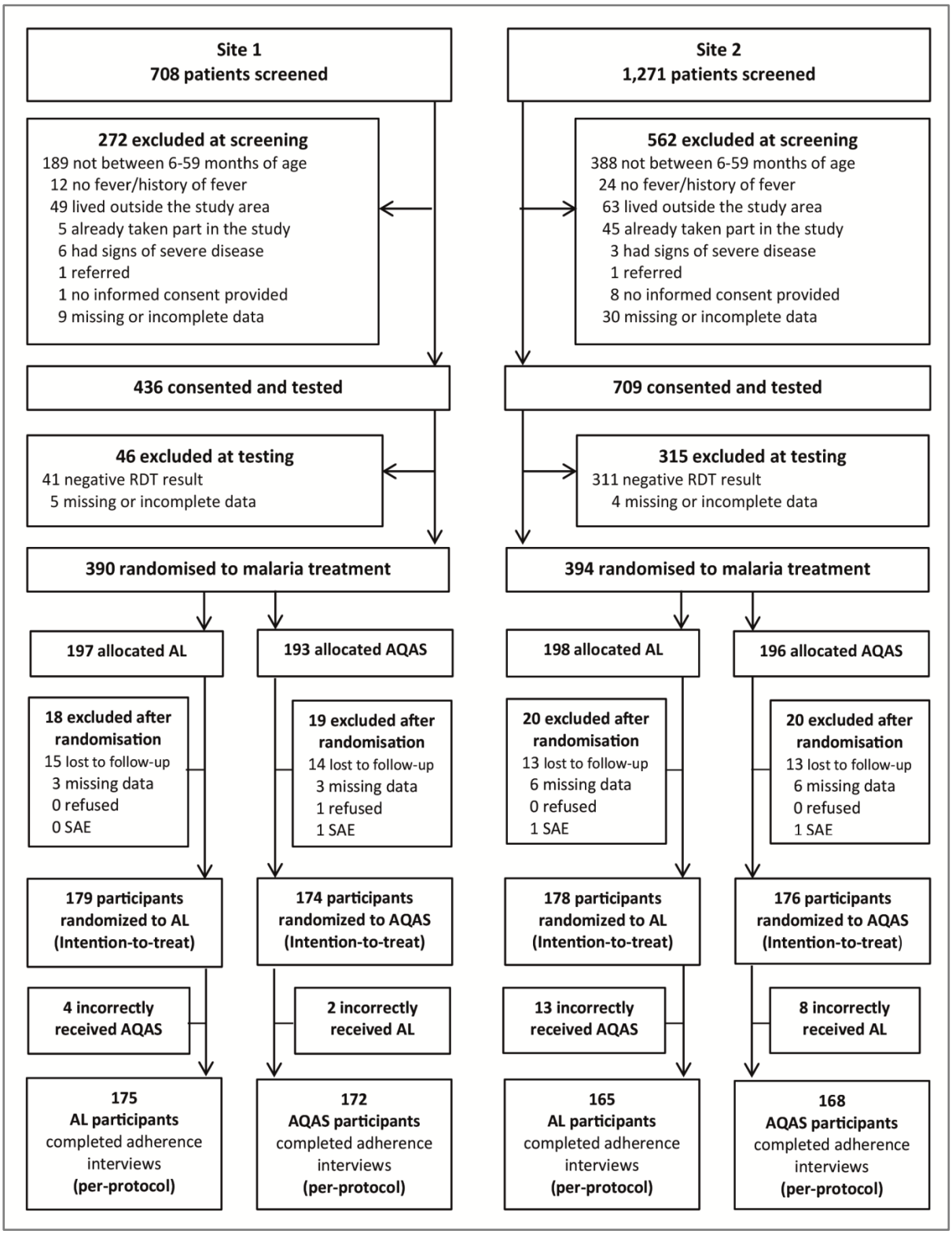

Fig. 2 Study profile. *RDT*, rapid diagnostic test; *AQAS*, fixed-dose combination amodiaquine–artesunate; *AL*, artemether–lumefantrine; *SAE*, serious adverse event

Characteristics of participants, caregivers, and households

The characteristics of participants and their caregivers and households were significantly different at the two study sites, therefore, all results are presented stratified by site (Table 1). Participants at Site 1 were younger than those at Site 2 (mean age 15 months vs 24 months, respectively, $p < 0.001$). No child at either site had been treated previously with AL, while some had received fixed-dose AQAS (41.3% at Site 1; 28.6% at Site 2; $p = 0.025$). Few caregivers reported that their child disliked AL, but complaints about AQAS were more common (19.8% at Site 1; 15.5% at Site 2; $p = 0.550$). At both sites, only caregivers in the AQAS arm reported that their child complained of bitter taste.

Caregivers were also younger at Site 1 (median age of 25 years at Site 1 vs 27 years at Site 2, $p< 0.001$); most caregivers (> 70%) spoke Krio (the local language) at both sites. In Site 1, caregivers in the AL arm were more educated than those in the AQAS arm (61.1% vs 50.0%, respectively, $p=0.040$). At both sites, approximately half of caregivers reported that health workers instructed them to finish the anti-malarial treatment. Caregiver knowledge about ACT was low at both sites, more so in Site 1.

The Muslim religion was practised by substantially more households at Site 1 than at Site 2 (85.9% vs 49.2%, respectively, $p<0.001$). Households at Site 2 were significantly poorer than at Site 1, with 149 (44.7%) households assigned to the poorest category at Site 2 vs 87 (25.1%) in Site 1 ($p< 0.001$). Otherwise, there were no additional differences in characteristics of participants, caregivers or households, between trial arms, at either site.

Table 1 Characteristics of participants, caregivers and households[a]

	Site 1		Site 2	
	AL (N = 175)	AQAS (N =172)	AL (N = 165)	AQAS (N = 168)
Participant characteristics				
Weight[b], kg [median (IQR)]	10 (8, 11)	10 (8, 11.4)	10 (8, 13)	10 (9, 13)
Age, months [median (IQR)]	15 (10, 24)	16 (11, 32.5)	24 (14, 37)	24 (14, 42.5)
Age categorized				
6 to 24 months	132 (75.4%)	116 (67.4%)	88 (53.3%)	85 (50.6%)
25 to 59 months	43 (24.6%)	56 (32.6%)	77 (45.7%)	83 (49.4%)
Gender (% female)	82 (46.9%)	72 (41.9%)	79 (47.9%)	76 (45.2%)
Previously taken the antimalarial treatment				
No	173 (98.9%)	97 (56.4%)	165 (100%)	118 (70.2%)
Yes	0 (0.0%)	71 (41.3%)	0 (0.0%)	48 (28.6%)
Unknown	2 (1.1%)	4 (2.3%)	0 (0.0%)	2 (1.2%)
Disliked the antimalarial treatment				
No	156 (89.1%)	128 (74.4%)	153 (92.7%)	130 (77.4%)
Yes	2 (1.1%)	34 (19.8%)	7 (4.2%)	26 (15.5%)
Unknown	17 (9.7%)	10 (5.8%)	5 (3.0%)	12 (7.1%)
Complained of bitter taste	0 (0.0%)	31 (18.0%)	0 (0.0%)	18 (10.7%)
Caregiver characteristics				
Age, years [median (IQR)]	25 (21, 30)	25 (21, 29)	27 (22, 34)	27 (23, 34)
Gender (% female)	169 (96.6%)	166 (96.5%)	156 (94.6%)	162 (96.4%)
Fluent in Krio	123 (70.3%)	124 (72.1%)	116 (70.3%)	118 (70.2%)
Any education	107 (61.1%)	86 (50.0%)	109 (66.1%)	116 (69.1%)
Told to finish treatment by health worker	101 (57.7%)	101 (58.7%)	85 (51.5%)	73 (43.5%)
Knowledge about ACTs	31 (17.7%)	35 (20.4%)	54 (32.7%)	51 (30.4%)
Household characteristics				
Religion[c]				
Christian	27 (15.4%)	22 (12.8%)	77 (46.7%)	91(54.2%)
Muslim	148 (84.6%)	150 (87.2%)	87 (52.7%)	77 (45.8%)
Household wealth index[d]				
1 (poorest)	40 (23.7%)	47 (27.5%)	77 (47.0%)	72 (43.1%)
2	59 (34.9%)	61 (35.7%)	42 (25.6%)	47 (28.1%)
3 (least poor)	70 (41.4%)	63 (36.8%)	45 (27.4%)	48 (28.7%)

[a] Demographic data were collected during follow-up visits; therefore, this information is only available from participants that were located and consented for the follow-up interviews (the per-protocol population)

[b] Scale availability was problematic at both sites on select days, so weight data is not available for some participants. Denominators for weight: Site 1: AL = 165; AQAS-164; Site 2: AL = 151; AQAS = 152

[c] Religion: information on religion is missing from one participant in the AL group at Site 2 (n = 164)

[d] Wealth index denominators: Site 1 AL = 169 and AQAS = 171; Site 2 AL = 164 and AQAS = 167

Adherence

At both sites, the odds of definite adherence (defined as self-reported adherence in the presence of an empty drug package) were higher for AL than AQAS (Table 2). Self-reported adherence (ignoring the results of the drug package inspection) was > 90% for both regimens, but varied between the sites. At Site 1, self-reported adherence to AL was slightly higher than to AQAS, but at Site 2, self-reported adherence to AQAS was greater than to AL. However, adherence determined by inspecting drug packaging alone was higher for AL than AQAS at both sites; adherence (defined by empty packaging) to both regimens was higher at Site 1 than Site 2. This variability in findings reflects differences in the retention of the drug package by caregivers, which was significantly higher at Site 1 than at Site 2 (263 [75.8%] vs 185 [52.6%], respectively, $p < 0.001$; Additional file 1). In addition, at both sites, significantly more caregivers saved AL packages than AQAS packages (Site 1: AL 147 [84.0%] vs AQAS 116 [67.4%], $p < 0.001$; Site 2: AL 103 [62.4%] vs AQAS 72
[42.9%], $p < 0.001$).

Table 2 Primary adherence outcomes

	Site 1			Site 2		
	AL	**AQAS**	**OR (95%CI) p-value***	**AL**	**AQAS**	**OR (95%CI) p-value***
Per-Protocol	**N=175**	**N=172**		**N=165**	**N=168**	
Primary adherence outcome[1]						
—Definitely non-adherent	2 (1.1%)	3 (1.7%)	2.16 (1.34-3.49)	10 (6.1%)	5 (3.0%)	1.53 (1.00-2.33)
— Probably non-adherent	4 (2.3%)	4 (2.3%)	0.001	4 (2.4%)	1 (0.6%)	0.049
—Probably adherent	30 (17.1%)	56 (32.6%)		65 (39.4%)	99 (58.9%)	
—Definitely adherent	139 (79.4%)	109 (63.4%)		86 (52.1%)	63 (37.5%)	
Self-reported adherence[2]						
—Non-adherent	6 (3.4%)	7 (4.1%)	1.19 (0.39-3.63)	14 (8.5%)	6 (3.6%)	0.40 (0.15-1.07)
—Adherent	169 (96.6%)	165 (95.9%)	0.753	151 (91.5%)	162 (96.4%)	0.067
Adherence based on packaging[3]						
—Non-adherent	36 (20.6%)	63 (36.6%)	2.23 (1.38-3.61)	79 (47.9%)	105 (62.5%)	1.81 (1.17-2.81)
—Adherent	139 (79.4%)	109 (63.4%)	0.001	86 (52.1%)	63 (37.5%)	0.008
Intention-to Treat	**N=179**	**N=174**		**N=178**	**N=176**	
Primary adherence outcome[1]						
—Definitely non-adherent	2 (1.1%)	3 (1.7%)	2.15 (1.35-3.44)	11 (6.2%)	6 (3.4%)	1.40 (0.93-2.10)
— Probably non-adherent	4 (2.3%)	4 (2.3%)	0.001	4 (2.3%)	1 (0.6%)	0.109
—Probably adherent	32 (17.9%)	58 (33.3%)		73 (41.0%)	101 (57.4%)	
—Definitely adherent	141 (78.8%)	109 (62.6%)		90 (50.6%)	68 (38.6%)	
Self-reported adherence[2]						
—Non-adherent	6 (3.4%)	7 (4.0%)	1.21 (0.40-3.67)	15 (8.4%)	7 (4.0%)	0.45 (0.18-1.13)
—Adherent	173 (96.7%)	167 (96.0%)	0.738	163 (91.6%)	169 (96.0%)	0.090
Adherence based on packaging[3]						
—Non-adherent	38 (21.2%)	65 (37.4%)	2.21 (1.38-3.55)	88 (49.4%)	108 (61.4%)	1.62 (1.06-2.48)
—Adherent	141 (78.8%)	109 (62.6%)	0.001	90 (50.6%)	68 (38.6%)	0.024

** Odds Ratios were calculated using ordinal logistic regression for the primary adherence outcome and logistic regression for the binary outcomes with ORs calculated using AQAS as the reference group*

[1] Definitely adherent= self-reported adherence + empty package; probably adherent= self-reported adherence (no package); probably non-adherent= self-reported non-adherence (no package); definitely non-adherent= self-reported non-adherence + package with tablets remaining

[2] Adherent= definitely adherent + probably adherent

[3] Adherent = only definitely adherent

Quality of treatment

Overall, the quality of treatment was high (Table 3). At both sites, nearly all participants received the total required tablets for both regimens. At Site 1, the mean proportion of number of tablets taken was higher, but not significantly, for AL (99.8%), while the opposite was found at Site 2, where the mean proportion of tablets received was marginally higher for AQAS (99.2%). Subtle differences in treatment patterns were found at both sites. At Site 1, significantly fewer AQAS participants received the appropriate number of tablets for their weight (correct dose), but fewer AL participants were treated the correct number of times per day (correct timing), and for the correct number of days (correct duration), although these findings were not statistically significant. At Site 2, AL participants were significantly less likely to be treated with the appropriate number of tables and for the correct number of times per day (correct dose and correct timing), and were less likely to receive the correct treatment overall (correct dose +timing +duration), than AQAS participants.

Adverse events

A total of 106 caregivers reported that their child experienced an adverse event to treatment. Significantly more adverse events were reported at Site 2 than at Site 1 (66 [19.8%] vs 33 [9.5%], respectively, $p< 0.001$). At both sites, significantly more caregivers in the AQAS arm reported adverse events (Table 4), with vomiting, weak- ness-fatigue, and dizziness most commonly reported. At Site 1, significantly more caregivers in the AQAS arm reported that their child vomited, or was weak or dizzy. Similar results were seen at Site 2, but only weakness was reported by significantly more caregivers in the AQAS arm. Three serious adverse events, including two hospitalizations for severe malaria and one death, were reported during the study period, but none were felt to be related to the study medications. The cause of death was unknown for the child that died. However, the child was noted by the study staff to have danger signs suggestive of severe disease, and was referred, but unfortunately the caregiver did not seek further care.

Table 3 Quality of treatment with ACT

Per-Protocol	**Site 1**					**Site 2**				
Treatment adherence[a]	**AL (N = 176)**	**AQAS (N = 176)**	**Difference in means**	**95% CI**	**p-value**	**AL (N = 173)**	**AQAS (N = 181)**	**Difference in means**	**95% CI**	**p-value**
Mean % of treatment (SD)[b]	99.8% (2.5)	98.6% (7.9)	1.17	− 0.09, 2.42	0.068	97.0% (12.8)	99.2% (6.3)	− 2.19	− 4.37, 0.00	0.050
Correct treatment[c]	**AL (N = 179)**	**AQAS (N = 174)**	**Odds Ratio**	**95% CI**	**p-value**	**AL (N = 178)**	**AQAS (N = 176)**	**Odds ratio**	**95% CI**	**p-value**
Correct dose[d]	163 (93.1%)	144 (83.7%)	2.64	1.30, 5.39	0.008	128 (77.6%)	149 (88.7%)	0.44	0.24, 0.81	0.008
Correct timing[e]	163 (93.1%)	166 (96.5%)	0.49	0.18, 1.34	0.165	136 (82.4%)	163 (97.0%)	0.14	0.05, 0.38	< 0.001
Correct duration[f]	172 (98.3%)	170 (98.8%)	0.67	0.11, 4.09	0.668	156 (95.6%)	164 (97.6%)	0.42	0.13, 1.40	0.159
Correct treatment[g]	154 (88.0%)	140 (81.4%)	1.68	0.92, 3.04	0.089	125 (75.8%)	148 (88.1%)	0.42	0.23, 0.76	0.004
Intention-to-treat	**Site 1**					**Site 2**				
Treatment adherence[a]	**AL (N = 176)**	**AQAS (N = 176)**	**Difference in means**	**95% CI**	**p-value**	**AL (N = 173)**	**AQAS (N = 181)**	**Difference in means**	**95% CI**	**p-value**
Mean % of treatment (SD)[b]	99.8% (2.5)	98.7% (7.9)	1.14	− 0.09, 2.36	0.069	97.0% (12.7)	99.1% (6.0)	− 2.30	− 4.40, − 0.19	0.032
Correct treatment[c]	**AL (N = 175)**	**AQAS (N = 172)**	**Odds Ratio**	**95% CI**	**p-value**	**AL (N = 165)**	**AQAS (N = 168)**	**Odds Ratio**	**95% CI**	**p-value**
Correct dose[d]	166 (92.7%)	146 (83.9%)	2.45	1.22, 4.90	0.011	138 (77.5%)	155 (88.1%)	0.47	0.26, 0.83	0.010
Correct timing[e]	166 (92.7%)	168 (96.6%)	0.45	0.17, 1.23	0.120	149 (83.7%)	170 (96.6%)	0.18	0.07, 0.45	< 0.001
Correct duration[f]	179 (97.8%)	174 (98.9%)	0.51	0.09, 2.81	0.439	169 (94.9%)	171 (97.2%)	0.55	0.18, 1.67	0.291
Correct treatment[g]	156 (87.2%)	142 (81.6%)	1.53	0.85, 2.74	0.153	135 (75.8%)	154 (87.5%)	0.45	0.26, 0.79	0.005

[a] Proportion of all tablets received – information on the number of tablets taken is missing from one participant in the AL group at Site 1 (n = 174). Measure of Effect = Difference of means; AQAS is the reference group

[b] Percent of treatment = total number of tablets taken by the patient/total number of tablets prescribed

[c] Odds Ratios were calculated using logistic regression, with ORs calculated using AQAS as the reference group

[d] Dose is defined as the number of tablets prescribed by weight or age. For AQAS: 1 tablet per day for three days. For AL: 5 to < 15 kg = 1 tablet twice a day for 3 days, 15 to < 25 kg = 2 tablets twice a day for three days

[e] Timing is defined as the number of times per day the treatment should be taken. For AQAS: once daily. For AL: two times per day

[f] Duration is defined as the number of days the treatment should be taken. For both AQAS and AL: 3 days

[g] Correct treatment = correct dose + correct timing + correct duration, in which the criteria for all three factors (as above) are met

Table 4 Reported adverse events (side effects)

	Site 1			Site 2		
	AL (N = 175)	**AQAS (N = 172)**	**p-value***	**AL (N = 165)**	**AQAS N = 168)**	**p-value***
Any adverse event						
Caregiver reported	6 (3.4%)	27 (15.7%)	< 0.001	25 (15.2%)	41 (24.4%)	0.039
Specific adverse events						
Vomiting	4 (2.3%)	16 (9.3%)	0.005	13 (7.9%)	18 (10.7%)	0.452
Weakness-Fatigue	0 (0.0%)	12 (7.0%)	< 0.001	9 (5.5%)	29 (17.3%)	0.001
Dizziness	0 (0.0%)	10 (5.8%)	0.001	7 (4.2%)	4 (2.4%)	0.376
Diarrhoea	1 (0.6%)	3 (1.7%)	0.369	2 (1.2%)	2 (1.2%)	1.000
Other gastrointestinal complaints[a]	1 (0.6%)	5 (2.9%)	0.119	2 (1.2%)	4 (2.4%)	0.685
Other AE reported[b]	1 (0.6%)	2 (1.2%)	0.621	4 (2.4%)	4 (2.4%)	1.000

* Fisher's exact test

[a] Reported one or more of the following: diarrhoea, anorexia, nausea or abdominal pain

[b] Other AE's reported: Site 1— AL: 1 pruritic; AQAS: 1 headache & 1 not specified. Site 2—AL: 2 change in urine colour, 1 cold/flu, & 1 sweating; AQAS: 1 change in urine colour, 1 fever, 1 mouth sores & 1 unspecified

Discussion

With progress on malaria control slowing and resistance to artemisinin resistance emerging, it is vital that every effort is made to protect the efficacy of ACT [32]. Patient adherence to prescribed anti-malarial regimens is a key step in the pathway to treatment effectiveness [4]. Yet, evidence on the impact of co-formulation of drug regimens, and comparative data on adherence to available ACT, is limited [3]. In this randomized trial, self- reported adherence was high for both co-formulated AL and AQAS, but varied by study site. At both sites, definite adherence was significantly higher for AL than AQAS. However, this outcome was influenced by the likelihood of retention of the drug package by caregivers, which was significantly higher for AL. Overall, the quality of treatment was high; however, disadvantages to both regimens were identified that could negatively impact adherence. AL was less likely to be administered correctly at one site, which is not surprising given the greater complexity of the dosing regimen. AQAS was less well-tolerated at both sites, and was associated with bitter taste and significantly more adverse events. To better understand adherence to ACT, and how adherence might impact on treatment effectiveness, additional studies are warranted, particularly comparative studies including ACT and new drug regimens as these become available. Standardizing methodologies for evaluating adherence would also improve the evidence base on ACT adherence.

Currently, the available evidence on ACT adherence is limited by variation in study designs and outcomes, differences in drug regimens, and lack of comparative studies [3]. In prior randomized trials, adherence to AL has ranged from 64 to 99% [33–38]. Similarly, adherence to co-packaged AQ + AS and AQAS has varied widely in prior studies. In Sierra Leone, adherence to co-packaged AQ+AS was only 48% [20], while in Zanzibar and Ghana adherence to AQ + AS was much higher (77 and 93%, respectively) [39, 40]. Two recent studies from The Democratic Republic of Congo reported adherence to fixed- dose AQAS to be 75 and 62% [41, 42], and in a study in Madagascar, adherence to AQAS was even higher (90%) [28].

The one other study that directly compared adherence to AL and AQAS in Benin found that ‘full adherence’ to the two regimens was not significantly different [24]. However,

this study primarily evaluated treatment effectiveness, with adherence as a secondary outcome; little information was provided about how adherence was defined and measured. Apparently, adherence was assessed during a home visit on Day 3 of treatment and drug packages were collected when available, but it is not clear how 'full adherence' was defined, limiting the ability to compare their results to findings from this study.

The results reported here build on the available evidence, suggesting that self-reported adherence to both AL and AQAS are high, and highlighting methodological challenges that should be addressed in future studies.

This study also identified specific characteristics which may impact adherence to AL and AQAS. AL was less likely to be taken correctly at one site, but was better tolerated than AQAS at both sites. The complexity of the AL dosing regimen, including the number of tablets, twice daily dosing, the requirement to give the second dose 8 h after the first, and to administer with fatty food [43], has been shown to negatively impact treatment adherence [44, 45]. In contrast, while AQAS has been optimized to be dosed only once daily [46–48], its bitter taste and greater likelihood of adverse events make it more difficult to administer to children [49, 50], and may reduce adherence as found in this study. Pharmaceutical companies have focused on producing child-friendly ACT formulations, including smaller tablets, dispersible tablets, and improved weight-for-age dosing recommendations [10, 12, 51, 52]. As new anti-malarial drugs are developed and evaluated for effectiveness, it will be important to assess child-friendly regimens that are palatable and easy to administer, in order maximize treatment adherence and outcomes in those affected most by malaria [53].

In this study, adherence to AL and AQAS varied depending on the outcome definition applied. Although definitions of adherence outcomes, based on self-report of treatment completion plus package inspection, which have been used in previous anti-malarial studies were adopted [3, 29, 30], limitations to these definitions were found. Both indicators used to define adherence are subject to bias. Self-reported adherence is open to social desirability bias, with caregivers more likely to report what they perceive

to be 'correct' answers, potentially leading to over-estimation of adherence. Package inspection and pill counts, while more 'objective' measures [54, 55], are dependent on the availability of packaging. In the Benin study, more AQAS packages were found (84.4% of AL vs 93.7% of AQAS packages) [24], in contrast to this study, in which more AL packages were retained. Factors that influence desirability of retaining packaging could also impact on adherence. Prior research suggests that novel drug packages, that aim to educate or market a drug regimen, may be more attractive or appealing, and thus may be more likely to be retained [56, 57], thus impacting on measures of adherence that incorporate data from package examinations, or may impact adherence directly [58].

A variety of approaches have been used to incorporate package inspection in the classification of adherence outcome [36, 59, 60]. Under trial conditions, blister packages have been retained and inspected with results successfully incorporated into the outcome measurement [61]. In other studies, package inspection has been included in the methods, but either excluded from the analysis [62], or not utilized altogether. For example, although the packaging was part of the outcome definition, the proportion of packaging available was not reported in a number of studies [35, 41, 42]. In others, the package information although collected, was not utilized and only self-reported (probable) adherence rates were reported [44, 63, 64]. In Ghana, an intervention study used package inspection as a secondary outcome to validate self- reported adherence, but found that only 60% of patients were able to produce their package, suggesting that this may not be the most accurate measurement of ACT adherence [36]. Likewise, in Ethiopia, difficulties with package retention over many days were reported, suggesting that presence of packaging may not be indicative of true adherence [50].

Although package inspections and pill counts serve as a gold standard for measuring adherence to treatment of other diseases [54, 65] the heterogeneity of this outcome measure in malaria studies limits comparison of adherence to regimens across studies. Instead, examining the quality of treatment, including whether the correct number of tablets were given at the correct frequency for the correct number of days, may provide a more accurate picture of treatment adherence [35, 37, 59, 63, 66]. Recently studies measuring anti-malarial adherence have presented per-dose adherence measurements

[36, 59, 61], this approach is useful as it can illustrate at which point patients stop taking their medications. However, this approach like those mentioned earlier relies on self-report, with or without package validation. Standardizing methodologies for evaluating adherence is necessary to improve the evidence base on ACT adherence.

This study had several limitations, in addition to the challenges with the adherence outcome classification. First, the characteristics of the participants, caregivers, and households enrolled in the two sites varied substantially, which was unexpected. Specifically, variations in the age of participating children, level of caregiver education, household religion and socioeconomic position were found, all of which may influence treatment adherence [3, 29, 67, 68]. To address these differences, the analysis was stratified by study site. Stratification did not impact on the power to detect differences in adherence outcomes, as the sample size calculations were done independently for the two sites, in case differences in the sites were found. Second, an unexpectedly high number of children were excluded after testing with RDT and after randomization, particularly at Site 2. In addition, several children received the incorrect treatment, again more commonly at Site 2. These exclusions and the imbalance between sites were likely due to characteristics of the health centres, and random error. No systematic biases were suspected. Furthermore, to examine the validity of the findings, a sensitivity analysis was conducted comparing outcome measures in the ITT and PP populations, which found that outcome measurements were almost identical for both analytical approaches, suggesting that the exclusions after randomization did not impact the outcomes presented here. Third, the design of this study may have led to an overestimation of adherence. Effectiveness trials and cross-sectional studies have been shown to report higher adherence levels than prospective observational studies; however, even results from such studies vary [3, 30]. Moreover, although this study did occur under 'normal conditions', the fact that providers and caregivers were observed, may have altered their behaviour as a result of participating in the study (participation bias), and influenced adherence outcomes [29, 69]. Finally, the limitations of only looking at statistical significance should be noted, as statistically significant differences do not always equate to clinical importance. This study was powered to detect a 15% difference in rates of adherence between AL and AQAS, with the thinking that if the absolute difference in adherence between the two regimens was 15%

or more that this would be a big enough difference from a clinical or public health perspective to favour one treatment over the other. From a public health perspective, the findings of this study did not find a difference large enough to favour one regimen over another; however, the secondary outcome (correct treatment and its associated components) does highlight operational areas where ACT administration could be improved.

Conclusion

Maximizing adherence to anti-malarial drug regimens is essential for ensuring treatment effectiveness; however, measuring adherence remains challenging. The results from this study suggest that although self-reported adherence to both AL and AQAS was high, the difference between the two regimens was not significant. However, potential disadvantages were identified for each regimen that might impact optimal treatment adherence. With the emergence of resistance to artemisinins in Southeast Asia fuelling the development of new drug formulations, information on adherence to different ACT regimens will become increasingly important to help guide drug delivery, improve treatment effectiveness, and inform drug policy. However, the methodology of measuring adherence in anti-malarial studies requires further advancement. This study highlights the limitations of package inspection, and suggests that an outcome measure based on correct treatment could have greater utility. Standardizing methodologies for evaluating adherence across diverse contexts would improve the evidence base on ACT adherence and effectiveness.

Additional file

Additional file 1: Package availability by drug and site

Abbreviations

ACT: artemisinin-based combination therapy; AL: Artemether–lumefantrine; AQAS: fixed-dose combination amodiaquine–artesunate; AQ AS: co-packaged amodiaquine plus artesunate; DRC: The Democratic Republic of Congo; FDC: fixed-dose combination; GFATM: The Global Fund to Fight AIDS, Tuberculosis and Malaria; ITT: intention-to-treat; MDA:

mass drug administration; NMCP: National Malaria Control Programme; PP: per-protocol; RDT: rapid diagnostic test; WHO: World Health Organization; 95% CI: 95% confidence interval.

Authors' contributions

KB was the principal investigator of the study. She conceived, designed and implemented the study and conducted the data analysis, interpretation and first draft of the paper. ELW provided essential input in the design, data analysis and interpretation. SJS provided substantial input into the design and implementation of the study. DC & SGS supported the study design, data analysis and interpretation of the data. SGS also provided a critical review of the first draft. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol was reviewed by the London School of Hygiene and Tropical Medicine (LSHTM) Clinical Trials Sub-committee. Approval for the study was granted by the LSHTM Research Ethics Committee and the Sierra Leone Ethics and Scientific Review Committee. The trial was registered at Clinical Trials.gov (NCT01967472). All participants provided written informed consent at the time of recruitment and again before administration of the follow-up survey in their homes.

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Additional File 1. Package Availability

Table S1. Package availability

	By Site			By Drug		
	Site 1	Site 2		AL	AQAS	
Intention to treat analysis	N=353	N=354	P value*	N=350	N=357	P value*
Package available						
—No	87 (24.7%)	169 (47.7%)	**<0.001**	94 (26.9%)	162 (45.4%)	**<0.001**
—Yes	266 (75.4%)	185 (52.3%)		256 (73.1%)	195 (54.6%)	
Per protocol analysis	N=347	N=333	P value*	N=340	N=340	P value*
Package available						
—No	84 (24.2%)	158 (47.5%)	**<0.001**	90 (26.5%)	152 (44.7%)	**<0.001**
—Yes	263 (75.8%)	175 (52.6%)		250 (73.5%)	188 (55.3%)	

*chi-squared test

Table S2. Package availability by site and drug

	Site 1			Site 2		
	AL	AQAS		AL	AQAS	
Intention to treat analysis	N=179	N=174	P value*	N=178	N=176	P value*
Package available[1]						
—No	29 (16.2%)	58 (33.3%)	**<0.001**	71 (39.9%)	98 (55.7%)	**0.003**
—Yes	150 (83.8%)	116 (66.7%)		107 (60.1%)	78 (44.3%)	
Per protocol analysis	N=175	N=172	P value*	N=165	N=168	P value*
Package available						
—No	28 (16.0%)	56 (32.6%)	**<0.001**	62 (37.6%)	96 (57.1%)	**<0.001**
—Yes	147 (84.0%)	116 (67.4%)		103 (62.4%)	72 (42.9%)	

*chi-squared test

CHAPTER 7: EXPLORING FACTORS ASSOCIATED WITH NON-ADHERENCE TO ACTS IN SIERRA LEONE

7.1 Introduction

Chapter 6 addresses the question, "what is the level of adherence to ACTs in Sierra Leone?" Specifically, it presents the results of the randomised controlled trial (RCT), which compared the levels of adherence to AL to the levels of adherence to AQAS at two government health facilities in Freetown, Sierra Leone (Objective 2). This chapter explores the factors associated with non-adherence to these two ACTs in the RCT study population (Objective 3).

Adherence to treatment, the primary outcome for the RCT, was categorical in nature (four different outcome categories were possible –see Figure 7.1). Thus, there were a number of approaches that could be utilised for the analysis, all of which required different assumptions to be made. I explored the use of three approaches: 1) analysis of a three-category outcome variable using ordinal logistic regression; 2) analysis of a three-category outcome variable using multinomial logistic regression; and 3) recoding the original outcome variable (using three approaches) as a binary variable and analysing using logistic regression. The results of these approaches are described and compared in this chapter.

7.2 Methods

7.2.1 Outcome and Covariate Definitions

Primary Outcome Measure

The primary outcome variable, treatment adherence, was initially classified into four ordered categories (Figure 7.1), and was based on the definition of adherence from previously published literature for antimalarial adherence [1-3]. However, as non-adherence was a rare event, the probable and definite non-adherence categories were collapsed into one category (non-adherence). Therefore, a three-category outcome was considered the primary outcome measure for this chapter. Definite adherence/correct treatment was set as the reference category, so that results are interpreted as associations with non-adherence and probable adherence.

Definite Adherence— The caregiver reported that the child had completed the treatment and the blister packaging was observed and found to have no tablets left.

Probable Adherence—The caregiver reported that the child had taken the correct dose, however, the packaging was not available for observation (self-reported adherence)

Probable Non-adherence—The Caregiver reported that the child has not taken all tablets and the status of the packaging was not available for observation or the blister package is empty (self-reported non-adherence).

Definite Non-adherence—The Caregiver showed a blister package still containing remaining tablets at the time of the home visit.

Figure 7.1 Adherence outcome definitions

Secondary Outcome Measures

One approach for the analysis of a nominal outcome, such as the original four-category adherence variable in this study, is to convert it to a dichotomous outcome by combining categories [4]. Following this approach, the primary outcome variable was transformed into three dichotomous secondary outcomes with different classifications of the outcome categories to define adherence.

The first binary outcome investigated package-based non-adherence, in other words, using an empty package as evidence of adherence. Participants with an empty package (originally classified as 'definite adherence') were coded as 0 (adherent). Otherwise, those that did not have an empty package (either had remaining tablets or no package—originally classified as: 'probable adherence,' 'probable non-adherence,' or 'definite non-adherence') were coded as 1 (non-adherent). Definite adherence was the reference category, so that results are interpreted as associations with non-adherence.This outcome did not take into account self-reported adherence.

The second binary outcome investigated self-reported non-adherence. All caregivers that reported not to have given all of the malaria treatment ('probable non-adherence' or 'definite non-adherence') were coded as 1 (non-adherent) otherwise those that did report

completing treatment (originally classified as either 'definite adherence' or 'probable adherence') were coded as 0 (adherent). Thus, self-reported adherence was the reference category, so that results are interpreted as associations with non-adherence. In this model, package inspection results were not taken into consideration.

The third and final binary outcome investigated **incorrect treatment**. Information on the correct dose, timing and duration were collected during the follow-up interviews. These three variables were then combined to form a composite measure for correct treatment. Incorrect treatment was coded as 1 and receiving the correct treatment ('correct dose + correct timing + correct duration') was coded as 0. Thus, correct treatment was the reference category, so that results are interpreted as associations with incorrect treatment.

7.2.2 Analytic approach

Three different analytic approaches were used to evaluate factors associated with adherence, namely: 1) Ordinal logistic regression using the three-category adherence primary outcome variable; 2) Multinomial logistic regression using the three-category adherence primary outcome variable; and 3) Binary logistic regression using the three binary secondary outcome variables described above. All regression models have assumptions that dictate their suitability for analysis.

1) Ordinal Logistic Regression Assumptions

Ordinal models are used for categorical outcomes which can be considered as ordered. The key assumption, the proportional odds assumption (also called the parallel regression assumption), is that the relationship between consecutive groups of outcome categories is the same [5, 6]. In other words, the coefficients that describe the relationship between the lowest versus the higher categories of the outcome variable are the same as those that describe the relationship between the next level and the highest and so forth. Below is a list of all the assumptions required for an ordinal logistic regression model:

1. *The dependent (outcome) variable is nominal (categorical).*
2. *There are one or more independent variables.*
3. *There is no multicollinearity*

4. *Proportional odds assumption or parallel regression assumption (i.e. the relationship between the outcome categories is equal)*
5. *There are no outliers*

2) Multinomial Logistic Regression Assumptions

Multinomial models do not assume the data are ordered, but also have assumptions that should be met *[7]*. Assumptions of multinomial logistic regression models are:

1. *The dependent (outcome) variable is nominal (categorical).*
2. *There are one or more independent variables*
3. *There is independence of observations, and the outcome/dependent variables have mutually exclusive categories.*
4. *There is no multicollinearity*
5. *There are no outliers*

3) Binomial Logistic Regression Assumptions

The main assumption for binomial logistic regression is that the dependent variable is binary, however, there are other assumptions that should be met as well [8]. The assumptions for binomial logistic regression models are:

1. *The dependent (outcome) variable is binary or dichotomous*
2. *There are one or more independent variables*
3. *There is independence of observations*
4. *There is no multicollinearity*
5. *There are no outliers*

7.2.3 Data analysis

Stata Version 12 (StataCorp, College Station, TX USA) was used for all analyses. Before building the models, descriptive statistics were used to summarise the data. Additionally, crude associations for associations between independent predictor variables and each outcome were first examined using Chi-square or Fisher's exact tests where appropriate. Results with a p-value < 0.05 were considered significant.

Independent variables were chosen for inclusion in the multivariable models based on findings from the literature [1, 2, 9]. The *a priori* covariates included were: age and gender of the child, the age and gender of the caregiver, household religion, caregiver education level, socio-economic status of the household, ACT formulation, caregiver knowledge of treatment and confirmatory diagnosis received. Other covariates considered for evidence of association were: study site, caregiver fluency in Krio, child disliked drug, adverse events, the child had taken the drug before, and whether fees were paid for health services for this fever episode. Only confirmatory diagnosis was not included in the model as all participants received a confirmatory blood test before treatment. Household socioeconomic status was based on a principal components analysis (PCA) of household assets [10].

All covariates were tested for collinearity using Pearson's correlation test, and covariates identified to be strongly correlated ($r \geq 0.8$) were excluded from the regression models. Collinearity was only found between "child disliked the drug", and "child complained of bitter taste" (r=0.8344). As bitter taste can be a reason why a child may not like the drug, it was removed from all of the models, as "child disliked the drug" was broader in scope.

Below are the specific details of the three different analytic approaches used for these data: 1) Ordinal logistic regression; 2) Multinomial logistic regression; and 3) Binary logistic regression.

1) Analytic Approach for Ordinal Logistic Regression

In order to use Ordinal Logistic Regression, it is necessary to test the proportional odds assumption or parallel regression assumption (i.e. the relationship between the exposure variable and odds of the outcome in each consecutive group is the same). To determine whether these data met the proportional odds assumption two tests were conducted. First, I implemented a user-written command for STATA (*omodel*) which runs a likelihood ratio test [5]. Second, I ran a Brandt test of parallel regression assumption (proportional odds assumption). For both tests, a significant test statistic (p-value<0.05) provides evidence that the assumption has been violated; in such a case the ordinal logistic

regression results may be invalid and should, at best, be treated with caution, or discounted.

2) Analytic Approach for Multinomial Logistic Regression

Using a multinomial logistic regression model, the crude and adjusted odds ratios and their 95% confidence intervals were obtained to assess the strength of the association between the independent variables and the outcome categories. For the multinomial model, both probably adherent and non-adherent were compared to definitely adherent (the reference). The results were expressed as relative risk ratios (RRR).

3) Analytic Approach for Binomial Logistic Regression

Similarly, for the binomial regression models, the crude and adjusted odds ratios and their 95% confidence intervals were obtained to assess the strength of the association between the independent variables and each of the three dichotomous outcome variables. The reference for the binary logistic regression was adherence or correct treatment, and the measure of effect used was Odds Ratio (OR).

7.3 Results

7.3.1 Ordinal Logistic Regression Results

Results from the omodel test produced a significant test result (X^2 = 52.1; p<0.001) (Table 7.1). The Brandt test also produced a significant test statistic (X^2=41.1; p<0.001) (Table 7.2). In summary, there was strong evidence that when modelled together, these data did not meet the proportional odds assumption (parallel regression assumption), with the type of ACT treatment given, the study site, whether the child dislikes the drug and reporting of adverse events showing strong evidence of non-proportional odds. Therefore a multinomial logistic regression model (which does not require the proportional odds assumption to be met) would need to be used for this categorical outcome, the results of which are presented in the next section.

7.3.2 Multinomial Logistic Regression Results

These data met all of the assumptions for a multinomial logistic model. This section presents results for both the unadjusted (crude) and adjusted analyses.

Unadjusted multinomial regression results

To explore factors associated with probable adherence or non-adherence compared to definite adherence, a crude analysis assessing the association of independent variables with each outcome category was conducted (Table 7.3). Unadjusted results for non-adherent compared to definitely adherent (reference) suggest that participation at study site 2, reporting that the child disliked the drug, complained of bitter taste and reporting an adverse event (side effect) were all significantly associated with non-adherence versus definite adherence. The unadjusted results for probably adherent compared to definitely adherent (reference) suggest that receiving AL, participating in the study at Site 2, and reporting an adverse event were significantly associated with probable versus definite adherence. In other words, these factors were associated with people being a bit less likely to be adherent.

Adjusted multinomial regression results

Results from the adjusted multinomial logistic regression model are presented in Table 7.4. In the adjusted analysis, the relative risk ratio (RRR) of non-adherence compared to definite adherence was significantly higher for caregivers reporting the child disliked the drug compared to those who did not (RRR=8.04; 95%CI 2.69-23.98; p<0.001) and those that reported adverse events/side effects compared to those who did not (RRR=4.48; 95%CI 1.78-11.24; p=0.001). However, although study site was associated with non-adherence compared to definite adherence in the unadjusted analysis, it was not found to be a predictor of non-adherence in the adjusted model (RRR=2.05; 95% CI 0.76-5.67; p=0.164).

In the adjusted results, the relative risk ratio of probable adherence (compared to definite adherence) was significantly lower for children receiving AL compared to AQAS (RRR=0.37; 95% CI 0.25-0.56; p<0.001) and higher for those participating in the study at Site 2 compared to Site 1 (RRR=3.65; 95%CI 2.44-5.47; p<0.001). Additionally, children aged 25-

59 months had a slightly higher risk of probable adherence versus definite adherence (RRR=0.69; 95%CI 0.48-1.00; p=0.048) compared to those that were aged 6-24 months.

7.3.3 Binomial Logistic Regression Results

These data met the assumptions for binomial logistic regression; therefore three different models were run, the results of which are presented below. As a reminder, the dichotomous secondary outcomes used were: a) packaged-based non-adherence; b) self-reported non-adherence; and c) incorrect treatment.

a) Package-based non-adherence

Three covariates were found to be significantly associated with package-based non-adherence (Table 7.5). Children receiving AL had 56% lower odds of being non-adherent than those receiving AQAS (OR=0.44; 95%CI 0.30-0.65; p<0.001). The study site was strongly associated with non- adherence, with those at Site 2 having over three times the odds of non-adherence compared to children at Site 1 (OR=3.46; 95%CI 2.35-5.10; p<0.001). Additionally, children who were aged 25-59 months had 30% lower odds of non-adherence (based on packages) than those aged 6-24 months (OR=0.70; 95%CI 0.49-1.00; p=0.049).

b) Self-reported non-adherence

Similarly, there were three covariates associated with self-reported non-adherence (Table 7.6). Children receiving AL had significantly higher odds of non-adherence (self-reported) than those taking AQAS (OR=3.21; 95%CI 1.19-8.62; p=0.021). Furthermore, children with caregivers reporting that the child disliked the drug or experienced an adverse event (side effects) were also significantly more likely to have been classified as non-adherent.

c) Incorrect treatment

There were six covariates associated with incorrect treatment with an ACT (Table 7.7). Children receiving AL had significantly higher odds of having received incorrect treatment compared to those receiving AQAS (OR=3.15; 95%CI 1.64-6.03; p=0.001), with males having half the odds of receiving incorrect treatment compared to female children (OR=0.53; 95% 0.32-0.88; p=0.014). Similarly, children with caregivers who reported that

the health worker instructed them to complete the treatment were also less likely to receive incorrect treatment compared to those not receiving completion instructions from the health workers (OR=0.51; 95%CI 0.29-0.88; p=0.015). Reporting that the child disliked the drug or experienced an adverse event (side effect) were both strongly associated with incorrect treatment (disliked drug OR=7.80; 95% CI 3.63-16.76; p<0.001 and adverse event OR=12.93; 95% CI 6.95-24.07; p<0.001). Finally, those reporting to have paid for services had 63% lower odds of receiving incorrect treatment than those that did not report paying for services (OR=0.37; 95%CI 0.14-0.99; p=0.04).

7.4 Discussion

Given the complexity and challenges with the defined adherence outcome, three analytic approaches were used to explore factors associated with non-adherence in the RCT study population. First, I attempted to use ordinal logistic regression. However, this method was not feasible; both the omodel likelihood ratio test and Brandt test statistics were highly significant indicating that the data did not meet the proportional odds assumption, meaning that, when modelled multivariably, the relationship between some of the key exposures and the different outcome levels was not equal. These data did, however, meet the assumptions for the multinomial logistic regression model, suggesting this is an appropriate model for analysing these data. However, due to the nature of comparing the outcome pairs separately, reporting and interpreting the output can be challenging.

Binary logistic regression was by far the easiest to execute, however, choosing how to define the binary outcome has limitations. Package-based non-adherence is influenced by package availability, and thus the analysis may be measuring associations with retention of the package rather than adherence. For self-reported non-adherence, the small numbers of non-adherent participants may have made the findings less robust, and reduced power to detect associations. Finally, factors associated with the secondary outcome incorrect treatment (which is based not on completion, but on components of adherence: dose, timing and duration), did not seem to have any apparent limitations other than this is a newer adherence outcome and thus there would be limited scope for comparison.

Despite the challenges highlighted above, there were trends identified between the different models. First, the multinomial and package-based binary outcomes produced similar results, both of which used the primary outcome definition and would have been influenced by package availability. Both models found associations with study drug, study site and age of the child. The multinomial analysis found that participants that were older and received AL were less likely to be probably adherent compared to participants classified as definitely adherent. Package-based non-adherence was also less likely for AL and children aged 25-60 months. Additionally, both models found that participants at Site 2 were more likely to be probably adherent compared to definitely adherent as well as non-adherent (package-based) compared to those that were adherent (package-based). In contrast, self-reported non-adherence and receiving incorrect treatment were more likely for participants receiving AL. Our findings are consistent with other published literature.

The component of adherence that affected the correct administration of AL was timing. It is recommended that AL be given twice a day. For younger children, this is one tablet two times a day, but for older this is two tablets twice a day. A Kenyan study reported overall treatment completion to be high (97.8%), however, when taking into account the correct timing of the individual doses adherence fell to 69.2% [11]. Similarly, Bruxvoort *et al*. have also reported timely completion of AL to be much lower than completed treatment measurements (37% timely to 64% completion) [12]. Furthermore, in their review in 2014 Funangchan *et al*. reported that convenient dosing regimens improve antimalarial adherence rates in two studies [13]. In The Gambia, rates of adherence for once daily chloroproguanil-dapsone were reported to be significantly higher than those reported for AL (94% compared to 67% respectively [14]. Likewise, Faucher *et al*. reported adherence was higher for once daily AQAS compared to the twice-daily dose of AL in Benin, however, the difference was not significant (0p=0.16) [15].

The binary logistic regression models that assessed self-reported non-adherence and incorrect treatment uncovered strong associations with child disliking the drug (which included bitter taste) or experiencing side effects/adverse events and non-adherence; with children disliking the medication or experiencing an adverse event or side effects more likely to be non-adherent or receive incorrect treatment. Specifically, bitter taste has been

shown to impact paediatric adherence to medications [16, 17]. This was the rationale for making dispersible AL palatable to children [18].

Finally, as the secondary outcome incorrect treatment is not influenced by the availability of package bias, this outcome may be useful in terms of better understanding of the contextual data which will be presented in Chapter 8.

Determining factors associated with non-adherence using the data from this RCT had some limitations. First, the outcome measure was complex and was made up of two components (self-reported adherence and package inspection), which is in line with previously published adherence studies [1-3]. However, the availability of packaging differed between study arms and sites, thus biasing the outcome measure to those that kept the package. Packaging was retained more for AL than for AQAS at both study sites. Furthermore, caregivers at Site 1 retained the packaging more than those at Site 2. This shortfall with the outcome impacted my ability to use ordinal logistical regression, which had the outcome data been reliable, would have been the preferred method for analysis given the ordinal nature of the outcome.

Second, as non-adherence was a rare event, using logistic regression methods may not be appropriate when the numbers for predictor variables are low. Specifically, the associations reported for the self-reported non-adherence outcome may be weakened by the lack of data and thus impact what conclusions can be made. Similarly, this may have impacted the multinomial comparison of definite non-adherence versus definite adherence, for which the power was also limited. Finally, using statistical approaches to determine associated factors with non-adherence identifies the mathematical probability of an association, but does not provide contextual information or reasons behind the proposed associations, which may be more useful for a behavioural outcome such as adherence.

7.5 Conclusions

Although this analysis cannot difinitively answer the question, “What are the factors associated with ACT adherence?”, it does provide evidence on what factors may have

influenced ACT adherence in this study population, with results suggesting that children that received AL were more likely to receive an incomplete dose, compared to those that received AQAS. Furthermore, the process of conducting these analyses has demonstrated how different analytic methods can be used for exploring factors associated with multinomial categorical outcomes.

7.6 Chapter References

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7.7 Tables

Table 7.1—Testing the proportional odds assumption using the "omodel" likelihood ratio test

```
Iteration 0:   log likelihood = -554.99513
Iteration 1:   log likelihood = -509.43711
Iteration 2:   log likelihood = -508.86329
Iteration 3:   log likelihood = -508.86232

Ordered logit estimates                           Number of obs   =        670
                                                  LR chi2(13)     =      92.27
                                                  Prob > chi2     =     0.0000
Log likelihood = -508.86232                       Pseudo R2       =     0.0831

------------------------------------------------------------------------------
     adhere3 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     ittact2 |   .6203925   .1882903     3.29   0.001     .2513504    .9894346
       site2 |  -1.153654   .1906991    -6.05   0.000    -1.527417   -.7798903
      agecat |   .3732938   .1746703     2.14   0.033     .0309463    .7156413
       sexch |   .1154379   .1656941     0.70   0.486    -.2093165    .4401923
        krio |  -.2005888   .1859014    -1.08   0.281    -.5649489    .1637712
       anyed |   .0264061   .1829564     0.14   0.885    -.3321819     .384994
    tertile3 |   .0012468   .1070347     0.01   0.991    -.2085373    .2110308
        rel2 |   .0671246    .189109     0.35   0.723    -.3035222    .4377713
    finishtx |   .0315729   .0409305     0.77   0.440    -.0486494    .1117952
  dislike_yn |  -.4878462   .3003115    -1.62   0.104    -1.076446    .1007535
         ae2 |  -.6006216   .2476432    -2.43   0.015    -1.085993   -.1152499
childtaked~2 |   .3600671   .2371059     1.52   0.129    -.1046518    .8247861
        paid |   .5308225    .309359     1.72   0.086    -.0755099    1.137155
-------------+----------------------------------------------------------------
       _cut1 |  -3.958769   .6965461          (Ancillary parameters)
       _cut2 |  -1.129034   .6734329
------------------------------------------------------------------------------

Approximate likelihood-ratio test of proportionality of odds
across response categories:
         chi2(13) =     52.07
       Prob > chi2 =    0.0000
```

Table 7.2 Brandt Test of Parallel Regression Assumption (proportional odds assumption)

Estimated coefficients from j-1 binary regressions

	y>0	y>1
ittact2	-1.1433035	.81321014
site2	-.0536008	-1.2405253
agecat	.28480239	.39323603
sexch	.18936068	.07834857
krio	.35136339	-.25668318
anyed	-.59536123	.08052936
tertile3	-.18264878	.01939935
rel2	.23519671	.07101586
finishtx	.48114145	.02558466
dislike_yn	-2.1469692	-.21348085
ae2	-1.4024989	-.43588607
childtakedrug2	1.1821534	.37074963
paid	.63429346	.49701763
_cons	3.539344	1.1158936

Brant Test of Parallel Regression Assumption

Variable	chi2	p>chi2	df
All	41.05	0.000	13
ittact2	15.42	0.000	1
site2	7.20	0.007	1
agecat	0.07	0.791	1
sexch	0.09	0.770	1
krio	1.89	0.169	1
anyed	2.27	0.132	1
tertile3	0.65	0.421	1
rel2	0.15	0.701	1
finishtx	1.43	0.231	1
dislike_yn	14.16	0.000	1
ae2	4.72	0.030	1
childtaked~2	0.95	0.330	1
paid	0.03	0.860	1

A significant test statistic provides evidence that the parallel regression assumption has been violated.

Table 7.3— Factors associated with ACT non-adherence and probable adherence versus definite adherence: unadjusted results using multinomial logistic regression (n=680)

Variables	N	Non-adherence n(%)	Probable Adherence n(%)	Definite Adherence n(%)	non-adherent vs definitely adherent RRR	95% CI	P value	probably adherent vs definitely adherent RRR	95% CI	P value
Antimalarial treatment										
—AQAS	340	13 (3.8%)	155 (45.5%)	172 (50.6%)	ref			ref		
—AL	340	20 (5.9%)	95 (27.9%)	225 (66.2%)	1.18	0.60 – 1.43	0.661	0.47	0.34 – 0.65	**<0.001**
Site										
—Site 1	347	13 (3.8%	86 (24.8%)	248 (71.5%)	ref			ref		
—Site 2	333	20 (6.0%)	164 (49.3%)	149 (44.7%)	2.56	1.23 – 5.30	**0.011**	3.17	2.28 – 4.42	**<0.001**
Child age (months)										
—6-24	421	21 (5.0%)	157 (37.3%)	243 (57.7%)	ref			ref		
—25-59	259	12 (4.6%)	93 (35.9%)	154 (59.5%)	0.90	0.43 – 1.88	0.783	0.93	0.67 – 1.30	0.685
Child Gender										
—female	309	18 (5.8%)	114 (36.9%)	177 (57.3%)	ref			ref		
—male	371	15 (4.0%)	136 (36.7%)	220 (59.3%)	0.67	0.33 – 1.37	0.272	0.96	0.70 – 1.32	0.800
Caregiver fluency in Krio										
—No	199	9 (4.5%)	64 (32.2%)	126 (63.3%)	ref			ref		
—Yes	481	24 (5.0%)	186 (38.7%)	271 (56.3%)	1.24	0.56 – 2.74	0.596	1.35	0.95 – 1.93	0.096
Caregiver education										
—No	262	9 (3.4%)	98 (37.4%)	155 (59.7%)	ref			ref		
—Yes	418	24 (5.7%)	152 (36.4%)	242 (57.9%)	1.71	0.77 – 3.77	0.185	0.99	0.72 – 1.37	0.968
Socio-economic status[1]										
—1 (poorest)	236	10 (4.2%)	99 (42.0%)	127 (53.8%)	ref			ref		
—2	209	11 (5.3%)	69 (33.0%)	129 (61.7%)	1.08	0.44 – 2.64	0.861	0.69	0.46 – 1.02	0.060
—3 (least poor)	226	12 (5.3%)	75 (33.2%)	139 (61.5%)	1.10	0.46 – 2.62	0.836	0.69	0.47 – 1.02	0.061
Household Religion[2]										
—Christian	217	13 (6.0%)	97 (44.7%)	107 (49.3%)	ref			ref		
—Muslim	462	20 (4.3%)	153 (33.1%)	289 (62.6%)	0.60	0.27 – 1.19	0.132	0.58	0.42 – 0.82	**0.002**

Variables	N	Non-adherence n(%)	Probable Adherence n(%)	Definite Adherence n(%)	non-adherent vs definitely adherent RRR	95% CI	P value	probably adherent vs definitely adherent RRR	95% CI	P value
HW said finish treatment										
—No	320	17 (6.1%)	133 (41.6%)	170 (53.1%)	ref			ref		
—Yes	360	16 (4.4%)	117 (32.5%)	15 (34.9%)	0.70	0.35 – 1.44	0.335	0.66	0.48 – 0.91	**0.010**
Caregiver Knowledge ACTs										
—No	509	28 (5.6%)	183 (36.0%)	298 (58.6%)	ref			ref		
—Yes	171	5 (2.9%)	67 (39.2%)	99 (57.9%)	0.54	0.20 – 1.43	0.214	1.10	0.77 – 1.58	0.597
Child disliked the drug										
—No	611	20 (3.5%)	225 (36.8%)	366 (59.9%)	ref			ref		
—Yes	69	13 (18.8%)	25 (36.2%)	31 (44.9%)	7.67	3.49 – 16.87	**<0.001**	1.31	0.76 – 2.28	0.336
Complained of bitter taste[3]										
—No	631	24 (3.8%)	230 (36.5%)	377 (59.8%)	ref			ref		
—Yes	49	9 (18.4%)	20 (40.8%)	20 (40.8%)	7.07	2.91 – 17.18	**<0.001**	1.64	0.86 – 3.11	0.131
Adverse event (side effects)										
—No	581	17 (2.9%)	208 (35.8%)	356 (61.4%)	ref			ref		
—Yes	99	16 (16.2%)	42 (42.4%)	41 (41.4%)	8.17	3.84 – 17.39	**<0.001**	1.75	1.10 – 2.79	**0.017**
Child has taken drug before										
—No	561	31 (5.6%)	204 (36.4%)	326 (58.1%)	ref			ref		
—Yes	119	2 (1.7%)	46 (38.7%)	71 (59.7%)	0.30	0.07 – 1.27	0.101	1.04	0.69 – 1.56	0.868
Paid for services										
—No	620	31 (5.0%)	229 (36.9%)	360 (58.1%)	ref			ref		
—Yes	60	2 (3.3%)	21 (35.0%)	37 (61.7%)	0.63	0.14 – 2.73	0.535	0.89	0.51 – 1.56	0.690

[1] *SES denominator=671*

[2] *Religion denominator=679*

[3] *bitter taste is correlated with "child disliked the drug" (r=0.8344). As bitter can be one reason for not liking a drug, disliked the drug was kept in the model and bitter taste dropped*

Table 7.4—Factors associated with ACT non-adherence and probable adherence versus definite adherence: adjusted results using multinomial logistic regression (n=670)[1]

Variables	non-adherent vs definitely adherent			probably adherent vs definitely adherent		
	RRR	95% CI	P value	RRR	95% CI	P value
Antimalarial treatment						
—AQAS	ref			ref		
—AL	2.05	0.76 – 5.67	0.164	0.37	0.25 – 0.56	**<0.001**
Site						
—Site 1	ref			ref		
—Site 2	1.70	0.69 – 4.23	0.252	3.65	2.44 – 5.47	**<0.001**
Child age (months)						
—6-24	ref			ref		
—25-59	0.65	0.28 – 1.50	0.309	0.69	0.48 – 1.00	**0.048**
Child Gender						
—female	ref			ref		
—male	0.81	0.37 – 1.78	0.606	0.96	0.68 – 1.36	0.812
Caregiver fluency in Krio						
—No	ref			ref		
—Yes	0.80	0.32 – 1.97	0.623	1.41	0.95 – 2.09	0.086
Caregiver education						
—No	ref			ref		
—Yes	1.76	0.70 – 4.40	0.227	0.88	0.60 – 1.29	0.503
Socio-economic status†						
—1 (poorest)	ref			ref		
—2	1.10	0.40 – 3.04	0.859	0.84	0.54 – 1.31	0.438
—3 (least poor)	1.39	0.50 – 3.86	0.522	0.92	0.59 – 1.44	0.710
Household Religion						
—Christian	ref			ref		
—Muslim	0.77	0.32 – 1.85	0.561	0.94	0.63 – 1.41	0.772
HW said finish treatment						
—No	ref			ref		
—Yes	0.61	0.28 – 1.30	0.196	0.98	0.90 – 1.07	0.724
Caregiver Knowledge ACTs						
—No	ref			ref		
—Yes	0.45	0.16 – 1.27	0.132	1.04	0.88-1.23	0.623
Child disliked the drug						
—No	ref			ref		
—Yes	8.04	2.69 – 23.98	**<0.001**	0.89	0.46 – 1.70	0.716
Adverse event (side effects)						
—No	ref			ref		
—Yes	4.48	1.78 – 11.24	**0.001**	1.25	0.74 – 2.14	0.405
Child has taken drug before						
—No	ref			ref		
—Yes	0.26	0.05 – 1.36	0.111	0.74	0.45 – 1.21	0.226
Paid for services						
—No	ref			ref		
—Yes	0.45	0.09 – 2.20	0.324	0.63	0.33 – 1.19	0.153

[1]The denominators from SES and religion influenced the overall denominator for the multivariate model

Table 7.5—Factors associated with package-based non-adherence – (per-protocol)

			Unadjusted analysis			Adjusted analysis[3]		
	n/N	%	OR	95% CI	P value	OR	95% CI	P value
Antimalarial treatment								
—AQAS	168/340	49.4%						
—AL	115/340	33.8%	0.52	0.38 – 0.72	**<0.001**	0.44	0.30 – 0.65	**<0.001**
Site								
—Site 1	99/347	28.5%						
—Site 2	184/333	55.3%	3.09	2.22 – 4.30	**<0.001**	3.46	2.35 – 5.10	**<0.001**
Child age (months)								
—6-24	178/421	42.3%						
—25-59	105/259	40.5%	0.93	0.68 – 1.28	0.655	0.70	0.49 – 1.00	**0.049**
Child Gender								
—female	132/309	42.7%						
—male	151/371	40.7%	0.92	0.68 – 1.25	0.595	0.91	0.65 – 1.28	0.596
Caregiver fluency in Krio								
—No	73/199	36.7%						
—Yes	210/481	43.7%	1.34	0.95 – 1.88	0.093	1.20	0.82 – 1.76	0.356
Caregiver education								
—No	107/262	40.8%						
—Yes	176/418	42.1%	1.05	0.77 – 1.44	0.745	0.95	0.65 – 1.38	0.787
Household Religion[1]								
—Christian	110/217	50.7%						
—Muslim	173/462	37.5%	0.58	0.42 – 0.81	**0.001**	0.91	0.62 – 1.35	0.650
Socio-economic status[2]								
—1 (poorest)	109/236	46.2						
—2	80/209	38.3	0.85	0.71 – 1.03	0.091	1.00	0.80 – 1.25	0.984
—3 (least poor)	87/226	38.5						
HW said finish treatment								
—No	150/320	46.9						
—Yes	133/360	36.9	0.66	0.49 – 0.90	**0.009**	0.75	0.53 – 1.08	0.122
Caregiver Knowledge ACTs								
—No	211/509	41.5						
—Yes	72/171	42.1	1.03	0.72 – 1.46	0.881	0.82	0.56 – 1.22	0.333
Child disliked the drug								
—No	245/611	40.1						
—Yes	38/69	55.1	1.83	1.11 – 3.03	**0.017**	1.33	0.72 – 2.45	0.356
Adverse event								
—No	225/581	38.7						
—Yes	58/99	58.6	2.24	1.44 – 3.47	**<0.001**	1.49	0.90 – 2.48	0.124
Child has taken drug before								
—No	235/561	41.9%						
—Yes	48/119	40.3%	0.94	0.63 – 1.40	0.755	0.66	0.40 – 1.08	0.095
Paid for services								
—No	260/620	41.9						
—Yes	23/60	38.3	0.86	0.50 – 1.48	0.589	0.59	0.32 – 1.11	0.102

[1] *Religion denominator=679*

[2] *SES denominator=671*

[3] *Due to missing data for religion and SES status covariates, the denominator for the adjusted analysis was n=670*

Table 7.6—Factors associated with self-reported non-adherence – (per-protocol)

			Unadjusted analysis			Adjusted analysis[3]		
	n/N	%	OR	95% CI	P value	OR	95% CI	P value
Antimalarial treatment								
—AQAS	13/340	3.8%						
—AL	20/340	5.9%	1.57	0.77 – 3.22	0.212	3.21	1.19 – 8.62	**0.021**
Site								
—Site 1	13/347	3.8%						
—Site 2	20/333	6.0%	1.64	0.80 – 3.36	0.171	1.15	0.47 – 2.83	0.754
Child age (months)								
—6-24	21/421	5.0						
—25-59	12/259	4.6	0.93	0.45 – 1.92	0.834	0.76	0.33 – 1.73	0.508
Child Gender								
—female	18/309	5.8						
—male	15/371	4.0	0.68	0.34 – 1.38	0.282	0.76	0.35 – 1.63	0.477
Caregiver fluency in Krio								
—No	9/199	4.5						
—Yes	24/481	5.0%	1.11	0.51 – 2.43	0.797	0.68	0.28 – 1.66	0.399
Caregiver education								
—No	9/262	3.4%						
—Yes	24/418	5.7%	1.71	0.78 – 3.75	0.174	1.84	0.75 – 4.51	0.180
Household Religion[1]								
—Christian	13/217	6.0%						
—Muslim	20/462	4.3%	0.71	0.35 – 1.46	0.348	0.80	0.34 – 1.89	0.605
Socio-economic status[2]								
—1 (poorest)	10/236	4.2						
—2	11/209	5.1	1.12	0.74 – 1.71	0.592	1.18	0.72 – 1.96	0.511
—3 (least poor)	12/226	5.3						
HW said finish treatment								
—No	17/320	5.3						
—Yes	16/360	4.4	0.83	0.41 – 1.67	0.599	0.76	0.33 – 1.77	0.531
Caregiver Knowledge ACTs								
—No	28/509	5.5						
—Yes	5/171	2.9	0.52	0.20 – 1.36	0.175	0.49	0.17 – 1.38	0.175
Child disliked the drug								
—No	20/611	3.3						
—Yes	13/69	18.8	6.86	3.18 – 14.81	**<0.001**	7.97	2.77 – 22.95	**<0.001**
Adverse event								
—No	17/581	2.9						
—Yes	16/99	16.2	6.40	3.06 – 13.39	**<0.001**	4.80	1.93 – 11.91	**0.001**
Child has taken drug before								
—No	31/561	5.5						
—Yes	2/119	1.7	0.29	0.07 – 1.24	0.076	0.38	0.07 – 1.98	0.252
Paid for services								
—No	31/620	5.0						
—Yes	2/60	3.3	0.66	0.15 – 2.81	0.567	0.51	0.10 – 2.55	0.409

[1] *Religion denominator=679*

[2] *SES denominator=671*

[3] *due to missing data for religion and SES status covariates, the denominator for the adjusted analysis was n=670*

Table 7.7—Factors associated with incorrect treatment – (per-protocol)

			Unadjusted analysis			Adjusted analysis[3]		
	n/N	%	OR	95% CI	P value	OR	95% CI	P value
Antimalarial treatment								
—AQAS	52/340	15.3%						
—AL	61/340	17.9%	1.21	0.81 – 1.82	0.354	3.15	1.64 – 6.03	**0.001**
Site								
—Site 1	53/347	15.3%						
—Site 2	60/333	18.0%	1.22	0.81 – 1.83	0.337	0.59	0.33 – 1.06	0.078
Child age (months)								
—6-24	69/421	16.4%						
—25-59	44/259	17.0%	1.04	0.69 – 1.58	0.839	0.89	0.52 – 1.50	0.651
Child Gender								
—female	66/309	21.4%						
—male	47/371	12.7%	0.53	0.35 – 0.81	**0.003**	0.53	0.32 – 0.88	**0.014**
Caregiver fluency in Krio								
—No	23/199	11.6%						
—Yes	90/481	18.7%	1.76	1.08 – 2.89	**0.023**	0.92	0.51 – 1.67	0.789
Caregiver education								
—No	40/262	15.3%						
—Yes	73/418	17.5%	1.17	0.77 – 1.79	0.454	1.49	0.85 – 2.61	0.163
Household Religion[1]								
—Christian	44/217	20.3%						
—Muslim	69/462	14.9%	0.69	0.45 – 1.05	0.082	0.59	0.33 – 1.04	0.069
Socio-economic status[2]								
—1 (poorest)	49/236	20.8%						
—2	29/209	13.9%	0.80	0.63 – 1.02	0.073	0.78	0.56 – 1.09	0.150
—3 (least poor)	33/226	14.6%						
HW said finish treatment								
—No	67/320	20.9%						
—Yes	46/360	12.8%	0.55	0.37 – 0.84	**0.004**	0.51	0.29 – 0.88	**0.015**
Caregiver Knowledge ACTs								
—No	82/509	16.1%						
—Yes	31/171	18.1%	1.15	0.73 – 1.82	0.540	1.03	0.57 – 1.87	0.918
Child disliked the drug								
—No	76/611	12.4%						
—Yes	37/69	53.6%	8.14	4.63 – 14.30	**<0.001**	7.80	3.63 – 16.76	**<0.001**
Adverse event								
—No	55/581	9.5%						
—Yes	58/99	58.6%	13.53	7.80 – 23.46	**<0.001**	12.93	6.95 – 24.07	**<0.001**
Child has taken drug before								
—No	98/561	17.5%						
—Yes	15/119	12.6%	0.68	0.38 – 1.22	0.196	0.83	0.36 – 1.93	0.666
Paid for services								
—No	103/620	16.6%						
—Yes	10/60	16.7%	1.00	0.49 – 2.05	0.992	0.37	0.14 – 0.99	**0.048**

[1] *Religion denominator=679*

[2] *SES denominator=671*

[3] *due to missing data for religion and SES status covariates, the denominator for the adjusted analysis was n=670*

CHAPTER 8: EXPLORING BARRIERS AND FACILITATORS OF ACCESS AND ADHERENCE TO PAEDIATRIC ARTEMISININ-BASED COMBINATION THERAPIES IN FREETOWN, SIERRA LEONE

8.1 Chapter Introduction

This chapter presents the results of a qualitative study that used in-depth interviews to "explore the barriers and facilitators of adherence to ACTs in Sierra Leone" (Objective 4).

8.2 Research Paper

The cover sheet is on the next page followed by the manuscript.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Kristin Banek
Principal Supervisor	Sarah Staedke & Daniel Chandramohan
Thesis Title	Evaluation of Adherence to Artemisinin-based Combination Therapy for the Treatment of Uncomplicated Malaria in Sierra Leone

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*		Was the work subject to academic peer review?	

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Global Public Health
Please list the paper's authors in the intended authorship order:	Kristin Banek, Sarah G. Staedke, Daniel Chandramohan
Stage of publication	Ready for submission

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study, collected the data, conducted the analysis and wrote the first draft of the manuscript.

Student Signature: [redacted] **Date:** 27 June 2018

Supervisor Signature: [signature] **Date:** 12 July 2018

Exploring barriers and facilitators of access and adherence to paediatric artemisinin-based combination therapies in Freetown, Sierra Leone

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Abstract

Introduction

Medication adherence is an important step in the treatment effectiveness pathway. However, medicine-taking behaviours do not occur in isolation, but are influenced by the environment in which the medicine is taken or administered. This qualitative study was embedded within a randomized controlled trial comparing adherence to artemether-lumefantrine (AL) and co-formulated amodiaquine-artesunate (AQAS) for the treatment of uncomplicated malaria in children under-five, to explore contextual factors and identifying barriers to and facilitators of access and adherence to artemisinin-based combination therapy at two public health facilities in Freetown, Sierra Leone.

Methods

Caregivers of children enrolled in the trial were purposively selected based on thier study arm assignment group (AL or AQAS) and their primary adherence outcome, and were invited to participate in an in-depth interview (IDI). IDI took place in the homes of the respondents or in a private area of the study site. All interviews were conducted in Krio or English and were electronically recorded, transcribed, and translated into English when required. Interview transcripts were coded and aggregated into themes, applying a thematic content approach.

Results

Interviews with 49 caregivers were analysed (Site 1=27; Site 2=22). Thirty caregivers were from the AL treatment group and 19 were from the AQAS group; 40 were classified as adherent to treatment and 9 as non-adherent. Caregivers' responses highlighted three key aspects of the treatment effectiveness pathway that influenced access to medications and adherence to treatment: (1) characteristics of the medications; (2) health system related factors; and (3) caregivers' previous experience with malaria treatment. Caregivers reported confidence in the public health system and said they trusted the health workers, which may have translated into better health behaviours. Ease of administration of the medication and perceived risk of side effects (namely weakness and vomiting) coupled with caregivers' prior experience with treating malaria influenced the way medications were administered to their children and whether they adhered to the prescribed treatment.

Conclusions

In order to improve adherence, the contextual factors in which medication-taking behaviours occur, such medication characteristics, health system factors and prior caregivers' experiences must be considered. Moreover, further development and deployment of antimalarials that are easier to administer (i.e. dispersible or chewable formulations) may improve treatment adherence in children.

Keywords: malaria, adherence, ACTs, Sierra Leone, qualitative

Introduction

The treatment effectiveness pathway has five components contributing to the overall success of prescribed medications, namely: 1) drug efficacy; 2) access to treatment; 3) targeting treatment; 4) health worker compliance; and 5) patient adherence [1]. Adherence, the final step along the pathway, is considered a vital element of the pathway and deemed essential for optimal treatment outcome [2]. The World Health Organization defines adherence as "*the extent to which a person's behaviour---taking medications, following a diet, and/or executing lifestyle changes—corresponds with the agreed recommendations from a health care provider*" [3]. Medication-taking behaviours can be influenced by various contextual factors including: socioeconomic factors, health system characteristics, aspects of the disease, treatment characteristics and other patient-related factors [3-5].

Antimalarials are recommended primarily based on their efficacy, that is their ability to clear parasites from the body and cure patients of malaria. In addition to efficacy, other characteristics of the medicines, such as taste, colour, packaging, number of tablets, perceived side effects and ease of administration, can all influence the ultimate effectiveness of the treatment. A number of older studies highlighted interventions that may improve patient adherence to antimalarial treatment [6-8], but only a few looked specifically at factors that directly influence patient adherence, such as the role communication may play in improving antimalarial adherence [9, 10], packaging and dosing inserts [11-14] and interventions aiming to improve community awareness around malaria treatment [15].

Although the evidence base on antimalarial adherence is growing, the published literature lacks consensus on factors associated with non-adherence to antimalarial regimens [16, 17] as well as information on the context in which adherence or non-adherence to antimalarials occurs. Understanding both the individual and contextual factors influencing adherence behaviours is necessary for the development of interventions to improve adherence to antimalarials [7]. Qualitative research methods provide a way to understand the environment of phenomena – in this case, barriers and facilitators influencing medication-taking. However, few qualitative studies have specifically examined adherence to ACTs and the context in which these medicines are administered [18-22]. In Sierra Leone, where this study was conducted, only one observational study measuring adherence to co-packaged amodiaquine

plus artesunate (AQ+AQ) has been conducted, which reported low treatment adherence (only 48.3% of participants were classified as probably adherent) [23].

This qualitative sub-study was conducted alongside a randomized controlled trial that compared adherence to two artemisinin-based combination therapies (ACT) for the treatment of uncomplicated malaria (artemether-lumefantrine (AL) and amodiaquine-artesunate (AQAS) in children under-five at two public health facilities in Freetown, Sierra Leone [24]. We interviewed selected caregivers of participating children to explore the circumstances that contribute to or prevent optimal adherence to ACTs for the treatment of uncomplicated malaria in children under five in this study population.

Methods

Study setting

This study took place in the catchment area of two government-run health facilities in Freetown, Sierra Leone. The first clinic (Site 1) was located in a densely populated area near the port in the eastern part of Freetown. The second clinic (Site 2) was located in the western part of Freetown. Both health facilities are classified as Community Health Centres by the Ministry of Health and Sanitation—Sierra Leone and primarily provide outpatient, preventative, laboratory and curative services as well as limited inpatient services for uncomplicated births and childhood illness not considered too severe [25].

The adherence trial

This qualitative study was embedded within the randomized trial conducted between September to December 2013, which compared caregiver adherence to AL and AQAS for the treatment of uncomplicated malaria in children under five [24]. A total of 680 caregivers completed follow-up (Site 1 =347 and Site 2 = 333). The self-reported adherence was high for both ACTs at both sites (Site 1: AL=96.6% and AQAS=95.9%; Site 2: AL=91.5% and AQAS=96.4%). However, the likelihood of administering the correct dose of medication at the correct time differed between the two treatment groups and between the study sites. At Site 1, the odds of receiving the correct dose was significantly higher for AL compared to AQAS (93.1% AL vs. 83.7% AQAS; OR = 2.64; 95%CI = 1.30-5.39); p=0.008), but was only boarder

line significant for correct treatment (88.0% AL vs 81.4% AQAS; OR = 1.68; 95%CI = 0.92-3.04; p=0.089. At Site 2, correct dosing and timing of treatment was significantly lower for AL compared to AQAS (dose: 77.6% AL vs 88.7% AQAS; OR = 0.44; 95%CI = 0.24-0.81; p=0.008 and timing: 82.4% AL vs 97.0% AQAS; OR=0.14; 95%CI=0.05-0.38; p<0.001) as was correct treatment (75.8% AL vs 88.1% AQAS; OR = 0.42; 95%CI = 0.23-0.76; p=0.004)

Study Design & Sampling

The primary objective of this qualitative study was to explore factors that influenced caregiver adherence to ACTs in this study population. The study involved in-depth interviews (IDIs) with caregivers from both treatment arms and study sites, including those classified as adherent and non-adherent to treatment. We aimed to enrol at least 20 caregivers per site into this sub-study. A sampling matrix was constructed (Table 8.1) to guide the estimated number of IDIs with caregivers. However, the total number of caregivers enrolled was determined by the content of the interviews. Recruitment was ongoing, once saturation of emerging themes was reached, study recruitment ended.

Table 1 Estimated number of IDIs with caregivers

Participants	*Number of Interviews*		
	Adherent	Non-adherent	Total
Co-formulated AQAS	5	5	10
Co-formulated AL	5	5	10
Total for one site	*10*	*10*	*20*
Total for two sites	*20*	*20*	*40*

A combination of purposive and convenience sampling was used. Caregivers who completed follow-up were purposefully selected by field workers and invited to participate in the qualitative study. Selection criteria included: 1) the treatment their child received; 2) their adherence outcome classification; and 3) consented to participate in the sub-study. Additionally, study staff identified caregivers who seemed comfortable speaking about their experience with treatment and asked them to participate in the qualitative study.

Data Collection

The interviews were conducted in the home of the participant or a private space at the health facility. The respondent designated the location of the interview. Interviews were conducted by KB or one of two selected field-workers at each study site. The interviews were conducted one-on-one between the participant and one field-worker unless a translator was required or the participant requested to have another person present. Interviews took place in Krio, although a few were conducted in English at the request of the respondent. Although KB is proficient in Krio, two interviews conducted by KB required a second field worker to be present to facilitate communication if required. All interviews were recorded and summary sheets prepared for each interview. Demographic, study drug and outcome data on the summary sheets were all validated by cross-checking the trial case record forms.

Data Analysis

Analysis of the IDIs was conducted using a thematic content approach [26, 27]. Recorded interviews were first transcribed and translated into English as necessary. The first phase of data analysis involved KB listening to the recordings then reading the English transcripts to ensure familiarity with the data as well as to confirm the quality of the translations. The second stage of analysis involved coding the data and identifying common themes and patterns across the data. Coding was initially completed by hand and subsequently uploaded into qualitative data analysis software, MAXQDA Analytics Pro 12 [28], to aggregate the codes into themes.

Ethical Considerations

The study was approved by the London School of Hygiene and Tropical Medicine (LSHTM) Research Ethics Committee and the Sierra Leone Ethics and Scientific Review Committee. The full trial protocol was also registered at ClinicalTrials.gov (NCT01967472; https://clinicaltrials.gov/ct2/show/NCT01967472). After explaining the purpose of this study, selected participants provided additional written informed consent to participate in the qualitative sub-study, including approval to be audio recorded and to quote them anonymously. For participants that could not write, a thumbprint was substituted for the signature.

Results

Participants

A total of 57 caregivers were enrolled in the sub-study (Site 1= 27; and Site 2= 30), with 8 IDIs excluded from Site 2 due to lack of consent, recording or incorrect recruitment (Table 8.2). The analysis was based on 49 fully transcribed and translated interviews (27 from Site 1 and 22 from Site 2), which was approximately 7% (49/680) of caregivers completing the main adherence trial. The majority (91%) of caregivers were women with a mean age of 30 years. The average age of the children who had been prescribed antimalarials in the study was 24 months. Self-reported non-adherence was a rare event in the main trial (range 3.4%-8.5%); as a result, only 9 (18.4%) of caregivers interviewed were classified as non-adherent (AL=5 and AQAS=4) (Table 8.3). Eight non-adherent caregivers were from Site 2 (AL=4 and AQAS=4), and one non-adherent caregiver was from Site 1 (AL treatment group). By chance, more caregivers were interviewed from the AL study arm (n=30) than the AQAS study arm (n=19).

Table 2 Characteristics of IDI participants

	Site 1 n(%)	Site 2 n(%)	Total N(%)
Number of IDIs conducted	**27**	**30**	**57**
Excluded[1]	0	8	8 (14.0%)
Total number of IDIs Analysed	**27**	**22**	**49 (86.0%)**
ACT received during the trial			
AQAS	10 (37.0%)	9(40.9%)	19 (37.3%)
AL	17 (63.0%)	13 (59.1%)	30 (61.2%)
Treatment uptake			
Non-adherent	1 (3.7%)	8 (36.4%)	9 (18.4%)
Adherent	26 (96.3%)	14 (63.6%)	40 (81.6%)
Caregiver Age Categories[2]			
<25	8 (29.6%)	8 (36.4%)	16 (32.7%)
25-34	11 (40.7%)	5 (22.7%)	16 (32.7%)
35-44	3 (11.1%)	5 (22.7%)	8 (16.3%)
45+	3 (11.1%)	3 (13.6%)	6 (12.2%)
Caregiver Gender			
Female	24 (88.9%)	21 (95.5%)	45 (91.3%)
Male	3 (11.1%)	1 (4.5%)	4 (8.2%)
Child Age Categories			
6-23 months	15 (55.6%)	9 (40.9%)	24 (47.1%)
24-59 months	12 (44.4%)	15 (68.2%)	27 (52.9%)

[1]Excluded: 1=no recording, 4= consent not varified; 3=excluded from RCT after recruitment
[2]Three caregivers did not provide their age (Site 1= 2; Site 2= 1)

Table 3 Outcome (self-reported adherence) and Treatment of IDI participants

	AL	AQAS	Total
Site1			
Adherent	16	10	26
Non-Adherent	1	0	1
Site 1 Total	**17**	**9**	**27**
Site2			
Adherent	9	5	14
Non-Adherent	4	4	8
Site 2 Total	**13**	**9**	**22**
Total			
Adherent	25	15	40
Non-Adherent	5	4	9
Combined Total	**30**	**19**	**49**

Factors influencing Adherence

We identified three key aspects of the treatment effectiveness pathway that influence optimal ACT adherence in this study population: 1) medicine characteristics; 2) health system factors; and 3) caregiver past and present experience with malaria illness and treatment.

Medication Characteristics

Caregivers reported that medicine characteristics were key factors influencing the acceptability of treatment and ease of administration, with taste dominating the majority of responses. Respondents described the ACTs as "*sweet*" or "*bitter*." "*Sweet*" was seen as a positive trait caregivers reported that "*sweet*" medicines are easier to administer to children.

> *"It [AL] tastes sweet, and also tastes nice."*
> ***(S2-13, female caregiver, adherent, AQAS)***

> *"Because this one is not bitter like that yellow and white one. For this one, it has that flavour, that orange-like flavour."*
> ***(S1-15, female caregiver, adherent, AL)***

"*Bitter*" medicines, on the other hand, were viewed both positively and negatively by caregivers. Some caregivers cited bitter taste as a barrier to administration, while others reported that the bitter taste implied that the drug was strong and thus more effective.

> *"No, she was not willing, but she didn't vomit it also. She didn't like it because it was bitter."*
> ***(S1-02, female caregiver, adherent, AQAS)***

> *"Only that they do vomit because it seems to be very bitter."*
> ***(S1-01, female caregiver, adherent, AQAS)***

> *"It is very bitter, but it is for your well bodi [health]"*
> (***S2-0, female caregiver, non-adherent, AQAS)***

Very few caregivers used the biomedical names of the malaria treatments given during the study or received previously. There were mentions of chloroquine and quinine, but in general, the majority of caregivers used the term "*malaria treatments*" or "*malaria medicines*." When caregivers were shown a sample or told the commercial brand-name of

the drug (i.e. Lokmol for AL, which has radio advertisements), they very quickly identified the malaria medications. Other names used were "*government medicines*", and a few used the acronym, "*ACTs*". Often only the colour and other descriptors of the medication were given to identify the medication. However, lack of knowledge of the biomedical name of the ACTs did not imply a lack of familiarity with the treatment. Caregivers have experience with antimalarials and other medications and can describe the appearance of each medication and their experience with it.

Caregivers associated yellow tablets as anti-malarial medicines that cause weakness, which generally meant amodiaquine (which caregivers identified by pointing to the medication during the interview). Interestingly, AL is also yellow, but as it was packaged in a very different blister-pack card and had a sweet smell and taste and was not mistaken for amodiaquine by most caregivers. Otherwise, most tablets commonly used by caregivers (i.e. acetaminophen tablets commonly called "Panadol") are white and could not be easily identified if outside of a distinct package.

Caregivers had some difficulty differentiating paediatric medicine and adult formulations of ACTs. This difficulty could be due to the common practice of cutting and separating blister-packs of adult doses to administer to children when there are shortages of paediatric formulations. This practice contributed to the idea that more tablets meant that a drug was "stronger" or more "powerful." One respondent specifically stated that the co-packaged AQ+AS was for adults and not for children, so she did not give it to her child.

> *"I have never used it [AQAS co-pack] with a child, with my children because that one is not meant for children. It is for grown-up people, because even myself, I used to use Artesunate."*
> (S1-16, female caregiver, non-adherent, AL)

Caregivers also equated more tablets with the strength of the medication. While more tablets were sometimes seen as good, some caregivers feared that the two tablet dose for AL would be "too strong" for their children.

> *"Even though they said I should administer it two each time, although I was afraid to give two at a time because I thought it would be strong for her, but*

> *those two at a time that I was giving to her, I thank God for that. Those two to three days she became very playful once again."*
> ***(S2-25, female caregiver, adherent, AL)***

Some respondents associated multiple tablets with side-effects such as when a child would become weak following treatment, either as a symptom of malaria or as a perceived or real side-effect of the medicine. Caregivers also commented on the difficulty of administering the number of tablets required for treatment with AL.

Potential side effects or adverse events

Caregivers also reported being afraid of administering too many tablets as they thought that too many tablets would be too strong and thus harmful to the child, influenced how caregivers would administer the ACT, both in terms of timing or dosing of the medication. Some caregivers reported that they would complete the entire dose prescribed, but would deliver it over four or more days and not within the recommended three days. Other caregivers reported cutting the AQAS tablets in half or only gave one AL tablet rather than two tablets to avoid overdosing their children.

> "Well, the reason for giving her two tablets was because she was seriously sick at that night; she was very weak at that night. The following morning, I only gave her one tablet. And the other day, I continued giving her two tabs again."
> ***(S2-17, female caregiver, non-adherent, AL)***

In addition to their child's weakness, caregivers altered behaviour based on other side effects and symptoms related to malaria: vomiting, lack of appetite and constipation. Vomiting, in particular, was cited as a reason to stop giving their children the medicines.

> *"When I gave him the malaria tablets [type not specified], he vomited twice. I didn't give the medicine again. I didn't give him at all. I went to the doctor."*
> ***(S2-15, female caregiver, adherent, AL)***

Caregivers had different practices regarding the administration of medications with food. Some caregivers felt that giving the medication with food helped to avoid vomiting and other side effects, while others felt that administering the medication without food was a better option to prevent adverse events.

> *"Once the child can eat, he should eat enough because that medicine too [AL, but also said it about AQ+AS] can cause the child to become weak if he does not eat enough."*
> (S2-22, female caregiver, adherent, AL)

One caregiver mentioned that the quantity and timing of giving the food were altered to avoid vomiting.

> *"No, he doesn't vomit. This is because after I have fed him, I wait for sometimes before giving him the medicine [AQAS]. Also, when I give him the medicine, I don't give him too much water to drink. If I give him too much water, he will vomit. I make sure that I put small water and I grind it very good in that small water and then put it in his mouth, so it all goes down and no vomiting."*
> *(S2-04, female caregiver, non-adherent, AQAS)*

Packaging

Medications in these settings are often dispensed from large containers with individual tablets counted and wrapped in paper or placed into small bags. The results from this study suggest that caregivers often identified ACTs not only by their colour, but also by their packaging. The exception to this was when there were stock-outs of paediatric ACTs and tablets were removed from the adult blister-packs, cut in half and given in paper to the caregivers.

Packaging was not only an identifier for antimalarials; it also served as reminders to the caregiver about how to administer treatment, particularly for AL. Little was mentioned about the packaging for AQAS, other than because it was in a package and therefore considered malaria medicine.

> *"The malaria tablets are specially wrapped on their cards and as you see them; you know that they are malaria medicines/drugs."*
> *(S2-04, female caregiver, non-adherent, AQAS)*

More caregivers commented that the packaging for AL was helpful as well as attractive. This may have been because it is quite colourful, contains pictures to aide treatment

administration, or has more physically durable packaging than that of AQAS. Furthermore, respondents mentioned that they liked to keep the package so they would have the name and an example of the package if they wanted to access this "new" malaria treatment at a later date from a pharmacy.

> *"The [AL] card helped me on how to administer the medicine."*
> ***(S1-25, female caregiver, adherent, AL)***

> *"I even grew annoyed that I did not have the empty card that I would have showed the pharmacies…but just telling them that you wanted Coartem, they couldn't know the medicine. But if there was the card, that could have helped."*
> ***(S1-16, male caregiver, adherent, AL)***

Treatment administration

Caregivers were quick to respond with the administration directions for AQAS with, "*one today, one tomorrow and one next tomorrow* [the day after tomorrow]." Caregivers also knew that AL was to be given twice a day, and depending on if they received the infant or child dose, knew it was one or two tablets at each administration point.

Methods of administration varied. For AQAS, almost all caregivers reported grinding the tablets and adding it to water and dispensing it either with a spoon or a dropper. A few reported that their child swallowed the tablets whole to avoid the bitter taste, but one mother of an older child only mentioned this. The primary method of administering AL was by dissolving it in water, and then the child would drink it, which was rather straightforward and easy for the caregivers to administer and contributed to its appeal as the dispersible formulation is very similar to syrups.

> *"Why I said it is good? I said it is good because it is a medicine but does not resemble ... it is syrup like when you mix it – the flavour. It has a very nice flavour. When I gave it to my child, she would drink it."*
> ***(S2-16, female, non-adherent, AL)***

Many caregivers mentioned that their child actually chewed the tablets and drank the water afterwards (Box 1). This was most common for AL although a few caregivers did mention that the child chewed AQAS. All mentioned that they bought bottled water to administer the ACTs.

"The child has the urge to take it [AL]. At times he takes it [AL] without drinking water. He can just chew it like that, in whole."
(S2-19, female caregiver, adherent, AL)

"Whenever I gave it [AL] to her, she would chew it and drink water…she was chewing every bit of it because she is a child that likes chewing medicines."
(S2-28, female caregiver, adherent, AL)

"This medicine is nice; it has a nice smell. It is nice. It has a strawberry smell. That is why I like it. Whenever I gave it to my child, he would just chew it. He likes it too [very] much."
(S2-23, female caregiver, adherent, AL)

Box 1. Quotes about chewing ACTs

Health system influences on treatment effectiveness

Access to Health Services

Quality of health services was very important to caregivers as was the ease of access (including location and free-services). The caregivers defined the quality of care as being treated well by health facility staff, receiving good medications, a clean and well-maintained facility and the availability of testing to confirm malaria. Health workers were generally seen as knowledgeable and helpful, with those showing kindness to the child and caregiver seen as more competent. This was particularly evident at Site 2 (Box 2).

"The reason being is that, when I go there [HF], they treat my child nicely and we the parents like hospitals where our children are nicely treated. The hospital is the best in the community. That is why I prefer to take my child there when he is sick."
(S2-19, female caregiver, adherent, AL)

"Well over there [the hospital] the nurses know how to talk to someone. It is not like in another hospital where nurses will shout at you, 'look at how you have made that child.' In this hospital, the nurses talk to you nicely; they give you words of encouragement and are very friendly. And even the doctors know how to talk to someone well. Even when they are treating your child, you will be happy about it. Because they can do proper diagnoses—checking his eyes, his ears, nose, pressure, everything. So over there, the nurses and the doctors know how to attend to a patient and how to talk to a patient whenever you pay a visit there."
(S2-22, female caregiver, adherent, AL)

Box 2. Quotes about Quality of Care at Site 2

Community connection to the health facility

Caregivers reported that feeling connected to the community health centre was also important. In particular, at Site 2, caregivers described feeling loyal to the health centre because it is where they had received antenatal care and delivered their children.

"It is there that I delivered this child, they [the nurses] treated me well. They talked to me nicely. They attended to me properly and helped me deliver safely. Whenever my child is sick, I will take him there, and they welcome me nicely and talk to me nicely."
(2.559/S2-20, female caregiver, adherent, AL)

"As for me, to be frank with you, since I gave birth to my child until now that she is three years of age, I have never taken her to any other hospital."
(S2-24, female caregiver, adherent, AL)

Additionally, Site 2 was considered the neighbourhood clinic, much like there is a neighbourhood market or school; it is where people from that community access health

services. Caregivers reported wanting to go there because the services were good and the health facility was well maintained and clean.

> *"Well, the first reason I like taking my child to [that clinic] is that it is located in my community. It is not situated far off. Second, the hospital is clean, the nurses are caring, and they talk with us patients nicely that is why I like taking my child there, whenever my children are affected by fever."*
> (S2-12, female caregiver, adherent, AQAS)

Site 1 was slightly different in that it served not only the community, but also those seeking care at the nearby children's hospital who were not sick enough for tertiary care and were referred down to the primary care facilities. This resulted in a slightly less community-focused facility. However, caregivers from Site 1 also stated that they were treated nicely by staff and would choose to seek care there again because they had delivered their children at that health centre.

> *"When I went there, the nurses treated my child nicely. We were treated very well."*
> *(S1-04, female caregiver, adherent, AQAS)*

Targeting malaria treatment

Caregivers also described the importance of diagnostic testing for malaria and confirming the diagnosis with a positive test. Caregivers associated the presence of testing with better service and more reliable care.

> *"For me, it is especially for the good treatment and the test that they do to determine the illness affecting the child."*
> *(S2-25, female* caregiver, adherent, AL)

> *The test is very important. Because sometimes some children will only be affected with fever and nothing else…..but if you do a medical test, the test will be able to prove if she has malaria."*
> *(S2-28, female caregiver, adherent, AL)*

> *"….it is the test that they conduct that would tell that it is malaria affecting her.*
> *(S1-13, female* caregiver, adherent, AL)

The key role of health workers

Almost universally, caregivers deferred to health facility staff to diagnose their child's illness and to guide them on fever management. Health facility staff who were kind and friendly were seen to provide even better care.

> *"Doctors and nurses will advise me what is wrong with my child."*
> *(S1-08, female* caregiver, adherent, AQAS*)*

> *"These quack doctors were never trained, they too only buy and sell. But as for the nurses and doctors, they went through training. And they thus know the correct medicines to prescribe."*
> *(S2-12, female caregiver, adherent, AQAS)*

Patient-Provider Interaction

Responses from caregivers also reported that the patient-provider interaction during the consultation was satisfactory and that the health worker took the time to show them how to administer the ACTs.

> *"He [the health worker] observed my child, diagnosed her. He looked inside her mouth. He looked at her eyes, and he even looked in her ears. And then he had to prescribe medicine for me. After prescribing the medicine, he showed me how to administer the medicine."*
> *(S2-23, female caregiver, adherent, AL)*

The caregivers' interaction with the health system appeared to have a large impact on positive health behaviours. Almost all of the caregivers interviewed could correctly describe how to administer not only the medication they received for the study, but also those they received previously. Furthermore, previous experiences with which culminated in positive outcomes contributed to the increase in trust the caregivers had in the health workers and the health system.

> *"The medicines that were supplied to us were very good. They will never come to tell us lies. The doctors and nurses that are there are specialised, and they have never falsely diagnosed any sickness on my child, so I believe them."*
> *(S2-19, female* caregiver, adherent, AL*)*

> *"Even myself as an adult, when I do go there [to the clinic] for treatments; they would treat me well and ensured that I went through all the procedures that I should until I meet the CHO [community health officer] and the CHO examined me. So that is why I like them. They are really doing their job."*
> *(S2-02, male* caregiver, adherent, AL*)*

Health system challenges

Not all health facility characteristics were seen as positive. Delays in receiving the blood test or treatment in addition to regular stock-outs were described by caregivers as specific barriers to accessing care. The patient load was high at both clinics, particularly on immunization days or therapeutic feeding days. All patients are triaged at the registration desk, so there is no distinction between children who are sick and those for routine services until they are registered. With high patient volume, this triage system can delay care and put a strain on resources and drug stocks and impact prescribing practices and the amount of time available for each patient consultation.

> *"If there is less number of people I will not wait long, but if the people are many, I will wait for a long time."*
> *(S2-04, female caregiver, non-adherent, AQAS)*

> *"They don't give enough medications…..I normally decide to go to buy the medicines [at the pharmacy]."*
> *(S2-16, female caregiver, non-adherent, AL)*

Prior to the study, both health facilities experienced regular stock-outs of infant and child dose ACTs. This translated into health workers using adult doses of AQAS to meet the paediatric ACT needs; AQAS adult tablets would be cut in half so that the children were receiving the correct dose. This practice became part of the caregivers' experience with ACTs and impacted what they did with future malaria medications.

> *"I will go by the instruction of the doctor. They will tell me, give him half in the morning and half in the evening. That's what I do."*
> *(S2-05, female caregiver, non-adherent, AQAS)*

Individual Level Facilitators and Barriers

The caregiver's own fears, previous malaria episodes (both their own and their child's) along with prior experiences with antimalarials were found to be key influences on their adherence behaviours. Caregivers were particularly concerned for the welfare of their children and are afraid when their child is ill. *"I'm badly afraid of fever" (S1-07, female caregiver, adherent, AL)*. Most knew that malaria could be fatal, understood the importance of seeking treatment early, and were genuinely concerned with doing what is right to protect their children. They also understood the importance of completing the medication; otherwise, their child's condition would not improve.

> *"Malaria is a bad killer disease. If immediate treatment is not taken, it kills quickly. The child will not be cured because he has not been given the complete dosage."*
> ***(S1-05, female caregiver, adherent, AQAS)***

> *"As long as you follow the doctor's instructions and take all of the dosages, you will be cured by it."*
> ***(S2-12, female caregiver, adherent, AQAS)***

> *"It [AQAS] is also a good cure for malaria…But once you are done taking the dose, you feel comfortable because you have taken the correct malaria treatment."*
> ***(S1-24, female caregiver, adherent, AQAS)***

Mothers know when their children are unwell. The child does not eat, does not play, can be lethargic, have bright urine or clings to the mother. Caregivers reported that when symptoms of illness are evident it is easier to be more vigilant and more attuned to the need to provide medication in order to see improvement in the child's condition. However, once the child starts to play and begins eating again and becomes more active, the "emergency" has passed, and caregivers shift their focus back to their normal daily routine. At this point, some caregivers reported forgetting to administer the medication as prescribed. Although most caregivers appeared to understand the importance of finishing the medications, they might not adhere strictly to the recommended dosing frequency or timing.

"When there is an improvement in the health of the child, I would forget to administer it to the exact time, but before the end of the day, I would remember and give it back to him. I would make sure that I gave him all the treatment even if it isn't administered at the correct time. I give it all."
(S2-04, female caregiver, non-adherent, AQAS)

Caregivers' personal experience with malaria medicines and recovery influenced how they administered medications for their children. Specifically, medications that work quickly resulting in a rapid improvement in the child's health were considered strong or more effective. Caregivers also reported that if the curative effect of the medication lasted for some time, meaning they did not need to revisit the health facility, the medication was seen to be superior as it contributed to the immediate recovery and longer-term health of their child (Box 3).

"This medicine is good……whenever you give a medicine to the child, and they recover you must know it is good. I think it is good."
(S1-13, female caregiver, adherent, AL)

"Because upon using it [AQAS] my child recuperated properly. I didn't have any problem [sickness] again with her up till now."
(S1-14, female caregiver, adherent, AL)

"At the time I was sick I drank [malaria] medicine I immediately recovered. So when my children fell sick too, I was giving the [malaria] medicine to them too."
(S1-08, female caregiver, adherent, AQAS)

"Well my child had a severe fever, but when I gave it [AL] to her, I discovered that she recovered.
(S1-13, female caregiver, adherent, AL)

Box 3. Quotes about prompt recovery

Discussion

Quantifying adherence to prescribed medications should be complemented by an understanding of how and why patients choose to take their medications [29, 30]. This study identified three key domains along the treatment effectiveness pathway that influenced access and adherence to ACTs in this study population, namely: medication characteristics, health system characteristics and individual caregiver experience and perceptions.

Medication Characteristics

Children under five are at the highest risk of malaria infection [31], yet relatively few child-friendly formulations have been developed [32].Prior to the roll-out of ACTs, chloroquine syrup was the primary antimalarial prescribed for paediatric malaria. However, adherence to this child-friendly formulation was subject to errors in dosage due to different measuring tools and understanding of the dosing schedule [11]. This led to the development of pre-packaged chloroquine doses which were user friendly, as the pre-packaging assisted with the correct administration of the antimalarial [13, 14]. This practice was maintained when antimalarial treatment policies evolved from monotherapies to combination treatments such as CQ+SP and AQ+SP [33-35]. However, combination treatments could be dosed incorrectly if one of the medications was seen to be less desirable, such as amodiaquine [36-38]. To overcome these limitations of co-packaging, ACTs were combined into co-formulated formulations to improve adherence and limit the administration of monotherapies [39].

The Drugs for Neglected Diseases Initiative (DNDi) aimed to improve the dosing of ACTs by optimising the dosing of AQAS and artesunate-mefloquine (ASMQ). The DNDi strategy included improving the weight-based dosing of ACT by developing co-formulated regimens with fewer and smaller tablets which were easier to administer to children [40]. Subsequently Novartis created the first dispersible ACT, artemether-lumefantrine (AL). The dispersible formulation of AL also included a flavour mask, which facilitated administration to children [41]. The need to develop paediatric ACTs has also influenced the development of the two newer paediatric ACT formulations, dihydroartemisinin-piperaquine (DHAPQ) (water-dispersible tablets) and pyronaridine-artesunate (water-dispersible granules). The newer pyrimidine-artesunate, which is recommended by WHO to be used in countries where other ACTs are failing, has incorporated these key elements (i.e. fewer tablets, flavour masking and

dispersible formulations) during drug development [32, 42, 43]. However, the granules are only for children less than 20kg, leaving a gap for older or heavier children who may still struggle with medication adherence.

It has been reported elsewhere that users have a preference for certain anti-malarial drugs particularly those with simple dosing schedules [44-46]. Likewise, Caregivers in this study suggested that flavoured medications, that were easy to drink, improved administration. Therefore, it is likely these medication characteristics were key influencing factors of adherence for this study population. While the newer ACTs have included many of the desirable medication characteristics such as simple dosing schedule, flavouring and ease of administration, they all still require water for administration.

Caregivers in our study population reported that their children would chew the tablets rather than have them be dispersed in water. New antimalarial therapies should consider chewable tablets as a therapeutic delivery option because access to clean water for taking medications is lacking in many resource-poor countries (only 68% in Sub-Saharan Africa [47] or even lower for poorer households [48]). The caregivers in this study population reported they used a commercial brand of water, indicating that they purchased water as part of the treatment. While urban populations may have access to bottled water, poor or more remote populations may not. Providing a chewable option could improve adherence not only from medication administration perspective, but also a household economic perspective.

Health System Factors that Influence Adherence

In addition to medication characteristics, the results from this study suggest that in the context of Sierra Leone, the caregivers' experience with previous malaria episodes and antimalarials along with their interaction with the health system had a large influence on how medications are administered. The participants of our study were not only accepting, but more trusting of the treatment received from the health system. The definition of "good care" seems to stem from the patient-provider interaction. When the health worker is seen as kind and helpful, the quality of the health services provided was interpreted to be better.

Specifically, caregivers in this population reported that they depend on the health workers to tell them what to do in order for their child get better. The literature suggests that a collaborative relationship to care may improve adherence [49]. Moreover, having a trusting patient-provider relationship or having very high trust in primary providers has been shown to promote cooperation, access, utilization of services and adherence [50-52]. It is important that further understanding is sought on the importance and value of patient and caregiver trust in health systems, as it may not only impact treatment adherence, but access and overall service delivery [50-52].

We found that caregivers in this population were generally satisfied with their care, which has been demonstrated elsewhere to improve recall of treatment advice and thus adherence [53]. Furthermore, there was a great emphasis by participants in this study on the high quality of the care received at the study sites, in particular how kind the health workers were to them. Sympathetic health workers, and positive patient-provider communication and interactions have been noted to improve adherence for chronic illnesses [51, 54] as well as for the treatment of malaria [9].

Additionally, diagnostic testing appears to be widely accepted if not even preferred by this population. The extent to which access to free commodities (drugs and diagnostics) influences this acceptability is unknown in this study population. Furthermore, responses from the caregivers suggest that they relied on the health workers to diagnose their children and to tell them how to manage the illness. This finding is in agreement with other literature which notes that trust in the health workers and the wider health system improves adherence [50, 51].

While health systems can influence adherence in positive ways, health systems can also be a negative influence. Based on observations before, during and after the study, the quality of care and functionality of the health centres were altered when the study was running versus when it was not. Thus, these broader contextual factors may have influenced adherence differently at diverse time points. For example, the supply chain of ACTs and RDTs was dramatically improved during the study, with study members ensuring adequate

supplies. When stocks of supplies were low before study initiation, different prescription practices were observed when paediatric doses or RDTs were not available. This was most evident with the practice of cutting tablets so that they would not be "too strong," as adult doses were often cut in half to meet the paediatric ACT needs. This practice then became a part of the knowledge practices of the caregivers. This finding is supported by other studies that suggest that effective malaria case management can only be achieved if antimalarials and diagnostics are available [55].

Knowledge practices how & what caregivers know is influenced by their experiences

Results from this study also suggest that the caregivers themselves also have intrinsic knowledge based on their previous experience with malaria treatment. Caregivers know what they have experienced. Caregivers in this study population recognized the malaria medication packages, even if they were not familiar with their biomedical names, drawing from their prior experience using the medications to treat themselves or their children. This experience (both good and bad) influenced their opinion of the medication, how best to administer it (crushing, chewing, dissolving, with/without food etc.) and ultimately if they or their child were able to complete the treatment.

Moreover, caregivers were more attuned to treatment administration when their child's symptoms were severe, and became more relaxed once the child started to eat and play again. For example, caregivers reported being more vigilant when their child was sick because they were afraid for their child's health and life. As the ACT began to work and symptoms resolved, the caregivers would transition out of this emergency mode into a more relaxed state. At this point, non-adherent caregivers admitted that they would then forget to give the medication. A Kenyan study had comparable results, finding that lack of fever or severe disease was associated with non-adherence to ACTs [56]. Similarly, it has also been suggested that caregivers discontinued other antimalarials if symptoms resolved prior to completing the treatment, including the three-day treatment of chloroquine [11, 29, 57] or the longer 7-day quinine treatment [57].

Although caregivers in this study may have forgotten to give the dose at the recommended interval, this only prevented optimal timing of the medication, not complete discontinuation of the treatment as some caregivers reported completing the entire dose even if it was later in the day. So a caregiver may have completed the treatment, but did not give the treatment as prescribed (i.e. "correct treatment").

Adherence does not occur in isolation

The findings from this study found three categories of factors that influence adherence behaviours: characteristics of the medications, health system factors, and prior caregiver experience. These findings are similar to factors reported by Sabaté *et al.* for long term therapies who cite two additional categories: socioeconomic and disease related factors [3]. Caregivers in this study did not cite economic reasons for non-adherence, but this domain may be more relevant for accessing treatment rather than completing treatment.

This study population has access to treatment free of charge as directed by the Ministry of Health and Sanitation—Sierra Leone, the impact of this accessibility on adherence was beyond the scope of this study. Familiarity with the malaria medications did not seem to be a leading influencer of adherence in this population as adherence was high for both treatment arms, and even non-adherent caregivers still recognised the medications. Although caregivers in this population also mentioned disease-related factors, it was usually with regard to their own experience treating their child, and as such, we did not classify it separately.

The findings from this study mirror earlier study assessing non-ACT antimalarials, which suggest that adherence does not occur in isolation, with a range of factors influencing how malaria illnesses are managed [58]. Additionally, these data suggest that additional characteristics of an ACT, in addition to drug efficacy, such as ease of administration, should be considered more carefully when designing new antimalarials. Given the complexity of adherence more holistic interventions focusing on medication characteristics, patient and caregiver preferences and experiences as well as strengthening health system factors that influence adherence are needed to ensure that ACTs achieve their maximum effectiveness.

Limitations

The main limitation of this study is the imbalance with regard to the sampling frame. Although we attempted to select participant caregivers based on their outcome classification and study arm, this was not as easy to implement as envisioned. During the randomized trial, IDIs took place after the main trail enrolment period (i.e. after the final follow-up interview to measure adherence). At times some caregivers were not willing to participate again or could not be found again. Additionally, due to delays in data entry, the selection was done in the field and was subject to transcription error. In order to find enough caregivers willing to participate, convenience sampling was used. Those willing to participate were, on large, from the adherent group rather than the non-adherent group.

Second, selection criteria were based on self-reported adherence (completed treatment), which was quite high in this population (>90%). However, during the course of the IDIs, it was realized that the type of non-adherence in this population might not be related to treatment completion but rather how the treatment is administered. Had the sample selection used correct and incorrect treatment, we may have had a larger number of participants in the incorrect (non-adherent) group as well as well as more information on the other components of adherence, such as dose, timing and duration.

Third, the IDIs were conducted in Krio and transcribed and translated into English by non-medical personnel. Therefore some words and phrases may have been lost or misinterpreted. To mitigate this effect, KB cross-checked each transcript while listening to the original Krio recordings and made edits when necessary. For the most part, all Krio terms were understood, but if there was doubt other study staff or the NMCP were consulted.

Finally, it is possible that caregivers provided answers they seemed would be acceptable to the researchers as a result of participating in the study or out of a desire to please the interviewer. This was mitigated by using a conversational approach in which the caregiver told the story of how the medications were administered. However, a longer-term ethnographical approach may have built more rapport over time and yielded richer data; however, as this was a sub-study with a focus on caregivers' experience and perceptions and not strictly an anthropological study; interviews were the preferred data collection method.

Conclusions

Adherence behaviours have multiple influences. We identified three broad areas of influence: medication characteristics, health system factors, and prior caregiver experience with malaria illness and treatment. In order to improve adherence, the contextual factors in which medication-taking behaviours occur must be considered. Furthermore, continued development of newer antimalarials that are easier to administer (i.e. dispersible or chewable formulations) may improve treatment adherence in children.

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No potential conflict of interest was reported by the authors.

Authors' contributions

KB was the principal investigator of the study. She conceived, designed and implemented the study and conducted the data analysis, interpretation and first draft of the paper. DC & SGS supported the study design, data analysis and interpretation of the data. SGS also provided a critical review of the first draft. All authors read and approved the final manuscript.

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CHAPTER 9: DISCUSSION

9.1 Chapter Introduction

This chapter will summarize and discuss the key results from this thesis. Specifically, section 9.2 provides a summary of the key findings presented in this thesis and introduces a synthesis of the results and their implications. Sections 9.3 unpacks the notion that adherence is multidimensional with different components that define adherence. Section 9.4 presents adherence as a system problem and delves further into factors found to be associated with adherence as outlined in this thesis. Section 9.5 discusses the challenges of measuring adherence and provides some recommendations going forward. Section 9.6 highlights future directions and applications for measuring adherence, while sections 9.7 and 9.8 outline the thesis strengths and contributions as well as limitations. And finally, Section 9.9 presents my closing conclusions.

9.2 Summary of Key Findings

A systematic review of the evidence on artemisinin-based combination therapy (ACT) adherence presented in Chapter 3 highlighted the weak evidence base for ACT adherence, specifically for co-formulated ACTs other than artemether-lumefantrine (AL). Furthermore, the review highlighted the lack of methodological standardization regarding measuring adherence to ACTs and the limited number of studies in West Africa. With these gaps in knowledge in mind, I set out to quantify the level of adherence for ACTs and to identify and explore factors that influence adherence ACT behaviours.

This thesis used data from two studies conducted in Sierra Leone to answer the following research questions: (1) What are the levels of adherence to ACTs in Sierra Leone?; and (2) What factors are associated with adherence/non-adherence to ACTs in Sierra Leone? The four specific objectives of this thesis were: I) To calculate population-level adherence and the factors associated with adherence/non-adherence to antimalarial treatment in Sierra Leone; II) To evaluate and compare the level of adherence to co-formulated amodiaquine-artesunate versus artemether-lumefantrine for the treatment of uncomplicated malaria in children aged 6 to 59 months seeking care at two government health facilities in Sierra

Leone; III) To identify factors associated with patient adherence/non-adherence to these two ACTs formulations; and IV) To explore barriers and facilitators of adherence to ACTs in Sierra Leone using qualitative methods. An overview of the key findings for each research objective (Chapters 5-8) is presented in Table 9.1.

A synthesis of the results from this thesis produced three key conclusions. First, adherence to ACTs is multidimensional with a number of components that contribute to the notion that a patient is adherent. Second, adherence behaviours do not occur in isolation, with factors external to the patient potentially impacting medication-taking behaviours. Third, measuring medication adherence is challenging and consists of more than one quantitative measurement. Adherence should be measured in a number of ways with each method providing information on a different aspect of adherence in order to triangulate findings and generate a more holistic understanding of how patients take medications, such as ACTs for the treatment of malaria.

Table 9.1 Summary of thesis research objectives and key findings

Research Objective	Chapter	Key findings
Objective I: To calculate population adherence and the factors associated with adherence/ non-adherence to antimalarial treatment in Sierra Leone.	5	• Low levels of adherence to ACT; 47.2% of children took ACT for the recommended 3 days. • Children were more likely to receive an ACT if they sought care at a public health facility or were 25-60 months of age. • Children receiving an ACT within 24 hours were 40% less likely to complete treatment, compared to those that received an ACT after 24 hours of symptom onset.
Objective II: To evaluate and compare the level of adherence to co-formulated ASAQ compared to AL for treatment of malaria in children aged 6 to 59 months seeking care at government health facilities in Sierra Leone.	6	• Definite adherence was significantly higher for AL at both study sites, but this outcome was biased by package availability. • Self-reported adherence was high for both ACTs with no significant difference between the two. • AL was less likely to be taken correctly at site 2 • AQAS was less well tolerated at both sites • Potential disadvantages were identified for both regimens that could impact optimal adherence
Objective III: To identify factors associated with patient adherence to these two ACTs formulations.	7	• These data could only be analysed using multinomial logistic regression or by transforming the outcome into a binary outcome. • The multinomial and package-based adherence outcomes generated similar results; receiving AL, participating at study site 2 or being a child age 24-59 months were all identified as factors associated with non-adherence. • For the binomial logistic regression, children who took AL, disliked the medication (including bitter taste) or experienced an adverse event/side effects were more likely to be non-adherent (self-reported) • Receiving incorrect treatment was more likely for children receiving AL, male, who disliked the medication (including bitter taste), who experienced an adverse event/side effect or who paid for services.
Objective IV: To explore barriers and facilitators of adherence to ACTs in Sierra Leone using qualitative methods.	8	• Medication characteristics, health system factors and caregivers' prior experiences were all found to influence adherence behaviours. • Patient preference and ease of administration appear to influence adherence behaviours.

9.3 Adherence is multidimensional

Chapter 5 presents a self-reported adherence estimate of 47.2% for any ACT using a national malaria knowledge attitudes and practices survey (mKAP). At the time of the mKAP survey, co-packaged amodiaquine + artesunate (AQ+AS) was the only available ACT at public health facilities. The adherence estimate from the mKap survey used the duration of treatment (3 days) as the measurement for treatment adherence. The sample included children from the selected households who were reported to have had a fever in the 2 weeks prior to the survey. The findings were similar to the observation study conducted by Gerstl *et al.* in Eastern Sierra Leone in 2008, who reported probable adherence (correct intake) to AQ+AS to be 48.3% [1]. Despite the differences in study design and adherence definitions between the two studies, the estimate for co-packaged AQ+AS for both studies was low (<50%), validating the national malaria control programmes concerns about this ACT formulation.

In contrast to the mKAP survey estimate, Chapter 6 presents on average higher adherence estimates for two co-formulated ACTS AL and co-formulated amodiaquine-artesunate (AQAS) measured within the context of a randomized trial and with a shorter follow-up period (4 days). The primary outcome for the study was definite adherence, defined as having an empty ACT package. Definite adherence was found to be different at each site and for each study arm (Site 1: AL = 79.4% vs. AQAS = 63.4%; p=0.001 and Site 2: AL = 52.1% vs. 37.5%; p=0.049) [2]. However, this difference was influenced by the significant difference in package availability at each study sites (Site 1 = 75.4%; Site 2 = 52.3%; p<0.001) and between study arms (AL = 73.1%; AQAS = 54.6%; p<0.001). Self-reported adherence was very high, more homogenous with no significant differences in the estimates between sites or study arms (Site 1: AL = 96.6% vs. AQAS = 95.9%; p=<0.753 and Site 2: AL = 91.5% vs. AQAS = 96.4%; p=0.067).

Data from Chapter 8 suggests that caregivers were completing the treatment, but maybe not at the prescribed intervals. Therefore in addition to treatment completion, other aspects of adherence that may influence effectiveness should be measured (such as dose, timing, and duration) [3]. The household survey only looked at one component of adherence by collecting data on correct duration as the estimate for adherence (rather

than treatment completion). Since completion may have taken place over the course of more than 3 days in this population, this estimate may have underestimated completion rates, but might be a more realistic estimate for correct treatment based on duration.

Although the RCT used treatment completion as the primary outcome, data was also collected on the other aspects of adherence such as dose, timing, and duration and presented as a secondary outcome (treatment quality). Self-reported adherence (treatment completion) was high for both study arms and sites. However, there were differences in the treatment quality by study arm and site.

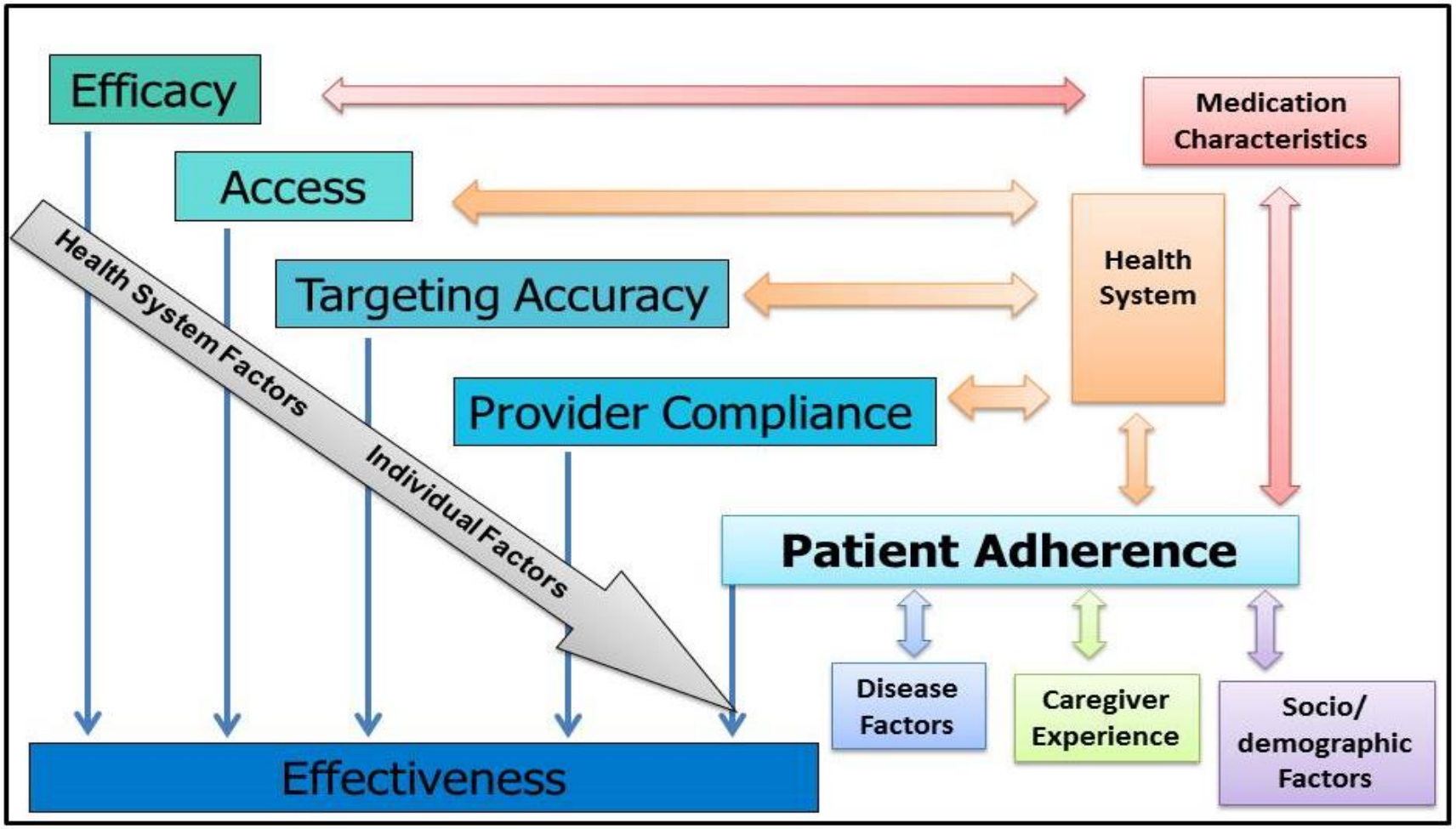
What remains unknown is whether one component of adherence is more important to measure than others as well as what impact completing a treatment, but not at the recommended intervals has on treatment effectiveness. The assumption is that treatment completion improves effectiveness. However, if the pharmacokinetics of a medication requires specific timing to be efficacious (as is recommended in the accompanying literature with Coartem©) then only having information on treatment completion and not data on how that medication was administered may limit the scope of interventions (including medication characteristics) designed to improve effectiveness. Only by teasing out measurements for the different components of adherence can we better understand adherence behaviours.

9.4 Adherence as a system problem

In Chapter 1, I introduced a figure outlining the pathway to effectiveness for malaria treatment (Figure 1.3). This pathway is linear and implies that each mitigating factor along the pathway occurs in isolation, with overall effectiveness a result of the multiplicative relationship between the steps. Although all 'steps' along the pathway are critical to success, this thesis focused primarily on the final step of the pathway, patient adherence. However, the findings from this thesis suggest that the figure oversimplifies the reality in which adherence behaviours take place; the different "steps" are conditional and interactive, with each step not only being influenced, but also influencing the efficacy/performance of each of the other steps, and ultimately treatment effectiveness.

It is often assumed that the entire responsibility of adherence lies with the patient or caregiver [4, 5]. However, factors that make up the adherence 'environment' may also impact the other steps along the pathway such as access, targeting and provider compliance and not only patient adherence (Figure 9.1).

Similarly, literature in relation to chronic therapy adherence has outline comparable factors (disease-related factors, medication characteristics, health care system factors, socio-economic factors and patient-related factors (i.e. knowledge, experience etc.) that influence adherence behaviours [6-8], suggesting that adherence may be more of a system problem instead of a "problem" at the individual patient level.



Source : Original figure courtesy of Marcel Tanner, personal communication 2012

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Figure 9.1 Revised treatment effectiveness pathway including the factors that influence adherence

9.4.1 Factors influencing adherence

To fully improve treatment effectiveness factors that impact optimal medication adherence need to be measured and addressed. This thesis used both quantitative methods to measure factors associated with adherence and qualitative methods to explore factors that prevent or facilitate adherence behaviours.

Published literature has suggested that a lack of knowledge of malaria [9], the antimalarial treatment dose [10-12] or lower levels education [13-16] are associated with non-adherence. Furthermore, even if users have knowledge of malaria and correct dosing, this does not guarantee it will influence practice [17]. Logistic regression results presented in Chapters 5 and 7 did not find associations between knowledge of malaria, knowledge of ACTs or education and adherence. While lack of specific formal knowledge may be a mediating factor, the responses from caregivers in this study (presented in chapter 8) revealed that prior experience with the medications influenced adherence behaviours. Similarly, there was weak or no evidence of an association between socioeconomic factors and adherence. This is consistent with the literature which suggests that socioeconomic and demographic factors are not statistically nor consistently associated with ACT adherence [18].

Results from the qualitative study presented in Chapter 8 suggest that medication characteristics such as ease of administration, taste and perceived side effects were all important factors influencing ACT adherence among children in this population. Likewise, results from the logistic regression results presented in Chapter 7 found associations between the child disliking the drug (including bitter taste) and two outcomes, self-reported non-adherence and incorrect treatment. Similarly, experiencing an adverse event or side effect was also found to be associated with both self-reported non-adherence and incorrect treatment.

These findings are similar to studies conducted in Malawi and Kenya which also found that patient preferences for the study ACT (AL) or a dislike or preference about a medication were both associated with adherence [11, 19]. While drug preference has not been studied or reported to be associated with antimalarial adherence in all antimalarial adherence

studies, this finding does suggest that medication characteristics, specifically those related to patient preference, may be relevant when developing new drugs or interventions to improve adherence.

Therefore a more comprehensive approach should be taken when designing interventions to improve adherence. The review by Yeung and White found that adherence to antimalarials was higher when "interventions focusing on provider knowledge and behaviour, drug packaging and provision of correct dosage" were implemented [20]. This echoes earlier research that highlighted the importance of patient education, provider communication and community sensitization [21-23]. Similarly, taking into account the complexity of the diagnosis and treatment process as well the role the different actor (both health workers and patients) behaviours play in effective treatment should be considered [24].

9.4.2 The importance of child-friendly medications and adherence

Prior to the introduction of ACTs, challenges with correct dosing and patient adherence were documented for chloroquine syrups and tablets [25, 26] and other antimalarial drugs, namely quinine [27]. Efforts to improve adherence led to the use of co-packaged and later co-formulated ACTs, some of which are dispersible and thus easier to administer [28]. While dispersible and co-formulated drugs are a move in the right direction to improve paediatric adherence to ACTs [29-31], the need for child-friendly ACTs remains unmet [32]. Specifically, there is still a need to create paediatric formulations that are not only palatable but easy to administer [33]. However, it is likely that the high cost of developing child-friendly treatments has limited the development of a paediatric ACT formulation with all of these characteristics.

The two ACTs used in Sierra Leone (AQAS and AL) fall short. AQAS has a simple dosing schedule, but remains bitter. AL is both dispersible and flavoured; however, the twice-a-day dosing schedule is not ideal for some caregivers as demonstrated by the lower levels of correct timing reported in this thesis. Additionally, the recommendation that AL be given with a fatty meal is not realistic in this population. Data on administration of ACT with food

was only available from Site 2, and found that the majority of caregivers (88.7%) administered the mediation without food (unpublished data).

In our study population, it was common practice to cut or crush tablets to aid administration, which can lead to suboptimal dosing [34]. Furthermore, while bitterness can be masked by a tablet coating, once the tablet is crushed the medication can have an unpleasant taste which can be a barrier for medication adherence, particularly in children who are more sensitive to bitter tastes than adults [35]. The move to dispersible formulations which are palatable, such as AL tablets or pyronaridine-artesunate granule sachets, may improve the dosing accuracy, but these formulations require water to be administered.

We found that children in this study population were chewing both AQAS and AL tablets, even if the water was available. In 2002, there were over 60 chewable tablet formulations registered in the United States [36]. Yet despite their many advantages include palatability, stability, precise dosing, portability, and ease of delivery [36], there is not yet a chewable antimalarial available. While developing paediatric formulations requires special consideration of physiology and pharmacology, ensuring new antimalarials are also both acceptable and easy to administer, may improve adherence and ultimately treatment effectiveness.

9.5 Methodological challenges & solutions for measuring adherence

Based on the previously reported methods of measuring antimalarials adherence, this thesis used the two most common indirect methods for measuring adherence: self-report and package inspection (pill count). However, this thesis demonstrates that measuring adherence remains challenging. This challenge arises primarily from researchers' reliance on indirect rather than direct methods for measuring adherence [37]. The only accurate way to know if a patient had taken their medication is to directly observe them [5, 38], which is the method of choice for chronic illnesses such as tuberculosis [39-41]. However, direct observation of medication intake is neither practical nor cost-effective and requires a number of supportive components to be successful [4, 42].

One challenge faced when measuring adherence is a bias of the measurement. This can be in terms of recall bias (remembering exactly how and when the medication was taken), social desirability bias (participants providing answers they feel the interviewer wants to here) or participation bias (as a result of taking part in a study) [4, 37]. Moreover, in the case of our RCT, we found that the primary outcome (definite adherence) was biased due to package availability being more common for AL than for AQAS.

Secondly, Bruxvoort *et al.* suggest in their review that study participation influences adherence outcome measurements [43]. Additionally, participating in a study may not be the only aspect that impacts adherence, but also the study design itself may influence the adherence results. Results from the systematic review presented in chapter 3 found that adherence was generally higher for RCTs compared to descriptive studies or cross-sectional surveys [18], possibly due to this notion that participation in a trial can alter the behaviour of both the participants and the health workers. A qualitative study conducted in Kenya to explore factors that impacted the high level of adherence in a randomized adherence trial. The authors concluded that in addition to outcome definitions, measurements and enrolment procedures, researchers should also consider the impact the trial or intervention might have on the quality of service provision and how quality may impact adherence [44].

Guidelines for good clinical practice dictate that participants are required to have the study explained to them followed by the provision of written informed consent [45]. It has been suggested that the act of consenting may bias study results [46]. While we tried to limit the impact the informed consent process had on our participants by not disclosing that there would be a follow-up visit, the act of consenting may have still influenced the participants' responses and behaviours. Additionally, in the first encounter field-staff only discussed the clinical portion of the study in the hopes that caregivers would behave as they normally do when seeking treatment for their children. We then sought a second informed consent at the time of the follow-up visits. While this may have reduced the bias introduced by the consent process, it would not negate any of the above-mentioned biases. Furthermore, our focus was primarily focused on the caregivers and not on the health workers. As discussed in chapter 8, the presence of the trial ensured adequate drugs

and supplies at both study sites, which would have helped the health workers to diagnose and treat malaria as per the guidelines.

Third, the outcome definitions for quantifying antimalarial adherence are not fixed. In some studies, self-reported adherence is used as the primary outcome measure. Other studies incorporate package inspection to varying degrees; similar to our study, some included packaging as part of the outcome [47, 48], while others used the package as a validation tool [49]. Moreover, when package inspection or pill counting was used for assessing antimalarial adherence in the published literature, limited details were provided as to the proportion packages found and inspected or how this information was incorporated into the outcome measure. Furthermore, the complexity of the outcome definition may have led to misclassification of some participants.

Further exploration and comparison of the different methodologies to measure adherence are needed to inform guidance on further research on adherence. To date, there has been only one direct comparison of methodology conducted which compared self-reported adherence to electronic "smart" blister packaging [3]. Additionally, studies should move to a combined approach of measuring adherence, to improve the precision of adherence measurements and capture all aspects of medication taking [4, 37, 38]. Finally, with adherence as the lynchpin for effective treatment, there is a need for formal standardization and guidance on best practices to measure adherence to antimalarial medications as was done for antimalarial efficacy and insecticide resistance.

9.6 Future directions & applications for measuring adherence

As a key aspect of effective malaria treatment, adherence should remain on the malaria research agenda. This is not only important for curative treatment, but also for chemoprevention interventions. This is particularly important if ACTs are to be used for these interventions in the future

9.6.1 Adherence and limiting artemisinin resistance

Measuring the levels of adherence to ACTs remains important, notably as artemisinin resistance has emerged in South East Asia [50-52]. In an effort to curb resistance, it has

been proposed that rotating regimens or using multiple first-line therapies could preserve ACT efficacy [53-55]. This suggestion could take many forms either by rotating or cycling ACTs in and out of circulation based on efficacy (as in Cambodia) [56] or targeted to different populations or interventions (i.e. one for curative treatment and one for chemoprevention or one for adults and another for children) [55]. Boni et al. defined multiple first-line therapies as "*a drug policy in which several therapies are made available in both the public and the private sectors, and patients and clinicians can choose which therapy to use*" [53]. If multiple first-line strategies using ACTs are to be successful, then patient preference, acceptability and adherence of the different therapies would need to be comparable.

Furthermore, it has been suggested that to save the efficacy of currently available ACT regimens, the duration of treatment could be extended from 3 days to a 5 or 7-day duration [57] or changed to sequential treatment with two different ACTs [56]. However, Achan *et al.* found that patients were less adherent to quinine, which had a 7-day treatment course [58]. While non-adherence is not attributed solely to the duration of treatment, the authors did demonstrate that levels of non-adherence increased over the course of the treatment duration (13% on day 3; 19% on day 5; 31% on day 6; and 44% on day 7) [58], suggesting that adherence to treatments that are longer in duration may be problematic. Similarly, studies evaluating adherence to a 7-day primaquine regimen have also reported lower adherence estimates [20, 59]. Thus it will be important to understand patient adherence to longer treatment regimens better if ACT treatment durations are to be extended.

Currently, Schallig *et al.* are testing whether sequential ACT administration can eliminate potentially resistant parasites in three African settings representing differing malaria epidemiology [60]. As part of the study, they will assess health worker, patient and caregiver acceptability and adherence of each ACT regimen. This is important because even if equally efficacious ACTs are paired, but are not equally acceptable, it may lead to non-adherence of one of the treatment courses and thus limit the potential effectiveness of using a sequential administration strategy.

9.6.2 The role of adherence and ACTs as chemoprevention

WHO currently recommends three chemopreventive interventions for vulnerable groups in high transmission areas, namely: seasonal malaria chemoprevention (SMC), intermittent preventive treatment in school children (IPTc) and intermittent preventive treatment in infants (IPTi) during routine immunization [28]. All three interventions depend on sufficient coverage to be effective, coverage in terms of reaching a large enough population as well as in terms of adequate uptake (adherence) of the antimalarial regimen by individuals. Currently, the recommended antimalarial treatments for these interventions do not include ACTs [61-63]. However, with the potential development of resistance to amodiaquine or sulfadoxine-pyrimethamine artemisinin-based combinations, such as long-acting forms of ACT (LACT), such as dihydroartemisinin-piperaquine (DHA-PQ) and artesunate-mefloquine (AS-MQ), may need to be considered [64].

The results in chapters five and eight suggest that treatment adherence is lower for those that do not feel their child is sick. As such, it would be essential to investigate this further in the context of chemopreventive interventions such as these. One study looking at the protective efficacy of three ACTs for chemoprevention in Uganda between 2010-2013 has already suggested there might be an issue. The authors found that 52% of malaria cases diagnosed in the DHQPQ arm had levels of piperaquine (PQ) levels below the detection limit, which they propose is due to non-adherence [65].

Similarly, the impact of adherence on mass drug administration (MDA) has proven to be important. In response to the 2014-2016 Ebola outbreak in West Africa, the WHO released temporary recommendations to reduce the number of fever cases in the affected countries [66]. The recommendations included changes to the malaria testing practices, LLIN distribution and included MDA using ACTs in areas of high transmission.

The Ministry of Health and Sanitation in Sierra Leone carried out an MDA campaign in 2015 with the aim of reducing the malaria burden and the number of febrile cases that could be considered suspected Ebola cases [67]. The MDA campaign was conducted in high Ebola and high malaria transmission area using the first line ACT, AQAS. Self-reported compliance (adherence) for participants >13 years of age was reported to be 71% for the

implementation areas [68]. While coverage was reported to be high (on average 97%), the acceptability of AQAS was found to be suboptimal as a result of 95% of respondents reporting a mild adverse drug reaction. This ultimately led Sierra Leone to switch to AL as the recommended first choice for malaria treatment in Sierra Leone [69].

Similar to the chemopreventive interventions named above, high coverage of MDA is the key to success, and therefore it will be essential to understand the acceptability and levels of adherence for ACTs chosen for MDA in light of asking people to take medications without having signs or symptoms of the disease.

9.7 Thesis Strengths and Contributions

This thesis responded to gaps in the literature on ACT adherence in general and more explicitly for Sierra Leone. Specifically, this thesis addresses the gap in limited information on adherence to co-formulated versions of ACTs, in particular, co-formulated AQAS. While there have been other qualitative studies exploring ACT adherence, chapter 8 is the first qualitative study exploring adherence to malaria treatment in Sierra Leone. Furthermore, there have been few comparative studies of adherence of ACT compared to other ACTs. The majority of previous studies comparing adherence levels of more than one ACT were primarily designed to test the effectiveness of the ACT, not to measure adherence. This thesis presents the first direct comparative trial primarily measuring adherence of two co-formulated ACTs. Furthermore, there has been limited discussion about the challenges of measuring adherence, the manuscripts presented in this thesis not only highlight challenges to measuring adherence but also suggest alternatives.

9.8 Thesis Limitations

While limitations have been discussed previously for each manuscript or chapter, this section presents cross-cutting limitations, namely: working in challenging environments, the influence of the research team on the findings, and limits to generalizability.

Working in a developing country context, in particular in countries that are recovering from years of instability, such as Sierra Leone, can mean that experienced research staff are difficult to find. The field-staff recruited to collect data for this thesis had previous

experience with household surveys conducted by Statistics Sierra Leone or International Non-governmental Organizations. However, their experience with qualitative data collection was more limited. Despite pre-study and on the job training and data reviews, field workers struggled with collecting data using open-ended questions and thus required continuous coaching.

While open-ended questions were used both for the follow-up adherence survey and for the IDIs, the difficulties were more evident for the qualitative study. To accommodate the differences in abilities, field-workers that showed more confidence and skill with this type of interview format, were assigned to do the qualitative work. The additional training and study staff selection resulted in an improvement in data quality, evidenced by improved case record forms and IDI recordings.

While every attempt was made to limit the influence the study and research team had on the research findings, the position, gender and nationality of the research staff may have influenced how the data was collected and analysed. Although, I have lived and worked in Sierra Leone since 2008 and know the language and the culture I am still a foreigner and as such will approach the research from a different perspective. Likewise, participants, the Ministry of Health and clinic health workers treated me quite differently than they did the Sierra Leonean research staff. For example, it was easier for me to secure sufficient ACTs and RDTs for the clinic than the clinic officer in charge because I was a foreigner in charge of a research study. Similarly, as a woman and a mother, I was also able to extract different stories and information from the caregivers than my predominantly male field-workers. Conversely, the field-workers had greater access to participants both in terms of language but also culture.

While the results of this study are comparable to findings in nearby Ivory Coast, where 97.2% of participants completed treatment [70], the generalizability of the results elsewhere may be limited. However, the results from this thesis are valid for the Sierra Leonean context at the time of data collection (2012), but results may be less relevant since the Ebola outbreak occurred in 2015-2017 and the subsequent changes to access to health care and service delivery.

9.9 Overall Conclusions

Although adherence to ACTs in the national survey was low, adherence to both AL and AQAS in the RCT were much higher, but were influenced by the criteria used to define adherence. The number of tablets or doses (such as those required for AL), dislike of the medication (including bitter tastes), and perceived side effects may contribute to poor adherence. Child-friendly formulation and patient-centred services may positively impact adherence to ACTs as may caregiver prior experience with ACTs. The responsibility of adherence to ACTs lies not only with the patient and caregiver, but also more broadly with the health workers and the health system. This thesis contributes to the knowledge base on adherence by providing a population estimate for adherence in Sierra Leone, comparative estimates of two co-formulated ACTs as well as expands on the methodological challenges highlighting the need to standardize the methodology for defining and measuring adherence.

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APPENDICES

List of appendices:

Adherence to Artemisinin-based Combination Therapy (ACT) in Sierra Leone: *A secondary analysis of national survey data*

Protocol Version:	1.0
Protocol Date:	28 December 2012
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1 KAP Secondary Analysis Table of Contents

1 Background

In 2011, the Government of Sierra Leone was awarded and signed an agreement to implement a Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) Round 10 grant for Malaria. Catholic Relief Services (CRS) is a co-Principal Recipient (co-PR) with the Ministry of Health and Sanitation (MoHS) for this grant. CRS's main responsibilities include: strengthening information systems related to medicine and commodities; community behaviour change communication; mass-media communication; and major research studies. The activities will be implemented by CRS Sierra Leone in partnership with the MoHS (in particular with the National Malaria Control Program (NMCP) and the Department for Planning & Information (DPI)) as well as through Sub-Recipients (SRs). The main responsibilities of the MoHS under this grant include: prompt & effective treatment, including procurement and supply management (PSM) and health worker training; home management of malaria (HMM); and malaria in pregnancy prevention and treatment. The overall goal of the Global Fund Round 10 Malaria project is: *to achieve the malaria-related Millennium Development Goals (MDGs) by 2015, not only by national aggregate, but also among the poorest groups across Sierra Leone* [1].

To achieve this, all stake holders must have an understanding of current barriers, opportunities as well as knowledge, attitudes and practices (KAP) relating to malaria and malaria control. As a national malaria KAP study has never been conducted in Sierra Leone, one of the first activities to be conducted under this grant was a nationwide survey carried out in January 2012. The 2012 KAP study provided much needed information to guide malaria control endeavours in Sierra Leone and also served as a baseline for the subsequent 2012 and 2014 combined Malaria Indicator Survey (MIS)/KAP studies and was the first survey to pilot the use of iPhones for data collection in Sierra Leone. Key partners in the malaria KAP study were the Ministry of Health and Sanitation (NMCP & DPI), Statistics Sierra Leone and Catholic Relief Services.

The focus of the KAP survey was primarily to understand the level of knowledge of households as well as what prevention and treatment practices they embrace. With regard to malaria treatment, questions focused on the knowledge and treatment seeking behaviour and whether they received timely and effective treatment. Although questions were asked with regard to how antimalarials were taken, this part of the survey has to date not been fully analysed. The aim of this additional analysis is to comprehensively examine the data to identify potential determinants of adherence to ACT in Sierra Leone.

2 KAP Study Objectives

The overall goal of the KAP Study was to gather information which will inform the national communication strategy for Behaviour Change Communication and Information Education and Communication. Information from this study will be used to create a communication strategy to be implemented with support from the Global Fund. Follow-up MIS/KAP studies will assess the impact of Behaviour Change Communication/Information, Education and Communication (BCC/IEC) activities funded by the Global Fund and serve to inform modifications of communication strategies and mass media messaging by NMCP and its partners.

Specific Objectives

- To determine the current knowledge, attitudes and practices of households to the recommended malaria prevention and treatment strategies
- To determine to what extent communities are accessing the needed malaria prevention and treatment services and identify any facilitators and/or barriers to that access.
- To determine which prevention and treatment practices and/or behaviours communities are already practicing and to determine which practices beneficiaries are more inclined to adopt and why.
- To document the perspectives and perceptions of communities that may positively or negatively impact malaria control efforts.
- To determine the primary sources for information concerning malaria prevention and treatment practices and behaviours and/or other key channels that might be useful for the roll out of the behaviour change strategy.
- To ascertain whether certain groups within the population (e.g. disaggregated on the basis of gender, socio-economic status, district, etc.) have lower rates of adoption and why.

3 Adherence to ACTs

In 2005, Yeung and White wrote a comprehensive review about how antimalarials were used by patients. Although comprehensive, it was done in the infancy of the ACT era [2]. At the time of the review, a total of 24 studies were identified, half of which were conducted in Africa and the other half in Asia and South America. Eight of the cited studies looked at artemisinin-based treatments, two of which looked only at monotherapies [3, 4]. The remaining six studies looked at Artemisinin-based Combination Therapies; four in Asia [5-8] and two in Africa [9, 10]. Only the study carried out in Uganda looked at a co-formulated ACT (AL) [10]. Results for adherence varied,

but were generally better when "interventions focusing on provider knowledge and behaviour, packaging and provision of correct dosage" were implemented. The authors concluded that there was inadequate information on the adherence to ACTs and that there was a need for further studies to determine their effectiveness in Africa as well as to evaluate interventions that may improve effectiveness (i.e. Blister package, co-formulations).

Since then, ACTs, and in particular co-formulated versions of ACTs have been scaled up across Africa. The majority of recent studies have looked primarily at adherence to the combination artemether-lumefantrine, primarily in East or southern Africa [10-25]. The research is even more scant with regard to adherence to amodiaquine-artesunate (AQAS) [26-32]. However, despite its wider availability only two studies (one in Benin and one in Madagascar) have looked at co-formulated AQAS [31, 33-35], with levels of adherence estimated to be 91% and 83.4% respectively. Reported adherence to co-packaged AQ+AS ranged from 48.7% in Sierra Leone to 97% in Ghana [28, 36].

However, it should be noted that the context, delivery system, study design, definitions of adherence and methods of measurement differed across the studies, this heterogeneity may have over or underestimated adherence. Furthermore, very few studies have looked at adherence to any type of ACT in larger populations [11, 36].

Additionally, little is known with regard to the determinants of adherence to ACTs. Findings and trends are not consistent across studies. Demographic factors, such as sex, socio-economic status or age do not seem to be factors strongly or consistently associated with adherence [10, 13, 23, 26, 28, 37]. However, it is important to note that some studies were not actually powered to look at age groups [10] Although two studies [19, 38] did have the power to look at age group, only one found that children less than five were less adherent [19] the other found no association between age and adherence [38].

Strategies, such as co-packing antimalarials, have been shown to improve adherence, however they do not reduce the number of tablets or the frequency at which the drugs need to be taken (Connor, Rafter et al. 2004; Orton and Barnish 2009). To further improve the efficacy and effectiveness of ACTs co-formulated versions (combining medications into the same tablet) have been produced to address dose frequency and quantity of medications.

Factors surrounding the administration of the drugs, and patient knowledge of dose or preference for a specific drug [17, 19, 27, 38], signs and symptoms of patients [38] and literacy [13, 18, 37] have

been found to be associated with ACT adherence. Factors that have to do with dispensing ACT such as package, simplicity, and number of pills (thought to make a difference) are not prominent factors investigated. However, one study found that giving the exact number of tablets for the prescribed dose was associated with adherence [27] Almost all of the patients in a Tanzanian study reported that the pictogram and the blister packaging were helpful, but the impact of this on adherence was not assessed [16].

This limited information on adherence is particularly important for Sierra Leone as the ACT of choice in Sierra Leone is amodiaquine plus artesunate (AQ+AS). To further understand the effectiveness of ACTs in Sierra Leone, Médecins Sans Frontières (MSF) conducted a study on the adherence to co-packaged AQ+AS, which concluded that despite efforts to improve access to ACTs, patient adherence was low with only 48.7% probably or definitely adherent (Gerstl, Dunkley et al. 2010). Recently the NMCP has decided to also provide a limited number of health facilities with co-formulated (also termed fixed-dose combination [FDC]) Amodiaquine + Artesunate as a pilot prior to larger scale introduction; however this has not been formally evaluated.

4 Objectives of the Additional analysis

- To calculate population adherence to Artemisinin-based Combination Therapy (ACT) in Sierra Leone
- To identify the determinants of adherence to ACT at the population level in Sierra Leone.

5 Study Population and Site

Sierra Leone, located on the West Coast of Africa, is subdivided into 14 administrative districts, two of which (Western Urban and Rural) encompass the greater Freetown area. The population at the 2004 Census consisted of 4.9 million people and was projected to be roughly 6,037,660 people by 2011 [39]. Under 15 year olds are estimated to constitute 49% of the population [40]. There are two major seasons, a summer rainy season (May to October) with heavy rains in July and August, and a winter dry season (November to April).

Malaria is endemic in Sierra Leone, with stable and perennial transmission in all parts of the country. Malaria accounts for about 40% of outpatient morbidity [41]. In 2010, only 46% of children under five who sought care at public health facilities received prompt and effective treatment for malaria with the first line malaria treatment: AQ+AS [41]. More recent data from

the fourth Sierra Leonean Multiple Indicator Cluster Survey (MICS4) suggest that this number has not changed much with only around half of children under 5 being treated with any antimalarial the same or next day from the onset of fever [42].

6 Survey Design & Methods

Sampling & Sample Size

Using the 2004 census sampling frame, a two stage cluster design was used to generate a probability sample of households within each of the 14 administrative districts in Sierra Leone (survey domains). During the first stage of sampling, thirty (30) clusters (Enumeration Areas-EAs) were randomly selected per survey domain (420 clusters total). An EA was defined as a city block in urban areas and a village, part of a village or a group of villages in the rural areas; each EA was approximately 200 households. The sampling frame was stratified by urban and rural areas to obtain a sample that is proportional to population size.

Each of the 420 clusters were enumerated in December 2011 and a household listing was produced in January 2012. The second stage of sampling used the household listing to randomly select 14 households per cluster for participation in the survey. The study protocol was approved by the Sierra Leone Ethics and Scientific Review Committee prior to commencement of activities.

Due to lack of data for most malaria indicators, values were conservatively estimated to be 50%. Therefore, a sample size of 420 households per district was used; 5,880 households nationally. Calculations were made using a 95% confidence level, a .07 level of precision and accounted for a contingency of 5% in order to compensate for refusal to participate or data quality issues. As a cluster design was utilized, a design effect of 2 was also applied.

KAP Data Collection & Analysis

The survey used the Roll Back Malaria, Malaria Indicator Survey questionnaire and had four sections: demographics, Head of Household knowledge and practice, women of child bearing age knowledge and practice and a treatment seeking section for children under 5. The data collection tool for the KAP study can be found in Appendix A.

Data was collected using Apple iPhones. The devices were programmed using the iFormBuilder mobile platform. All electronic data was transferred from the Apple devices into a cloud database regularly while in the field using the local 3G mobile network. Upon completion of the fieldwork, any

remaining forms that needed to be transferred were uploaded via wireless internet connections at Statistics Sierra Leone and CRS offices in Freetown.

Paper questionnaires were provided to teams to use only as a backup in case of electronic equipment failure. When necessary, data entered onto paper forms were then entered into an iPhone as soon as it was possible. Back-up files of the database were stored on two external servers (iFormBuilder and a specially created Google email account) as well as stored on the iPhones. For quality control, validation and built in skip logic was written into the iFormBuilder program.

Data were cleaned and analysed using Excel and STATA statistical software packages. Descriptive statistics were used to summarize survey data. When applicable, categorical variables were compared using chi-square tests or Fisher's exact tests. In such instances a p-value of < 0.05 was considered significant. Principle Component Analysis (PCA) was used to create the Socioeconomic Status (SES) index [43].

Consent

All district, chiefdom, village community leaders, and village committees/councils were informed of the survey. Village leaders and committee's will helped create awareness of the study within their communities. As per the Ministry of Health and Sanitation normal operating procedures for national household surveys, witnessed verbal consent was obtained from each respondent prior to administration of the questionnaire. Respondents were informed that participation in the study is completely voluntary and that they could refuse to answer a question or discontinue their participation at any time without penalty.

Confidentiality

Each household was given a unique identification number that did not contain personal identifiers. The information obtained from interviews was only used by the project researchers and stored in password protected databases and paper forms were stored in a secure location within the CRS office in Freetown. Every effort was made to ensure that the personal information gathered for this study was kept confidential.

Risks and Discomforts

This study was a descriptive study; there were no anticipated risks or discomforts. Participants were asked to volunteer their time (up to 1 hour) and could discontinue involvement at any time.

Ethical Considerations

The KAP study protocol was approved by the Sierra Leone Ethics and Scientific Review Committee (Appendix B).

7 Summary of KAP Results

A total of 5,169 households were approached and the head of household and one woman of child bearing age per household were interviewed. Overall knowledge of malaria is higher than was expected. Factors such as age, gender, education and socioeconomic status do play into different aspects of knowledge and should be considered when designing the malaria communication strategy. The greatest knowledge was centred on malaria prevention. This is most likely due to the nationwide universal coverage campaign that took place in late 2010.

Information around malaria signs and symptoms appears to be confusing. Danger signs are not differentiated and this could be an important intervention area. Key messages on danger signs that are simple and clear are recommended.

Knowledge about the drugs that are used to treat malaria was low, with less than half of respondents citing ACT as a drug to treat malaria (47.2%; 95%CI [44.7 to 49.7]). Answers were similar for all ages. Women were significantly more likely to mention ACT (52.3%; 95%CI [49.3% to 55.2%]) compared to men (42.2%; 95%CI [39.2% to 45.3%]; p <0.001). Respondents with any education (54.4% vs. 43.2%) and higher socioeconomic status (60.9% vs. 36.5%) were also significantly more likely to know ACT compared to the poorest or least educated respondents (p= <0.001 for both).

Brand or name recognition seems low and this may be due, in part, to a lack of sufficient drugs or the availability of multiple brands of ACTs through the public health system as a result of receiving ACT from multiple sources in order to fill gaps in drug supply. ACT in Sierra Leone is currently available with various trade names, packaging, doses and even formulations.

Despite the fact that Chloroquine is not recommended to treat malaria in Sierra Leone, 41.6% (95%CI [39.2% to 44.0%]) still mentioned it as a drug to be used. Two thirds of respondents mentioned that traditional medicines and herbs are used to treat malaria. Respondents mentioning herbs were more likely to be women either without education or in the lowest

economic group. Other drugs cited were panadol/paracetamol (45.9%; 95%CI[43.2% to 48.6%]), SP/Fansidar (27.6%; 95%CI[25.5% to 29.8%]), aspirin (8.2%; 95%CI[7.0%

Treatment Seeking Results

The treatment seeking section of the questionnaire was administered to 1,528 caretakers of children under five who had fever in the last two weeks to measure knowledge of malaria medications and to measure treatment seeking behaviour for fever. Due to the novelty of using iPhones for data collection in Sierra Leone only 1,427 households had complete records and were included in the analysis.

In the 1,427 households, there were 1,641 children that had fever in the two weeks preceding the survey. Sixty-three percent of all caretakers sought treatment for the child, and there were no significant differences in the proportion seeking treatment based on the district of residence, household education or socioeconomic status. Caregivers primarily sought treatment from public health facilities (hospitals 30.8% or PHUs 51.3%).

Of those seeking treatment, 94.6% received medication for that fever. There were no differences by district, educational level or socioeconomic status. Less than half (47.4% received ACT, the nationally recommended treatment. Chloroquine, although no longer recommended, was still reported by almost half (48.7%) of all caretakers.

Of those receiving ACT for treatment, none except for one child received ACT on the same day as the onset of fever. Two thirds (67.3%) reported to have received ACT the next day after the onset of fever; and 19.6% received ACT within 48 hours. Only 47% of caretakers of children under 5 receiving ACT, reported that ACT was given for the correct duration (3 days).

8 Analysis Plan

During the initial phase of the analysis only the number of days children took ACT was examined. The primary outcome for this analysis will be adherence to ACT by caregivers with children under 5 receiving ACT in Sierra Leone. Adherence will be defined as taking the treatment for 3 days. This additional analysis will also explore factors associated with adherence to ACT.

First a univariate analysis of potential factors that may have influenced adherence to ACT (specifically: knowledge of malaria treatment, demographic and socioeconomic factors, treatment source, time to treatment, age of child and caregiver) will be conducted.

Following this, the factors that are deemed to have an association with adherence based on the statistical significance ($p < 0.1$) in the univariate analysis will be included in a multivariable logistic regression model to determine the effect of various factors on adherence after adjusting for covariates.

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10 KAP Appendices

Appendix A: Sierra Leone KAP Survey Tool

Sierra Leone KAP Survey
Catholic Relief Services & National Malaria Control Program
January 2012

No.	A. Household Identification	
A1.	Region…….	☐
A2.	District……	☐☐
A3.	Chiefdom name and code:_____	☐☐☐☐
A4.	Village/Neighborhood Name: _____	
A5.	Cluster/EA Number……	☐☐☐☐☐☐☐☐
A6.	Household Number……..	☐☐
A7.	Urban or Rural……	☐
A8.	GPS Coordinates…….	Not Applicable for Paper version.
A9.	Name of Household Head:_____	

		Visits		
		1	2	Final
	Name of Interviewer:	_____	_____	_____
	Date of Interview:	_____	_____	_____
	Result*	☐	☐	☐
	*RESULT CODES: 1 COMPLETED 2 NO HOUSEHOLD MEMBER AT HOME OR NO COMPETENT RESPONDENT AT HOME AT TIME			

	OF VISIT 3 ENTIRE HOUSEHOLD ABSENT FOR EXTENDED PERIOD OF TIME 4 POSTPONED 5 REFUSED 6 DWELLING VACANT OR ADDRESS NOT A DWELLING 7 DWELLING DESTROYED 8 DWELLING NOT FOUND 9 OTHER (SPECIFY) _____
	INFORMED CONSENT Hello. My name is _____and I am working with the Ministry of Health & Sanitation, Statistics Sierra Leone and Catholic Relief Services. We are conducting a national survey about malaria. We would very much appreciate your participation in this survey. The information you provide will help the government to plan health services. The survey usually takes around 30 minutes to complete. Whatever information you provide will be kept strictly confidential and will not be shown to other persons. Participation in this survey is voluntary and you can choose not to answer any individual question or all of the questions. However, we hope that you will participate in this survey since your views are important. At this time, do you want to ask me anything about the survey? May I begin the interview now?
	INFORMED CONCENT OBTAINED Yes☐ No☐ ⟶> END
	Signature of interviewer: _____ Date:_____
	Please complete the following information for the paper version.
	Name of Supervisor: _____
	Survey Checked by Supervisor? Yes ☐ No ☐

B. Household Demographic Information

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B1	How many people live in this Household? *Household Members are defined as those who <u>regularly</u> eat from the same pot*.	☐☐	
B2	How many are Male?	☐☐	
B3	How many are Female?	☐☐	
B4	How many children are <5 years of age are in the Household?	☐☐	
B5	How many children are 5-14 years of age are in the Household?	☐☐	
B6	How many household members are 15 years and above?	☐☐	
B7	How many women of child bearing age 15-49 are in the Household?	☐☐	
B8	How many women of child bearing age 15-49 in the Household are currently pregnant?	☐☐	
B9	What is the main language spoken in this household?	Krio.....1 Mende.....2 Temne.....3 Limba.....4 Fullah .....5 Kissi.....6 Susu.....7 Loko.....8 Kono.....9 Madingo.....10 English.....11 Other (specify)_____ _____.....12	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B10	What is the main religion in this household?	Christian……1 Muslim……2 Other (specify)_____.....3	
B11	For the **head of household**, what is the highest level of school attended: primary, secondary, or higher?	No Schooling……0 Primary ..... 1 Secondary ..... 2 Higher ..... 3 Technical/Vocational School……..4 Other (specify)_____.5	
B12	What is the main source of drinking water for members of your household?	Piped water……1 Tube well or borehole..... 2 Dug well……3 Water from spring……4 Rainwater..... 5 Tanker truck..... 6 Cart with small tank..... 7 Surface water (river/dam/ lake/pond/stream/canal/ irrigation channel..... 8 Bottled water..... 9 Plastic bag…… 10 Other (specify)_____ 11	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B13	What kind of toilet facility does your household use?	Flush or pour flush toilet……1 Pit latrine……2 Pit latrine without slab/open pit……..3 Composting toilet .....4 Bucket toilet.....5 Hanging toilet/hanging latrine.....6 No facility/bush/field .....7 Other (specify)_____ …..8	
B14	Does your household have the following assets?	YES NO	
	Electricity from grid?	Electricity/NPA.....1 2	
	A generator?	Generator…… 1 2	
	Solar panels?	Solar panels…… 1 2	
	A radio?	Radio.....1 2	
	A television?	Television 1 2	
	A mobile telephone?	Mobile telephone 1 2	
	A refrigerator?	Refrigerator 1 2	
	An electric iron?	Iron 1 2	
	A bicycle?	Bicycle……1 2	
	A motorcycle or scooter?	Motorcycle/scooter 1 2	
	A cow, goat, or sheep?	Cow/goat/sheep…… 1 2	
	A canoe or boat?	Canoe/boat……1 2	
	An electric fan?	Fan 1 2	
	A domestic worker (unrelated to household head)?	Domestic worker……1 2	
	A CD or cassette player?	Cd/cassette player 1 2	
	A plough?	Plough……1 2	
	A vehicle (car or truck)?	Vehicle 1 2	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B15	What type of fuel does your household mainly use for cooking?	Electricity/NPA.....1 LPG/Natural gas.....2 Biogas.....3 Kerosene.....4 Charcoal.....5 Firewood/straw.....6 Dung.....7 Other (specify)_____ 8	
B 16	Main material of the floor. RECORD OBSERVATION.	Natural floor Earth/sand.....11 Dung.....12 Rudimentary floor Wood planks.....21 Palm/bamboo.....22 Finished floor Parquet or polished wood.....31 Vinyl or asphalt strips.....32 Ceramic tiles.....33 Cement.....34 Carpet.....35 Other (specify) _____ 36	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B17	Main material of the roof. RECORD OBSERVATION.	Thatch ..... 11 Bamboo..... 12 Wood ..... 21 Tarpaulin ..... 22 Iron sheets ..... 31 Concrete ..... 32 Other (specify) _____ 33	
B18	Does any member of the household own any agricultural land?	Yes.....1 No.....2	
B19	Does this household own any livestock, herds other farm animals, or poultry?	Yes.....1 No.....2	
B20	Does your household have any mosquito nets ("tent") that can be used while sleeping?	Yes.....1 No.....2	→**C1**
B21	How many mosquito nets does your household have? IF 7 OR MORE NETS, RECORD '7'.	☐	
B22a	Are any of the mosquito nets in your household treated with medicine?	Yes.....1 No.....2 Don't Know.....99	→**C1** →**C1**
B22b	How many of the mosquito nets in your house are treated with Medicine?	☐	
B23	Did you sleep under a treated mosquito net last night?	Yes.....1 No.....2 Don't Know.....99	→**B25** →**B25**
B24	Why did you sleep under the treated mosquito net last night? MULTIPLE RESPONSES POSSIBLE	Protect from malaria.....1 Prevent mosquito bites.....2 Prevent other insects from disturbing me…3 Other	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
		(specify)_____..... 4 Don't know……..99	
B24b	In general, how often do you sleep under a treated mosquito net?	Always ……1 Sometimes…….2 Never…….3	
B25	Did any other household members sleep under a treated mosquito net last night?	Yes……1 No……2 Don't know…….....9	 →**C1** →**C1**
B26	Who are all the people who slept under a treated mosquito net last night? MULTIPLE RESPONSES **PROBE ONCE (ANYTHING OTHERS?)**	Children under 5……1 Other children……2 Pregnant woman…….. 3 Other Adult……4 Elderly……5 Other (specify)_____ …….6	
B27	In general, how often do your children under 5 sleep under a treated mosquito net?	Always ……1 Sometimes…….2 Never…….3	→**C1**
B28	Why do the children under 5 who sleep in this house sometimes **NOT** sleep under a treated mosquito net? MULTIPLE RESPONSES **PROBE ONCE (ANYTHING ELSE?)**	Too hot……..1 Too cold……2 Child afraid……3 Child cries……4 Not enough nets……5 Net not hung up……6 Used by adults……7 Net not used when traveling……8 Net worn out / poor condition……9 Nets bad for childens' health……10 Other (specify)_____ …..11 Don't know……99	

C. Household Knowledge

****This can be either the head of household or their representative****

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
C-I	Gender of Respondent	Male.....1 Female.....2	
C-II	How old are you (*in completed years*)?	☐☐	
C-III	What is the highest level of education you have reached?	No Schooling……0 Primary.....1 Secondary.....2 Higher.....3 Technical/Vocational School……4 Other (specify)_____.5	
C1	Have you ever heard of an illness called malaria? ➔ **PROMPT** using local name for malaria	Yes.....1 No.....2	 ➔ **C14**
C2	Can you tell me the main signs or symptoms of malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Fever/Excessive sweating……1 Feeling cold/chills……2 Headache……3 Nausea and Vomiting……4 Diarrhea……5 Dizziness……6 Loss of appetite……7 Body ache or joint pain……8 Pale eyes……9 Body weakness……10 Refusing to eat or drink……11 Other (Specify)_____..12 Don't know……99	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
C3	Can you tell me danger signs or symptoms for severe malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Shaking/Convulsions……1 Vomiting everything……2 Confusion……3 Low blood (severe anemia)……4 Difficulty Breathing……5 Dizziness……6 Other (Specify)_____..7 Don't Know……99	
C4	In your opinion, what causes malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Mosquito bites……1 Eating immature sugarcane……2 Eating cold food……3 Eating other dirty food……4 Drinking beer or palm wine……5 Drinking dirty water……6 Getting soaked with rain……7 Cold or changing weather……8 Witchcraft……9 Injections/Drugs……10 Eating oranges or mangos……11 Eating plenty oil……12 Sharing razors/blades……13 Bed bugs……14 Other (Specify)._____....15 Don't know……99	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
C5	How can someone protect themselves against malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Sleep under a mosquito net……..1 Sleep under Treated net……..2 Use mosquito repellent……..3 Avoid mosquito bites……..4 Take preventive medication……..5 Spray house with insecticide……..6 Use mosquito coils……..7 Cut the grass around the house……8 Fill in puddles (stagnant water)……9 Keep house surroundings clean……10 Burn leaves……11 Don't drink dirty water……..12 Don't eat bad food (immature sugarcane/leftover food)……13 Put mosquito screens on the windows…..14 Don't get soaked with rain……..15 Other (Specify)_____.....16 Don't know……99	
C6	In your opinion, which people are most affected by malaria in your community? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Everyone……1 Children……..2 Adults……..3 Pregnant women……4 Older adults……5 Other (specify)_____....6 Don't know.....99	
C7	What drugs are used to treat malaria? CIRCLE ALL ANSWERS MENTIONED	ACT ……1 Chloroquine……2 SP/Fansidar……..3 Quinine ……4 Aspirin. ……5 Panadol/Paracetomol……6 Traditional medicine/Herbs……7 Other	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
		(specify)_____.....8 Don't know……99	
C8	Have you ever heard or seen any messages / information about malaria?	Yes.....1 No.....2	→ **SEC D**
C9	Where did you see or hear these messages/information? MULTIPLE RESPONSES POSSIBLE **PROBE ONCE (ANYTHING ELSE?)**	Government clinic/hospital……..1 Community health worker……2 Friends/family……3 In my home……4 Drama groups……5 Peer educators……6 Community meeting……7 Town crier……8 Posters/billboards……9 On TV……10 On the radio……11 In the newspaper……12 Faith/religious leader……13 Other (specify)_____..14 Don't know……99	
C10	How long ago did you see or hear these messages? (If Don't Know enter 99)	☐☐ COMPLETED MONTHS	
C11	What language was used to deliver the message? MULTIPLE RESPONSES	Krio.....1 Mende……2 Temne……3 Limba……4 Fullah ……5 Kissi……6 Susu……7 Loko……8 Kono……9 Madingo……10 English……11 Other (specify)_____.....12	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
C12	How many times did you hear this message?	Once.....1 Twice.....2 More than Twice.....3 Don't Know.....99	
C13	What type of malaria messages/information did you see or hear? MULTIPLE RESPONSES POSSIBLE **PROBE ONCE (ANYTHING ELSE?)**	Fight Malaria.....1 Malaria is dangerous.....2 Malaria can kill.....3 Mosquitoes spread malaria.....4 Sleeping under mosquito net important.....5 Who should sleep under mosquito net.....6 Seek treatment for fever.....7 Seek treatment for fever within 24 hours/promptly.....8 Importance of house spraying.....9 Not plastering walls after spraying.....10 Environmental sanitation activities.....11 Other (specify)_____.....12 Don't know.....99	
Proceed to women's questionnaire. Randomly select one eligible woman and complete the women's survey. If no eligible women in the house hold please thank the respondent for their time, the survey is complete.			
C14	Is there an eligible Woman (age 15-49) that agrees to be interviewed?	Yes.....1 No.....2	→ **SEC D** → **END**

D. Women's Questionnaire

A2.	District……	☐☐
A3.	Chiefdom name and code:_____	☐☐☐☐
A5.	Cluster/EA Number……	☐☐☐☐☐☐☐☐
A6.	Household Number……..	☐☐

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D1	What is the woman's Name?	_____	
D2	How old are you (*in completed years*)?	☐☐	
D3	What is the highest level of education you have reached?	No Schooling……0 Primary .....1 Secondary .....2 Higher .....3 Technical/Vocational School……4 Other (specify)_____.....5	
D4	Has this woman already answered the knowledge questions in section C?	YES.....1 NO.....2	→**D18**
D5	Have you ever heard of an illness called malaria?	YES.....1 NO.....2	→**D18**

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D6	Can you tell me the main signs or symptoms of malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Fever/Excessive sweating……1 Feeling cold/chills……2 Headache……3 Nausea and Vomiting……4 Diarrhea……5 Dizziness……6 Loss of appetite……7 Body ache or joint pain……8 Pale eyes……9 Salty tasting palms……10 Body weakness……11 Refusing to eat or drink……12 Other (Specify)_____..13 Don't Know……99	
D7	Can you tell me danger signs or symptoms for severe malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Shaking/Convulsions……1 Vomiting everything……2 Confusion……3 Low blood (severe anemia)……4 Difficulty Breathing……5 Dizziness……6 Other (Specify)_____..7 Don't Know……99	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D8	In your opinion, what causes malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Mosquito bites……1 Eating immature sugarcane……..2 Eating cold food……..3 Eating other dirty food……..4 Drinking beer or palm wine……..5 Drinking dirty water……..6 Getting soaked with rain……..7 Cold or changing weather……8 Witchcraft……9 Injections/Drugs……10 Eating oranges or mangos……11 Eating plenty oil……12 Sharing razors/blades……13 Bed bugs……14 Other (Specify)._____....15 Don't know.....99	
D9	How can someone protect themselves against malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Sleep under a mosquito net……..1 Sleep under Treated net……..2 Use mosquito repellent……..3 Avoid mosquito bites……..4 Take preventive medication……..5 Spray house with insecticide……6 Use mosquito coils……..7 Cut the grass around the house……8 Fill in puddles (stagnant water)……9 Keep house surroundings clean……10 Burn leaves……11 Don't drink dirty water……12 Don't eat bad food (immature sugarcane/leftover food)……13 Put mosquito screens on the windows…..14 Don't get soaked with rain……..15 Other (Specify)_____.....16 Don't know……99	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D10	In your opinion, which people are most affected by malaria in your community? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Everyone……………………………………1 Children……………………………………2 Adults………………………………………3 Pregnant women…………………………4 Older adults………………………………5 Other (specify)________________________...6 Don't know…………………………………99	
D11	What drugs are used to treat malaria? CIRCLE ALL ANSWERS MENTIONED	ACT ……………………………………… …..1 Chloroquine ……………………………………2 SP/Fansidar ……… ……………………………3 Quinine ……… …………………………………4 Aspirin……………………………………………5 Panadol …../Paracetomol………………………6 Traditional medicine/Herbs……………….7 Other (specify)________________________.....8 Don't know…………………………………99	
D12	Have you ever heard or seen any messages / information about malaria?	Yes……………………………………………1 No………………………………………………2	 →D18
D13	How long ago did you see or hear these messages? (If Don't Know enter 99)	☐☐ COMPLETED MONTHS	
D14	What language was used to deliver the message? MULTIPLE RESPONSES	Krio…………………………………………………1 Mende…………………………………………2 Temne…………………………………………3 Limba…………………………………………4 Fullah …………………………………………5 Kissi……………………………………………6 Susu……………………………………………7 Loko……………………………………………8 Kono……………………………………………9 Madingo……………………………………10 English………………………………………11 Other (specify)______________________.....12	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D15	How many times did you hear this message?	Once.....1 Twice.....2 More than Twice.....3 Don't Know.....99	
D16	Where did you see or hear these messages/information? MULTIPLE RESPONSES POSSIBLE **PROBE ONCE (ANYTHING ELSE?)**	Government clinic/hospital.....1 Community health worker.....2 Friends/family.....3 In my home.....4 Drama groups.....5 Peer educators.....6 Community meeting.....7 Town crier.....8 Posters/billboards.....9 On TV.....10 On the radio.....11 In the newspaper.....12 Faith/religious leader.....13 Other (specify)_____..14 Don't know.....99	
D17	What type of malaria messages/information did you see or hear? MULTIPLE RESPONSES POSSIBLE **PROBE ONCE (ANYTHING ELSE?)**	Fight Malaria.....1 Malaria is dangerous.....2 Malaria can kill.....3 Mosquitoes spread malaria.....4 Sleeping under mosquito net important.....5 Who should sleep under mosquito net.....6 Seek treatment for fever.....7 Seek treatment for fever within 24 hours/promptly.....8 Importance of house spraying.....9 Not plastering walls after spraying.....10 Environmental sanitation activities.....11 Other (specify)_____.....12 Don't know.....99	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D18	Have you ever been pregnant?	Yes.....1 No.....2	 → **D36**
D19	Have you been pregnant in the last 2 years?	Yes.....1 No.....2	 → **D36**
D20	Are you pregnant now?	Yes.....1 No.....2 Don't know.....9	 → **D28** → **D28**
D21	How many months pregnant are you?	I____I I____I completed months *If don't know, enter '99'*	
D22	Have you received any antenatal care during this pregnancy?	Yes.....1 No.....2 Don't know.....9	 → **D24** → **D24**
D23	From whom did you first receive antenatal care?	Hospital.....1 Clinic (PHU).....2 TBA (traditional birth attendant).....3 BFV (blue flag volunteer).....4 Herbalist.....5 Spiritual.....6 Drug peddler.....7 Drug Shop/Pharmacy.....8 Private Doctor.....9 Other (specify)_____....10	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D23b	Did you receive antenatal care from anyone else? *(i.e. Where did they go next?)*	Didn't receive additional care……..…..0 Hospital……1 Clinic (PHU)……..2 TBA (traditional birth attendant)……..3 BFV (blue flag volunteer)……4 Herbalist……..5 Spiritual……..6 Drug peddler……..7 Drug Shop/Pharmacy……8 Private Doctor……9 Other (specify)_____....10	
D24	Have you taken any medication to prevent malaria during this pregnancy?	Yes.....1 No.....2 Don't know……9	 → **D28** → **D28**
D25	If yes, what type of medicine did you take? ***Circle all that apply***	Don't know the type……..0 SP/Fansidar……1 Chloroquine……2 Other (Specify)_____.....3	
D26	For how many days did you take this medicine?	Just 1 day……1 2 days……..2 3 days or more……3 Don't know……9	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D27	Where did you get the medication?	Hospital……1 Clinic (PHU)……..2 TBA (traditional birth attendant)……..3 BFV (blue flag volunteer)……4 Herbalist……..5 Spiritual……..6 Drug peddler……7 Drug Shop/Pharmacy……8 Private Doctor……9 Other (specify)_____....10	
D28	Have you had any other pregnancies in the last two years?	Yes.....1 No.....2 Don't know……9	 → **D36** → **D36**
D29	How many months ago was your last pregnancy?	I____I I____I completed months *If don't know, enter '99'*	
D30	Did you receive any antenatal care during your last pregnancy?	Yes.....1 No.....2 Don't know……9	 → **D32** → **D32**
D31	From whom did you first receive antenatal care?	Hospital……1 Clinic (PHU)……..2 TBA (traditional birth attendant)……..3 BFV (blue flag volunteer)……4 Herbalist……..5 Spiritual……..6 Drug peddler……7 Drug Shop/Pharmacy……8 Private Doctor……9 Other (specify)_____....10	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D31b	Did you receive antenatal care from anyone else? *(i.e. Where did they go next?)*	Didn't receive additional care……..…..0 Hospital……1 Clinic (PHU)……..2 TBA (traditional birth attendant)……...3 BFV (blue flag volunteer)……4 Herbalist……..5 Spiritual……..6 Drug peddler……..7 Drug Shop/Pharmacy……8 Private Doctor……9 Other (specify)_____....10	
D32	Did you take any medication to prevent malaria during your last pregnancy?	Yes.....1 No.....2 Don't know……9	→ **D36** → **D36**
D33	If yes, what type of medicine did you take? ***Circle all that are mentioned**	Don't know the type……..0 SP/Fansidar……1 Chloroquine……..2 Other (Specify)_____....3	
D34	For how many days did you take this medicine?	Just 1 day……1 2 days……..2 3 days or more……3 Don't know……..9	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
D35	Where did you get the medication?	Hospital……1 Clinic (PHU)……..2 TBA (traditional birth attendant)……..3 BFV (blue flag volunteer)……4 Herbalist……..5 Spiritual……..6 Drug peddler……7 Drug Shop/Pharmacy……8 Private Doctor……9 Other (specify)_____....10	
D36	Are you the primary care-taker for any child(ren) under 5?	Yes.....1 No.....2	→ **END**
D37	How many children under 5 do you care for?	☐☐	
D38	How many children under 5 that you care for had fever in the last 2 weeks?	☐☐	**IF 0 → END**

E. Care-seeking Questionnaire for Children under 5

***** Complete one (1) care-seeking questionnaire for each of the children from D38.Start with the youngest child (under 5 years), then proceed up to a maximum of 3 children < 5 with fever in the last 2 weeks.***

Child #1

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
E1	Child #1's name _____		
E2	What is the age of your child *(years)*? **only continue for children 4 or less** *Enter '00', if less than 1 year*	☐☐ *completed years*	
E3	Does *(name)* have a fever now?	Yes.....1 No.....2 Don't know.....9	 → **E5** → **E5**
E4	How many days ago did the fever start? *If the fever started today, enter '00'* *If don't know, enter '99.*	☐☐ *Days*	
E5	Did you seek advice or treatment for *(name's)* fever?	Yes.....1 No.....2 Don't know.....9	 → **E14** → **E14**
E6	How soon did you seek advice or treatment for (name's) fever?	Same day.....1 Next day.....2 Two days.....3 3 days or more days.....4 Don't know.....9	

E7	Where did you **first** go for treatment?	Hospital……..1 Clinic (PHU)……..2 CBP……3 TBA……4 BFV……5 Herbalist……6 Spiritual……7 Drug peddler/pepper doctor/quack……8 Drug Shop/Pharmacy……9 Private Doctor……10 Other (Specify)_____.11	
E8	Who decided that you should go there for treatment for *(name's)* fever?	Self……1 Husband……2 In-laws……3 Family Member……4 Friend……5 Health Worker……6 Other (Specify)_____..7	
E9	Where did you go **next** for treatment?	Didn't seek second treatment……..0 Hospital……1 Clinic (PHU)……2 CBP……3 TBA……4 BFV……5 Herbalist……6 Spiritual……7 Drug peddler/pepper doctor/quack……8 Drug Shop/Pharmacy……9 Private Doctor……10 Other (Specify)_____.11	
E10	Was *(name)* treated with any medicine during his/her fever?	Yes……1 No……2 Don't know……9	 → **END** → **END**

	Medicine Name (show job aide with medicine)	**E11**. Did *(child name)* take *(medicine name)* during his or her fever? No……0 → **skip to next type of medicine** Yes…….1	**E12** How many days after the fever started did *(child name)* start taking *(medicine name)*? Same day……..0 Next day……..1 Two days ……2 Three days or more.....3 Don't know……4	**E13**. For how many days did *(child name)* take *(medicine name)*? *If 'don't know', enter '99'*
a.	Chloroquine (syrup or tablets)			I__I I__I *days*
b.	ACT (tablets)			I__I I__I *days*
c.	Panadol (syrup or tablets)			I__I I__I *days*
d.	Herbs/Traditional Medicine			I__I I__I *days*
e.	Fansidar (tablets)			I__I I__I *days*
f.	Other (Specify)_____			I__I I__I *days*

E14	Are there any additional Children under 5 years of age with fever in the last 2 weeks?	Yes.....1 No.....2	→ **END**

Child #2

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
E1-2	Child #2's name _____		
E2-2	What is the age of your child *(years)*? **only continue for children 4 or less** *Enter '00', if less than 1 year*	☐☐ *completed years*	
E3-2	Does *(name)* have a fever now?	Yes.....1 No.....2 Don't know.....9	 → **E5-2** → **E5-2**
E4-2	How many days ago did the fever start? *If the fever started today, enter '00'* *If don't know, enter '99.*	☐☐ *days*	
E5-2	Did you seek advice or treatment for *(name's)* fever?	Yes.....1 No.....2 Don't know.....9	 → **E14-2** → **E14-2**
E6-2	How soon did you seek advice or treatment for (name's) fever?	Same day.....1 Next day.....2 Two days.....3 3 days or more days.....4 Don't know.....9	

E7-2	Where did you **first** go for treatment?	Hospital……..1 Clinic (PHU)……..2 CBP……3 TBA……4 BFV……5 Herbalist……6 Spiritual……7 Drug peddler/pepper doctor/quack……8 Drug Shop/Pharmacy……9 Private Doctor……10 Other (Specify)_____.11	
E8-2	Who decided that you should go there for treatment for *(name's)* fever?	Self……1 Husband……2 In-laws……3 Family Member……4 Friend……5 Health Worker……6 Other (Specify)_____..7	
E9-2	Where did you go **next** for treatment?	Didn't seek second treatment……..0 Hospital……1 Clinic (PHU)……2 CBP……3 TBA……4 BFV……5 Herbalist……6 Spiritual……7 Drug peddler/pepper doctor/quack……8 Drug Shop/Pharmacy……9 Private Doctor……10 Other (Specify)_____.11	
E10-2	Was *(name)* treated with any medicine during his/her fever?	Yes……1 No……2 Don't know……9	→ **END** → **END**

	Medicine Name (show job aide with medicine)	**E11-2**. Did *(child name)* take *(medicine name)* during his or her fever? No……..0 → **skip to next type of medicine** Yes…….1	**E12-2**. How many days after the fever started did *(child name)* start taking *(medicine name)*? Same day……..0 Next day……..1 Two days ……2 Three days or more.....3 Don't know……..4	**E13-2**. For how many days did *(child name)* take *(medicine name)*? *If 'don't know', enter '99'*
a.	Chloroquine (syrup or tablets)			I__I I__I *days*
b.	ACT (tablets)			I__I I__I *days*
c.	Panadol (syrup or tablets)			I__I I__I *days*
d.	Herbs/Traditional Medicine			I__I I__I *days*
e.	Fansidar (tablets)			I__I I__I *days*
f.	Other (Specify)_____			I__I I__I *days*

E14-2	Are there any additional Children under 5 years of age with fever in the last 2 weeks?	Yes.....1 No.....2	→ **END**

Child #3

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
E1-3	Child #2's name _____		
E2-3	What is the age of your child *(years)*? **only continue for children 4 or less** *Enter '00', if less than 1 year*	☐☐ *completed years*	
E3-3	Does *(name)* have a fever now?	Yes.....1 No.....2 Don't know.....9	 → **E5-2** → **E5-2**
E4-3	How many days ago did the fever start? *If the fever started today, enter '00'* *If don't know, enter '99.*	☐☐ *days*	
E5-3	Did you seek advice or treatment for *(name's)* fever?	Yes.....1 No.....2 Don't know.....9	 → **E14-2** → **E14-2**
E6-23	How soon did you seek advice or treatment for (name's) fever?	Same day.....1 Next day.....2 Two days.....3 3 days or more days.....4 Don't know.....9	

E7-3	Where did you **first** go for treatment?	Hospital……..1 Clinic (PHU)……..2 CBP……3 TBA……4 BFV……5 Herbalist……6 Spiritual……7 Drug peddler/pepper doctor/quack……8 Drug Shop/Pharmacy……9 Private Doctor……10 Other (Specify)_____.11	
E8-3	Who decided that you should go there for treatment for *(name's)* fever?	Self……1 Husband……2 In-laws……3 Family Member……4 Friend……5 Health Worker……6 Other (Specify)_____..7	
E9-3	Where did you go **next** for treatment?	Didn't seek second treatment……0 Hospital……1 Clinic (PHU)……2 CBP……3 TBA……4 BFV……5 Herbalist……6 Spiritual……7 Drug peddler/pepper doctor/quack……8 Drug Shop/Pharmacy……9 Private Doctor……10 Other (Specify)_____.11	
E10-3	Was *(name)* treated with any medicine during his/her fever?	Yes……1 No……2 Don't know……9	→ **END** → **END**

	Medicine Name (show job aide with medicine)	**E11-3**. Did *(child name)* take *(medicine name)* during his or her fever? No……0 → **skip to next type of medicine** Yes…….1	**E12-3**. How many days after the fever started did *(child name)* start taking *(medicine name)*? Same day……..0 Next day……..1 Two days ……2 Three days or more.....3 Don't know……..4	**E13-3**. For how many days did *(child name)* take *(medicine name)*? *If 'don't know', enter '99'*
a.	Chloroquine (syrup or tablets)			I__I I__I *days*
b.	ACT (tablets)			I__I I__I *days*
c.	Panadol (syrup or tablets)			I__I I__I *days*
d.	Herbs/Traditional Medicine			I__I I__I *days*
e.	Fansidar (tablets)			I__I I__I *days*
f.	Other (Specify)_____			I__I I__I *days*

Sierra Leone Ethical Approval

GOVERNMENT OF SIERRA LEONE
Office of the Sierra Leone Ethics and Scientific Review Committee
Directorate of Training, Non-Communicable Diseases and Research
Connaught Hospital
Ministry of Health and Sanitation

16th December, 2011

Ms. Kristin E. Banek
Catholic Relief Services
29 Kingharman Road
Freetown

Dear Ms. Banek,

Sierra Leone Malaria Knowledge, Attitudes and Practices (KAP) Study

This letter refers to the above proposed study submitted for review.

The Committee hereby grants Ethical and Scientific clearance for this study to be conducted in Sierra Leone

The Committee stipulates as follows: that,

1. It must be notified in advance, if you decide to amend the research design and/or methodology at any time during the conduct of the study.
2. It must be informed if for any reason, the study is terminated prematurely.
3. On the conclusion of the study, you submit a report or any publication based on the study.

Yours sincerely,

[redacted]

Professor Hector G. Morgan
Chairman, SLESRC

Email: hgmorg2007@yahoo.com / williettav@yahoo.com

Adherence to Artemisinin-Based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone

Protocol Version: 1.5

Protocol Date: 30 September 2013

Principal Investigator: Kristin Banek, PhD Candidate

Advisors:
Daniel Chandramohan, Professor
Sarah Staedke, Senior Lecturer

Collaborators in Sierra Leone:
Samuel Juana Smith, Programme Manager, NMCP
Anitta Kamara, Case Management Focal Point, NMCP
Musa Kanu, Head of Surveillance, Monitoring & Evaluation, NMCP
Wiltshire Johnson, Director/Register, Pharmacy Board
Sahr Gbomor, Head of Pharmacovigilance, Pharmacy Board

London School of Hygiene and Tropical Medicine
Faculty of Infectious and Tropical Diseases
Department of Clinical Research

1 Study Summary

Title	Adherence to Artemisinin-Based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone
Study design	Open-labelled randomised controlled study
Participants	• Children aged 6 to 59 months and their parents/caregivers • Health workers at the two study sites
Sample size	• 440 (220 per arm) patients & their parent caregivers per study site • 6-12 Health Worker Interviews & 40 parent/caregiver In-depth Interviews
Study site	The study will be conducted at two primary health units (Ross Road & George Brook) in the capital city of Freetown
Selection criteria	1. Patient is a child between 6 to 59 months 2. Visiting health facility for treatment of fever 3. Do not have signs of severe disease 4. Are not being referred to another health facility 5. Living within a defined distance from the health facility (<5 km/ 3 miles) 6. Have not taken part in the study already or are not part of a household that has already taken part in the study 7. Responsible caretakers/parents provide additional informed consent
Study intervention	Participants will be randomized to one of two ACTs and followed up after completion of treatment (4 days): 1. Co-formulated Amodiaquine-Artesunate (AQAS) 2. Co-formulated Artemether-Lumefantrine (AL)
Study Aim	The aim of this study is to measure and compare the level of provider compliance with malaria treatment guidelines and patient adherence to co-formulated AQAS compared to AL under routine conditions in Sierra Leone.

Specific Objectives	1. To evaluate the level of compliance to malaria treatment guidelines by health workers at two government health facilities in Sierra Leone under routine conditions and to assess how health worker compliance may affect patient adherence. 2. To evaluate and compare the level of adherence to co-formulated ASAQ compared to AL for treatment of malaria in children aged 6 to 59 months seeking care at government health facilities in Sierra Leone. 3. To identify determinants of adherence to the two co-formulated ACTs by both health workers and caregivers at government health facilities in Sierra Leone.

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List of Abbreviations & Acronyms

ACT	Artemisinin-based Combination Therapy
AL	Artemether-Lumefantrine (Coartem)
AQ	Amodiaquine
AQ+AS	Amodiaquine+Artesunate co-packaged
AQ+SP	Amodiaquine + Sulfadoxine-pyrimethamine
ANC	Antenatal Clinic
AS	Artesunate
AQAS	Artesunate + Amodiaquine co-formulated
AS+SP	Artesunate + Sulfadoxine-pyrimethamine
BMQ	Brief Medical Questionnaire
CDP	Chlorproguanil-dapsone (Lapdap®)
CQ	Chloroquine
CQ+SP	Chloroquine + Sulfadoxine-pyrimethamine
CHC	Community Health Centre
CHP	Community Health Post
CRS	Catholic Relief Service
DHMT	District Health Management Team
DHA-PQ	Dihydroartemisinin-Piperaquine
DHS	Demographic and Health Survey
DNDi	Drugs for Neglected Diseases Initiative
DPPI	Department for Policy, Planning & Information
FDC	Fixed Dose Combination
FGD	Focus Group Discussion
GFATM	Global Fund to Fight AIDS, Tuberculosis, and Malaria
GoSL	Government of Sierra Leone
GPS	Global Positioning System
IDI	In-depth Interview
KAP	Knowledge, Attitudes & Practices
LLIN	Long-Lasting Insecticidal Net
MCH	Maternal and Child Health
MCHaide	Maternal and Child Health Aide
MCHP	Maternal and Child Health Post
MDG	Millennium Development Goals
MEMS	Medical Event Monitoring Services
MICS	Multiple Indicator Cluster Survey conducted by UNICEF
MIS	Malaria Indicator Survey
MoHS	Ministry of Health & Sanitation
MSF	Médecins Sans Frontières
NMCP	National Malaria Control Program
OIC	Officer In Charge
PHU	Peripheral Health Unit
QNN	Quinine
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
SP	Sulfadoxine-pyrimethamine, also known as Fansidar
SSL	Statistics Sierra Leone
UNICEF	United Nations Children's Fund
WHO	World Health Organization

1 Introduction

1.1 Artemisinin-Based Combination Therapy (ACT)

Despite increased support for malaria control over the past decade, the burden of malaria remains high in many endemic countries, particularly in sub-Saharan Africa [1]. Prompt treatment with effective antimalarial drugs targeted towards those confirmed to have malaria is a key malaria control strategy [2, 3]. The cornerstone of this strategy is Artemisinin-Based Combination Therapy (ACT). To further improve malaria case management, the World Health Organization (WHO) updated the malaria treatment guidelines in 2010, recommending that ACT treatment should be targeted to only parasitologically confirmed cases of malaria [2, 3].

In 2003, less than twenty countries had adopted ACT as the first line treatment for uncomplicated malaria [4, 5]; by 2009, that number had increased to 77 countries. With the support of donors, specifically the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM), the number of countries that have deployed ACT has increased dramatically allowing for treatment to be more widely available [5]. By 2010, 84 countries had adopted ACTs, with 60 countries providing ACTs free of charge to all ages in the public sector as well as 8 have piloted the provision of subsidized ACT through the private sector [2, 6, 7].

The two primary ACT regimens scaled up over the past ten years in sub-Saharan Africa are artemether-lumefantrine (AL) and amodiaquine plus artesunate (AQ+AS) [8]. Decision-making for antimalarial treatment policy in individual countries is based on both efficacy and availability, with the requirement that the formulation is prequalified by the WHO. AL was chosen for much of East and Southern Africa where resistance to amodiaquine has emerged [8]. However, in the West African region, AQ has retained a relatively high efficacy(median treatment failure rate of 12%; minimum <5%, maximum ~65%), and thus it is assumed that the combination AQ+AS will be also be effective [8]. As AQ+AS was also substantially cheaper than AL initially, as well as being effective, 23 countries in Africa, including Sierra Leone, have chosen AQ+AS as the first- and/or second-line treatment for uncomplicated malaria (Figure 2).

However, the choice of AQ+AS does not come without concerns. As amodiaquine is cross-resistant with Chloroquine the overall efficacy of the combination is at risk when resistance to amodiaquine increases [8]. Moreover, some studies have suggested that recurrent exposure to AQ may cause toxicity, such as instances where amodiaquine has been used

for chemoprophylaxis [9]. However, AQ appears to be much safer when used for shorter duration [10]. Adherence to the amodiaquine + artesunate regimen is also a concern due to the multiple tablets per dose as well as patient tolerability to amodiaquine, particularly in adults [9, 11-14].

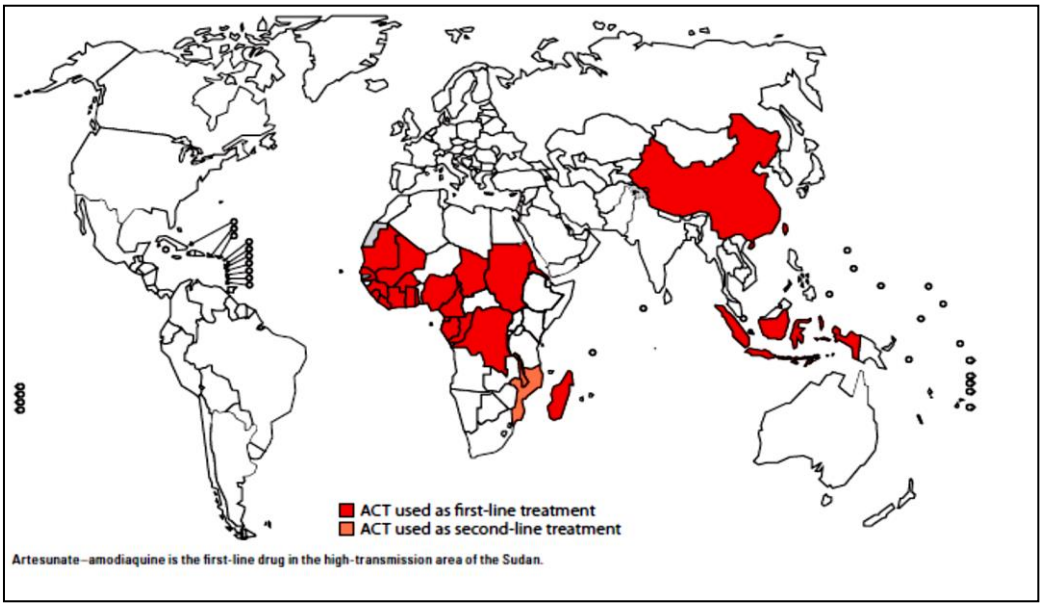

Figure 2. Countries in which artesunate–amodiaquine is recommended [8]

1.2 Translating Treatment Policies into Practice

Changing antimalarial treatment policy to ACTs is not enough to ensure proper treatment of malaria; addressing access and targeting of these efficacious treatments are necessary [15]. The delivery of effective treatment for malaria is often challenged by limited health-care infrastructure and skilled human resources, particularly in Africa [16, 17]. Over the last few years, efforts have been made to improve access to lifesaving treatment by expanding delivery systems to the community level as well as through the private sector.

Increasing access to effective drugs does not guarantee patient acceptability and ultimately adherence to the medications [18]. Focusing on the health system challenges (i.e. access and targeting) without addressing factors determining adherence, will ultimately lead to suboptimal outcomes for malaria treatment. Strategies that address 'therapy-related' factors [19], such as co-packing antimalarials into blister packs, have been shown to improve adherence, and stop the practice of using mono-therapies (thus preserving efficacy) [18, 20, 21].

While co-packaging antimalarial combinations assists both provider and patient in ensuring the correct treatment dose, it does not reduce the number of tablets or the frequency the drugs need to be taken. In addition, co-packaging does not necessarily change any perceptions that patients may already have about individual drugs, and patients may choose not to take all of the tablets or choose to take only one of the medications.

In an effort to overcome the limitations of co-packed antimalarial drugs and to improve adherence, several ACTs have been co-formulated; the most common of these are artemether–lumefantrine (AL), chlorproguanil, dihydroartemisinin-piperaquine (DHA-PQ), and the co-formulated versions of amodiaquine-artesunate (AQAS) and artesunate-mefloquine (ASMQ).

AL was the first co-formulated antimalarial that contained an artemisinin derivative[22]. AL has given twice a day for three days. Children weighing 5-14 kg (roughly under 12 months of age) take 1 tablet twice a day for three days (
Figure). Children 12-59 months (15-24 kg) take 2 tablets, twice a day for three days (total of 12 tablets). AL should be taken with food to be the most effective [23].

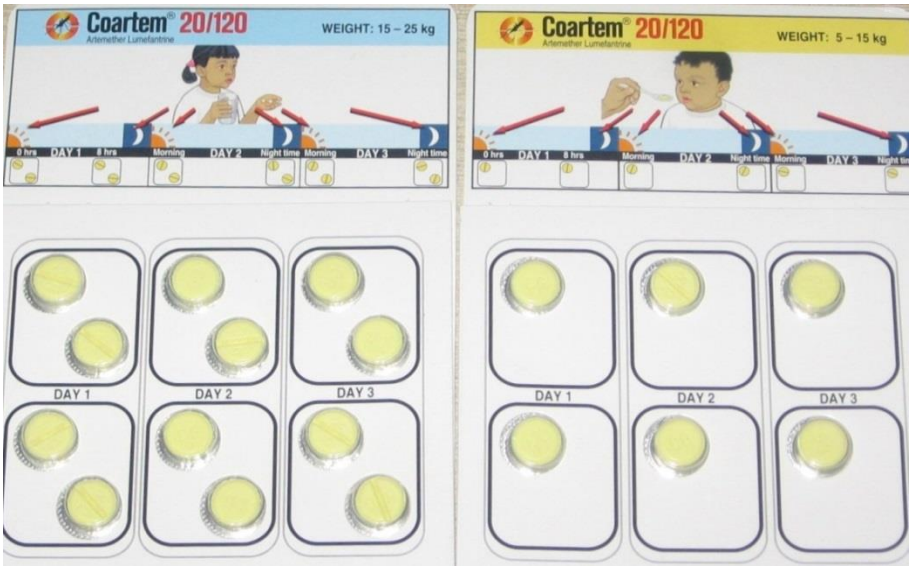

Figure 3. Artemether-Lumefantrine Dosing for children 5-25kgs [24]

Co-formulated AQAS (branded Winthrop® for the public sector or Coarsucam® for the commercial sector) was recently developed by the public-private partnership Drugs for

Neglected Diseases Initiative (DNDi) [25, 26] with the objective to create a product that would “improve patient compliance” [27]. The new product has a simple dosing schedule: 1 dose a day for 3 days. Children under the age of 14 only take one tablet, while patients 14 years and over, take 2 (Figure). The co-formulation reduces the number of tablets to be taken compared to the co-packaged version of the same combination, thus easing treatment intake and hopefully improving patient adherence. However, the switch to co-formulated AQAS by countries has been slow due to availability and cost implications. It is envisioned that over time the co-formulated version will be the predominant formulation in a few years.

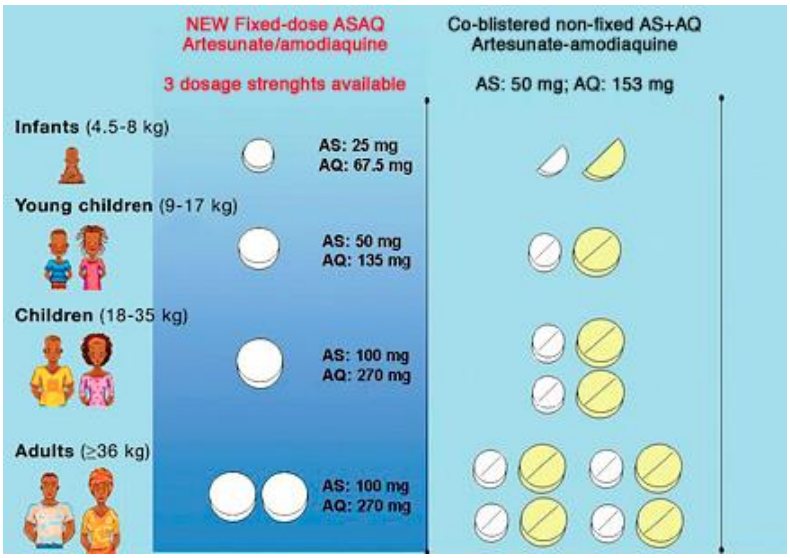

Figure 4. Dosing for co-formulated AQAS versus co-packaged AQ+AS [27]

1.3 Antimalarial Medications in Sierra Leone

In 2004, the Government of Sierra Leone (GoSL) changed the national treatment policy for uncomplicated malaria from Chloroquine to ACTs [28]. The ACTs of choice in Sierra Leone are amodiaquine plus artesunate (AQ+AS) or artemether-lumefantrine (AL) as an alternative if AQ+AS is unavailable. The ACT combination AQ+AS was chosen as the preferred choice due to its availability, affordability and efficacy [29]. Since that time partners, in particular the GFATM, have supported the procurement and distribution of antimalarial treatments to all levels of the health system. The National Malaria Control Program (NMCP) has provided this combination in pre-packaged blisters by age group and has repeated drug efficacy studies on both co-formulated ASAQ and AL in 2011 with results due out in 2013 (personal communication, NMCP June 2012). To further understand the effectiveness of ACTs in Sierra Leone, Médecins Sans Frontières (MSF)

conducted a study on the adherence to co-packaged AQ+AS in Bo district, which concluded that despite efforts to improve access to ACTs, patient adherence was low with only 48.7% probably or definitely adherent to the treatment regimen [30]. Only the knowledge that mosquito bites can lead to malaria was associated with adherence.

Recently the NMCP has switched from co-packaged AQ+AS to the co-formulated version of amodiaquine-artesunate (also termed fixed-dose combination [FDC]) GFATM. Additionally, the NMCP is planning ahead and considering if, when and how AL should be introduced into practice in the country, The national policy for malaria treatment states that cases should be parasitologically confirmed, whenever possible [28]. Clinical diagnosis is acceptable only in the instance that parasitological confirmation is not possible. The impact of the policy change, on provider and patient adherence and the overall effectiveness of malaria treatment, is unknown.

1.4 Adherence to Antimalarials

In 2005, Yeung and White wrote a comprehensive review about how antimalarials were used by patients. Although comprehensive, it was conducted in the infancy of the ACT era [31]. At the time of the review, a total of 24 studies were identified, half of which were conducted in Africa and the other half in Asia and South America. Eight of the cited studies looked at artemisinin-based treatments, two of which looked only at monotherapies [32, 33]. The remaining six studies looked at ACTs; four in Asia (Myanmar, Thailand, Cambodia) [34-37] and two in Africa (Uganda and Zambia).[38, 39]. The study in Zambia looked at adherence to AS+SP, while only the study carried out in Uganda looked at a co-formulated ACT (AL). Since this review has been published, ACTs, and in particular co-formulated versions of ACTs, have been scaled up across Africa. Results found for adherence varied due to study design, context and treatment regimen, but were generally better when “interventions focusing on provider knowledge and behaviour, packaging and provision of correct dosage” were implemented.

The majority of recent studies looking at antimalarial adherence have looked at patient adherence to AL, all but three of which took place in East or southern Africa [39-55]. Of the three that did not, one was conducted in Ghana [41] within a study looking at the feasibility of Home Management of malaria, and the other two took place in southern Asia (Bangladesh & India) [50, 52]. Six additional studies looked at AL in comparison to one or two other antimalarial drugs [56-61]. Levels of adherence for AL ranged from as low at 38% in Ethiopia to 96% in South Africa [40, 46]. The cross-sectional household surveys [40, 62] and

effectiveness studies, which followed patients for 28 days or more tended to have higher levels of adherence.

The combination amodiaquine+artesunate was investigated in eight studies [30, 63-69]. However, despite its wider availability only two studies (one in Benin and one in Madagascar) have looked at co-formulated AQAS [65, 67], with levels of adherence estimated to be 91% and 83.4% respectively. Reported adherence to co-packaged AQ+AS ranged from 48.7% in Sierra Leone to 97% in Ghana [30, 62]. However, it should be noted that the context, delivery system, study design, definitions of adherence and methods of measurement differed across the studies, this heterogeneity may have over or underestimated adherence.

Little is known with regard to the determinants of adherence to ACTs. Findings and trends are not consistent across studies. Demographic factors, such as sex, socio-economic status or age do not seem to be factors strongly or consistently associated with adherence [30, 37, 42, 51, 54, 70]. However, it is important to note that some studies were not actually powered to look at age groups [54]. Although two studies [47, 71] did have the power to look at age group, only one found that children less than five were less adherent [47]; the other found no association between age and adherence [71].

In contrast, factors surrounding the administration of the drugs, and patient knowledge of dose or preference for a specific drug [45, 47, 64, 71], signs and symptoms of patients [71] and literacy [42, 46, 70] have been found to be associated with ACT adherence. Factors that have to do with dispensing ACT such as package, simplicity, and number of pills (thought to make a difference) were not prominent factors investigated. However, one study found that giving the exact number of tablets for the prescribed dose was associated with adherence [64], suggesting that pre-packaged doses should improve adherence. Almost all of the patients in a Tanzanian study reported that the pictogram printed on the packages and the blister packaging depicting the correct treatment doses were helpful, but the impact of this on adherence was not assessed [44]. In summary, individual patient factors associated with adherence that have been reported in the literature are inconsistent.

1.5 Study Rationale

Better treatment, targeting and improved access may improve the coverage of malaria treatment. However, these aspects only address health system factors, but do not adequately address individual factors that improve the overall effectiveness of malaria

treatment. In an era of malaria elimination strategies and developing resistance to artemisinin compounds in South East Asia [72], provider compliance to malaria treatment guidelines and patient adherence to treatment are vital.

It is often assumed that co-formulated antimalarials will facilitate adherence in the same way that co-packaged treatments have previously. It is assumed that the co-formulated version, should not only improve dispensing, but should also improve patient adherence. However, other factors may influence patient/caregiver adherence to treatment. Although a co-formulated antimalarial, AL's still has a dosing schedule that requires multiple administrations a day and recommends that it be taken with food, both of which may impact on patient adherence. AQAS, although currently available and efficacious, may lose efficacy in the coming years and the NMCP is interested in testing effective alternatives. Only one in Benin [65] has compared the adherence to these two co-formulated ACTs, and there is no study to date that has rigorously evaluated, either individually or in comparison, the adherence of these two to co-formulated ACTs in Sierra Leone.

Currently both AQAS and AL are available and recommended for the treatment of uncomplicated in Sierra Leone, however, AL is only found in the private sector. It has yet to be established if one formulation is better tolerated by patients in Sierra Leone. Despite the assumption that the co-formulated versions of ACTs will yield higher adherence and hence better treatment outcomes, information on factors affecting adherence to ACTs remain unclear.

2 Research Aims & Objectives

The aim of this study is to measure and compare the level of provider compliance with malaria treatment guidelines and patient adherence to co-formulated AQAS compared to AL under routine conditions in Sierra Leone. It is hypothesized that caregivers will adhere to the co-formulated AQAS at least 15% more than those that receive AL. Additionally, this study will explore the key factors that influence adherence to both of these antimalarial treatment formulations.

Specific Objectives:

I. To evaluate the level of compliance to malaria treatment guidelines by health workers at two government health facilities in Sierra Leone under routine conditions and to assess how health worker compliance may affect patient adherence.

II. To evaluate caregiver acceptance and adherence to negative rapid diagnostic test (RDT) results and subsequent treatment for their child's febrile illness.

III. To evaluate and compare the level of adherence to co-formulated ASAQ compared to AL for treatment of malaria in children aged 6 to 59 months seeking care at government health facilities in Sierra Leone.

IV. To identify determinants of adherence to the two ACTs formulations by both health workers and caregivers at government health facilities in Sierra Leone.

3 Study Setting

3.1 Background

Sierra Leone, located on the West Coast of Africa, is subdivided into 14 administrative districts, two of which (Western Urban and Rural) encompass the greater Freetown area. The population at the 2004 Census consisted of 4.9 million people and was projected to be roughly 6,037,660 people by 2011 [73]. Under 15 year olds are estimated to constitute 49% of the population [74]. There are two major seasons, a summer rainy season (May to October) with heavy rains in July and August, and a winter dry season (November to April).

Malaria is endemic, with stable and perennial transmission in all parts of the country. Malaria accounts for about 40% of outpatient morbidity [75]. In 2010, only 46% of children under five who sought care at public health facilities received prompt and effective treatment for malaria with the first line malaria treatment: AQ+AS [75]. More recent data from the fourth Sierra Leonean Multiple Indicator Cluster Survey (MICS4) suggest that this number has not changed much with only around half of children under 5 being treated with any antimalarial the same or next day from the onset of fever [76].

3.2 Health System Structure

In Sierra Leone, health care is delivered at three levels: (*i)* primary or first point of care through Peripheral Health Units (PHUs); (*ii)* secondary care through district level hospitals; and (*iii)* tertiary or specialized care through regional or national hospitals [77]. However the system is focused largely on a primary health care framework with the majority of care delivered through PHUs [78]. There are three types of PHUs (from largest to smallest): 1) Community Health Centres (CHCs); 2) Community Health Posts (CHPs); and 3) Maternal & Child Health Posts (MCHPs).

3.3 Study Sites & population

This study will take place in the capital Freetown, which is located in the Western Area Urban administrative district (Figure 5). Two public health facilities and their catchment areas will serve as the study sites (Ross Road and George Brook CHCs).

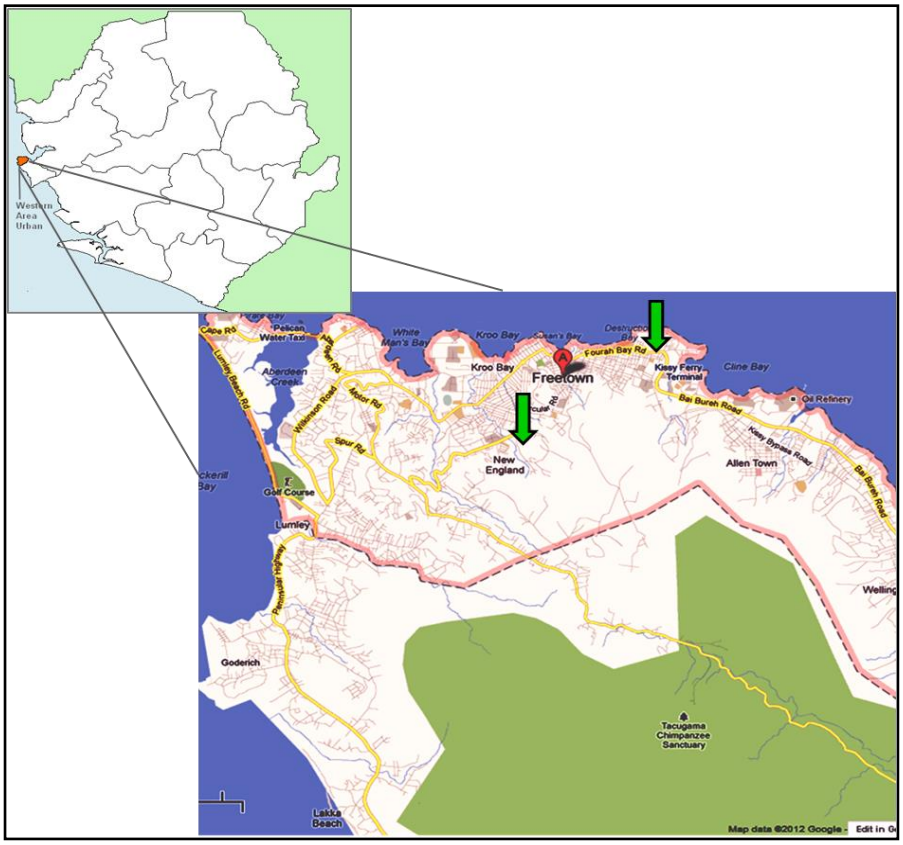

Figure 5. Map of Study Area

The Ross Road clinic is located in a densely populated area in the eastern part of Freetown called Cline Town. The clinic has an estimated catchment population of 21,324 people, approximately 10,000 of whom are under 15 years of age. The Ross Road CHC sees approximately 1,000 patients per month, the majority (50%) of which are children under 5 presenting with fever. On average, the Ross Road clinic has 400 children under 5 with confirmed malaria per month (Table).This clinic has two Community Health Officers (CHOs) that are responsible for the patient consultations and approximately 8-10 other support staff (MCHaides, nurses, midwives and dispensers).

The George Brook CHC is located in the western part of Freetown in an area called Dwarzak Farm. This CHC has an estimated catchment population of 27,855 people,

approximately 3,000 of which are under 5 years of age. The George Brook clinic sees approximately 800 patients per month, approximately 60% are children under 5 presenting with fever and an estimated 240 of which have confirmed malaria each month (Table). George Brook has around 15 health workers, only one of which is a CHO.

Table 1. Confirmed Malaria Cases for Children Under 5

HEALTH FACILITY	J	F	M	A	M	J	J	A	S	O	N	D	Total	Avg
Ross Road	169	200	288	310	437	622	300	202	615	411	609	613	**4,776**	**398**
George Brook	194	190	356	203	331	220	179	318	315	169	272	166	**2,913**	**243**

4 Methods

4.1 Overall Study Design

This is an open-labelled randomised controlled study which will use a mixed method approach (Figure 6). Prior to the recruitment of patients semi-structured interviews with health workers will be undertaken to gain a better understanding of the health workers and their practices with regard to the diagnosis and treatment of malaria. The second component of the study entails observations of health worker consultations with patients aged 6 to 59 months and their caregivers and will look at how health workers diagnose and treat malaria. Prior to the consultation, patients will be randomized to receive either co-formulated AQ+AS or AL at the time of prescription. Consultations will be followed by short exit interviews at the health facility with the same caregivers, which will be used to measure patient satisfaction with services, as well as to confirm the way in which diagnosis and treatments were received and understood. The observed caregivers will serve as the sampling pool for these exit interviews.

Under Component 4, patients and their caregivers that participate in the exit interviews will then be followed-up at their home four days later in order to measure the adherence of participants to AQAS or AL and potential factors that affect adherence. Additionally, data will be collected from a sub-set of caregivers using in-depth interviews (IDIs) to collect supplementary information with regard to adherence/non-adherence and factors that may affect behavioural choices and/or attitudes with regard to adherence (Component 5).

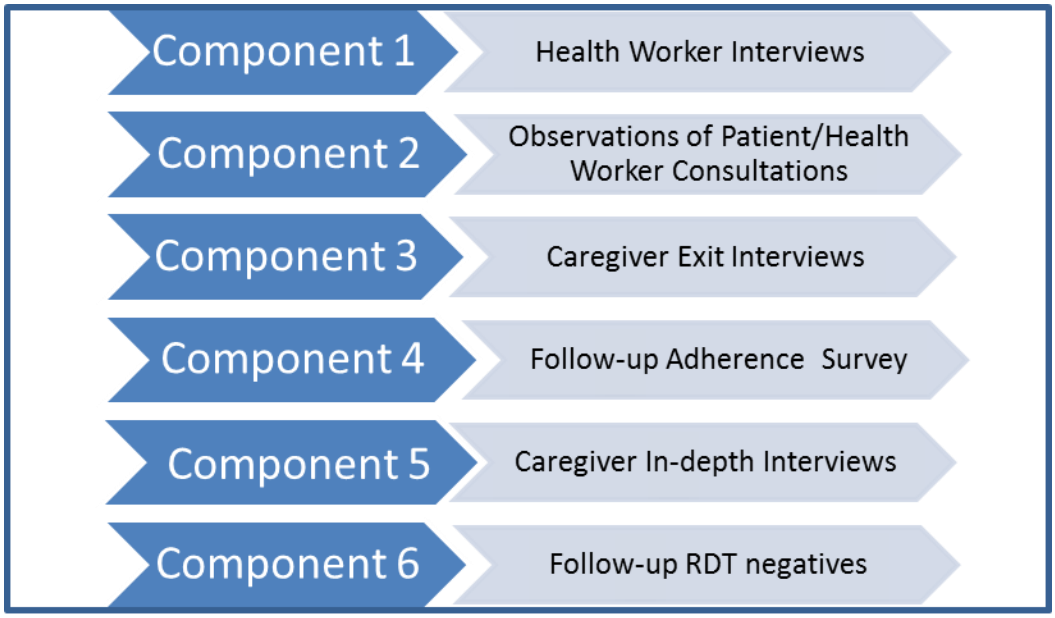

Figure 6. Study Components

4.2 Component 1: Health Worker Interviews

Health workers at the two study sites will be interviewed in order to understand the context of the working environment and their familiarity with the malaria treatment guidelines. After agreeing to be interviewed and providing written consent, each health worker will be asked general questions about how health workers diagnose and treat patients with malaria. Then the health worker will be prompted to share his/her thoughts about why physicians might prescribe or not prescribe AQAS or AL. Additionally, they will be asked about their opinion on patient adherence, factors that contribute to non-adherence and practices they employ to address this (Appendix A).

After the completion of the interviews, health workers will also be asked if they would agree to have their patient interactions observed over the subsequent months. Only those providing written informed consent will be included in the remaining components of the study.

At least three health workers (Table 2) will be purposefully selected per site in order to represent the different types of health workers present at that site (Community Health Officer, Nurse, and Midwife, etc.).

Table 2. Number of Health Worker In-depth Interviews

Health Facility	Interviews*
Ross Road	3-6
George Brook	3-6
Total	**6-12**

*Numbers are dependent on the number of health workers available at each health facility

4.3 Components 2-4: Observations, Exit Interviews & Follow-up Survey

4.3.1 Component 2: Observations of Patient/Health Worker Consultations

To gather further information on the on the context of treatment allocation and to better measure health worker compliance to malaria treatment guidelines patient-provider consultations at the two study sites will be observed over the course of the study period. This will be conducted in two phases. Initially, health workers will be observed just administering AQAS to better understand current malaria diagnosis and treatment practices of the study site health workers. At both study sites, each health worker that consults with patients will be observed until a minimum of 20 consultations with patients with fever are observed [79]. Following this initial observation period health workers will receive a refresher training on both treatment regimens and the randomization scheme will be introduced and the randomized controlled trial to compare adherence to AQAS to AL will commence.

Approximately 6-10 structured observations will take place per day, but this will be dictated by the number of health workers conducting consultations that day, patient numbers and the number of study team members available. Both the health worker and parent/caregiver will need to agree to be observed before the consultation begins. Only consultations for fever will be recorded. The observer will take notes and complete a structured checklist for each patient observation (Appendix B). Examination procedures (history taking, physical examination, recommended laboratory tests) will be noted. Each consulting clinician (primarily the CHOs) at the health facility will be observed a minimum of 20 times each [80]. However, the total number of observations at each site will equal the total number of exit interviews & follow-up adherence surveys (see section 4.3.9 for sample size calculations).

4.3.2 Component 3: Caregiver Exit Interviews

Upon completion of the clinic visit, patient/caregivers will be asked to take part in a short exit interview survey. Participants will be asked about the type/quality of care received at the health facility will be obtained. Patients will be asked about their treatment seeking practices,

care and treatment received during the visit, satisfaction with services, as well as demographic information, including contact information (i.e. address and mobile number) (Appendix C). To limit bias and to avoid influencing treatment taking practices, patients will not be informed that the study team may follow them up later at their homes for an additional interview. However the purpose of the interview and further consent will be obtained before the assessment of adherence at homes [81].

4.3.3 Component 4: Follow-up Adherence Survey

Caretakers/parents of the patients will be visited at their homes on Day-4; the day after the last prescribed treatment dose should be taken. If the interview cannot be completed on Day-4, the interviewer can try again on Day-5. No interviews will be carried out after Day-5. Any interview done after Day-5 will not be taken into account in the analysis. The caretakers/parents who gave the treatment to the patient (child) must be present to answer the adherence survey questionnaire. Participation will be on a voluntary basis, and the visit will only proceed after additional written informed consent is given. If the clinical condition of the patient requires further medical attention at the time of the home visit, she/he will be referred to the nearest health centre immediately, and the adherence assessment will be conducted later (up to Day-5) if possible, once the patient's condition has improved.

A structured questionnaire will be administered to assess patient adherence (Appendix D). It will start with some general questions about the patient and the household. Then patients will be asked to account how the tablets were taken, and will be asked to show the original blister packaging. If the blister packaging is found, any remaining tablets will be counted. Finally, there will be a few additional questions about their experience with the treatment, any side effects (adverse events) experienced, why or why they didn't complete the treatment and about general malaria knowledge. All patients or caretakers/parents will be thanked for participating and encouraged to return to the health facility soon if patient's health condition is of concern. If treatment has not been completed the patient will be encouraged to complete the full treatment course.

4.3.4 Participant Selection & Consent

Patients attending the health facility for the treatment of fever for their child 6 to 59 months will be screened and invited to take part in the study (Appendix C). Only those parents/caregivers that are visiting the health facility for the treatment of fever in a child 6 to 59 months and meet the inclusion criteria (Box 1) will be included in the study.

- *Patient is a child between 6 to 59 months*
- *Visiting health facility for treatment of fever*
- *Do not have signs of severe disease*
- *Are not being referred to another health facility*
- *Living within a defined distance from the health facility (<5 km/ 3 miles)*
- *Have not taken part in the study already or are not part of a household that has already taken part in the study*
- *Responsible caretakers/parents provide additional informed consent*

Box 1 Inclusion Critera for Components 2-6

Parents/caregivers will be provided information on study components 2 and 3 (observation, treatment and exit interviews) and will be asked if they are willing to participate. Only those providing written informed consent to participate in the study activities that day will be enrolled and receive a patient study inclusion card, which they will present to the health worker at the time of consultation.

4.3.5 Treatment Assignment and Allocation

Currently, AQAS is available at both study sites. AL is available in the private sector and is often prescribed when AQAS is unavailable. However, the cost is prohibitive and wide use remains limited. AL will be provided by the research team to the study sites for the purpose of this study. The AL will be checked and approved by the Pharmacy Board prior to study commencement. Participants in the study will be randomly assigned to receive one of the two formulations. However, in every other aspect diagnosis and treatment will be carried out as per the normal operation of the health facility. Randomization will be determined based on a pre-prepared randomization list. Treatment assignment will be determined by the health worker performing the patient consultation.

4.3.6 Randomization

A computer generated randomization list (in blocks of 10) will be created by a member of the project that will not be directly involved in the conduct of the study. Prior to the onset of the study, the randomization list will be used to create individual treatment allocation slips, which will be in opaque sealed envelopes and will be opened by the health worker during the consultation at the time of prescription and dispensing of medications.

4.3.7 Blinding

The study medications are not identical in appearance and taste nor are the number of tablets per dose the same. Neither the participants, health workers nor the study team will be blinded to the treatment assignments as they are the ones responsible for either: 1)

prescribing and administering the treatment to the child (health workers); 2) administering the medication to the child (parent/caregiver); or 3) collect information about treatment practices and opinions (study team).

4.3.8 Study Medications

Co-formulated ASAQ will be distributed by the Ministry of Health & Sanitation (MoHS), district health management team to the health facilities as per normal procurement procedures. AL will be provided to the study sites at the beginning of the study period. A brief introduction and refresher session will be carried out by the NMCP with the health staff. The treatments that will be evaluated during the study period are displayed in Table 3.

All participants will receive a full treatment course for their child, which will include one treatment dose a day for three days for AQAS and two doses a day for three days for AL. Treatments will be will be prescribed according to the national guidelines and as recommended by the manufacturer (See Figure above) Parents/caregivers will be responsible for administering the treatments to their child as instructed by the health worker (Table 4).

Table 3. Treatments to be observed

Regimen	Trade name	Age Group	Concentration
Amodiaquine + Artesunate (co-formulated)	Winthrop/ Coarsucam (Sanofi)	Infant (2-12 months) (4.5- 8 kg)	Amodiaquine: 67.5 mg Artesunate: 25 mg
		Young Children 12-59 months (9-17kg)	Amodiaquine: 136 mg Artesunate: 50 mg
Artemether-lumefantrine	Coartem	Infant 2-11 months (5-14 kg)	Artemether: 20 mg Lumefantrine: 120 mg
		Young Children 12-59 Months (15-24 kg)	Artemether: 20 mg Lumefantrine: 120 mg

Table 4. Treatment Doses

Treatment group		Day 1	Day 2	Day 3
Amodiaquine + Artesunate (co-formulated)	Infant (2-12 months)	1 tablet	1 tablet	1 tablet
	Young Child (13-59 months)	1 tablet	1 tablet	1 tablet
Artemether-lumefantrine	Infant (2-12 months)	1 tablet 1 tab 8 hrs later	1 tab A.M. 1 tab P.M.	1 tab A.M. 1 tab P.M.
	Young Child (13-59 months)	2 tablets 2 tabs 8 hrs later	2 tabs A.M. 2 tabs P.M.	2 tabs A.M. 2 tabs P.M.

4.3.9 Sample Size Calculations

The prevalence of adherence to co-packaged AQ+AS in Sierra Leone is estimated to be 50% [30]. It is estimated that the co-formulated version of ASAQ will yield a higher level of adherence (conservatively estimated to be 75%). There is currently no data on adherence levels to AL in Sierra Leone, but it is hypothesized that it will be greater than co-packaged AQ+AS, but less than AQAS. In order to determine a 15% or greater difference between the different treatment groups (α-error of 5%, 80% power, 20% contingency, a total of 198 patients are required for each treatment arm. As differences in context, health system and/or socioeconomic factors may influence adherence, the study is powered adequately to measure adherence at each site with a precision of +/- 5%. Thus, the total number of observations, exit interviews and follow-up adherence surveys for each site will be 396 (Table 5).

Table 5. Sample Size for Observations, Exit Interviews & Adherence Surveys

	Co-Formulated ASAQ	Co-Formulated AL	Total
Ross Road	198	198	396
George Brook	198	198	396
Total	396	396	**792**

4.4 Component 5: Caregiver In-depth Interviews

In addition to the surveys, in-depth interviews will be carried out with a subset of both adherent and non-adherent caregivers to get a more textured picture of the potential factors that affect adherence. Participants will be purposefully selected based on the treatment they received and whether they were adherent or non-adherent to the treatment regimen. The interviews will be conducted in private in the home of the participant. The location where interview will take place will be designated by person being interviewed. The interviews will be one-on-one unless the participant requests to have another person in the room.

The interviewer will start by first asking general questions about what the parent/caregiver does when their child is ill. Next the interviewer will ask the parent to identify some common medications used to treat fever. The discussion will then turn to inquiring about the parent/caregivers' experience with malaria treatment, understandings and expectations of treatment, tolerability, and barriers faced with regard to treatment adherence. See attached draft topic guide for the topics to be covered (Appendix F). At the end of the meeting, the interviewer will thank the participant for their time.

A sampling matrix has been constructed (Table), which outlines the estimated number of parent/caregiver in-depth Interviews expected. However, these numbers are only estimation; sampling may be more or less than this based on whenever new ideas no longer appear.

Table 6. Number of In-depth Interviews with Caregivers

Participants	*Interviews*		**Total**
	Adherent	**Non-adherent**	
Co-formulated AQAS	5	5	10
Co-formulated AL	5	5	10
Total for one site	***10***	***10***	***20***
Total for two sites	***20***	***20***	***40***

4.1 Component 6: Follow-up RDT Negative Cases

According to the National Malaria Treatment Guidelines all fever cases should receive a confirmatory blood test prior to receiving malaria treatment. In order to ascertain caregiver acceptance of malaria test results and agreement and/or adherence to treatment advice given during their clinic visit a subset of caregivers from one of the study sites (George

Brook) will be included in this sub-study. Caregivers, who are already participating in the study and whose child received a negative RDT test and no ACT, will be followed up on day 4 and interviewed. Those not found and interviewed between days 4-7 will be considered lost during follow-up.

Caregivers will be asked questions about their acceptability of the new policy of testing before treating for malaria and actions taken for their child's current illness (Annex G). They will also be asked questions with regard to how exactly they treated their child's current illness in order to ascertain if additional medications or consultations were sought beyond those given at the health facility visit that occurred 4 days earlier. Additionally, questions on adherence to any antimalarials administered, demographics and the child's current health status will be asked. Children found whose health is not improving and/or getting worse will be advised to return to the health facility immediately.

4.1.1 Sample Size Calculations for RDT Negative Survey

The prevalence of caregiver acceptance of malaria test results in Sierra Leone is unknown and therefore estimated to be 50%. Based on calculations using an α-error of 5%, 80% power, a .08 level of precision and accounting for a contingency of 15% for refusal to participate or loss to follow-up, 177 caregivers will need to be interviewed.

5 Ethical Considerations

5.1 Informed Consent

Witnessed written consent will be obtained from each participant prior to the observations and interviews. Respondents will be informed that participation is completely voluntary and that they may refuse to answer a question or discontinue their participation at any time without penalty (see Appendix H & I). All participants will have the study purpose explained to them in English or Krio. If another language is needed then a translator will be used to ensure that they fully understand the purpose of the study. Everyone will be offered the opportunity to refuse participation at any time during the study without penalty.

5.2 Confidentiality

Participant will be informed that participation in the study may result in a loss of privacy. Information exchanged during the interactions with patients will be record (onto data tools

and in-depth interviews will be digitally recorded). The names of participants will not be used in any reports. The names mentioned during interviews will also not be used. No quotes or other results arising from your participation in this study will be included in any reports, even anonymously, without consent. The information obtained from these interviews will only be used by the project researchers and stored in a secure location. We will do our best to make sure that the personal information gathered for this study is kept private.

5.3 Drug Safety

In Sierra Leone, both amodiaquine-artesunate and artemether-lumefantrine are recommended first-line treatments for uncomplicated malaria in Sierra Leone [28]. Furthermore, as AQAS is supplied through international donor funding (specifically GFATM), as a condition to sustained support, only WHO prequalified pharmaceuticals and health products that comply with national regulations and authorization are used in public health facilities [82].

Although, some studies have suggested that recurrent exposure to AQ may cause toxicity [9] a Cochrane review found that there was still evidence that AQ was both effective and safe for the treatment of uncomplicated malaria [10]. Serious adverse events, such as central nervous system (CNS) effects have been reported to be more for amodiaquine compared to Chloroquine [83]. However the most serious adverse events (agranulocytosis, hepatotoxicity and aplastic anaemia) have been in relation to its previous use for chemoprophylaxis for longer periods of time (total case fatality rate estimated to be 1:15,650)[10].

The combination of amodiaquine plus artesunate is one of the five ACTs recommended by the WHO for the treatment of uncomplicated malaria [3] and in has an encouraging safety profile [84]. Additionally, the move to improve adherence by combining amodiaquine with artesunate into one tablet and one dose per day has also been found to be safe [85].

AL is also recommended by the WHO for the treatment of uncomplicated malaria [3]. AL was the first co-formulated ACT and is the first line treatment in much of Sub-Saharan Africa. Overall, AL is considered both tolerable and safe to use, however, there is still a risk of adverse drug reactions [86]. The most common adverse events for AL include headache, dizziness, gastrointestinal disturbances (vomiting, nausea, diarrhoea, and

anorexia), pruritus, cough, fatigue, pyrexia, and irregular heart palpitations [87, 88]. Although there are concerns about neurotoxicity and artemisinin derivatives, no serious adverse events or neurotoxic adverse events have been reported; however, there were initial concerns that there would be cardio-toxicity as a result of the lumefantrine component which is similar in structure to halofantrine [89].

However, as no drug is completely without risk, information on adverse events will be collected throughout the course of the study. Data will be collective actively through a checklist and open ended "other" category on the follow-up adherence questionnaire (Appendix E). Other adverse events will be monitored passively if/when patients return to the health facilities for additional care for the same febrile illness.

5.4 Risks & Benefits

As this will be a randomized controlled study, one treatment regimen may prove to be more or less tolerated, efficacious or safe than the other. However, a recent drug efficacy study carried out in Freetown in 2012 found that efficacy and safety were similar for both regimens (personal communication, NMCP February 2013).

Although all medications including AQAS and AL are associated with some risk of side effects; there are no major anticipated risks or discomforts as the medications to be studied are already widely used and available in Sierra Leone. AQAS and AL are the recommend first line treatments for uncomplicated malaria in Sierra Leone and are currently recommended by WHO for the treatment of uncomplicated malaria [3, 28].

Participants will be asked to volunteer their time for interviews (approximately 1 hour maximum) and can discontinue involvement at any time. Patient care will be the same at the health facility as it would be if there was not a study taking place, however to assist with monitoring drug safety caregivers will be told to come back to the health facility if their child becomes worse.

5.5 Ethics

The study protocol will be reviewed by the London School of Hygiene & Tropical Medicine Clinical Trials Sub-committee. Approval for the study will be sought by the Sierra Leone Ethics and Scientific Review Committee and the London School of Hygiene & Tropical Medicine Research Ethics Committee prior to commencement of activities.

6 Data Collection & Management

6.1 Quantitative Data Collection

Observation data will be collected using a checklist and via notes from the researcher. Observation checklists and health worker interviews will be entered into an electronic database. Additionally, open-ended questions and researcher notes from the observations & interviews will be exported into Nvivo for analysis. All survey data will be collected using paper questionnaires. Data will be double entered into a computerized database (EpiInfo) to verify accuracy of entry. Back-up files of the database will be stored on an external hard drive or server. For quality control, validation and built in skip logic will be written into the database to limit the entry of incorrect data and to ensure entry of data into required fields. Data management, cleaning and analysis will be primarily performed using EpiInfo and STATA software packages.

6.2 Qualitative Data Collection

Qualitative teams will consist of an interviewer and at times an assistant/translator who will record observations and take notes during the interviews. All interviews will be carried out anonymously, meaning that all data collected from the individuals will not have personal identification information included. However, social demographic data describing the type of person answering the questions will be collected.

Information from interviews will be captured with written notes and will also be recorded. The audio recordings will be downloaded from the digital recording devices and then transcribed. In instances where the interview is not in English or Krio, interview transcripts will be translated into English.

The Health Worker interviews will be conducted at the health facility where the health worker is based. The location within the health facility where interviews will take place will be designated by the health worker being interviewed. The interviews will be one-on-one unless the health worker requests to have another person in the room.

As the caregiver in-depth interviews will be a subset of the adherence survey sample, the interviews will take place as a continuation of the follow-up surveys. Caregivers will be interviewed in their homes or another designated place where they feel comfortable. The interviews will be one-on-one unless the health worker requests to have another person in the room.

6.3 Quality Assurance

All members of the study team will receive training on the project objectives, methodology and expected operating procedures such as communication and data collection skills prior to commencement of the field work. Trainings will include a detailed review of the study tools and procedures, role plays and field tests. Knowledge of study procedures will be assessed and documented with a post-training questionnaire. Training manuals and relevant study documentation will be provided. Prior to study commencement a pilot study will be conducted to ensure teams are comfortable with the data collection tools and procedures and to identify any areas for improvement. Team meetings will be held regularly to discuss progress, identify challenges and recognize achievements.

7 Analysis Plan

7.1 Outcome Definitions

Definitions for Correct Prescription (provider compliance)

The proportion of correct prescribing practice by health workers will be assessed during clinic observations and through patient exit interviews. The definition of correct prescription was adapted from WHO indicators [1] . Prescription will be considered correct if all of the following occur:

1) The case was confirmed using RDT/microscopy
2) The provider prescribed ACT
3) The correct dosage of ACT was prescribed (based on weight/age)
4) The correct number of tablets were given

Definition of Correct Dose Taken

Definition of correct dose will be based on the caregiver's verbal account. The dose taken will be considered correct if all of the following occur:

1) The specified number of tablets were taken
2) The dose was not spat out or vomited
3) The complete dose was taken only once per day for three days

Definition of Adherence

Full Adherence—Caregiver reports that the child has taken the correct dose .The blister packaging was observed and found to have no tablets left.

Probable Adherence—Caregiver reports that the child has taken the correct dose. There is no blister packaging available for observation.

Probable Non-adherence—Caregiver reports that the child has not taken all tablets (did not receive correct dose). No medication blister packaging available for observation or the blister packaging is empty.

Certain Non-adherence—Any Caregiver who showed a blister package still containing any remaining tablets at the time of the home visit.

7.2 Health Worker Interviews & Observations

Basic descriptive statistics will be generated for both sets of data where appropriate. Open ended questions will be analysed in Nvivo. Using thematic content analysis, themes will be coded as they emerge from the data. The expected output is a general picture of the context of the prescribing practices of the health workers in each study site.

7.3 Exit Interviews

Data will be analysed using the definition for proper prescription presented in above in section 7.1. Descriptive statistics will be used to summarize exit interview data. The proportion (and associated 95% confidence interval) of patients who reported receiving correct treatment provision will be calculated.

7.4 Follow-up Adherence Surveys

Data will be analysed using the definitions for adherence described above in section 7.1. Descriptive statistics will be used to summarize survey data. Crude associations for adherence to ACT treatment will first be examined using chi-square tests. A multivariable logistic regression model will then be used to determine factors associated with adherence. Factors will be chosen for inclusion in the multivariable model based on the results the univariate analysis as well as based on the findings from a literature review. However, the expected (a priori) covariates include: age of patient, sex of patient, age of caregiver, sex of caregiver, socio-economic status, ACT formulation, knowledge of treatment and confirmatory diagnosis received. To assess whether any differences in adherence between treatment formulations vary by age group, interaction terms between age and treatment type will also be examined in multivariable logistic regression models.

7.5 Follow-up RDT Negative Surveys

Descriptive statistics will be used to summarize RDT negative survey data. Crude associations for adherence to test results will first be examined using chi-square tests. A

multivariable logistic regression model will then be used to determine factors associated with adherence to test results. Factors will be chosen for inclusion in the multivariable model based on the results the univariate analysis. However, the expected (a priori) covariates include: demographic and socio-economic factors, knowledge of malaria as well as treatment and confirmatory diagnosis received.

7.6 Caregiver In-Depth Interviews

Translated transcripts and interview notes from the caregiver interviews will be read and re-read to ensure familiarity with the data. Using thematic content analysis, themes will be coded as they emerge from the data. Coding will be done by hand initially in the field in order to inform data collection. Qualitative data analysis software, NVivo (QSR International, Cambridge, MA) will be used to code data electronically. The NVivo software program will be used to aggregate the codes into themes.

8 Study Timeline

The estimated time frame for this field study from start to finish is one year (Table 7). Time needed for preparation and data collection is estimated to be 5-6 months and will take place in Freetown, Sierra Leone.

Table 7. Study Timeline

Activity	***F***	***M***	***A***	***M***	***J***	***J***	***A***	***S***	***O***	***N***	***D***	***J***	***F***	***M***	***A***	***M***
Finalize Protocol	x				x											
Ethical Approvals		x	x	x	x	x	x									
Study Preparations			x	x	x		x									
Pilot								x								
Health Worker Interviews								x								
HW Observations								x	x	x	x					
Exit Interviews								x	x	x	x					
Adherence Survey								x	x	x	x					
RDT Negative Follow-up									x	x	x					
In-Depth Interviews								x	x	x	x					
Transcribe & Translate								x	x	x	x	x				
Coding Qualitative Data								x	x	x	x	x	x			
Data Entry								x	x	x	x	x				
Data Cleaning									x	x	x	x	x	x		
Data Analysis										x	x	x	x	x	x	x
Writing up of Results												x	x	x	x	x

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10 Adherence Trial Appendices

Appendix 1--Component 1: Health Worker Questionnaire

	Health Facility	Ross Road……..……..…..…1 George Brook……..…..…..2
	Interviewer Initials	
	Date	
	INFORMED CONSENT OBTAINED?	☐ **Yes (1) → CONTINUE** ☐ **No (0) → END**

Background information on informant (health worker)

	Interview Number	
	Sex	Female ...……1 Male ……2
	Age (years)	
	Qualification/Designation	

A. Training

A1	Have you received any specific training on malaria diagnosis and treatment?	No.....0 Yes.....1	
A2	When was the training?	< 1 month.....1 < 6 month.....2 6-12 months.....3 12+ months…….4	
A3	Where was the training?	Health Facility.....1 District HQ.....2 NMCP/MOH.....3 Other (specify)_____.....4	

A4	How many times were you trained? (Enter number)		
A5	Could you tell me a bit about the training (Details: Was the training helpful? Why? Why not?)		
A6	How could the training be better in the future?		

B. Drugs, treatment and procedures

B1	Do you have treatment guidelines for malaria at this facility	No.....0 Yes.....1 Don't Know.....9	→B3 → B3
B2	Which treatment guidelines for malaria case management do you use at this facility? (Give details if necessary, e.g. national guidelines etc.)		
B3	Are the drugs specified in these guidelines always available?)	No.....0 Yes.....1 Don't Know.....9	
B4	Have you had periods where your patients have not been able to get their medications because there were stock outs?	No.....0 Yes.....1 Don't Know.....9	→B6 → B6
B5	What do you advise patients to do when there are stock outs?		
B6	Can you give me more details about how malaria is diagnosed and treated at this Health Facility?		
B7	How do you test for malaria at this health facility?	RDT.....1 Microscopy.....2 Both.....3 Other (specify)_____.....4 Don't know……..9	

B8	How do you determine treatment doses for patients?	Weight.....1 Age.....2 Both.....3 Other (specify)_____.....4 Don't know……..9	
B9	How are patients informed/educated about their treatment?		
B10	Who is giving this information?		
B13	What kind of information do they receive?		

C. Adherence

C1	Do you think your patients, generally speaking, adhere to co- packaged AQ+AS?	No.....0 Yes.....1 Don't Know.....9	
C2	Can you tell me why you think that is the case?		
C3	What about co formulated AQAS?	No.....0 Yes.....1 Don't Know.....9	
C4	Can you tell me why you think that is the case?		

C5	In your opinion, is adherence to the fixed-dose AQAS same, better or worse compared to AQ+AS co-packaged?	same.....0 better.....1 Worse……..……2 Don't Know.....9		
C6	Can you tell me why you think that is the case?			
C7	What other ACTs do they take?			
C8	In your opinion do they adhere to the treatment regimen? Why? Why not?			
C9	What factors do you think impact patient adherence to malaria medications?			
C10	Can you tell me what you do to encourage patients to adhere to their medications?			
C11	Can you demonstrate for me? For example, if I am the mother of a child with malaria what would you say and do?			
C12	Could you estimate the percentage of your patients who you think take their entire malaria treatment?(record the number/percentage)	AQAS (FDC)		
		AQ+AS co-pack		
		AL		
		Other ACT (specify)		
C13	Is there anything else you would like to tell us or ask us?			

Appendix 2--Component 2: Health Worker Observation Checklist

No.	A. Health Worker Identification & Information	
A1	Observation Number	
A2	Health Worker Name	
A3	Health Worker ID Number	☐☐☐
A4	Health Facility	Ross Road……..…1 George Brook……..…..……..2
A5	Researcher Initials	
A6	Date	
A7	Gender of Health Worker	Female ..……1 Male …….2
A8	Role of HF Staff being observed today	OIC……..……1 Nurse/midwife……..……..……2 Dispenser…….…..3 Other (Specify)_____...4
A9	Qualifications of HF Staff being observed Today	CHO…….…1 SECHN…….……2 Nurse/midwife…….……3 Dispenser……..……..4 Other (Specify)_____...5
A10	Previously trained in malaria case management with ACT	No.....0 Yes.....1

B. Patient Assessment			
B1	Did the Health worker ask the patient and/or the person accompanying the child about?	**Yes**	**No**
	History of Fever		
	Drinking and eating (lack of appetite)		
	Vomiting		
	Cough		
	Runny nose		
	Diarrhoea or constipation		
	Chills (feeling cold)		
	Headache		
	Weakness		
	Lethargy/sleeping		
	Restlessness or irritability		
	Other Consultations or medications recently taken		
	Nature of previous treatment		
	Allergies		
	Vaccination status		
	Other (specify):_____		
B2	Did the Health worker examine the patient for:	**Yes**	**No**
	Temperature		
	Pulse/ heart beat		
	RR/chest		
	Blood pressure		
	Abdomen palpation		
	Pallor		
	Signs of dehydration		
	Eyes		
	Ears		
	Throat		
	Cervical lymph nodes		
	Skin rash/infection		
	Local infection (wounds/abscess/boil)		
	Other (specify):_____		
B2	Did the Health worker request any lab tests for malaria:	**Yes**	**No**
	Malaria Rapid Test		
	Malaria Slide		
	Other (specify) _____		

C. Diagnosis & Treatment of Malaria Observations				
C1	Did patient actually receive a blood test for malaria?	No.....0 Yes.....1 Don't know……..…….9		
C2	What was the result?	Negative.....0 Positive.....1 Don't know……9		
C3	Did the health worker prescribe an antimalarial?	No.....0 Yes.....1 Don't know……..…….9		
C4	If yes, which antimalarial was prescribed?	AQAS……...1 AL……..……...2 Quinine……..…..3 Fansidar/SP……4 Chloroquine……..5 Other (specify)_____.....6 Don't know……..…..9		
C5	Were there any other medications given?	No.....0 Yes.....1 Don't know……..…….9		
C6	What medications were given	**Yes**	**No**	
	Antibiotic			
	Paracetamol			
	ORS			
	Other 1(Specify): _____			
	Other 2(Specify): _____			
	Other 3(Specify): _____			
C7	Who dispensed the drugs to the patient	Health worker consulting……..1 Nurse…….……2 Dispenser……..…….3 Other (specify)_____..4 Don't know……..……..9		

C8	Did the Health worker calculate the dosage of malaria medication based on the patient's weight or age?	Weight.....1 Age.....2 Both.....3 Other (specify)_____..4 Don't know……..9	
C9	Was the dose dispensed according to the patient's weight or age?	Weight.....1 Age.....2 Both.....3 Other (specify)_____...4 Don't know…..……...9	
C10	Were the drugs dispensed correctly?	No.....0 Yes.....1 Don't know…….…….9	
C11	Was the first dose taken on the spot (DOT)?	No.....0 Yes.....1 Don't know…….…….9	
C12	What was the reason for not taking the drug on the spot?	Clean water not available……..1 Fear taking the drug on empty stomach……...2 Dispenser not educated to that effect……..…3 Other (specify)_____.....4 Unknown……9	
C13	Was the patient educated about the antimalarial prescribed?	No.....0 Yes.....1 Don't know…….…….9	
C14	Were patients with danger signs/severe malaria treated and referred	Not treated or referred.....0 Both Treated & Referred.....1 Treated only.....2 Referred only.....3 Other (specify)_____.....4 Don't know…….……..9	

C15	Additional notes about patients with severe malaria/danger signs	
C16	Other observations or notes	

Appendix 3—Screening & Enrollment Form

Screening Number:	**2. Date:** ***(dd/mm/yy)***

Screening Questions		
	Yes	***No***
Patient is a child between 6 to 59 months		
Visiting health facility for treatment of fever		
Do not have signs of severe disease		
Are not being referred to another health facility		
Living within a defined distance from the health facility (<8 km/ 5 miles)		
Have not taken part in the study already or are not part of a household that has already taken part in the study		
Responsible caretakers/parents provide additional informed consent		
Does the patient meet the inclusion criteria? ***If any of the responses fall into the grey shaded area, exclude the patient from the study***		

If the patient meets the inclusion criteria please conduct informed consent and collect the enrollment information.

Patient Enrolment Information	
Assigned Study Number	☐-☐☐☐
Patient Name	
3. Patient Age (months):	_____**months**
Patient Gender (circle):	**Male** **Female**
Parent/Caregiver Name	

Parent/Caregiver Age (years):	**_____years**
Parent/Caregiver Gender	**Male Female**
Name of Spouse	
Names and ages of other Children in home	1) 2) 3)
Neighbourhood	
Home address including local identifiers	
Phone number available:	**Yes No**
f yes: **owner name and number**	1) 2) 3)

Appendix 4: Exit Interview Survey Tool

No.	A. Patient Identification & Information	
A1	Health Facility	Ross Road……..……..…..…1 George Brook……..…..…..2
A2	Patient Identification Number	☐-☐☐☐
A3	Patient Name	
A4	Parent/Caregiver Name	
A5	Interviewer ID number	
A6	Date of Interview	
A7	**INFORMED CONSENT OBTAINED?**	☐ **Yes (1) → CONTINUE** ☐ **No (0) → END**

C. Treatment Seeking

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
C1	Health Facility	Ross Road……..……..……..…1 George Brook……..……..…..2	
C1	What is the age of your child *(months)*?	☐☐ *Completed Months*	
C2	Gender of child	Female ..……1 Male ……2	
C3	How many days ago did the fever start? *If the fever started today, enter '00'* *If don't know, enter '99.*	☐☐ *Days*	
C4	How soon did you seek advice or treatment for (name's) fever?	Same day……1 Next day……..2 Two days……3 3 days or more days……4 Don't know……..9	
C5	Did you seek advice or treatment for *(name's)* fever elsewhere before coming to this health facility?	Yes.....1 No.....2 Don't know……..9	 → **C8** → **C8**

C6	Where did you **first** go for treatment?	This Health Facility……1 Hospital……2 Other Clinic (PHU)……..……..3 CBP……..…..……4 TBA……..……..…..……5 BFV……..……..…..……6 Herbalist……..……..……..7 Spiritual……..……..……8 Drug peddler/pepper doctor/quack…..……9 Drug Shop/Pharmacy……..……...10 Private Doctor/Clinic..……..……...11 Other (Specify)_____.12	
C7	Where did you go **next** for treatment?	Didn't seek second treatment……..…0 This Health Facility……1 Hospital……2 Other Clinic (PHU)……..……..3 CBP……..…..……4 TBA……..……..…..……5 BFV……..……..…..……6 Herbalist……..……..……..7 Spiritual……..……..……8 Drug peddler/pepper doctor/quack…..……9 Drug Shop/Pharmacy……..……...10 Private Doctor/clinic..……..……...11 Other (Specify)_____.12	
C8	How long did it take you to get to the health facility today?	Less than 15 min……..……1 15-30 minutes……..……2 30 -60 minutes……..……3 More than an hour……4 Other (Specify)_____.5 Don't know……..……..9	
C9	How much did you have to pay to get here (in Leones)? (if nothing insert 0)		

C10	How long did you have to wait to see a health worker today?	No wait……..……0 Less than 15 min……..……1 15-30 minutes……..……2 30 -60 minutes…….……3 More than an hour……4 Don't know……..9			
C11	Do you feel you had to wait too long	Yes.....1 No.....2 Don't know……..9			
C12	Was the health worker nice	Yes.....1 No.....2 Don't know……..9			
C13	Can you tell me what questions the health worker asked you about your child's illness?				
C14	Were you given any medications to treat your child?	No.....0 Yes.....1 Don't know……..9			→ **END** → **END**
C15	Which malaria medications did you receive? **Put a check mark (✓) under the one column that applies**	0=No	1=Yes	9=DK	
	Fixed dose AQAS				
	AL				
	Other ACT (specify)_____				
	QNN tablets				
	CQ tablets				
	SP				

C16	How did the health worker tell you how to take the medications?				
C17	Did you receive any other medications?	No.....0 Yes.....1 Don't know.....9			→ **END** → **END**
C18	What other medications did you receive? **Put a check mark (✓) under the one column that applies**	0=No	1=Yes	9=DK	
	Antibiotic				
	Paracetamol				
	ORS				
	Other 1(Specify): _____				
	Other 2(Specify): _____				
	Other 3(Specify): _____				
C20	Did the health worker tell you about any complications or situations in which you should return to the health facility?	No.....0 Yes.....1 Don't know.....9			→ **C22** →**C22**
C21	When should you return to the health facility?				
C22	Are you satisfied with your visit to the health facility today?	Yes.....1 No.....2 Don't know.....9			 → **END**
C23	Can you please tell me why or why not?				

Appendix 5--Component 4: Adherence Questionnaire

No.	A. Household Identification			
A1.	Patient Identification Number	☐ - ☐☐☐		
A2.	Patient Name			
A3.	Parent/Caregiver Name			
A4.	Village/Neighbourhood Name:			
A5.	Location Identifiers			
Visit				
		1	2	3
Interviewer ID number				
Date of Interview				
Interview Result				
Result Codes:		1 = Respondent found and consented to interview 2 = Respondent found but refused consent 3 = Respondent not home 4 = Respondent not found		
Survey Checked by supervisor		No.....0 Yes.....1		
A6.	**INFORMED CONSENT OBTAINED?** ☐ **Yes (1)** → **CONTINUE** ☐ **No (0)** → **END**			

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
A1	Has anyone in this household had this interview before?	No.....0 Yes.....1	→ **END**
A2	What medication were you prescribed for malaria? *(Do not read out the options)*	AQAS……1 AL……2 Quinine……3 Fansidar/SP……4 Chloroquine…….. 5 Other (specify)_____.....6 Don't know……99	
A3	Have you (*the respondent*) ever seen this drug before?	No.....0 Yes.....1 Don't know……9	
A4	Have you *(the respondent)* ever taken this drug before?	No.....0 Yes.....1 Don't know……9	
A5	Has your child ever taken this drug before? *(If the patient is a child)*	No.....0 Yes.....1 Don't know……9	
A6	Did you have to pay for this malaria medication?	No.....0 Yes.....1 Don't know……9	→**A8** → **A8**
A7	How much did you have to pay for the malaria medication? (Leones)		
A8	Did you pay any other fees at the health facility?	No.....0 Yes.....1 Don't know……9	→**A11** → **A11**
A9	What did you pay for?		

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES			SKIP
A10	How much did you pay? (Leones)				
A11	Who explained to you how to take the malaria medication?	Doctor/ clinical officer……..…….1 Clinic pharmacist/dispenser……..……..2 Private pharmacy……..……..3 Family ember/friend……..……..4 Other (specify)_____.….5 Don't know……..…..99			
A12	Please describe to me what the health worker told you about giving this medication to your child				
A13	Ask whether the health worker gave them any of the following advice	**No (0)**	**Yes (1)**	**DK (2)**	**N/A (9)**
	Take first dose straight away				
	Take 1 tablet a day for 3 days				
	Take 2 tablet a day for 3 days				
	Finish the treatment (take all 3 tablets)				
	Repeat the dose if child vomits within 30mins				
	Return to health facility if deteriorates/ symptoms not resolved in 3 days.				
	Other (specify)_____				
A14	Did you have any difficulties understanding how to give the malaria medication?	No.....0 Yes.....1 Don't know……..….9			**→A16** **→A16**
A15	What difficulties did you have?				

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES		SKIP
A16	Did you or your child have any dislikes about the malaria medication?	No.....0 Yes.....1 Don't know…….……9		→A18 →A18
A17	What dislikes did you or your child have?			
A18	Did your child have any side effects (or adverse events) to the malaria medication?	No.....0 Yes.....1 Don't know…….……9		→A20 →A20
A19	What side effects did s/he have?	**No (0)**	**Yes (1)**	**DK (9)**
	Weakness/fatigue			
	Anorexia			
	Nausea			
	Vomiting			
	Abdominal pain			
	Diarrhoea			
	Pruritus (Itching)			
	Rash			
	Mouth Sores or sore throat			
	dizziness			
	Headache			
	Jaundice (yellow eyes/palms)			
	Cold/flu/cough			
	Other (describe)_____			
A20	Can you show me the treatment package given?	No.....0 Yes.....1 Don't know…….……9		→A23 → A23

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
A21	*FOR INTERVIEWER:* *Look at the package. Which package did they show you or tell you they were given?*	No package.....0 Infant.....1 Small Child/Toddler.....2 Other (specify)_____.....3 Don't know……..…….9	
A22	*FOR INTERVIEWER: Write the name on the package (if available)*		
A23	Please describe to me how you **GAVE** the malaria medication to your child		
A24	*FOR INTERVIEWER:* If they missed any doses, did not complete the treatment or took any at the wrong time ask them to explain why?		

Just to cross check what you have told me, I am going to ask you again about how you gave your child the malaria medicine.

	FOR INTERVIEWER: **On the diagrams below do the following:** 1. Choose the correct diagram (co-blister package or co-formulated) 2. Colour in or mark the circles of tablets that were reported to be taken 3. Ask them when each of the pills were taken: what day the pills were taken on (Day 1, 2, 3), if they were taken in the morning or the evening 4. Ask how each dose was taken and whether they were taken with water, food, milk, crushed, whole etc... 5. Put an x through the tablets that you see are empty in the blister.

AL Package

Infant

Day 1		Day 2		Day 3	
					
Blister Empty	No.....0 Yes.....1	Blister Empty	No.....0 Yes.....1	Blister Empty	No.....0 Yes.....1
When taken:		When taken:		When taken:	
How taken:		How taken:		How taken:	

Toddler (small child)

Day 1		Day 2		Day 3	
					
Blister Empty	No.....0 Yes.....1	Blister Empty	No.....0 Yes.....1	Blister Empty	No.....0 Yes.....1
When taken:		When taken:		When taken:	
How taken:		How taken:		How taken:	

Fixed-Dose/Co-formulated Package

Infant (Pink)

Day 1		Day 2		Day 3	
○		○		○	
Blister Empty	No.....0 Yes.....1	Blister Empty	No.....0 Yes.....1	Blister Empty	No.....0 Yes.....1
When taken:		When taken:		When taken:	
How taken:		How taken:		How taken:	

Toddler (small child) Purple

Day 1		Day 2		Day 3	
○		○		○	
Blister Empty	No.....0 Yes.....1	Blister Empty	No.....0 Yes.....1	Blister Empty	No.....0 Yes.....1
When taken:		When taken:		When taken:	
How taken:		How taken:		How taken:	

FOR INTERVIEWER:	
A28	Any other comments or observations made (for either treatment):

B. Household Demographic Information

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B1	What is the age of your child (Name) that visited the clinic three days ago? * Enter '00', if less than 1 year	☐☐ *Completed years*	
B2	Gender of child	Female ..……..1 Male ……..2	
B3	What is the main language spoken in this household?	Krio.....1 Temne ……...2 Mende ……...3 Fullah ……..4 Other (specify)_____.....5	
B4	What is the main religion in this household?	Christian……..……1 Muslim……..……..2 Other (specify)_____.....3	
B5	Gender of Parent/caretaker	Female ..……..1 Male ……..2	
B6	Age of Parent/caretaker	☐☐	
B7	For the **parent/caretaker**, what is the highest level of school attended: primary, secondary, or higher?	No Schooling……..……..…0 Primary.....1 Secondary.....2 Higher .....3 Technical/Vocational School……...4 Arabic School.....5 Other (specify)_____.6	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B8	What is the main source of drinking water for members of your household?	Piped water……..……1 Tube well or borehole .....2 Dug well……..……3 Rainwater ..... 4 Tanker truck .....5 Cart with small tank .....6 Bottled water./plastic bag.....7 Other (specify)_____.8	
B9	What kind of toilet facility does your household use?	Flush or pour flush toilet……...1 Pit latrine……..……2 Pit latrine without slab/open pit……..3 Composting toilet.....4 Bucket toilet.....5 Hanging toilet/hanging latrine .....6 No facility/bush/field.....7 Other (specify)_____.8	
B10	What type of fuel does your household mainly use for cooking?	Electricity/NPA.....1 LPG/Natural gas.....2 Biogas.....3 Kerosene.....4 Charcoal.....5 Firewood/straw .....6 Dung .....7 Other (specify)_____.8	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES		SKIP
B11	Main material of the floor. RECORD OBSERVATION.	**Natural floor** Earth/sand.....11 Dung .....12 **Rudimentary floor** Wood planks.....21 Palm/bamboo .....22 **Finished floor** Parquet or polished wood.....31 Vinyl or asphalt strips .....32 Ceramic tiles.....33 Cement.....34 Carpet .....35 Other (specify) _____ 36		
B12	Main material of the roof. RECORD OBSERVATION.	**Basic roof** Thatch.....11 Bamboo.....12 **Rudimentary roof** Wood.....21 Tarpaulin .....22 **Finished roof** Iron sheets .....31 Concrete.....32 Other (specify) _____ 33		
B13	Does your household have the following assets?	**No (0)**	**Yes (1)**	
	Electricity from grid?			
	A generator?			
	Solar panels?			
	A radio?			
	A television?			
	A mobile telephone?			
	A refrigerator?			
	An electric iron?			
	A bicycle?			

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES		SKIP
	A motorcycle or scooter?			
	A cow, goat, or sheep?			
	A canoe or boat?			
	An electric fan?			
	A domestic worker (unrelated to household head)?			
	A CD or cassette player?			
	A plough?			
	A vehicle (car or truck)?			
	Agricultural land?			

C. Malaria Knowledge

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
C1	Can you tell me the main signs or symptoms of malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Fever/Excessive sweating……1 Feeling cold/chills……2 Headache……3 Nausea and Vomiting……4 Diarrheal……5 Dizziness……6 Loss of appetite……7 Body ache or joint pain……8 Pale eyes……9 Body weakness……10 Refusing to eat or drink……11 Other (Specify)_____..12 Don't know……99	
C2	What drugs do you use treat malaria? CIRCLE ALL ANSWERS MENTIONED	ACT …… …..1 Chloroquine……2 SP/Fansidar……3 Quinine……4 Panadol/ Paracetamol……5 Traditional medicine/Herbs……6	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
		Other (specify)_____.....7 Don't know……99	
C3	Which drug does the ministry of health recommend for the treatment of malaria? **CIRCLE ONE**	ACT ……..... …..1 Chloroquine……..……..……2 SP/Fansidar……..…….……..3 Quinine……..…..…..4 Other (specify)_____.....5 Don't know……99	

Appendix 6--Component 5: Caregiver In-depth Interview

	Health Facility	Ross Road……..……..…..…1 George Brook……..…..…..2
	Interviewer Initials	
	Date	
	Supervisor Initials	
	Survey Checked by supervisor	No.....0 Yes.....1
	INFORMED CONSENT OBTAINED?	☐ **Yes (1) → CONTINUE** ☐ **No (0) → END**

Background information on informant

	Interview Number	
	Sex	Female ...……1 Male …….2
	Age (years)	
	Parent/Caregiver Name	

Conducting the Discussion	
Introduction	1. What can people in your community do to treat fever?
Treatment Seeking	1. How soon do you seek treatment for fever? → ***Probe: Why wait or why go soon?*** 2. Can you tell me where you go when your child falls ill with fever? 3. Why do you choose to go to _____ (**say the source of care they mentioned**)? → ***Probe: Can you go anywhere else when your child falls ill?***

	4. Can you tell me what happened when you visited the clinic that last time you went there for your child's fever? → ***Probe: Did they do a blood test? Can you tell me about it?*** → ***Probe: What treatment/medicines did you receive?*** → ***Probe: Can you tell me how they gave you the medicines?*** → ***Probe: Where you told how to take the medicines?*** → ***Probe: Anything else you want to tell me about your visit?***
Malaria	1. Are there any other names that you or people in your community can use for malaria? 2. When a child has fever how do you know if it is malaria? → ***Probe: Anything else****?* → ***Probe: How do you know it wasn't another illness?*** 3. How do you treat malaria in this community? → ***Probe: Anything else****?* → ***Probe: Which are the most effective? Why?*** → ***Probe: Anything else****?* 4. For each of the three medications (AQ+AS, AQAS and AL) show them the package and ask: → ***Probe:*** Can you tell me what you call this malaria medicine? → ***Probe:*** What do you call this medicine?

Malaria—Treatment ***Co-Pack AQ+AS***	1. Could you tell me your experience with Amodiaquine + Artesunate that comes in this package (show blister pack) ***→ Probe: What do you like about this medicine? Dislike?*** ***→ Probe: Have you had any problems with this medication?*** ***→ Probe: Is there anything else you want to tell me?*** 2. When you take this medicine can you or your child finish the entire dose?
Malaria—Treatment ***Fixed-dose AQAS***	1. Could you tell me your experience with Amodiaquine + Artesunate that comes in this package (show FDC) ***→ Probe: What do you like about this medicine? Dislike?*** ***→ Probe: Have you had any problems with this medication?*** ***→ Probe: Is there anything else you want to tell me?*** 2. When you take this medicine can you or your child finish the entire dose?
Malaria—Treatment ***Fixed-dose AL***	1. Could you tell me your experience with artemether-lumefantrine that comes in this package (show package) ***→ Probe: What do you like about this medicine? Dislike?*** ***→ Probe: Have you had any problems with this medication?*** ***→ Probe: Is there anything else you want to tell me?*** 2. When you take this medicine can you or your child finish the entire dose?
Summary	• ***Is there anything else you want to say that you forgot to say before?*** ***→ Probe: Anything else?*** • Mention the main themes discussed and the responses given ***(be brief—DO NOT read out all of the notes).*** • ***Is there anything that you would like to correct or add?***

Appendix 7--Component 6: Follow-up RDT Negative Surveys

No.	A. Household Identification			
A1.	Patient Identification Number	☐ - ☐☐☐		
A2.	Patient Name			
A3.	Parent/Caregiver Name			
A4.	Village/Neighbourhood Name:			
A5.	Location Identifiers			
Visit				
		1	2	3
Interviewer ID number				
Date of Interview				
Interviewed in clinic or at home				
Interview Result				
Result Codes:		1 = Respondent found and consented to interview 2 = Respondent found but refused consent 3 = Respondent not home 4 = Respondent not found		
Survey Checked by supervisor		No.....0 Yes.....1		
A6.	**INFORMED CONSENT OBTAINED?** ☐ **Yes (1)** → **CONTINUE** ☐ **No (0)** → **END**			

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
A7	Has anyone in this household had this interview before?	No.....0 Yes.....1	 → **END**
A8	When you went to the clinic for your child's illness did your child receive a blood test?	No.....0 Yes.....1 Don't know……9	
A9	Can you tell me the result of the test?	Negative.....0 Postivie.....1 Don't know……9	
A10	Do you believe that the test was correct?	No.....0 Yes.....1 Don't know……9	
A11	Do you prefer that your child is tested for malaria to decide to give malaria treatment or do you prefer that your child is given malaria treatment every time they have fever?	Tested first……..1 Fever……2 Both……..3 Don't know/Care……4	
A12	What medications were you prescribed when you attended clinic? *(Do not read out the options)*	None……0 Septrin/ Co-trimox……..1 Amoxicillin……2 Paracetamol……3 ORS/Electrolytes……4 Vitamins/Multivitamin……5 Iron/Ferrous Sulphate……6 Zinc……7 Piriton……8 Other (specify) _____....9 Don't know……99	→ **A15** → **A15**
A13	Did you have to pay for this medication?	No.....0 Yes.....1 Don't know……9	→ **A15** → **A15**
A14	How much did you have to pay for the medication? (Leones)		
A15	Did you pay any other fees at the health facility?	No.....0 Yes.....1 Don't know……9	→ **A18** → **A18**

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES			SKIP
A16	What did you pay for?				
A17	How much did you pay? (Leones)				
A18	Ask whether the health worker gave them any of the following advice	**No (0)**	**Yes (1)**	**DK (2)**	**N/A (9)**
	Repeat the dose if child vomits within 30mins				
	Return to health facility if deteriorates/ symptoms not resolved in 3 days.				
	Other (specify)_____				
A19	Did you have any difficulties understanding how to give the medication you received from the clinic?	No.....0 Yes.....1 Don't know……9			→ **A21** → **A21**
A20	What difficulties did you have?				
A21	Did you give your child anything else to treat this illness?	No.....0 Yes.....1 Don't know……9			→ **A24** → **A24**
A22	What else did you give your child?				
A23	Where did it come from?				
A24	Is your child still unwell? **IF ANSWERS YES PLEASE ENSURE CHILD IS SEEN BY NURSE/DOCTOR/MEDICAL OFFICER**	No.....0 Yes.....1 Don't know……9			→**A26** →**A26**
A25	How many days after visiting clinic did the child get better?	1……1 2……2 3……3 4……4 5……5 6……6 7……7 Don't know……..99			

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
A26	After your visit to the clinic did you taken your child to see anyone else to help with this illness?	No……0 This Health Facility……1 Hospital……..2 Other Clinic (PHU)……..……..3 CBP……..……4 TBA……..……..……..……5 BFV……..……..……..……6 Herbalist……..……..……..7 Spiritual……..……..……..8 Drug peddler/pepper doctor/quack…..……9 Drug Shop/Pharmacy……..……...10 Private Doctor/Clinic...……..……...11 Other (Specify)_____.99	→**A35**
A27	How much did you pay to travel to that place? (IF NOTHING WRITE 0 (ZERO))		
A28	How much did you pay for the services? (IF NOTHING WRITE 0 (ZERO))		
A29	Were you given any medications or treatments?	No.....0 Yes.....1 Don't know……9	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
A30	Which medications were you given? **MARK ALL THAT ARE MENTIONED**	Nothing/no medications……0 Anti-malarial ……1 Septrin/ Co-trimox……2 Amoxicillin……3 Paracetamol……4 ORS/Electrolytes……5 Vitamins/Multivitamin……6 Iron/Ferrous Sulphate……7 Zinc……8 Piriton……9 Herbal medication……10 Other (specify) _____..11 Don't know……99	→**A35** →**A35** →**A35** →**A35** →**A35** →**A35** →**A35** →**A35** →**A35** →**A35** →**A35**
A30	What was the exact name of the antimalarial medication? (**IF THE PACKAGE IS AVAILABLE LOOK AT THE PACKAGE TO CONFIRM**)	Artesunate + amodiaquine……1 Artemether-lumefantrine (coartem/lokmal).2 Quinine……3 Unsure……4 Other (specify)……5 Don't know……99	
A31	How much did you pay for the antimalarial? (IF NOTHING WRITE 0 (ZERO))		
A32	Did your child take all of the antimalarial medication?	No……0 Yes……1 Some of it……2 Don't know……9	
A33	Please describe to me how you **GAVE** the malaria medication to your child		
A34	Do you feel this medication helped your child?	No……0 Yes……1 Don't know……9	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
A35	How would you describe your child's health now? **CHILDREN THAT ARE WORSE SHOULD RETURN TO THE HEALTH FACILITY IMMEDIATELY**	No change/same……..0 Better……1 Improving/Still a little sick……2 Worse……3 Don't know……9	**→A37** **→A37** **→A37**
A36	If the child is now well or improving, what do you think made the child better?	Treatment given in this clinic……0 Treatment caregiver gave……1 Treatment given elsewhere……....2 Child recovered naturally……...3 Other (please specify)……4 Don't know……9	
A37	If your child has another fever would you return to the government clinic?	No.....0 Yes.....1 Don't know……9	 **→A39** **→A39**
A38	If no, why not		
A39	Any other comments or observations		

B. Household Demographic Information

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B1	What is the age of your child (Name) that visited the clinic three days ago?	☐☐ *Months*	
B2	Gender of child	Female .....1 Male 2	
B3	What is the main language spoken in this household?	Krio.....1 Temne .....2 Mende .....3 Fullah .....4 Other (specify)_____.....5	
B4	What is the main religion in this household?	Christian.....1 Muslim.....2 Other (specify)_____.....3	
B5	Gender of Parent/caretaker	Female .....1 Male 2	
B6	Age of Parent/caretaker	☐☐ Years	
B7	For the **parent/caretaker**, what is the highest level of school attended: primary, secondary, or higher?	No Schooling.....0 Primary.....1 Secondary.....2 Higher .....3 Technical/Vocational School.....4 Arabic School.....5 Other(specify)_____.6	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
B8	What is the main source of drinking water for members of your household?	Piped water……..……1 Tube well or borehole .....2 Dug well…….……3 Rainwater ..... 4 Tanker truck .....5 Cart with small tank .....6 Bottled water./plastic bag.....7 Other (specify)_____.8	
B9	What kind of toilet facility does your household use?	Flush or pour flush toilet……...1 Pit latrine…….……2 Pit latrine without slab/open pit……..3 Composting toilet.....4 Bucket toilet.....5 Hanging toilet/hanging latrine .....6 No facility/bush/field.....7 Other (specify)_____.8	
B10	What type of fuel does your household mainly use for cooking?	Electricity/NPA.....1 LPG/Natural gas.....2 Biogas .....3 Kerosene.....4 Charcoal.....5 Firewood/straw .....6 Dung .....7 Other (specify)_____.8	
B11	Main material of the floor. RECORD OBSERVATION.	**Natural floor** Earth/sand.....11 Dung .....12 **Rudimentary floor** Wood planks.....21 Palm/bamboo .....22 **Finished floor** Parquet or polished wood .....31 Vinyl or asphalt strips .....32 Ceramic tiles.....33 Cement.....34 Carpet .....35 Other (specify) _____ 36	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES		SKIP
B12	Main material of the roof. RECORD OBSERVATION.	**Basic roof** Thatch.....11 Bamboo.....12 **Rudimentary roof** Wood.....21 Tarpaulin.....22 **Finished roof** Iron sheets.....31 Concrete.....32 Other(specify) _____ 33		
B13	Does your household have the following assets?	**No (0)**	**Yes (1)**	
	Electricity from grid?			
	A generator?			
	Solar panels?			
	A radio?			
	A television?			
	A mobile telephone?			
	A refrigerator?			
	An electric iron?			
	A bicycle?			
	A motorcycle or scooter?			
	A cow, goat, or sheep?			
	A canoe or boat?			
	An electric fan?			
	A domestic worker (unrelated to household head)?			
	A CD or cassette player?			
	A plough?			
	A vehicle (car or truck)?			
	Agricultural land?			

C. Malaria Knowledge

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
C1	Can you tell me the main signs or symptoms of malaria? MULTIPLE RESPONSES possible **PROBE ONCE (Anything else?)**	Fever/Excessive sweating……1 Feeling cold/chills……2 Headache……3 Nausea and Vomiting……4 Diarrheal……5 Dizziness……6 Loss of appetite……7 Body ache or joint pain……8 Pale eyes……9 Body weakness……10 Refusing to eat or drink……11 Other (Specify)_____..12 Don't know……99	
C2	What drugs do you use treat malaria? CIRCLE ALL ANSWERS MENTIONED	ACT …… …..1 Chloroquine……2 SP/Fansidar……3 Quinine……4 Panadol/ Paracetamol……5 Traditional medicine/Herbs……6 Other (specify)_____.....7 Don't know……99	
C3	Which drug does the ministry of health recommend for the treatment of malaria? **CIRCLE ONE**	ACT …… …..1 Chloroquine……2 SP/Fansidar……3 Quinine……4 Other (specify)_____.....5 Don't know……99	

Appendix 8--Information Sheets by Component

Information for Participants
Component 1— Health Worker Interview

Protocol Title:	Adherence to Artemisinin-Based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone
Site of Research:	Ross Road and George Brook PHU, Freetown, Sierra Leone
Sponsor:	London School of Hygiene & Tropical Medicine
Principal Investigator:	Kristin Banek, MPH and PhD Candidate
Date:	2 April 2013

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to talk to others about the study, if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Kristin Banek a PhD candidate from the London School of Tropical Medicine (LSHTM) and the Ministry of Health and Sanitation are doing a study to collect information on how patients are treated for fever/malaria in this area. We would like to understand which factors help and hinder the diagnosis and treatment of fever/malaria. This study involves several parts, including observing health workers and their patients and interviews with health workers and caregivers.

Why have I been chosen?

For this part of the study, we would like to learn more about how health workers diagnose and treat patients with fever and how they feel about the current malaria treatment options. To do this, we would like to interview health workers working at this clinic.

Do I have to take part?

You are free to choose not to participate in the study. We will describe the study and make sure you explain the study by using this information sheet. If you agree to take part, we will then ask you to sign a consent form. Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may change your mind at any time. No matter what decision you take, there will be no penalty to you in any way.

What will happen to me if I take part?

The study will take place over the next four months. However, your interview will only take around an hour to complete. If you agree to take part, a member of the research team will ask you some questions about the diagnosis and treatment of malaria. We will record the interview using a digital voice recorder and will make notes during the interview.

Costs and payments

There are no direct costs to you for taking part in this study, except for your time. You will not be paid for taking part in this study.

What are the possible disadvantages and risks of taking part?

Participation in any research study may involve a loss of privacy. Information exchanged during the interview will be recorded, but your name will not be used in any reports or publications. No quotes or other results arising from your participation in this study will be included in any reports or publications, even anonymously, without your agreement. The information obtained from these interviews will only be used by the project researchers and stored in a secure location. We will do our best to make sure that the personal information gathered for this study is kept private.

What are the possible benefits of taking part?

There will be no direct benefit to you from participating in this study. However, the information that you provide may help to improve health services and malaria treatment in Sierra Leone.

Will my taking part in the study be kept confidential?

Yes. We will attempt to keep all information collected about you during the course of the research strictly confidential. If you join the study, the data collected for the study may be looked at by authorized persons from the London School of Hygiene & Tropical Medicine and the Ministry of Health and Sanitation. They may also be looked at by LSHTM supervisors to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

What will happen if I don't want to carry on with the study?

You can decide to stop participating at any time. Just tell the project researcher right away if you wish to stop. We will only use the data that you consent to us using.

What will happen to the results of the research study?

The results of this research will be published in medical journals and disseminated to the Ministry of Health and Sanitation, to the study health facility and their catchment areas and to the wider international malaria community.

Who has reviewed the study?

This study was reviewed and approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, the LSHTM Clinical Trial Sub-committee and the Sierra Leone Ethics and Scientific Review Committee.

Contact Details

If you have any questions, comments or concerns about taking part in this study, you can contact Kristin Banek, Lead Investigator, 076324648 or Dr. Smith, Programme Manager, National Malaria Control Programme, 076611042. If for any reason you do not wish to do this, or you still have concerns about doing so, you may contact the Sierra Leone Ethics and Scientific Review Committee at telephone number 078463696.

Consent to participate in the study

You may keep this information sheet if you wish. Participation in this study is voluntary. You have the right to decline to participate in the study, or to withdraw from it at any point without penalty. If you do not wish to participate in the study, you should inform the researcher now. If you do not agree to quotes or other results arising from your participation in the study being included, even anonymously, in any reports about the study, please tell the researcher now. **Do you agree to participate in this study?** You will be given a copy of the information sheet and a signed consent form to keep. Thank you for considering taking the time to read this sheet.

Information for Participants
Component 2—Observations: Health Worker

Protocol Title:	Adherence to Artemisinin-Based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone
Site of Research:	Ross Road and George Brook PHU, Freetown, Sierra Leone
Sponsor:	London School of Hygiene & Tropical Medicine
Principal Investigator:	Kristin Banek, MPH and PhD Candidate
Date:	2 April 2013

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to talk to others about the study, if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Kristin Banek a PhD candidate from the London School of Tropical Medicine (LSHTM) and the Ministry of Health and Sanitation are doing a study to collect information on how patients are treated for fever/malaria in this area. We would like to understand which factors help and hinder the diagnosis and treatment of fever/malaria.

Why have I been chosen?

For this part of the study, we would like to learn more about how health workers actually diagnose and treat patients with fever. To do this, we would like to observe interactions between health workers and caregivers of ill children at this health centre. We are specifically interested in observing interactions with parents/caregivers and their children 6 to 59 months who have fever and no danger

signs of severe disease. We would like to learn about what usually happens between health workers, patients/ caregivers.

Do I have to take part?

You are free to choose not to participate in the study. We will describe the study and make sure you explain the study by using this information sheet. If you agree to take part, we will then ask you to sign a consent form. Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may change your mind at any time. No matter what decision you take, there will be no penalty to you in any way.

What will happen to me if I take part?

If you agree to take part, a member of the research team will join you during your work in the room where you see patients to record your interactions with patients and their caregivers. Both the health worker and parent/caregiver need to agree to the observation or we will not observe the consultation. We would like you to conduct your consultation with the patient as you would normally; you are not expected to do anything differently to your usual practice while we are present. The individual observation will only take as long as your regular consultations (15-20 min each). We would like to observe your interactions with patients over the next 3-4 months, starting today. Each day, we would like to record your interaction with at least one patient, and up to 10 patients.

Costs and payments

There are no direct costs to you for taking part in this study, except for your time. You will not be paid for taking part in this study.

What are the possible disadvantages and risks of taking part?

Participation in any research study may involve a loss of privacy. Information exchanged during the interview will be recorded, but your name will not be used in any reports or publications. No quotes or other results arising from your participation in this study will be included in any reports or publications, even anonymously, without your agreement. The information obtained from these interviews will only be used by the project researchers and stored in a secure location. We will do our best to make sure that the personal information gathered for this study is kept private.

What are the possible benefits of taking part?

There will be no direct benefit to you from participating in this study. However, the information that you provide may help to improve health services and malaria treatment in Sierra Leone.

Will my taking part in the study be kept confidential?

We will keep the study information private. Under certain conditions, people responsible for making sure that the research is done properly may review your study records. This might include people involved with sponsoring or monitoring the study. All of these people are also required to keep your identity confidential. Otherwise, the information that identifies you will not be given out to people who are not working on the study.

What will happen if I don't want to carry on with the study?

You can decide to stop participating at any time. Just tell the project researcher right away if you wish to stop. We will only use the data that you consent to us using.

What will happen to the results of the research study?

The results of this research will be published in medical journals and disseminated to the Ministry of Health and Sanitation, to the study health facility and their catchment areas and to the wider international malaria community.

Who has reviewed the study?

This study was reviewed and approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, the LSHTM Clinical Trial Sub-committee and the Sierra Leone Ethics and Scientific Review Committee.

Contact Details

If you have any questions, comments or concerns about taking part in this study, you can contact Kristin Banek, Lead Investigator, 076324648 or Dr. Smith, Programme Manager, National Malaria Control Programme, 076611042. If for any reason you do not wish to do this, or you still have concerns about doing so, you may contact the Sierra Leone Ethics and Scientific Review Committee at telephone number 078463696.

Consent to participate in the study

You may keep this information sheet if you wish. Participation in this study is voluntary. You have the right to decline to participate in the study, or to withdraw from it at any point without penalty. If you do not wish to participate in the study, you should inform the researcher now. If you do not agree to quotes or other results arising from your participation in the study being included, even anonymously, in any reports about the study, please tell the researcher now. **Do you agree to participate in this study?** You will be given a copy of the information sheet and a signed consent form to keep. Thank you for considering taking the time to read this sheet.

Information for Participants

Components 2, 3 & 4—Observations, Treatment & Exit Interview: Parent/Caregiver

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Protocol Title:	Adherence to Artemisinin-Based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone
Site of Research:	Ross Road and George Brook PHU, Freetown, Sierra Leone
Sponsor:	London School of Hygiene & Tropical Medicine
Principal Investigator:	Kristin Banek, MPH and PhD Candidate
Date:	2 April 2013

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to talk to others about the study, if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Kristin Banek a PhD candidate from the London School of Tropical Medicine (LSHTM) and the Ministry of Health and Sanitation are doing a study to collect information on how patients are treated for fever/malaria in this area. We would like to understand which factors help and hinder the diagnosis and treatment of fever/malaria.

Why have I been chosen?

For this part of the study, we would like to learn more about how health workers diagnose and treat patients with fever. To do this, we would like to observe interactions between health workers and caregivers of ill children at this health centre. We are specifically interested in observing interactions with parents/caregivers and their children 6 to 59 months who have fever and no danger signs of severe disease. We would like to learn about what usually happens between health workers, patients,

and caregivers. We would also like to learn more about how patients view their visit to the health facility. To do this, we would like to interview parents/caregivers of children 6 to 59 months that have come to the health facility for the treatment of fever. We would like to learn about what happened during your visit and your opinion about the services.

Do I have to take part?

You are free to choose not to participate in the study. We will describe the study and make sure you explain the study by using this information sheet. If you agree to take part, we will then ask you to sign a consent form. Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may change your mind at any time. No matter what decision you take, there will be no penalty to you in any way.

What will happen to me and my child if I take part?

If you agree to take part, a member of the research team will join you during your consultation with the health worker. Both the health worker and parent/caregiver need to agree to the observation or we will not observe the consultation. We would like you to act as you would normally; you are not expected to do anything differently while we are present.

If your child is diagnosed with malaria the health worker will give your child the national malaria treatment (amodiaquine+artesunate). Currently the Ministry of Health offers this medicine in two types of packets. Your child will be assigned through lottery to receive one version for the treatment of this malaria episode.

After you are finished with your clinic visit today, we would like to ask you some questions about your experience visiting the health Centre, provision of care for your child, and your normal practices with regard to seeking treatment for your child. We will write your answers on our survey forms.

What do I have to do?

Please go about your clinic visit as you would normally. We ask that you answer the interview questions as truthfully as you can. If for any reason your child's condition does not improve or gets worse once you return to your home, you should come back to the health facility immediately.

Costs and payments

There are no direct costs to you for taking part in this study, except for your time. Neither you nor the health workers at the clinic will be paid for taking part in this study.

What are the possible disadvantages and risks of taking part?

Risks involved with treatment

1) All drugs have the potential to have side effects. The side effects with some of these drugs may be more common when two drugs are taken together. However, serious health

problems, including death, have rarely been reported following treatment with the study medications.

a. Major side effects: Severe problems that have been reported include the following:
    i. Amodiaquine - lowering of blood counts, bone marrow failure, inflammation of the liver, and death
    ii. artesunate - lowering of the blood counts and inflammation of the liver
    iii. co-formulated Amodiaquine+Artesunate – lowering of the blood counts and inflammation of the liver
    iv. artemether-lumefantrine –allergic reactions and irregular heartbeats

b. Minor side effects. The following side effects have been reported in association with the study medications-
    i. amodiaquine - nausea, vomiting, diarrhoea, lethargy (tiredness)
    ii. artesunate - headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, tinnitus (ringing noise in ears), neutropenia (low blood count), abnormalities of liver tests.
    iii. co-formulated Amodiaquine+Artesunate – anorexia, nausea, vomiting, diarrhoea, abdominal pain, headache, lethargy (tiredness), weakness, cough.
    iv. artemether-lumefantrine – fever, cough, headache, anorexia, nausea, vomiting, dizziness,

2) Severe malaria: Your child may get sicker or develop malaria that is severe even after receiving treatment with study medications. If your child shows any evidence of severe malaria (including persistent vomiting, low blood counts, convulsions, confusion, or coma) please come back to the health facility as soon as possible where they can be assessed, treated and/or referred for possible admission to hospital.

3) Unknown Risks: The research treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about your child's participation in the study.

Risks involved in study procedures

1) Randomization: Your child will be assigned to a treatment group by chance. The treatment your child receives may prove to be less effective or to have more side effects than the other study treatments or than other available treatments. This will not be known until after the study is completed.

2) Confidentiality: Participation in research may involve a loss of privacy, but information about you and your child will be handled as confidentially as possible. Medical information related to malaria will be collected on your child, but only the people working on the study will see it. Anyone assigned to review this study will be granted direct access to your child's records, if necessary, for verification of the study procedures and data. No quotes or other results arising from your participation in this study will be included in any reports or publications, even anonymously, without your agreement. We will do our best to make sure that the personal information gathered for this study is kept private.

What are the possible benefits of taking part?

There will be no direct benefit to you from participating in this study. However, the information that you provide may help to improve health services and malaria treatment in Sierra Leone.

What happens when the research study stops?

After the study stops, treatment at this clinic will be provided at this health facility as per the policies of the Ministry of Health and Sanitation.

Will my taking part in the study be kept private?

We will keep the study information private. Under certain conditions, people responsible for making sure that the research is done properly may review your study records. This might include people involved with sponsoring or monitoring the study. All of these people are also required to keep your identity confidential. Otherwise, the information that identifies you will not be given out to people who are not working on the study.

What if relevant new information becomes available?

If the study is stopped for any reason, you will be told why and advised on what you should do the next time your child is ill.

What will happen if I don't want to carry on with the study?

You can decide to stop participating at any time. Just tell the project researcher right away if you wish to stop. We will only use the data that you consent to us using.

What will happen to the results of the research study?

The results of this research will be published in medical journals and disseminated to the Ministry of Health and Sanitation, to the study health facility and their catchment areas and to the wider international malaria community.

Who has reviewed the study?

This study was reviewed and approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, the LSHTM Clinical Trial Sub-committee and the Sierra Leone Ethics and Scientific Review Committee.

Contact Details

If you have any questions, comments or concerns about taking part in this study, you can contact Kristin Banek, Lead Investigator, 076324648 or Dr. Smith, Programme Manager, National Malaria Control Programme, 076611042. If for any reason you do not wish to do this, or you still have concerns about doing so, you may contact the Sierra Leone Ethics and Scientific Review Committee at telephone number 078463696.

Consent to participate in the study

You may keep this information sheet if you wish. Participation in this study is voluntary. You have the right to decline to participate in the study, or to withdraw from it at any point without penalty. If you do not wish to participate in the study, you should inform the researcher now. If you do not agree to quotes or other results arising from your participation in the study being included, even anonymously, in any reports about the study, please tell the researcher now. **Do you agree to participate in this study?** You will be given a copy of the information sheet and a signed consent form to keep. Thank you for considering taking the time to read this sheet.

Information for Participants

Components 4 & 5—Parent/Caregiver Follow-up Survey & In-Depth Interviews

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Protocol Title:	Adherence to Artemisinin-Based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone
Site of Research:	Ross Road and George Brook PHU, Freetown, Sierra Leone
Sponsor:	London School of Hygiene & Tropical Medicine
Principal Investigator:	Kristin Banek, MPH and PhD Candidate
Date:	2 April 2013

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to talk to others about the study, if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Kristin Banek a PhD candidate from the London School of Tropical Medicine (LSHTM) and the Ministry of Health and Sanitation are doing a study to collect information on how patients are treated for fever/malaria in this area. We would like to understand which factors help and hinder the diagnosis and treatment of fever/malaria.

Why have I been chosen?

For this part of the study, we would like to learn more about how parents/caregivers gave the malaria medication and how children took the medications provided at their visit to the health facility a few days ago. To do this, we would like to interview the parents/caregivers of children 6 to 59 months that

received treatment for fever/malaria. We would like to learn about what happened during your visit and your experience with the medication.

Do I have to take part?

You are free to choose not to participate in the study. We will describe the study and make sure you explain the study by using this information sheet. If you agree to take part, we will then ask you to sign a consent form. Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may change your mind at any time. No matter what decision you take, there will be no penalty to you in any way.

What will happen to me and my child if I take part?

Today, we would like to ask you some questions about your experience with treating your child for their most recent malaria illness. We will write your answers on our survey forms. The interview should last no more than 1 hour.

Twenty parents/caregivers will be selected for further questions. If you are willing, we will ask some additional questions beyond the survey about you and your child's experience and opinions about the malaria medication you were given. For this part of the interview we will take notes and will and will record the interview using a digital voice recorder. (Show voice recorder).

Costs and payments

There are no direct costs to you for taking part in this study, except for your time. You will not be paid for taking part in this study.

What are the possible disadvantages and risks of taking part?

Participation in research may involve a loss of privacy, but information about you and your child will be handled as confidentially as possible. Medical information related to malaria will be collected on your child, but only the people working on the study will see it. Anyone assigned to review this study will be granted direct access to your child's records, if necessary, for verification of the study procedures and data. No quotes or other results arising from your participation in this study will be included in any reports or publications, even anonymously, without your agreement. We will do our best to make sure that the personal information gathered for this study is kept private.

What are the possible benefits of taking part?

There will be no direct benefit to you from participating in this study. However, the information that you provide may help to improve health services and malaria treatment in Sierra Leone.

Will my taking part in the study be kept private?

We will keep the study information private. Under certain conditions, people responsible for making sure that the research is done properly may review your study records. This might include people

involved with sponsoring or monitoring the study. All of these people are also required to keep your identity confidential. Otherwise, the information that identifies you will not be given out to people who are not working on the study.

What will happen if I don't want to carry on with the study?

You can decide to stop participating at any time. Just tell the project researcher right away if you wish to stop. We will only use the data that you consent to us using.

What will happen to the results of the research study?

The results of this research will be published in medical journals and disseminated to the Ministry of Health and Sanitation, to the study health facility and their catchment areas and to the wider international malaria community.

Who has reviewed the study?

This study was reviewed and approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, the LSHTM Clinical Trial Sub-committee and the Sierra Leone Ethics and Scientific Review Committee.

Contact Details

If you have any questions, comments or concerns about taking part in this study, you can contact Kristin Banek, Lead Investigator, 076324648 or Dr. Smith, Programme Manager, National Malaria Control Programme, 076611042. If for any reason you do not wish to do this, or you still have concerns about doing so, you may contact the Sierra Leone Ethics and Scientific Review Committee at telephone number 078463696.

Consent to participate in the study

You may keep this information sheet if you wish. Participation in this study is voluntary. You have the right to decline to participate in the study, or to withdraw from it at any point without penalty. If you do not wish to participate in the study, you should inform the researcher now. If you do not agree to quotes or other results arising from your participation in the study being included, even anonymously, in any reports about the study, please tell the researcher now. **Do you agree to participate in this study?** You will be given a copy of the information sheet and a signed consent form to keep. Thank you for considering taking the time to read this sheet.

Information for Participants

Components 6—Parent/Caregiver Follow-up RDT Negative Survey

Protocol Title:	Adherence to Artemisinin-Based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone
Site of Research:	Ross Road and George Brook PHU, Freetown, Sierra Leone
Sponsor:	London School of Hygiene & Tropical Medicine
Principal Investigator:	Kristin Banek, MPH and PhD Candidate
Date:	29 Septemerl 2013

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to talk to others about the study, if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Kristin Banek a PhD candidate from the London School of Tropical Medicine (LSHTM) and the Ministry of Health and Sanitation are doing a study to collect information on how patients are treated for fever/malaria in this area. We would like to understand which factors help and hinder the diagnosis and treatment of fever/malaria.

Why have I been chosen?

For this part of the study, we would like to learn more about how parents/caregivers treat their child's current illness and what their opinion is about malaria testing after visiting the health facility health facility a few days ago. To do this, we would like to interview the parents/caregivers of children 6 to

59 months that received treatment for fever/malaria. We would like to learn about what happened during your visit and your experience with the clinic visit and treatment.

Do I have to take part?

You are free to choose not to participate in the study. We will describe the study and make sure you explain the study by using this information sheet. If you agree to take part, we will then ask you to sign a consent form. Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may change your mind at any time. No matter what decision you take, there will be no penalty to you in any way.

What will happen to me and my child if I take part?

We would like you to come back to the health facility in a few days so that we can Today, we would like to ask you some questions about your experience with treating your child for their most recent malaria illness. We will write your answers on our survey forms. The interview should last no more than 1 hour.

Costs and payments

There are no direct costs to you for taking part in this study, except for your time. You will not be paid for taking part in this study.

What are the possible disadvantages and risks of taking part?

Participation in research may involve a loss of privacy, but information about you and your child will be handled as confidentially as possible. Medical information related to malaria will be collected on your child, but only the people working on the study will see it. Anyone assigned to review this study will be granted direct access to your child's records, if necessary, for verification of the study procedures and data. No quotes or other results arising from your participation in this study will be included in any reports or publications, even anonymously, without your agreement. We will do our best to make sure that the personal information gathered for this study is kept private.

What are the possible benefits of taking part?

There will be no direct benefit to you from participating in this study. However, the information that you provide may help to improve health services and malaria treatment in Sierra Leone.

Will my taking part in the study be kept private?

We will keep the study information private. Under certain conditions, people responsible for making sure that the research is done properly may review your study records. This might include people involved with sponsoring or monitoring the study. All of these people are also required to keep your identity confidential. Otherwise, the information that identifies you will not be given out to people who are not working on the study.

What will happen if I don't want to carry on with the study?

You can decide to stop participating at any time. Just tell the project researcher right away if you wish to stop. We will only use the data that you consent to us using.

What will happen to the results of the research study?

The results of this research will be published in medical journals and disseminated to the Ministry of Health and Sanitation, to the study health facility and their catchment areas and to the wider international malaria community.

Who has reviewed the study?

This study was reviewed and approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, the LSHTM Clinical Trial Sub-committee and the Sierra Leone Ethics and Scientific Review Committee.

Contact Details

If you have any questions, comments or concerns about taking part in this study, you can contact Kristin Banek, Lead Investigator, 076324648 or Dr. Smith, Programme Manager, National Malaria Control Programme, 076611042. If for any reason you do not wish to do this, or you still have concerns about doing so, you may contact the Sierra Leone Ethics and Scientific Review Committee at telephone number 078463696.

Consent to participate in the study

You may keep this information sheet if you wish. Participation in this study is voluntary. You have the right to decline to participate in the study, or to withdraw from it at any point without penalty. If you do not wish to participate in the study, you should inform the researcher now. If you do not agree to quotes or other results arising from your participation in the study being included, even anonymously, in any reports about the study, please tell the researcher now. **Do you agree to participate in this study?** You will be given a copy of the information sheet and a signed consent form to keep. Thank you for considering taking the time to read this sheet.

Appendix 9--Standardized Consent Form

Consent form
Sierra Leone ACT Study

ID number						
Data Tool	HW	HW Ob	Ob/Tx Ex	Ad	IDI	RDT

WHAT YOUR SIGNATURE OR THUMBPRINT MEANS

Your signature or thumbprint below means that you understand the information given to you about your participation in the study and in this consent form. Your signature or thumbprint will confirm that:

1. You have read the information sheet concerning this study [or have understood the verbal explanation] and understand what will be required of you and what will happen to you and your child if you take part in the study.

2. Your questions concerning this study have been answered by a study researcher.

3. You ł understand that at any time you may withdraw from this study without giving a reason and without penalty.

4. You agree to take part in this study ☐ **Agree** ☐ **Do Not Agree**

5. If quotes are to be used, you agree to quotations from your participation in the study to be included anonymously in reports and papers about the study.
   ☐ **Agree** ☐ **Do Not Agree**

_____

Name of **Participant** *(*PRINTED)

_____

Signature or Fingerprint of **Participant** Date

_____

Name of **Research Staff** Administering Consent *(*PRINTED)

_____

Signature of **Research Staff** Administering Consent Date

_____

Name of **Person witnessing** Consent *(*PRINTED)

_____

Signature of **Person Witnessing** Consent Date

APPENDIX C: LSHTM ETHICAL APPROVAL FOR THE SECONDARY ANALYSIS

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Kristin Banek
Research Degree Student,
CRD/ITD
LSHTM
3 January 2013

Dear Kristin,

Study Title:	**Treatment seeking and adherence to ACT in Sierra Leone: A secondary analysis of national survey data**
LSHTM ethics ref:	**6342**

Thank you for your application of 30 December 2012 for the above research, which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion
Approval is dependent on local ethical approval having been received, where relevant.

Approved documents
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM ethics application	n/a	
Protocol	V1	28/12/2012

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form. All studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. At the end of the study, please notify the committee via form E5.

Yours sincerely,

[redacted]

Professor Andrew J Hall Chair
ethics@lshtm.ac.uk
http://intra.lshtm.ac.uk/management/committees/ethics/

APPENDIX D: APPROVAL TO USE KAP HOUSEHOLD SURVEY DATA

CRS
CATHOLIC RELIEF SERVICES

1

1 December 2017
Kristin Banek
Kristin.Banek@lshtm.ac.uk

As the publishers and rights holders of the "*Sierra Leone Malaria Knowledge, Attitudes and Practices (KAP) Study" report and data*, please consider this letter as formal permission for granted to Kristin Banek for the following:

1. To use data generated during the "*Sierra Leone Malaria Knowledge, Attitudes and Practices (KAP) Study*," to conduct a secondary analysis to look at factors associated with treatment completion.

2. To use part or all of the following report, including figures and tables. The final report must be cited as the source of the material. Any modifications to the material should be noted, so it is clear that the material is 'adapted from' the final report.

> Catholic Relief Services [Sierra Leone], National Malaria Control Programme (NMCP) [Sierra Leone], Statistics Sierra Leone: **Sierra Leone Malaria Knowledge, Attitudes and Practices (KAP) Study Final Report.** Freetown, Sierra Leone: CRS, NMCP and SSL; 2012.

Sincerely,

[redacted]
Name of CRS Representative

[redacted]
Name NMCP Programme Manager

[redacted]
Signature
18th Dec. 2017

[redacted]
Signature
15/12/2017

THE NATIONAL MALARIA CONTROL PROGRAMME

APPENDIX E: SIERRA LEONE ETHICAL APPROVAL FOR THE ACT ADHERENCE TRIAL

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Kristin Banek
Research Degree Student
CR / ITD
LSHTM
17 July 2013

Dear Ms Banek,

Study Title:	**Adherence to Artemisinin-based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone**
LSHTM ethics ref:	**6377**
LSHTM amend no:	**A435**

Thank you for your application of 1 July 2013 for the amendment above to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Interventions Committee.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion
Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM amendment application	n/a	30 June 2013
Protocol	1.4	30 June 2013

After ethical review
Any further changes to the application must be submitted to the Committee via an E2 amendment form. The Principal Investigator is reminded that all studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. An annual report form (form E3) is required on the anniversary of the approval of the study and should be submitted during the lifetime of the study. At the end of the study, please notify the committee via form E5.

Yours sincerely,

[redacted]

Professor John DH Porter, Chair
ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

London School of Hygiene & Tropical Medicine
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Observational / Interventions Research Ethics Committee

Kristin Banek
Research Degree
Student CR / ITD
LSHTM
17 July 2013

Dear Ms Banek,

Study Title:	**Adherence to Artemisinin-based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone**
LSHTM ethics ref:	**6377**
LSHTM amend no:	**A459**

Thank you for your application of 1 October 2013 for the amendment above to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Interventions Committee.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion
Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM amendment application	n/a	30 September 2013
Protocol	1.5	30 September 2013

After ethical review
Any further changes to the application must be submitted to the Committee via an E2 amendment form. The Principal Investigator is reminded that all studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. An annual report form (form E3) is required on the anniversary of the approval of the study and should be submitted during the lifetime of the study. At the end of the study, please notify the committee via form E5.

Yours sincerely,

[redacted]

Professor John DH Porter, Chair
ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

APPENDIX F: SIERRA LEONE ETHICAL APPROVAL FOR THE ACT ADHERENCE TRIAL

GOVERNMENT OF SIERRA LEONE

Office of the Sierra Leone Ethics and Scientific Review Committee Directorate of Training, Non-Communicable Diseases and Research Connaught Hospital Ministry of Health and Sanitation

6th August 2013

Ms. Kristen Banek
23C Pipleline/Lightfoot Boston Road
Off Wilkinson Road
Freetown

Dear Ms. Banek,

Adherence to Artemisinin-Based Combination Therapy (ACT) For the Treatment of Malaria in Sierra Leone: Revised Study Protocol Version 1.4 of 30th June 2013

This letter confirms ethical approval for amendments to the original research protocol and the supporting revised documentation.

You are reminded of the requirement to notify the Ethics Committee of any serious adverse events which occur during the study.

The Committee further stipulates as follows:

1. It must be notified in advance, if you decide to amend the research design and/or methodology at any time during the conduct of the study.
2. It must be informed if for any reason, the study is terminated prematurely.
3. On the conclusion of the study, you submit a report or any publication based on the study.

Yours sincerely,

[redacted]

Professor Hector G. Morgan
Chairman, SLESRC

Email: hgmorg2007@yahoo.com I williettav@yahoo.com

GOVERNMENT OF SIERRA LEONE
Office of the Sierra Leone Ethics and Scientific Review Committee
Directorate of Training, Non-Communicable Diseases and Research
Connaught Hospital
Ministry of Health and Sanitation

5th November, 2013

Ms. Kristen Banek
23C Pipleline/Lightfoot Boston Road
Off Wilkinson Road
Freetown

Dear Ms. Banek,

Additional Amendments to: Adherence to Artemisinin-based Combination Therapy (ACT) for the Treatment of Malaria in Sierra Leone (Protocol Version: 1.5)

This letter acknowledges the amendments contain in the revised version of the study protocol.

The Committee has considered these minor changes which were done in order to improve the quality of the study outcomes. The Committee accepts these changes.

Yours sincerely,

[redacted]

Professor, Hector G. Morgan
Chairman, SLESRC

Email: hgmorg2007@yahoo.com I williettav@yahoo.com