Providers' knowledge, preference and practice in treating patients with suspected malaria in Cameroon and Nigeria

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Declaration

I, Lindsay Jean Mangham Jefferies, 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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Abstract

Working as agents for their patients, health care providers often make treatment decisions on the patient's behalf. By establishing common standards, clinical guidelines are central to efforts to improve patient care and can expedite the introduction of new technologies. Each year considerable resources are used to disseminate clinical guidelines, though conventional public health interventions often have a limited effect in changing providers' practice.

Using economic theory and methods, research was undertaken to design and evaluate interventions to support the roll-out of malaria rapid diagnostic testing. This thesis contains five research papers on providers' knowledge, preference and practice in treating patients with malaria symptoms in Cameroon and Nigeria. In this setting, uncomplicated malaria is routinely diagnosed and treated by health workers in outpatient departments and primary health centres, or self-treated using antimalarials purchased at pharmacies and drug stores.

Major problems with malaria diagnosis and treatment were identified. Relatively few febrile patients were tested for malaria, many did not receive the recommended antimalarial, and when patients were tested for malaria the test result was often ignored when treatment was prescribed. Moreover, there was no significant relationship between providers' knowledge and their practice, and preferences over alternative antimalarials were similar among providers working in the same facility or locality.

The results of a cluster randomized trial in Cameroon demonstrated that introducing rapid diagnostic tests with enhanced training, which targeted providers' practice, was more cost-effective than introducing rapid diagnostic tests with basic training, when each was

compared to current practice. Since the trial concluded, the Ministry of Health has incorporated the enhanced training in the nationwide roll-out of rapid diagnostic testing. The findings are also relevant for policy makers elsewhere, and highlight the value in developing strategies to improve providers' adherence to malaria treatment guidelines when expanding access to malaria testing.

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I am also appreciate the love and laughter of my family and friends, not least my parents who support me in everything I do and no matter where it takes me.

Finally, I am deeply grateful to Mark for his love, and endless encouragement. He never doubted by ability to complete the PhD. This thesis is dedicated to him. The next challenge is a joint one, and I know he will offer much love, energy and support as we embark on the next stage of our lives together.

Contents

List of Figures and Tables

Abbreviations

ACT	Artemisinin Combination Therapy
AL	Artemether Lumefantrine
AM	Antimalarial
AQ	Amodiaquine
ASAQ	Artesunate Amodiaquine
ASMQ	Artesunate Mefloquine
ASSP	Artesunate Sulphadoxine-Pyrimethamine
BCC	Behaviour Change Campaign
CQ	Chloroquine
DHAPQ	Dihydroartemisinin Piperaquine
HW	Health Worker
IMCI	Integrated Management of Childhood Illnesses
MI	Multiple Imputation
MLM	Multilevel Modelling
N/A	Not Applicable
NGO	Non-Governmental Organization
NMCP	National Malaria Control Programme
OTC	Over the Counter
PMD	Patent Medicine Dealer
RCT	Randomized Control Trial
RDT	Rapid Diagnostic Test
REACT	Research on Economics of ACTs
SP	Sulphadoxine-Pyrimethamine
WHO	World Health Organization

Useful terminology

Febrile illness

Malaria is clinically suspected on the basis of fever or a history of fever since the signs and symptoms of malaria are nonspecific. In settings where the risk of malaria is high (which includes Cameroon and Nigeria), malaria should be suspected in patients that present with a fever or history of fever in the past 24 hours. Diagnosis based on clinical features alone has very low specificity and results in over-treatment. The World Health Organization (WHO) recommends parasitological confirmation of malaria in all patients before treatment is prescribed. Other possible causes of fever and the need for alternative or additional treatment should be carefully considered.

Uncomplicated Malaria

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium*. The parasites are inoculated into the human host by a feeding female anopheles mosquito. The WHO defines uncomplicated malaria as a symptomatic infection with malaria parasitaemia without signs of severity and/or evidence of vital organ dysfunction.

National Malaria Treatment Guidelines

In many countries (including Cameroon and Nigeria), national governments develop malaria treatment guidelines to advise how malaria should be diagnosed and what treatment is recommended. National guidelines are usually based on guidance published by the WHO and the local epidemiological setting. The guidelines establish a common standard which providers are expected to adhere to.

Malaria Diagnosis

Malaria can be confirmed using microscopy, which involves examining thick and thin blood slides under a microscope, or using a rapid diagnostic test (RDT), which is an antigen-based stick in which a coloured line indicates that plasmodial antigens have been detected. The WHO recommends prompt parasitological confirmation by microscopy or alternatively by RDT in all patients suspected of malaria before treatment is started. Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible.

Malaria Treatment

Malaria is treated using medicines known as antimalarials. There are different types of antimalarials, and the artemisinin combination therapy (see below) is the recommended first-line treatment for uncomplicated malaria through sub-Saharan Africa. Other types of antimalarial include: amodiaquine, chloroquine, sulphadoxine-pyrimethamine, quinine and artemisinin-monotherapy.

Artemisinin Combination Therapy (ACT)

ACT is the recommended first-line treatment for uncomplicated malaria. It is a combination of artemisinin or one of its derivatives with an antimalarial or antimalarials of a different class. The different generic types of ACT are: artemether-lumefantrine (AL); artesunate-amodiaquine (ASAQ); artesunate-mefloquine (ASMQ); artesunate-sulphadoxine-pyrimethamine (ASSP); and dihydroartemisinin-piperquine (DHAPQ). For each type there are multiple brands available. The most widely used brands include Coartem and Coarsucam.

Preface

This PhD thesis includes a collection of research papers. These papers are related, though they have been published, or submitted, as independent research contributions. As a result some information has been repeated and the terminology used is not uniformly consistent. The term 'provider' is used in many of the papers to refer to the individual health worker providing treatment, though in some instances health worker, clinician, doctor, nurse, pharmacist, patent medicine dealer and medicine retailer have been used. Similarly, facility and outlet have been used to refer to an organization where malaria treatment may be obtained, and may collectively include hospital outpatient departments, health centres, clinics, pharmacies and drug stores. However, in some instances, facility refers to public and mission hospitals and health centres. The term medicine retailer has also been used to refer collectively to private sector retail outlets, including pharmacies, drug stores, and patent medicine dealers. I should also add that having married in 2012 I changed my name, and my thesis includes papers authored as Lindsay Mangham and as Lindsay Mangham-Jefferies.

PART I

INTRODUCTION

1. Introduction

1.1 Malaria diagnosis and treatment in sub-Saharan Africa

Malaria is a major cause of mortality and morbidity in sub-Saharan Africa and an integrated strategy is recommended that combines preventive measures with prompt access to effective treatment [1]. Malaria places an enormous burden on the health system, and in areas of medium-to-high transmission, malaria should be suspected in all individuals who present with a fever, or had a fever in the past 24 hours. In sub-Saharan Africa, antimalarials may be obtained from a variety of facilities and outlets, including government and mission hospitals and health centres, private clinics, pharmacies, drug stores, general stores and itinerant medicine vendors. Individuals may also seek treatment from herbalists and traditional healers.

Uncomplicated malaria is routinely treated by health workers in outpatient departments and at the primary care level, though severe cases should be referred and admitted for inpatient care. Responsibilities for prescribing malaria treatment span a range of cadres, and nurses and junior staff often prescribe treatment in primary care facilities [2].

Self-treatment of uncomplicated malaria is also common, and many cases are treated at home using antimalarials left-over from previous illness or bought at retail outlets. Retail outlets are a major source of antimalarials [3-5]. Pharmacies are regulated and licensed to sell both prescription-only and over-the-counter medicines under the supervision of a qualified pharmacist, though clients may be served by staff without formal pharmacy training [6-8]. The legal status of drug stores varies; they are often permitted to sell a limited range of products, and can be owned and managed by someone without clinical or pharmacy qualifications [7, 9-12]. In some settings, antimalarials can also be purchased at general stores, or obtained from itinerant medicine sellers [5].

The resources available for diagnosing malaria vary by type of facility. Parasitological testing is available at hospitals and larger facilities, though health workers at many primary care facilities routinely diagnose malaria on the basis of clinical symptoms [13].

1.2 Clinical guidelines for the diagnosis and treatment of malaria

The World Health Organization (WHO) publishes clinical guidelines for the diagnosis and treatment of malaria based on biomedical evidence on the efficacy and safety of diagnostic methods and antimalarial medicines [1, 14]. There have been two major changes to malaria treatment guidelines over the last decade. First, artemisinin combination therapy (ACT) became the recommended treatment for uncomplicated malaria following evidence of resistance to older alternative antimalarials, such as chloroquine and sulphadoxine-pyrimethamine (SP). ACT has been widely adopted, and it is now the first-line treatment for uncomplicated malaria throughout sub-Saharan Africa. It comes in five generic combinations: artemether-lumefrantrine, artesunate-amodiaquine, artesunate-mefloquine, artesunate-sulphadoxine-pyrimethamine, and dihydroartemisinin-piperquine. Quinine and artemisinin-monotherapy can also be used to treat malaria, though they should be reserved for cases of severe malaria.

Second, in 2010 the WHO updated malaria treatment guidelines to recommend parasitological testing of all febrile patients before treatment is prescribed and confirm rapid diagnostic tests (RDTs) are a valid alternative to microscopy [1]. Parasitological testing was previously encouraged, since clinical symptoms are non-specific and the fever may have other causes [1], however, access to microscopy testing was limited by the availability of laboratory equipment and technicians able to prepare and read blood slides. In the absence of a malaria test presumptive malaria treatment is advised for febrile patients [13, 14]. As a result, it is common for antimalarials to be consumed based on symptoms alone.

RDTs offer considerable potential to expand access to malaria testing and reduce the over-consumption of antimalarials, since they require minimal infrastructure and training [15]. Interest in RDTs has grown substantially in recent years and governments across sub-Saharan Africa are now deciding how to expand access to malaria testing and whether to introduce RDTs in health facilities that already offer microscopy testing. These policy decisions will require governments to revise national malaria treatment guidelines, and consider what interventions could be used to expedite the introduction of RDTs and ensure policy changes are accompanied by changes in providers' practice.

1.3 Providers' knowledge, preference and practice in diagnosing and treating uncomplicated malaria

Ensuring providers adhere to clinical guidelines is essential for delivering high quality patient care. National malaria treatment guidelines can be used to assess the quality of malaria case management and the performance of health care providers. Although many studies describe access to clinical guidelines and in-service training, relatively few report on providers' knowledge of malaria treatment. Similarly, limited attention has been given to understanding providers' preferences, such as how they prefer to diagnose malaria and what treatment they prefer to give. Economic theory suggests providers frequently act as agents and make decisions on behalf of their patients. This agency relationship arises when patients lack information to diagnose the illness and select treatment. It is important, therefore, to understand providers' preference over different diagnostic methods or which antimalarial they prefer to supply, and who and what influences their preference. It can also be helpful to distinguish between providers' stated and revealed preference. Their stated preference would reflect the providers' choice in the absence of constraints, such as the resources available at the facility, the patients' ability to pay or specific information about the patient. In contrast, their revealed preference reflects their

actual choice given the prevailing constraints, and is more commonly referred to as their practice.

Available evidence indicates considerable variation in providers' knowledge across geographies and types of facility within sub-Saharan Africa. In Kenya, six months after ACT became the first-line antimalarial, 70% of government health workers were aware of the new drug policy, while in Cameroon more than a year after the policy change less than 15% of health workers knew the recommended antimalarial [16-18]. Concerns have been expressed about the knowledge of medicine retailers [10, 19-23]. In a recent study from Kenya, 65% of medicine retailers correctly identified artemether-lumefantrine (AL) as the first-line treatment, though only 48% would recommend AL to adults and 37% would recommend AL to children [23]. Also, medicine retailers in Nigeria have expressed confusion over antimalarials and antipyretics, and the correct antimalarial doses for children [11].

For many years, the literature on malaria case management was dominated by studies that described treatment following a symptomatic diagnosis and demonstrated problems with the choice of antimalarial [16, 24-35]. Studies undertaken since ACT became the first-line antimalarial have shown providers in government and mission facilities were slow to change their practice and prescribe ACT [16, 32, 35]. Providers' practice tends to improve over time, though surveys undertaken up to four years after the policy change found not all febrile children were prescribed the recommended antimalarial [16, 32, 36, 37]. There were also problems with ACT dispensing, with under-dosing common among children weighing 15-24kg and inadequate advice on the regimen [16, 32, 35]. Problems with the treatment supplied were also found at medicine retailers in Kenya, Nigeria, Tanzania, and Uganda, where less than half of mystery clients seeking malaria treatment were advised to buy the type of antimalarial recommended by the government [11, 22, 29, 30, 38-45]. Similarly, in 2010 only 39% of febrile patients at drug shops in Uganda received an ACT [38].

Several recent studies on malaria case management have focused on treatment following a malaria test [33, 36, 46-54]. The emphasis given to appropriate treatment reflects advanced in rapid diagnostic testing and concerns about the cost of ACT, as well as possible risks associated with missing non-malaria causes of febrile illness, and the potential to accelerate artemisinin resistance [55]. While these are powerful arguments for testing for malaria before supplying antimalarials, studies have shown diagnostic testing is often underused and antimalarials are often prescribed to patients with a negative malaria test. For example, in Kenya, only 43% of febrile patients attending government facilities with microscopy available were tested for malaria, and antimalarials were prescribed to 61% of cases with a negative blood slide [33]. Evidence of providers prescribing antimalarials to test-negative patients also occurred in Malawian, Tanzanian and Zambian health facilities that had diagnostic testing available (either with microscopy or RDT) and had ACT in stock [52-54]. However, there is some evidence of improvement over time, as cross-sectional surveys conducted at health facilities in Tanzania showed the national roll-out of RDTs was associated with an increase (from 16% to 55%) in the percentage of febrile patients tested for malaria, and a significant reduction (from 43% to 18%) in the overuse of ACT in patients without malaria parasites [56].

To design effective interventions and improve the quality of malaria case management, it is important to understand the influences on providers' practice. Qualitative methods have been used to study the practice of health workers and medicine retailers [57-65]. For instance, Kenyan nurses were interviewed to investigate why ACT was infrequently prescribed [59]. The nurses expressed positive perceptions about the efficacy and safety of ACT, though explained they would reserve ACT for patients under five years or with more severe symptoms because of concerns about the government's ability to sustain supply. Nurses also mentioned that patients may have preferences over different antimalarials, and with staff shortages and a busy workload there may be insufficient time to explain the treatment regimen. Other qualitative studies focused on providers' perceptions of RDTs and reasons why providers prescribed antimalarials to test-negative patients [57, 58, 62].

Many providers recognised the advantages of malaria testing, though they also expressed a lack of trust in test results and explained it would indefensible to miss a malaria case [57]. Providers' preferences were shaped by their initial training and their peers, but also by their patients, as providers noted a malaria diagnosis was often expected and readily accepted by their patients [58].

Influences on providers' practice has also been explored using quantitative methods, and logistic regression has been used to determine whether the treatment prescribed to febrile patients was associated with patient, provider or health facility characteristics [22, 24, 25, 31, 33-35, 38, 46, 66-69]. The presence of a fever or high temperature was positively associated with decisions to undertake a malaria test, treat for malaria, and prescribe the recommended treatment. Access to in-service training, malaria treatment guidelines, wall charts, and supervision were positively associated with the choice of antimalarial in some but not all studies. The effect of pre-service training, work experience, case load, consultation time, the age of the patient, and the level of facility also had mixed results on providers' decision to test for malaria and their choice of treatment.

While the evidence available on the quality of malaria case-management at different types of health facility and by different types of provider is reasonably extensive, some questions remain. The relationship between providers' knowledge and practice is not well understood; although some evidence suggests access to in-service training, job aids and clinical guidelines can have a positive effect on choice of treatment, the overall findings were mixed. We also have very little information on providers' stated preference, and understanding their preference may help to explain differences between providers' knowledge and practice and identify new approaches to intervention. Thus, we cannot assume efforts to disseminate malaria treatment policy will necessarily change providers' knowledge of the guidelines, the type of treatment that providers' prefer to supply, or the treatment actually supplied to febrile patients. It is also important to understand the degree to which providers are constrained resources available at the health facility or

outlet, the patient's ability to pay for treatment, or aspects of the institutional environment in which they work.

1.4 Aims and objectives

In this thesis I examine the care received by febrile patients seeking treatment at different types of facility in Cameroon and Nigeria. The research focuses on providers' knowledge, preference and practice and approaches a common public health problem, how to improve providers' adherence to clinical guidelines, from an economics perspective. This perspective has considerable potential to offer new insights, though alternative theories are available from other disciplines that could be applied to examine the practice of health care providers. For instance, psychology has a range of theories on behaviour change, such as the expectancy-value theory, theory of reasoned behaviour, attitude-behaviour-context theory and normative conduct theory [70-72]. Some of these theories focus on individual motivation and are based on expectations and values, while others emphasize social influences and external contextual factors. There are also theories on human behaviour in sociology, such as those that consider the role of social expectations and trust [73-75], and anthropological models of behaviour change, such as social learning theory in which behaviour change results from observing and imitating others [76].

Within the economics literature, analysis of human behaviour is often founded on rational choice theory, which assumes individuals make deliberative choices between distinct courses of action [77, 78]. Individuals are presumed to weigh up the expected benefits and costs of different actions and make choices that maximize their expected utility. This underpins my research, though I also emphasize that providers often make decisions in the context of the agency relationships. For example, a provider's interaction with a patient can be characterized as a principal-agent relationship when the patient relies on the provider to diagnose the condition and select treatment. I also acknowledge that

providers' preference and practice may reflect multiple agency relationships, and providers may be influenced by additional principals, such as their employer or supplier.

Moreover, my thesis draws on thinking from behavioural economics and new institutional economics. As explained further in Chapter 2, these theories suggest providers may be bounded in their ability to make rational decisions, or constrained by the prevailing social, cultural or institutional environment. While these theories tend to be located within the economics literature they have been heavily influenced by thinking in other disciplines. For example, the notion of informal institutions, which is central to new institutional economics, builds on work from sociology and cultural theory [79, 80] and behavioural economics integrates economics with psychology as it incorporates concepts such as habits, framing and social norms of behaviour [81].

The research on providers' preference and practice was used to design interventions to improve providers' adherence to the malaria treatment guidelines, and the cost-effectiveness of the interventions implemented in Cameroon were evaluated as part of this thesis.

The aim of the thesis was to analyse providers' stated and revealed preferences for treating febrile patients, when providers have imperfect information and are agents in multiple agency relationships, and to evaluate the cost-effectiveness of interventions that were designed to improve providers' adherence to clinical guidelines.

Specific objectives are:

- To describe the treatment supplied to febrile patients at health facilities and medicine retailers in Cameroon and Nigeria.
- To assess providers' knowledge of the national malaria treatment guidelines and investigate the determinants of providers' stated preference for treating uncomplicated malaria.

- To examine the determinants of providers' revealed preference (i.e. their practice) for treating patients with malaria symptoms.
- To evaluate the cost-effectiveness of interventions to improve providers' practice in diagnosing and treating uncomplicated malaria at public and mission facilities in Cameroon.

1.5 Structure of the thesis

The thesis is structured in three parts. Part I contains the introduction, literature review and an overview of the study setting, Part II contains five research papers, and Part III discusses the research findings and the overall contribution of the thesis.

Chapter 2 summarises conceptual and empirical literature. Providers' practice has been considered from an economics perspective, founded in agency theory and thinking from new institutional economics and behavioural economics. The empirical literature was reviewed to identify possible interventions to improve providers' ability to diagnose and treat uncomplicated malaria.

Chapter 3 provides overview of the study sites, and introduces the Research on the Economics of ACT (REACT) project, which was the context for the research included in this thesis. This chapter contains the trial protocol for the evaluation in Cameroon. The protocol describes the interventions that were developed following extensive formative research, and how they would be evaluated using a cluster-randomized trial.

Chapters 4 to 8 contain the five research papers:

I. Treatment of uncomplicated malaria at public health facilities and medicine retailers in south-eastern Nigeria.
II. Malaria prevalence and treatment of febrile patients at health facilities and medicine retailers in Cameroon.

III. What determines providers' stated preference for the treatment of uncomplicated malaria?

IV. Mind the gap: knowledge and practice of providers treating uncomplicated malaria at health facilities and medicine retailers in Cameroon and Nigeria.

V. Economic evaluation of a cluster randomized trial of interventions to improve health workers' practice in diagnosing and treating uncomplicated malaria in Cameroon.

Four of these papers report on findings arising from the formative research undertaken to inform the design of interventions to improve diagnosis and treatment of patients who present with symptoms of uncomplicated malaria. The first two papers describe the results of patient exit surveys undertaken at health facilities and medicine retail outlets in Nigeria and Cameroon and highlight problems with the treatment of uncomplicated malaria (Chapters 4 and 5).

As providers are often responsible for treatment decisions, providers' knowledge, preference and practice in treating uncomplicated malaria was the focus of further investigation. The paper in Chapter 6 reports on the determinants of providers' stated preference for the treatment of uncomplicated malaria, and thus examines their preference when not constrained by the resources available, information about the patient or the patient's ability to pay. Chapter 7 contains a research paper on the relationship between providers' knowledge and their practice. The knowledge-practice gap was examined by restricting the analysis to the subset of patients who relied on the provider to select treatment and were supplied an antimalarial, and by linking exit survey responses to the individual provider who supplied treatment.

The final research paper is presented in Chapter 8. This is the economic evaluation of training interventions that were implemented in Cameroon to support the introduction of malaria RDTs and encouraged providers to test febrile patients for malaria and to provide treatment that adhered to the test result. Two training interventions were designed, based

on the formative research: one-day 'basic' training that sought to ensure providers knew how to use malaria RDTs and the recommendations in the national malaria treatment guidelines; and three-day enhanced' training that explicitly focused on changing providers' practice.

Chapter 9 contains the discussion. The overall findings from the thesis are summarized and contribution of the thesis is discussed. The limitations of the thesis are acknowledged and areas for further research are outlined. The thesis concludes by considering the implications of the research for the design and evaluation of interventions to encourage providers to adhere to malaria treatment guidelines and on malaria treatment policy in Cameroon.

Finally, an appendix has been included. This contains the appendix to the empirical review included in Section 2.2 and two further research papers for which I am a co-author. The first presents findings from qualitative research in Cameroon, which was undertaken as part of the formative research. This paper complements the quantitative research reported in Chapters 5-7 and contributed to the design of interventions in Cameroon. The second paper reports on the effectiveness of the interventions evaluated in Cameroon. This paper complements the economic evaluation as it includes detail on the implementation and effectiveness of the training interventions.

1.6 Contribution of the candidate

The thesis was undertaken in the context of the Research on the Economics of ACT (REACT) project, which sought to improve the diagnosis and treatment of uncomplicated malaria in Cameroon and Nigeria. The project was implemented in four phases: formative research; intervention design; evaluation; and dissemination. By taking a phased approach the project sought to design interventions to address problems identified during the formative research and respond to the interests of policy-makers. As such, the project evolved differently in each country. An overview of REACT is provided in Section 3.2.

REACT was conceived by the principal investigators: Dr Virginia Wiseman, Professor Wilfred Mbacham, and Professor Obinna Onwujewke. I joined the project as a co-investigator after funding had been secured, though before any research commenced. I made a substantial scientific contribution to the project, and coordinated research activities and managed research teams in Cameroon and Nigeria.

The research contained in this thesis includes work conducted in the context of REACT, but for which I had a lead responsibility and undertook with considerable independence. I led the design and analysis of patient exit surveys and provider surveys in Cameroon and Nigeria, which included the development of research instruments, training of field teams to pilot and administer the surveys, and analysis of the survey data. Chapters 4 and 5 present the main findings of the exit surveys. These findings identified priorities for intervention.

From my reading on theory-based evaluation, I wanted to ensure the selection and design of interventions was founded on a conceptual and empirical understanding of the patient-provider interaction. This included a literature review on interventions to improve providers' practice in diagnosing and treating malaria (Section 2.2). I independently developed the search strategy, identified relevant papers, synthesized the evidence and interpreted the findings. The review was written up as a working paper for REACT and was approved by the principal investigators. Chapters 6 and 7 contain additional analyses on the knowledge, stated and revealed preferences of providers. For each, I led the conception of the research question, undertook the analysis, and prepared the research paper. I received support from my PhD supervisor, though the work was conducted with considerable independence and my co-authors understood this research was intended to contribute to a PhD.

My research was particularly pertinent to the selection and design of interventions in Cameroon as a decision was made to focus on malaria case management at public and mission facilities, where providers are routinely responsible for diagnosis and the choice

of treatment. In discussions with the National Malaria Control Programme (NMCP), it was agreed REACT should develop training interventions that not only sought to improve providers' knowledge of the malaria treatment guidelines, but also explicitly sought to change their practice. I led workshops with the Cameroon study team to develop the content of the training. During this design phase, I also prepared a logic model to articulate the causal mechanisms by which the training was expected to change providers' knowledge and practice (Section 3.2).

The trial design was led by the principal investigators, with support from co-investigators, including myself, Bonnie Cundill, a statistician, and Clare Chandler, social scientist. The trial protocol is included in Section 3.3.

Chapter 8 presents the economic evaluation I conducted in Cameroon. I led the design and analysis of the economic evaluation. I oversaw the collection of patient exit surveys and managed a Research Assistant, Tom Drake, who collected data on the cost of the interventions and the facility costs of malaria diagnosis and treatment. I worked independently on the cost-effectiveness and prepared the research paper. Co-authors provided feedback on a full draft and approved the final paper.

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2. Literature Review

This Chapter contains a review of conceptual and empirical literature and presents a conceptual framework. Section 2.1 presents economic theories relevant to understanding providers' practice and the patient-provider interaction. This includes agency theory and concepts from new institutional economics and behavioural economics. Section 2.2 contains a comprehensive literature review on interventions that had been used to improve providers' ability to diagnose and treat uncomplicated malaria. This literature review is a working paper undertaken for REACT and was used to identify potential interventions that could be used to improve the practice of providers diagnosing and treating uncomplicated malaria in Cameroon and Nigeria. Section 2.3 contains a conceptual framework I developed to inform the research and it illustrates who or what may influence providers' preference and their practice. Section 2.4 summarises the current evidence and rationale for further research.

2.1 Conceptual literature

2.1.1 Agency theory

Economics is concerned with the decisions that people make, and offers a perspective from which to consider the actions of providers supplying health care [1]. Agency theory is often used to provide a conceptual framework for examining the interaction between health care providers and their patients [2, 3]. The theory applies to situations where there is an asymmetry of information, and in the context of health care it is assumed that patients lack the knowledge to make rational decisions about the health care they require,

and once at a facility they rely on the provider to diagnose the condition and recommend treatment [3].

The information held by providers and patients is likely to depend on the nature of the illness and the complexity of treatment [4]. The degree of imbalance is likely to be greater when the patient's symptoms are severe, there are many treatment options, and clinical interventions require more advanced technology. In these situations the provider will have information that is complementary to that held by the patient, while for more familiar illnesses, such as the common cold, providers' information will largely substitute that held by the patient, since the patient may know the treatment options from previous care seeking. There may also be limits on the providers' information, which bounds their ability to make rational decisions, and provider's practice may be constrained by the resources available at the facility or by the patient's ability to pay for health care.

A perfect agent has been defined as someone who would use her superior knowledge to select the best good or service for the principal that is consistent with his preferences [5, 6]. In other words, the perfect agent would make the same choices as the principal, if the principal held all the necessary information from which to make a rational decision over the set of choices available [6]. However, agency theory contends that the agent will have her own preferences and has an incentive to exploit the information asymmetry for her benefit. Thus, both the principal and his agent want to maximize their individual utility functions. In standard agency theory, the utility functions are entirely independent of each other, and it follows that the self-interested agent would make choices for her own benefit, irrespective of the principal's preferences.

The economics literature typically assumes that the agent's utility function depends on her preferences over income and leisure time, and that the agent has a financial incentive to induce demand in order to increase her income until she has obtained her optimal combination of income and leisure, or at least achieved a threshold income [2, 7]. It can be

argued, therefore, that the provider's effort in diagnosis and the choice of treatment will depend on the monetary benefits she accrues, and that she may supply additional unnecessary medicines or services in order to increase her income. Supplier induced demand is said to occur when the agent supplies more of a good than would be demanded by the fully-informed principal. Redressing the information imbalance between providers and patients may mitigate supplier-induced demand, though there may be practical limits to the amount of technical knowledge and skills that can be transferred to the patient [6, 8].

Agency theory has traditionally focused on the bilateral relationship between the principal and their agent, however, the situation may be complicated further as the provider may be serving multiple principals [9, 10]. For instance, in addition to the provider's agency relationship with the patient, she may also be acting as an agent on behalf of her employer, policy-makers or programme managers in the Ministry of Health, or suppliers of pharmaceutical products. In some instances the provider will have a formal contract with the principal, though often the contractual relationship will be an implicit understanding in which the provider perceives a responsibility to act on behalf of the principal. For example, while it may be unusual for the patient and provider to have a written agreement for the health care transaction, the provider's actions in treating the patient may reflect a pledge to the Ministry of Health to practice ethically, or an intrinsic motivation to meet the patient's needs and supply effective treatment.

2.1.2 Financial incentives

The health economics literature on agency theory has concentrated on the providers' financial incentives under different types of organization and remuneration schemes [11]. In theory profit-maximising firms are more likely than government or NGOs to exploit the information advantage and induce demand, though provider practices will also depend on the method of remuneration [12]. Providers that receive income directly determined by

the services supplied have a financial incentive to provide treatment. These fee-for-service remuneration schemes are common in the private sector, and tend to apply to providers that own or part-own the clinic, pharmacy or drug store [13]. In contrast, providers paid a salary have no financial incentive to provide care and are presumed to work the minimum required to sustain their employment. These are two distinct provider payment methods, though there are also many complex employment and remuneration arrangements [14]. Allowances or bonuses may be provided in addition to a basic salary, dual employment is common, and there may be informal arrangements, in which providers receive commission from drug sales, or under-the-counter payments from patients [15, 16].

2.1.3 Contractual arrangements

Provider and patient incentives may be aligned if the payment received by the provider is contingent on the patient's health outcome rather than health care inputs [1]. Thus, the provider has an incentive to exert effort when diagnosing the patient's condition and provide effective treatment if her income depends on an observable improvement in the patient's health. There are, however, considerable challenges and costs involved in devising incentive-compatible contracts and expertise is required to monitor the agent's actions and enforce penalties should the contract be breached [2, 3, 17]. Consequently, outcome-contingent contracts are rare in modern medicine, though they have been used by traditional healers in some African countries [18, 19]. Input-based contracts are also problematic when the relationship between health care consumption and health outcomes is uncertain, health care inputs are difficult to measure and medical experts disagree on what is best for the patient [3, 19].

2.1.4 Dynamic relationships & reputation effects

Contractual difficulties may be overcome if the relationship is considered from a longer-term perspective since providers who are concerned about their ability to generate income in the future will want to establish and maintain a good reputation to encourage

repeat business. The provider's reputation is important because health care is an experience good and the quality of health care cannot be assessed in advance of consumption [20, 21]. Providers may also use advertising or observable attributes to signal the quality of their services. Reputation effects can incentivize providers to exert greater effort, offer effective care and achieve patient satisfaction. Providers are usually more responsive to reputation effects when there is considerable competition, while reputation is less important when patients have little choice over where they seek care [20].

2.1.5 Intrinsic motivation and patient attributes

It is argued that providers not only respond to financial incentives but also have an intrinsic motivation to provide care and improve the health of others [3, 22]. Economists do not consider agents to be altruistic, but argue that they remain self-interested, derive satisfaction from their work and enjoy the esteem that is associated with their profession [3, 23, 24]. Agency theory incorporates intrinsic motivation by extending the provider's utility function to include the utility derived from the anticipated improvement in the patient's health [3, 25, 26]. The degree of intrinsic motivation is likely to vary between providers and may depend on patient or facility characteristics. For example, providers at mission facilities may derive some intrinsic motivation from their faith, though factors such as improved supervision or greater job security may also be relevant [18]. Providers may distinguish between patients, and Ryan (1994) identified several sociological studies that report differential levels of care depending on the patients' gender, education or ethnicity [27]. Similarly, remarkable differences were observed in an ethnographic study on the treatment of patients attending a Ghanaian hospital that related to the patients' socioeconomic background and communication style [28].

2.1.6 Institutional & Social Context

Individual behaviour takes place within an institutional and social context [29]. This is well understood by anthropologists and sociologists, and authors from these disciplines have explored various dimensions including societal expectations that influence the role of doctors and patients in the medical consultation, power dynamics and the symbolic and social value of medicines, and potential for shared treatment-decision making [30-34].

Economists have also considered how social, cultural and political factors may influence behaviour by considering the role of institutions [35, 36]. Formal institutions, such as regulation, can constrain the providers' actions or medicines available at the facility [37], though the term institution has been defined broadly to include any form of constraint that may shape human interaction [38]. Thus, provider-patient interactions are considered embedded within social structures, cultural norms and values [39, 40]. Social networks were found to be an important source of information for individuals in rural Tanzania making choices about their health care consumption, and explained patterns of treatment seeking over time [41]. Providers' preferences and practices may also be shaped by others working at the facility, as social networks not only affect the flow of information but can be a source of reward and punishment [36].

2.1.7 Economic psychology

The growing literature on behavioural economics highlights limitations and inconsistencies in individuals' ability to make rational utility-maximizing decisions [42]. Individuals tend to assess choices with reference to the current situation, be reluctant to change preferences, and be risk averse [43]. Moreover, individuals prefer to make choices that conform to expectations and behavioural norms which may explain why providers are often slow to respond to changes in treatment policies. In the context of health and health care, these issues have been explored by sociologists, though the economics research has so far focused on influences over individual lifestyle choices, rather than

provider behaviour within an agency relationship [44]. Nevertheless, social and psychological factors are also likely to influence providers' preference and practice.

2.1.8 Summary

Agency theory provides a useful framework to consider the relationship between providers and their patients, and highlights many factors that may influence providers' knowledge and practice. Standard agency theory emphasizes the financial incentives that result from information asymmetry, though extensions to the theory recognise intrinsic motivation. The interaction may also depend on organization, social, cultural and psychological factors and may be constrained by the resources available, institutional environment and social structures.

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2.2 Empirical literature: A review of interventions to improve providers' ability to diagnose and treat uncomplicated malaria

A review of the empirical literature was undertaken to identify studies that report on interventions that were intended to improve the ability of providers to diagnose and treat uncomplicated malaria. The introduction summarises common problems with providers' practice, including the type of antimalarial supplied, the under-use of malaria testing, and the provision of antimalarials to patients who test negative for malaria. Various intervention have been developed to improve the ability of providers to diagnose and treat malaria.

This comprehensive literature review was undertaken to understand what interventions had been tried and tested, and to synthesize evidence on their effectiveness. The literature review synthesizes evidence from 27 studies and 32 different interventions. The different types of interventions were categorized using a pre-defined typology, based on the information provided about the intervention or intervention package. The majority of the studies included provider training or an educational process that sought to enhance the providers' knowledge and skills of malaria diagnosis and treatment.

The review concludes that provider training can have a significant effect on providers' knowledge and practice, though synthesis was limited by the amount of information available on the intervention and variation within each intervention category, as well differences in the setting, research methodology and outcome indicators used. Moreover, it was difficult to ascertain the merits of supplementary activities such as refresher training or supervision when they were included within an intervention package.

The findings from this literature review, along with quantitative and qualitative research conducted in Cameroon and Nigeria, were used to inform the design of interventions for the REACT project.

The literature was written up as a working paper for the REACT and has been published on the ACT Consortium website. The working paper has a relatively lengthy appendix, and this is included as an appendix to the thesis (Appendix A).

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Contribution: I am the sole author of the literature review. Colleagues reviewed the report and provided comments.

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Interventions to Improve Providers' Ability to Diagnose and Treat Uncomplicated Malaria:

A Literature Review

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Executive Summary

Prompt access to effective malaria treatment is important, and many individuals rely on providers to diagnose malaria and dispense the recommended treatment. Whether the emphasis is on presumptive or parasitological diagnosis, ensuring that providers are able to supply treatment in line with national guidelines is critical for patient care. There are, however, longstanding problems with the care available at many public health facilities and private sector outlets. Given these problems and the recent interest in the use of RDTs, there is a need for interventions that improve the ability and practice of providers to treat patients that present at a health facility with a fever. This literature review examines the evidence available on interventions to improve providers' ability to diagnose or treat uncomplicated malaria.

A comprehensive search of the published literature was undertaken using bibliographic databases. Relevant publications in the grey literature were identified from review articles, reference lists of relevant publications and from websites of development agencies. Publications since 1990 were eligible if they met all of the following inclusion criteria:

- The **intervention** was intended to improve providers' ability to diagnose or treat uncomplicated malaria.
- The **population exposed to the intervention** are providers.
- The **study design** included a comparison group.
- The effect was reported on a **malaria-related outcome.**
- The **study setting** was an area of endemic malaria transmission in sub-Saharan Africa or Asia.

Evidence on effectiveness was synthesized using three types of outcome: i) presumptive treatment of uncomplicated malaria; ii) appropriate treatment of uncomplicated malaria (following a diagnostic test); and iii) the accuracy of prescribing antimalarial treatment regimens.

Twenty-nine publications were eligible for the review, which report on 27 studies and 32 different interventions. The majority of the studies were from Africa, with 8 from Kenya, 5 from Tanzania, 4 from Uganda and 3 from Nigeria. The majority of the interventions were designed to focus on malaria, though several included malaria within the Integrated Management of Childhood Illnesses (IMCI). Provider training was dominant, and the principal activity in 21 of 32 interventions. The training interventions included studies focusing on presumptive treatment of malaria, and studies on diagnostic testing.

Most interventions had a significant positive effect on the presumptive treatment of uncomplicated malaria, and the accuracy of the doses and advice given. The provision of RDTs and training on diagnostic tests improved the appropriate treatment of malaria, though the proportion of test-negative patients receiving antimalarials often remained relatively high. No studies compared an intervention in both public and private sector providers and only two programmes reported on the cost-effectiveness of the intervention.

Further work on interventions to improve the appropriate treatment of febrile patients would be valuable. The studies show that provider training and the provision of RDTs can be beneficial, though suggest that conventional approaches may have only a limited effect.

Abbreviations

ACT	Artemisinin Combination Therapy
AL	Artemether Lumefantrine
AM	Antimalarial
AQ	Amodiaquine
ASAQ	Artesunate Amodiaquine
BCC	Behaviour Change Campaign
CQ	Chloroquine
HW	Health Worker
IMCI	Integrated Management of Childhood Illnesses
NGO	Non-Governmental Organization
N/A	Not Applicable
OTC	Over the Counter
RCT	Randomized Control Trial
RDT	Rapid Diagnostic Test
SP	Sulphadoxine Pyrimethamine

Table of Contents

Boxes, Figures & Tables

1. Background

Malaria is a major cause of mortality, and the majority of the disease burden falls in sub-Saharan Africa [1]. There are approximately 250 million episodes of malaria each year, and about one million malaria-related deaths, mostly in children under five years of age [1]. Prompt access to effective malaria treatment is important, and many individuals rely on providers to diagnose malaria and dispense the recommended treatment. The most effective treatment for uncomplicated malaria is artemisinin combination therapy (ACT) and this medicine is the first-line recommended antimalarial across sub-Saharan Africa [2]. ACT replaced less effective antimalarials, such as sulphadoxine-pyrimethamine (SP) and guards against drug resistance by combining the artemisinin derivative with another type of antimalarial, such as lumefantrine or amodiaquine (as in artemether-lumefantrine and artesunate-amodiaquine).

The introduction of ACT has, however, brought new challenges. The treatment regimen for ACT is more complex than the former first-line treatment SP, which was taken as a single dose, and should be taken twice daily for three days in a dose suitable for the patient's weight or age. ACT is also considerably more expensive than alterative antimalarials, and as it can cost up to ten times more than SP, affordability is a key concern. The high cost of ACT also brought into question the widespread use of presumptive treatment in areas of low to medium malaria transmission. A revived an interest in parasitological diagnosis also coincided with the release of rapid diagnostic tests (RDTs) for malaria. Malaria RDTs have been shown to have high specificity and sensitivity, and have the potential to transform access to malaria testing since they are suitable for use in resource-constrained settings and do not require laboratory equipment or specialist skills.

Whether the emphasis is on presumptive or parasitological diagnosis, ensuring that providers are able to supply treatment in line with national guidelines is critical for patient care. However, there are longstanding problems with the care available at many public health facilities and private sector outlets [3, 4]. For example, despite the efforts of the Zambian malaria control programme to disseminate guidance on the change in first-line treatment from sulphadoxine pyrimethemine (SP) to artemether lumefantrine (AL), two years after AL (a type of ACT) had been adopted as the first-line antimalarial only 42% of children under five years received treatment in line with national guidelines [5]. Ensuring patients receive the recommended type of antimalarial is the first step, though it is also important that they receive the appropriate dose and understand how to take the full course of treatment. In terms of the dosage, recent studies from Kenya and Uganda reported more than 90% of children received ACT in the recommended dose, however such accuracy in dosing has not always been the case [5, 6]. For example, a study on treatment in government health centres in Nigeria found that 39% of antimalarials were in the correct dose, with 30% receiving an insufficient dose and a further 30% receiving more than required [7]. The same study showed even greater problems in the private sector, with 28% of patients at patent medicine dealers obtaining the correct dose, while half of the patients received an inadequate amount [7]. The advice given by providers to patients on how to administer the medicine may be a further source of problem [8].

Given the problems with the delivery of ACTs in several settings, as well as the relatively recent interest in the use of RDTs, there is a need for interventions that improve the ability and practice of providers to treat patients that present at a health facility with a fever. This literature review

examines the evidence available on interventions to improve providers' ability to diagnose or treat uncomplicated malaria. The review has been undertaken as part of the Research on the Economics of ACTs (REACT) project. The objective of REACT is to design and evaluate interventions to improve the treatment of uncomplicated malaria in Cameroon and Nigeria. This literature review has been undertaken to inform intervention selection and design.

This is not the first paper to review the literature on interventions to improve malaria treatment. Smith *et al* (2009) recently reviewed interventions to improve provider practice and user behaviour in relation to prompt and effective malaria treatment in sub-Saharan Africa [9]. Goodman *et al* (2007) and Brieger *et al* (2005) both review the literature on the role of private practitioners and interventions that have been used to improve their practice [4, 10]. Other related review articles have focused on interventions to improve home-based management of malaria or on improving prescribing practices [11-14]. This review of interventions to improve providers' ability and practice in treating malaria is distinct insofar as it includes papers that report on a wider range of malaria-related outcomes and from settings across both Africa and Asia. The literature in this area is constantly evolving, and even since the review by Smith et al, there have been several new publications.

2. Objectives

The aim of the literature review is to synthesize evidence on interventions to improve the ability of providers to diagnose and/or treat uncomplicated malaria. Specific objectives of the review are:

a) to identify the range of interventions evaluated that sought to improve providers' ability to diagnosis or treat uncomplicated malaria;

b) to review the characteristics of the studies in terms of the approach and research methods used to evaluate the intervention; and

c) to compare the effectiveness of the interventions.

3. Methods

3.1 Literature Search Strategy

A comprehensive search of the published literature was undertaken using the following databases: Medline, Embase, Global Health, International Bibliography of Social Sciences (IBSS), CAB Abstracts and International Network for the Rational Use of Drugs (INRUD). The databases were last accessed on 26 November 2009.

From the research question four concepts were derived and underpin the search. The concepts were: malaria; treatment; intervention; and provider (as shown in Box 1 with their synonyms). The synonyms were used as keywords for title and abstract searches in Medline, Embase, Global Health, IBSS and CAB Abstracts. Truncation search terms were used to make the search inclusive. The outputs from the title and abstract searches for all the synonyms in each concept were combined using the Boolean operator "or". The four concepts were then brought together using the "and" operator. The search of the INRUD database was less restrictive, and used the keywords "malaria" or

"fever" or "febrile" in all indexed fields. The citations obtained from each of the databases were exported to Endnote reference management database, and all duplicates were removed.

Box 1. Search strategy

Concept: malaria	**Concept: treatment**	**Concept: intervention**	**Concept: provider**
fever	diagnos*	intervention	public
febrile	management	education	private
malaria	knowledge	training	personnel
	practice		clinician*
	treatment*		health worker*
	test*		retailer*
			seller*
			provider*

Within each concept terms were combined with the operator "or"
Results from each concept were combined using the operator "and"
Search was limited to publications since 1 January 1990

The search focused on publications available in peer-review academic journals since we are primarily interested in evaluation studies grounded in a rigorous study design. Relevant publications in the grey literature were identified from review articles, reference lists of relevant publications and from websites of development agencies.

3.2 Inclusion Criteria

Publications were eligible if they met all of the following inclusion criteria:

- The publication reports on an **intervention** that was intended to improve the ability or practice of providers to diagnose or treat uncomplicated malaria. Improving providers' ability or practice to treat uncomplicated malaria could be the primary focus, or contained within a range of objectives.

- The **population exposed to the intervention** are providers. The providers may be from any cadre, with any or no qualification and from any type of health facility or outlet. This population can therefore include individuals working in government, mission and private facilities, pharmacies and drug retail outlets as well as community-based actors.

- The **study design** was defined as a (cluster) randomized control trial, pre-post design with a control group, repeated cross-sectional studies, pre-post design without control, or a post-only evaluation which included a comparison group. One-time cross-sectional studies and post-only designs without a comparison were excluded as they lack a comparison group.

- The study reports the effect of the intervention on **malaria-related outcomes.** It can use any outcome measure for provider knowledge, provider competence, or treatment outcomes in relation to the care received by patients or their health status. The term malaria-related is defined to include confirmed and unconfirmed malaria cases, since it is common for malaria diagnoses to be based solely on febrile symptoms.

- The **study population** depends on the outcome reported, though may be patients for whom treatment is sought, mystery clients that seek treatment, or providers.

- The **study setting** was an area of endemic malaria transmission in sub-Saharan Africa or Asia.

Studies were excluded if the abstract was not available in the English language and if it was published before 1990.

Characteristics of publications that failed to meet the inclusion criteria include: interventions that directly target patients, caregivers or the community (e.g. home management of malaria interventions to educate mothers, or mass-media campaigns); interventions that introduce as well as train community based agents (e.g. recruit and train village malaria assistants); and interventions that focused on malaria prevention strategies (e.g. bednets or intermittent preventive treatment).

3.3 Data extraction and synthesis

The title and abstract of each citation were reviewed to identify publications for the full-text review. The full-text of identified publications were read to determine it if met all the inclusion and none of the exclusion criteria.

For each eligible publication summary details were extracted in a tabular form, capturing the nature of the intervention, study context, study design, research methods and outcomes reported. Based on the description of the intervention it was categorized both in terms the principal element of the intervention package, and any supplementary activities. The categories used in this review are listed and defined below and based on a recent World Health Organization report (Box 2) [15].

Box 2. Different categories of intervention

Consumer Education: *activities to improve the knowledge or awareness of patients, their caregivers or the community. These range from mass-media campaigns to displaying a poster or leaflets at a health facility.*

Economic Intervention: *economic incentives are created to change the practice of health providers.*

National Policy Initiative: *the intervention is part of a national programme of activities, or closely aligned to a government initiative.*

Pre-packaged Antimalarials: *drugs are repackaged and as such presented in age-specific packs or with additional information.*

Provider Educational Process: *providers are educated using an approach that differs to conventional workshop-based provider training.*

Printed Educational Materials: *participants receive written or pictorial documents, such as a training manual, clinical algorithm or another form of job aid.*

Provider Training: *participants attend workshop-based training, possibly including practice sessions. A variety of learning techniques may be used within the workshop-format including lectures, seminars, role-play and assessment.*

Rapid Diagnostic Testing (RDT) Provision: *providers have RDTs available to use.*

Refresher Training: *participants have the opportunity to attend a second training workshop.*

Enhanced Supervision: *providers receive additional supervision or support visits.*

To compare the effectiveness of the interventions on the ability of provider to diagnose and treat malaria we have focused on three types of outcome: 1) presumptive treatment of uncomplicated

malaria in febrile patients; 2) appropriate treatment of uncomplicated malaria in febrile patients (following a diagnostic test); and 3) the accuracy of prescribing antimalarial treatment regimens. Thus for synthesis, outcomes have also been assigned to the following categories:

1) Presumptive treatment of uncomplicated malaria in febrile patients:

- Provider knowledge of how to diagnose and/or treat malaria
- Proportion of patients who were presumptively prescribed or treated with an antimalarial
- Proportion of patients who were presumptively prescribed or treated with the recommended antimalarial

2) Appropriate treatment of uncomplicated malaria in febrile patients:

- Provider ability to conduct malaria diagnostic testing
- Proportion of patients who were prescribed or treated with an antimalarial following a malaria diagnostic test

3) Accuracy of prescribing antimalarial treatment regimens:

- Provider ability to prescribe or dispense an antimalarial in the correct dose
- Provider ability to prescribe or dispense an antimalarial with correct advice on the regimen

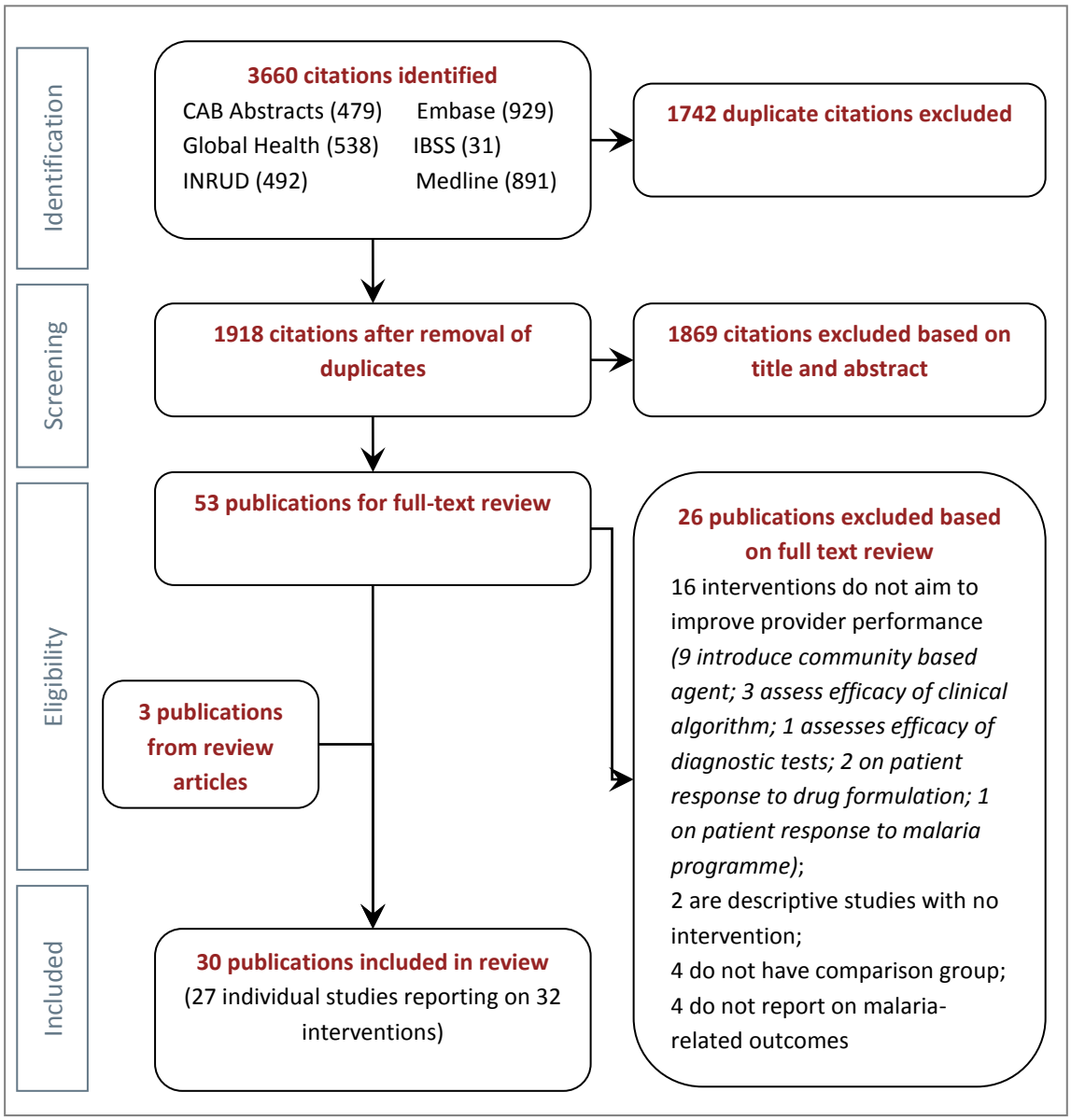
For those outcomes that report on the treatment prescribed or received we distinguish between outcomes obtained from simulated mystery client visits and outcomes from real-world patient-provider interactions. The latter, by definition, entail patient variation in terms of their symptoms, demographic and socio-economic characteristics. In contrast, the outcomes from the simulated mystery client visits present a standardized case with which to measure the competence of the provider. The providers' ability to conduct diagnostic testing is also considered a measure of their competence.

4. Results

4.1 Search results and selection of publications

The process for selecting publications is shown in Figure 1. A total of 1918 publications were identified from the database and reference lists, searches once duplicates were removed. From the title and abstract 53 publications were selected for full-text review. After the review of the full text, 26 publications were rejected as they did not meet the inclusion criteria (Appendix A). Sixteen were rejected because the intervention does not seek to improve the ability of providers, predominately because the intervention involved introducing a community-based agent, such as village health volunteer. Other publications were rejected because the study was descriptive (2 publications), there was no comparison group (4 publications) or because the publication did not report on malaria-related outcomes (4 publications). Twenty-six publications [16-41] were eligible and a further 3 publications [42-44] were identified from review articles and the reference lists of eligible articles.

Figure 1: Flow chart for selection of studies



4.2 Overview of the selected publications

Thirty publications were eligible for the review. These publications report on 27 studies, since some publications report on the same studies [17, 19, 20, 24, 31-33] and other publications report on multiple studies [20, 33]. Moreover, the publications report on a total of 32 interventions as 5 studies evaluate multiple interventions [21, 25, 29, 33, 35]. For instance, Harvey et al (2008) use a 3-arm intervention trial to consider the impact of provider training and job aid, a job aid alone in comparison to a control group[21].

The characteristics of the selected studies are summarized in Table 1 and Appendix B. The majority of the studies (17 of 27) were set in three countries in East Africa, with 8 from Kenya, 5 from Tanzania and 4 from Uganda [16, 17, 23-27, 29, 31-38, 40, 42]. A further 8 were from West Africa (of which 3 were from Nigeria) [18, 28, 30, 39, 41-44]. The remaining three studies were from Ethiopia, Zambia [21] and India [22].

The studies were reasonably balanced between public and private sector facilities. Fifteen studies were located in public facilities, predominately focusing on malaria diagnosis and treatment at the primary care level. Eleven studies engaged private sector actors; primarily drug retailers with no or little formal training though a few were from private health clinics. A couple of studies involved wholesalers of malaria treatment in addition to retail outlets [32, 37]. One study evaluated training of community health workers [21].

4.3 Different types of intervention

Thirty-two interventions were evaluated within the 27 studies. The majority of the interventions were designed to focus on malaria (21 of 32 interventions or 16 of 27 studies) (Appendix B). In the 12 remaining interventions, improving malaria diagnosis and treatment was part of a broader objective, often the management of a range of common childhood illnesses. There was one exception, in which the objective of the intervention was to improve the quality of laboratory services [18].

In 21 of the 32 interventions (or 19 of 27 studies), the principal activity was categorized as provider training, and in total provider training was used in 27 of the interventions (Box 3). The different types of studies and interventions are summarized in Box 3 and described in Appendix B. Within the category of provider training there was considerable variation. Improving diagnosis and treatment of malaria was the focus in the majority of the training interventions, though in some instances this was a component of a child health training programme. For example, 4 interventions were training implemented as part of the Integrated Management of Childhood Illnesses (IMCI) initiative [17, 22, 31, 39]. The use of malaria diagnostic tests, either using microscopy or rapid diagnostic tests, was covered in 6 training interventions [18, 25, 29, 35, 36, 40]. The training workshops used a range of learning techniques, and many sought active participation by including practical sessions and role-playing, in addition to seminars and presentations. The training workshops also varied in length, with courses lasting from one-hour to 11 days.

Box 3. Categorization of the studies and interventions

CATEGORY	INTERVENTION		STUDY
	Principal activities	Principal & supplementary activities	Principal activities
Consumer Education	-	7	-
Economic Intervention	3	3	2
National Policy or Initiative	-	4	-
Pre-packaged Antimalarials	1	4	1
Provider Educational Process	3	3	3
Printed Educational Materials	1	24	-
Provider Training	21	27	19
Provision of Rapid Diagnostic Testing	2	2	2
Refresher Training	1	3	-
Enhanced Supervision	-	9	-
TOTAL	**32**		**27**

Three interventions were categorized as a provider educational process, since they sought to improve providers' knowledge and practice but without taking a workshop-based training approach [37, 42, 44]. Two interventions used self-assessment in order to encourage participants to reflect on the quality of the services provided, and discussion with colleagues [42, 44]. The other educational intervention focused on peer-to-peer learning, with wholesalers trained and encouraged to educate their customers from drug retail outlets on new malaria treatment guidelines [37].

Nine interventions (within 7 studies) focused on conducting tests to diagnose malaria [18, 21, 25, 29, 35, 36, 40]. Three studies evaluated the impact of provider training on the ability of health workers to accurately conduct diagnostic tests [18, 21, 29]. Two studies evaluated the impact of training in microscopy, in addition to training in malaria management, on the treatment received by febrile patients [25, 36]. Finally two studies evaluated the impact of providing RDTs on the treatment received by febrile patients [35, 40].

Two studies focused on changing provider practices by adjusting economic incentives [32, 33]. These two interventions were country case studies undertaken in the context of preparatory work on the Affordable Medicines Facility – malaria (AMFm) [32, 33]. The AMFm proposes to subsidize ACT, with the aim of increasing the availability and affordability of ACT, whilst also crowding out artemisinin monotherapies whose use can contribute to drug resistance. One study reports on the impact of a price subsidy, shopkeeper training, and behaviour change communication activities in Tanzania, with an additional arm also evaluating the impact of including a suggested retail price [32]. The other case study was a franchise scheme in Kenya [33].

As the studies range from the early 1990s until 2009, they have been undertaken in the context of different national policies for the first-line recommended treatment for uncomplicated malaria. Only 6 of the 27 studies report on an intervention that has been undertaken in the context of ACT, and of these 4 focus on improving malaria diagnosis in public sector facilities, either by training on microscopy or RDTs or by making RDTs available [21, 35, 36, 40]. The remaining 2 studies are the AMFm case studies, which consider improving the availability and affordability of ACTs though private sector distribution channels [19, 32, 33].

While the interventions have been described by focusing on their principal component, it should be noted that the vast majority of the interventions involved a package of activities. For instance, provider training and provider educational process interventions were typically supplemented by printed educational materials such as training manuals, guidelines or wall charts displaying clinical algorithm for treating malaria. In 9 instances the interventions referred to an enhanced level of supervision [16, 23-25, 35, 38, 39] and in three of interventions there were opportunities for refresher training [23, 24, 29]. Activities that sought to enhance consumer awareness were mentioned in 7 interventions [16, 23, 24, 32, 33, 37, 43], while 4 interventions involved the distribution of repackaged antimalarials [32, 41, 43]. Finally, 4 of the interventions were closely aligned to a national government programme or initiative, such the dissemination of change of first-line treatment [16, 18, 35].

4.4 Evaluation methods

Studies were eligible to be included in the literature review if they adopted a study design which permitted the intervention to be evaluated with reference to a comparison group. Three studies applied a cluster randomized or individual randomized control design [16, 25, 41]. Ten studies used a pre-post design with a control group [18, 22-24, 26, 27, 30, 32, 33, 35] and 7 studies used a pre-post design without a control group [28, 29, 36, 38-40, 43]. The remaining 7 studies evaluated post intervention with a comparison group [17, 21, 31, 34, 37, 42, 44].

The studies used a variety of research methods to evaluate the impact of the intervention. They also tended to employ several methods of data collection to validate and contextualize their findings. The main methods used to assess the impact of the intervention on providers' ability to treat according to guidelines were direct observation of the patient consultation (in 10 studies) [17, 21, 23, 31, 34, 35, 39, 41, 42, 44] and exit surveys with patients or their caregiver (in 9 studies) [17, 25, 31, 32, 34, 35, 40-42]. The latter sometimes involved a re-examination of the patient, re-reading of blood slides or independent testing for malaria parasites. Mystery clients were used in 6 studies [16, 24, 26, 37, 38, 43], as an alternative method for assessing provider competence in delivering treatment, and with the advantage that the same scenario is presented in each case in order to control for variation in patient characteristics, such as their age or symptoms. In two studies patient records were consulted, though there were concerns about the reliability of these data [28, 35], and in two studies patients were followed up either on day 4 to obtain information on patient adherence to treatment or on day 7 to know the health status of patients [25, 41].

Additional research methods were used to assess the impact of the intervention. For instance, household surveys were used in 3 studies to examine the treatment seeking behaviour and treatment received by febrile patients [20, 24, 33]. Five studies used methods of assessing health worker knowledge of malaria treatment [18, 22, 27-29], and 5 studies involved a health facility survey or retail audit to determine, amongst other things, the availability of diagnostic services and medicines [16, 37, 40, 42, 43]. Qualitative research was undertaken in 8 studies, usually interviews or focus group discussions with the health care providers, though 2 studies sought the views of patients or caregivers[17, 33, 40-42, 44]. The objective of the qualitative work also varied, in some cases it sought to obtain a deeper understanding of the effect and acceptability of the intervention. In other cases, however, qualitative methods were used during the development stage, such as in the design of activities or materials, or more generally to explore the feasibility of the intervention. Finally, only two studies reported on the cost-effectiveness of the intervention [19, 22].

4.5 Effect of intervention

The evaluation studies report a range of different outcome measures, as summarized in Table 1. The outcome measures have been grouped to determine the effect of the intervention on the providers' ability to deliver presumptive treatment, appropriate treatment following a diagnostic test, and the accuracy of the treatment provided in terms of dosage and advice on regimen. These results are presented in Tables 2, 3 and 4, respectively. Evidence across the studies has been synthesized, though it is important to note direct comparison is limited by variation in the specific indicators used as well as differences in other dimensions such as the methods of data collection and the study context.

In the majority of cases the intervention had a significant positive effect on the presumptive treatment of uncomplicated malaria (Table 2). Three studies show provider training had a positive impact on providers' knowledge of how to treat malaria [22, 30, 37]. A further 8 studies show that provider training had a significant positive impact on whether febrile patients received either any antimalarial or the recommended antimalarial, and these studies cover interventions with providers in both public and private sector facilities [16, 23, 24, 26, 35, 37, 38, 43]. Studies that used mystery clients to assess provider competence consistently show that training is effective in improving presumptive treatment. However, in two instances was the effect was not significant [25, 39]. The first compares training on a clinical algorithm to diagnose malaria as has having no significant impact on whether the patient receives an antimalarial, though the proportion of febrile patients receiving an antimalarial is very high in the intervention and control arms [25]. The other study shows that provider training has no significant effect on proportion of febrile patients *without* malaria that receive an antimalarial, and as desired the proportion is relatively low in both groups [35].

Provider training and job aids designed to improve the accuracy of diagnostic testing show a positive effect, with the studies by Harvey and Ohrt reporting improvements in conducting the test and in understanding the test results (as in Table 3) [21, 29]. The appropriateness of the treatment received by febrile patients following a diagnostic test is also reported in Table 3. Treatment with an antimalarial is considered appropriate following a positive test result for the presence of malaria parasites, and inappropriate following a negative test result. The results from two interventions that introduced RDTs show that the introduction of RDTs reduced the proportion of RDT negative patients that received an antimalarial, though only in one of the two studies was the reduction statistically significant [35, 40]. In the two studies that evaluated the impact of provider training, it was found that the proportion of parasite negative patients that received an antimalarial was significantly reduced [25, 36].

Several studies assessed the accuracy with which health workers deliver treatment in the correct dose and with advice on how the treatment should be administered (Table 4). Overall the interventions had a significant positive effect on the proportion of patients that received an antimalarial in the correct dose or with correct advice on the treatment regimen. Only in one study was the effect not significant, and in this case prior to the intervention more than three-quarters of the patients were prescribed an antimalarial in the correct dose [36].

The other interventions which are not reported in these tables are the two AMFm cases studies which introduced an economic incentive. The study from Tanzania, which introduced a price subsidy and rolled out supporting interventions including shopkeeper training and behaviour change communication in the community showed a significant positive impact on the availability of ACTs in retail outlets and in the use of ACTs [32]. The inclusion of a suggested retail price also had a positive impact, though caution was noted in setting the price since the mean price charged was slightly higher in that district. Finally the results of a household survey in Kenya show an increase in the use of ACTs, though it is not possible to determine the source of the ACT and therefore the effect of the franchise scheme on their use.

5. Discussion

The review identified studies that have evaluated interventions to improve the ability of providers to diagnose malaria and treat patients. In total 30 publications met the eligibility criteria and these contained 27 studies and evaluated 32 different interventions. In the majority of studies the intervention involved provider training or an educational process intended to enhance providers' knowledge and skills when treating febrile patients, either specifically in the context of malaria or for a wider range of childhood illnesses. The most recent studies were undertaken since ACT was adopted, and included studies that sought to improve malaria diagnosis in the public sector facilities as well as others that promoted the availability and affordability of ACT in the private sector. This reflects the concerns about the higher price of ACTs and the need to limit resistance to artemisinin derivatives.

Overall the studies were found to have a positive effect on presumptive treatment of febrile patients, and the accuracy of the doses and advice given. This shows that provider training (and other interventions) can change the knowledge, competence and practice of providers working in the public and private sectors. The results also show that the provision of RDTs and training on diagnostic tests led to improvements in the appropriate treatment of malaria, with reductions in the proportions of patients receiving an antimalarial if they were found to be test negative. Despite the reductions, the proportions of test-negative patients receiving antimalarials were still relatively high, suggesting that more would be needed to prevent inappropriate treatment with antimalarials in patients who tested negative for malaria. The overprescribing of antimalarials following parasitic diagnosis has been the focus of research in Tanzania, which highlights the considerable change in mind-set required to influence the prescribing behaviour of public sector health workers [45, 46].

In synthesizing the effect of the interventions it is important to be cognizant of the differences in the context, actors, and research methodology, as well as the variations in the outcome indicators used. There was also variation in the study designs used. The more rigorous approaches employed a randomized, or cluster randomized design or alternatively a pre-post design with a control group. These designs mitigate bias, by controlling for comparatively more potential confounders, though are used in only 13 of the 27 studies.

None of the studies compared the implementation of an intervention across public and private sector providers. This may reflect the need to tailor the intervention to the type of provider, and what makes sense in the public sector may not be readily transferred to the private sector and vice versa. It might be useful to know the relative impact of, say, a training intervention with providers in the public and private sectors to know where best to direct efforts to improve treatment of uncomplicated malaria. However, such decisions ought also to take into account the patterns of treatment seeking and the relative cost-effectiveness of the interventions. In that vein, it was noteworthy that only two programmes reported on the cost-effectiveness of the intervention. The impact of the intervention from an equity perspective was also a notable gap in the research.

6. Conclusion

The review of the interventions to improve the ability of provider to diagnose and treat uncomplicated malaria provides valuable background to the design of interventions for the REACT project. It is useful to know what approaches have been tried and tested, as well as the methods used to evaluate their effect. The review also highlights areas for further work. For instance, while it has been shown that provider training and other educational processes can have a significant effect on providers' knowledge and practice, the magnitude of the effect varies considerably. Moreover, in developing a training package, it is clear the following aspects would benefit from further consideration: the length of the programme, learning techniques, importance of supervision and benefits of refresher training.

The studies also suggest that further work on interventions to improve the appropriate treatment of febrile patients would be valuable. The studies show that provider training and the provision of RDTs can be beneficial, though suggest that conventional approaches may have only a limited effect. The findings also indicate the focus of the REACT project on analysing the cost-effectiveness and equity implications of an intervention will be important since these perspectives have received limited consideration. Thus, REACT should demonstrate the feasibility and importance of bringing an economic perspective to evaluation of interventions targeting service delivery improvements.

Table 1. Overview of selected studies

Intervention	Country, Year	Facility or Outlet	First-line AM	Study Design	Research instruments	Outcome Measures	Study
Provider Training (malaria)	Kenya, 2005	60 Private sector drug retailers	AQ / SP for OTC	Cluster RCT	• Mystery clients • Retail audit	• % mystery clients sold (any) AM • % mystery clients sold recommended AM • % mystery clients sold recommended AM with correct advice on regimen	[16]
Provider Training (IMCI)	Tanzania, 2000	20 Primary health facilities	Not specified	Post + control (up to 3 years after training)	• Observation of consultation • Exit survey of febrile <5yrs (including re-examination) • Interviews with providers	• % febrile <5yrs observed that were correctly treated for malaria	[17, 20]
Provider Training (laboratory tests)	Ghana, 2000	205 Public sector peripheral laboratories	Not specified	Pre-Post (after 18 months)	• Provider survey	• % of laboratories surveyed with accurate results for malaria microscopy 6-months after training	[18]
Educational Process (self- assessment)	Guinea and Kenya, 2001	8 Primary care clinics in each country	Not specified	Post + control (after 15 months)	• Health facility survey • Observation of patient consultations • Exit survey of febrile <5yrs • Interviews & FDGs with staff	• % febrile <5yrs observed that were correctly prescribed malaria treatment	[42]
Provider Training & Pre-packaged AMs	Nigeria, 2003	200+ Private drug retailers	CQ and SP	Pre-post	• Mystery clients • Retail audit	• % of mystery clients sold the recommended AM	[43]
A) Provider Training (RDT) & Job Aid B) Job Aid	Zambia	79 Community health workers	Not-specified	3-arm study	• Observation of CHW performance using 16-item checklist • Responses to 10 standard test results	• % steps in using RDT performed correctly • % RDTs read correctly	[21]
Educational Process (self- assessment & peer feedback)	Mali, 2001	Public health facilities	Not specified	Post + control	• Observation of provider-client interaction; • Interviews with study participants	• % provider that comply to fever care standards	[44]

Intervention	Country, Year	Facility or Outlet	First-line AM	Study Design	Research instruments	Outcome Measures	Study
Provider Training (IMCI)	India	Public health facilities (85 health workers)	Not specified	Pre-Post (immediately after)	• Multiple choice and problem-based questionnaire	• Malaria knowledge score	[22]
Provider Training (malaria)	Kenya, 1995-1997	23 Private sector drug retailers	CQ	Pre-Post (after 1yr and after 2yrs)	• Observations of patient consultations	• % of those seeking treatment for fever that were sold an AM • % of AMs sold in correct dose • % of AMs sold with advice on use	[23]
Provider Training (malaria)	Kenya 1999-2000	Private sector drug retailers	CQ / SP	Pre-Post + control in two study sites*	• Mystery shoppers • Household survey (children <5yrs reporting fever in past two weeks)	• % mystery clients advised to buy an AM • % mystery clients sold CQ / SP that were given advice on regimen • % AM users taking adequate dose	[19, 24]
A) Provider Training (microscopy + clinical diagnosis) B) Provider Training (clinical diagnosis)	Tanzania 2003-2004	16 public health centres & 13 dispensaries	SP	Cluster RCT (3 arms)	• Exit survey of febrile <5yrs (including re-examination and microscopy test) • Follow up on day-7	• % febrile children attending facility that receiving AM prescription	[25]
Provider Training (childhood illness)	Tanzania, 2004	40 private sector drug retailers	SP	Pre-Post with control (after 6 months)	• Mystery clients	• % mystery clients sold the recommended AM (SP) • % mystery clients sold the recommended AM with correct advice on regimen	[26]
Provider Training (rational drug use)	Uganda, Not specified	private providers	Not specified	Pre-Post with control	• Mystery clients	• % mystery clients sold an AM • % mystery clients sold an AM and given advice on the regimen	[27]
Provider Training (malaria)	Ghana, Not specified	Medical assistants from 40 public health centres	CQ	Pre-Post, no control (after 3-9 months)	• Prescription survey from outpatient records • Knowledge assessment • FGDs	• % providers know correct dose for 3yr old • % providers know correct dose for 5yr old	[28]

Intervention	Country, Year	Facility or Outlet	First-line AM	Study Design	Research instruments	Outcome Measures	Study
Provider Training (microscopy) + Refresher Training (microscopy)	Kenya	Kenyan & international microscopists	Not specified	Pre-Post	• Pre-post examination / assessment (including reading slides)	• % point improvement on knowledge of microscopy • % point improvement on slide sensitivity and specificity	[29]
Provider Training (childhood illnesses)	Nigeria	28 private sector drug retailers	CQ	Pre-Post with control	• provider knowledge assessment	• Mean knowledge score	[30]
Provider Training (IMCI)	Uganda, 2000, 2001, 2002	public and NGO facilities	Not specified	Post + Control	• Observation of patient consultation • Exit survey of febrile >5yrs (including re-examination) • Interviews with providers	• % febrile <5yrs observed that were given an AM in the correct dose	[31] [20]
Economic Incentive A) Price subsidy, BCC, training, & suggested retail price B) Price subsidy, BCC & training C) No intervention	Tanzania, 2007-08	private sector drug retailers	AL	Pre-Post with control (after 6 months)	• Patient Exit Interviews	• % of consumers purchasing AMs that bought AL	[32, 33]
Economic Incentive (Franchise scheme)	Kenya, 2007	9 Community & family wellness shops that joined franchise	AL	Pre-Post (after 9 months)	• Household survey (reporting fever in past 2 weeks) • Interviews with franchisee • FGDs with caregivers	• Use of AL (but cannot be attributed to franchise scheme)	[33]
Provider Training	Ethiopia	3 public health facilities without laboratories (6 nurses)	CQ	Post + comparison	• Observation of patient consultation • Exit survey of febrile >5yrs (including re-examination)	• No. of children that providers diagnosed with fever compared to control (clinical diagnosis by study paediatrician)	[34]

Intervention	Country, Year	Facility or Outlet	First-line AM	Study Design	Research instruments	Outcome Measures	Study
A) RDT provision vs No RDTs B) Pre vs post training, guidelines, supervision	Kenya, 2006	60 government health facilities (hospitals, health centres, dispensaries)	AL	Pre-Post with control	• Observation of patient consultation • Exit survey of febrile >5yrs (including re-examination and microscopy test)	• % febrile >5yrs with and without uncomplicated malaria that received recommended AM • % febrile >5yrs who were RDT test positive and received recommended AM • % febrile >5yrs who were RDT test negative and received ACT	[35]
Provider Training (microscopy)	Uganda 2006	8 public facilities with microscopy services (also malaria surveillance sites)	AL	Pre-Post (after 4 months)	• Patient-level surveillance data from health facility (febrile patients, all ages) • Gold standard microscopy to determine diagnostic accuracy	• % febrile <5yrs / >5yrs who were parasite positive and received AM • % febrile <5yrs / >5yrs who were parasite negative and received AM • % <5yrs / >5yrs prescribed AM who were prescribed a correct dose	[36]
Provider Educational Process (peer educators)	Kenya, 2000	Private sector wholesalers and drug retail outlets	SP	Post & Control (Intervention arm if poster was visible)	• 2 mystery clients per facility. • Retail audit	• Mean malaria knowledge score (based on 10-question true/false quiz) • % mystery clients that were sold recommended AM (SP) • % outlets with the recommended AM in stock	[37]
Provider Training (childhood illness)	Uganda, 2002-2003	Private clinics and drug shops	CQ + SP	Pre-Post (after 3 months)	• Mystery clients	• % mystery clients supplied recommended AM • % mystery clients supplied recommended AM in the correct dose • % mystery clients supplied recommended AM with correct advice on regimen	[38]

Intervention	Country, Year	Facility or Outlet	First-line AM	Study Design	Research instruments	Outcome Measures	Study
Provider Training (IMCI)	Nigeria, Not specified	4 urban public health centres (32 health workers)	Not specified	Pre-post (after 3 months)	• Observation of patient consultation (for children <5yrs)	• % of children <5yrs correctly (clinically) diagnosed for malaria • % of children <5yrs observed that received an AM • % of children <5yrs observed correctly prescribed an AM	[39]
Provision of RDTs (including training)	Tanzania, 2005	6 rural public dispensaries (without microscopy services)	AL	Pre-Post (after 8 weeks)	• Health facility survey • Patient exit survey (incl. microscopy and RDT) • Qualitative exit interviews with patients • Qualitative interviews with providers	• % of AM prescriptions that were RDT test negative	[40]
Pre-packaged AMs (compared to routine prescription)	Ghana, Not specified	6 public health facilities	CQ	Cluster RCT (3 facilities as intervention, 3 facilities as control)	• Observations of patient consultations • Patient exit survey • Follow up on day-4 on adherence to AM • FGDs on perception of packaging	• % of clinical diagnosed malaria cases that were given the correct prescription	[41]

* First study site: no training 1998 vs CQ training 1999 vs SP trained 2000 and 2001; Second study site: no training 1998 and 1999 vs SP training 2000 and 2001
Abbreviations: ACT = artemisinin-based combination therapy; AL = artemether lumefantrine; AM = antimalarial; ARI = acute respiratory infection; AQ = amodiaquine; ASAQ = artesunate amodiaquine; BCC = behaviour change campaign; CQ = chloroquine; HW = health worker; IMCI = Integrated Management of Childhood Illnesses; NGO = nongovernmental organization; N/A = Not applicable; OTC = over the counter; RCT = randomized controlled trial; RDT = rapid diagnostic test; SP = sulphadoxine pyrimethamine

Table 2. Effect of interventions on providers' ability to presumptively treat uncomplicated malaria

Intervention	Outcome Indicator	Pre-Intervention or Control Arm	Post-Intervention or Intervention Arm	Significance	Study
Effect on providers' knowledge of how to treat malaria					
Provider Training	Mean knowledge score (out of 100)	43.2 (n=33)	71.6 (n=37)	P<0.001	[30]
Provider Training (8-day IMCI)	Mean knowledge score (out of 100)	28.5 (n=35)	80.0 (n=35)	P<0.05	[22]
Provider Training (5-day IMCI)	Mean knowledge score (out of 100)	20.0 (n=50)	80.0 (n=50)	P<0.001	[22]
Provider Educational Process (Peer Educators)	Mean malaria knowledge score (10-question true/false quiz)	7.1	8.7	P<0.001	[37]
***Effect* on ability of providers to clinically diagnose malaria**					
Provider Training (IMCI)	No. of children providers diagnosed with fever compared to control (clinical diagnosis by study paediatrician)	39	248	33% sensitivity 99% specificity	[34]
Effect on proportion of patients that were prescribed or treated with any antimalarial (AM)					
Provider Training	% mystery clients that were sold an AM	58% (n=135)	78% (n=143)	OR:2.6, Not specified	[16]
Provider Training	% mystery clients that were advised to buy an AM	2% (n=224)	54% (n=183)	Significant	[24]
Provider Training	% mystery clients that were sold an AM	33% (n=78)	27% (n=30)	Not significant	[27]
Provider Training (IMCI)	% febrile <5yrs observed that received an AM	87% (n=32)	100% (n=46)	Not specified	[39]
Provider Training (clinical diagnosis)	% febrile children attending facility that receiving AM prescription	control: 99% (n=1100)	algorithm only: 95% (n=1058)	Not significant	[25]
Provider Training	% of those seeking treatment for fever that were sold an AM	34% (n=289)	Post 1yr: 84% (n=237) Post 2yr: 79% (n=150)	P<0.001 P<0.001	[23]
Effect on proportion of patients that were prescribed or treated with the recommended antimalarial (AM)					
Provider Educational Process (Peer Educators)	% mystery clients sold the recommended AM (SP)	5% (n=302)	29% (n=202)	P<0.001	[37]
Provider Training	% mystery clients sold the recommended AM (SP)	55% (n=20)	85% (n=20)	P<0.01	[26]
Provider Training	% mystery clients sold the recommended AM	21% (n=135)	52% (n=143)	OR: 5.0, P<0.001	[16]
Provider Training	% mystery clients given or recommended correct AM	2% (n=57)	73% (n=66)	P<0.001	[38]
Provider Training + Pre-packaged antimalarial	% of mystery clients sold the recommended AM	48% (n=112)	87% (n=100)	P<0.01	[43]
Provider Training + Materials + Supervision	% of febrile patients >5yrs with uncomplicated malaria that received recommended treatment	7% (n=27)	48% (n=13)	P=0.05	[35]
Provider Training + Materials + Supervision	% of febrile patients >5yrs without uncomplicated malaria that received ACT	13% (n=401)	14% (n=297)	P=0.86	[35]

Table 3. Effect of interventions on providers' ability to appropriately treat malaria by improving malaria diagnosis

Intervention	Outcome Indicator	Pre-Intervention or Control Arm	Post-Intervention or Intervention Arm	Significance	Study
Effect on providers' competence in malaria diagnostic testing					
Provider Training (laboratory tests)	% of laboratories surveyed with accurate results for malaria microscopy 6-months after training	84% (n=58)	91% (n=54)	Not specified	[18]
Provider Training (microscopy)	Pre-test score and % point improvement following training: written examination on knowledge of microscopy	62% (n=77)	+ 27% (n=77)	P<0.001	[29]
Provider Training (microscopy)	Pre-test score and % point improvement following training: sensitivity and specificity of slide readings	74% (n=77) 76% (n=77)	+ 14% (n=77) + 17% (n=77)	P<0.001 P<0.001	[29]
Refresher Training (microscopy)	Pre-test score and % point improvement following training: written examination on knowledge of microscopy	82% (n=23)	+ 15% (n=23)	P<0.001	[29]
Refresher Training (microscopy)	Pre-test score and % point improvement following training: sensitivity and specificity of slide readings	89% (n=23) 94% (n=23)	+ 6% (n=23) + 3% (n=23)	Not significant Not significant	[29]
Provider Training (RDTs)	% steps in using RDT performed correctly	80% (n=21)	92% (n=26)	P<0.05	[21]
Provider Training (RDTs)	% RDTs read correctly	80% (n=21)	93% (n=26)	P<0.05	[21]
Printed Educational Materials (Job Aid on RDTs)	% steps in using RDT performed correctly	57% (n=32)	80% (n=21)	P<0.05	[21]
Printed Educational Materials (Job Aid on RDTs)	% RDTs read correctly	54% (n=32)	80% (n=21)	P<0.05	[21]
Effect on treatment with antimalarial					
RDT Provision + Provider Training	% of AM prescriptions who were RDT test negative	55% (n=365)	16% (n=168);	Significant	[40]
RDT Provision	% of febrile >5yrs who were RDT test positive and received recommended treatment	48% (n=13)	36% (n=13)	P=0.04	[35]
RDT Provision	% of febrile >5yrs who were RDT test negative and received ACT	14% (n=297)	11% (n=346)	P=0.30	[35]
Provider Training	% febrile <5yrs who were parasite positive (from microscopy) and receiving AM	95.0%	96.7%	P=0.06	[36]

Intervention	Outcome Indicator	Pre-Intervention or Control Arm	Post-Intervention or Intervention Arm	Significance	Study
Provider Training	% febrile >5yrs who were parasite positive (from microscopy) and receiving AM	90.4%	90.8%	P=0.87	[36]
Provider Training	% febrile <5yrs who were parasite negative (from microscopy) and receiving AM	47.9%	19.6%	P<0.001	[36]
Provider Training	% febrile >5yrs who were parasite negative (from microscopy) and receiving AM	38.8%	15.6%	P<0.001	[36]
Provider Training	% febrile children attending facility who received AM prescription	algorithm only: 95% (n=1058)	algorithm & microscopy training 61% (n=973)	Significant	[25]

Table 4. Effect of the interventions on providers' ability to give accurate dose and advice on regimen

Intervention	Outcome Indicator	Pre-Intervention or Control Arm	Post-Intervention or Intervention Arm	Significance	Study
Effect on providers' ability to provide correct dose of antimalarial					
Provider Training	% providers who know correct dose for 3yr old	25% (n=32)	58% (n=33)	Not specified	[28]
Provider Training	% providers who know correct dose for 5yr old	12.5% (n=32)	30% (n=33)	Not specified	[28]
Provider Training (IMCI)	% febrile <5yrs observed given an AM in the correct dose	25% (n=135)	88% (n=169)	P<0.001	[17]
Provider Training (IMCI)	% febrile <5yrs observed given an AM in the correct dose	In 2000: 24% (n=224) In 2001: 38% (n=73) In 2002: 30% (n=105)	48% (n=142) 47% (n=138) 52% (n=378)	P<0.001 Not significant P<0.05	[20, 31]
Provider Training (IMCI)	% febrile <5yrs observed given an AM in the correct dose	36% (n=32)	84% (n=46)	Not specified	[39]
Pre-packaged drugs	% of clinically diagnosed malaria cases who were received an AM in the correct dose	74% (n=340)	93% (n=314).	P<0.001	[41]
Provider Training	% patients <5yrs prescribed AM treatment who were prescribed a correct dose	86.3%	89.0%	P=0.39	[36]
Provider Training	% patients >5yrs prescribed AM treatment who were prescribed a correct dose	78.6%	79.5%	P=0.86	[36]
Provider Training	% mystery clients given or recommended correct AM in the correct dose	0% (n=57)	50% (n=66)	P<0.001	[38]
Provider Training	% of AMs sold in correct dose	32% (n=99);	Post 1yr: 83% (n=199) Post 2 yr:90% (n=119)	P<0.001 P<0.001	[23]
Provider Education Process (self-assessment)	% febrile children observed prescribed AMs in the correct dose	51% (n=160)	62% (n=160);	P<0.001	[42]
Effect on providers' ability to provide advice on treatment regimen					
Provider Training	% mystery clients who were sold the recommended AM with correct advice on regimen	5% (n=135)	31% (n=143)	OR: 8.8, P<0.001	[16]
Provider Training	% mystery clients who were sold SP who were given appropriate advice on regimen	0% (n=2)	98% (n=98)	Significant	[24]
Provider Training	% mystery clients who were sold the recommended AM with correct advice on regimen	13% (n=20)	40% (n=20)	P<0.01	[26]
Provider Training	% mystery clients who were given or recommended correct AM with correct advice on how to administer	8% (n=57)	49% (n=66)	P<0.001	[38]
Provider Training	% of AMs sold with advice on use	2% (n=99)	Post 1yr: 94% (n=199) Post 2 yr: 98% (n=119)	P<0.001 P<0.001	[23]

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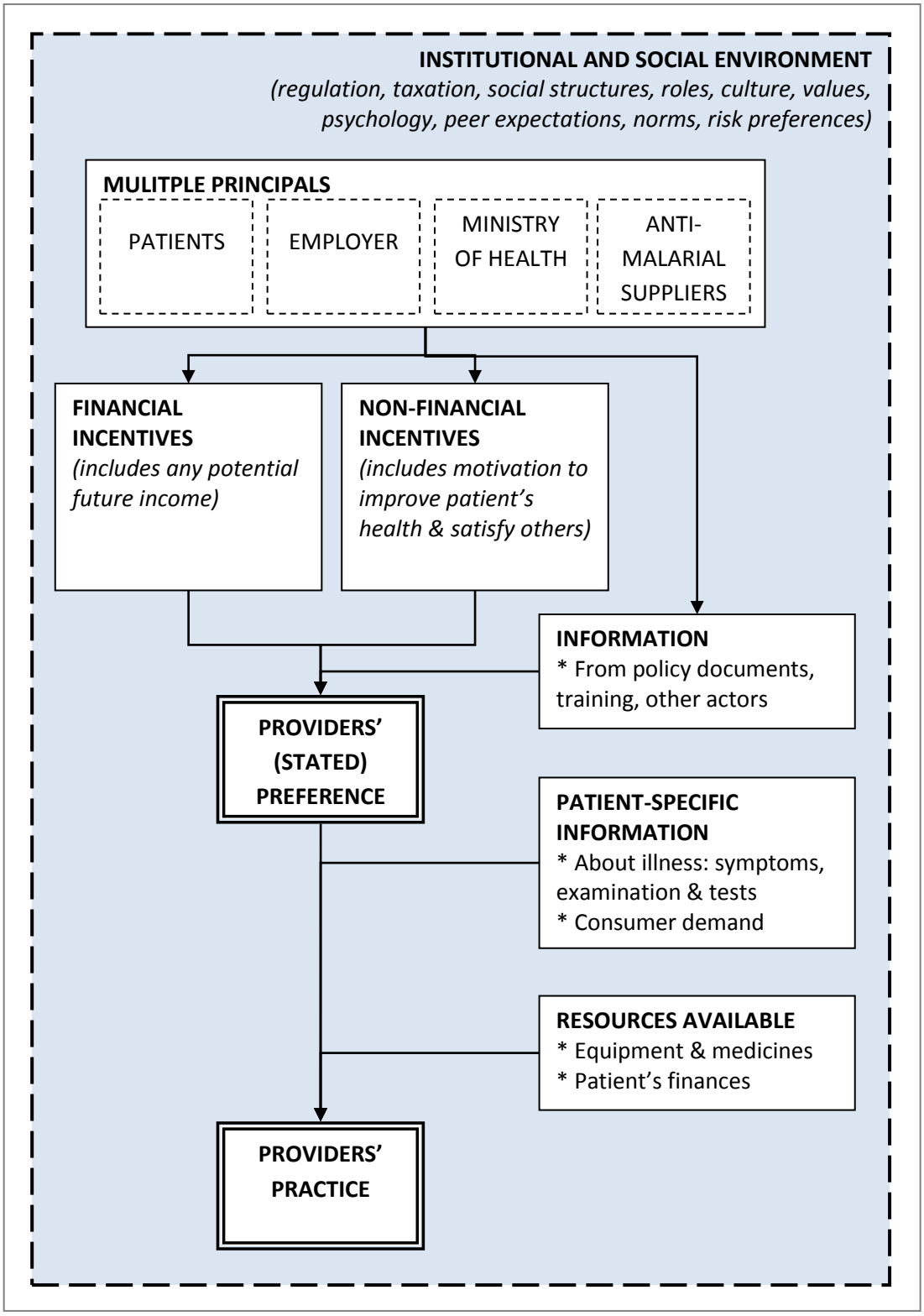
2.3 Conceptual framework

A conceptual framework was developed to integrate insights from the conceptual and empirical literature reviews and illustrate what factors may influence providers' preference over alternative antimalarials for uncomplicated malaria and their practice when treating patients with malaria symptoms (Figure 1).

The framework is founded in the agency theory and applies to patient-provider relationships that are characterised by information asymmetry in which the provider makes treatment decisions on behalf of the patient. The conceptual framework distinguishes between the treatment that the provider prefers to supply for a given illness and the treatment the provider actually supplies to an individual patient. Thus, it is acknowledged that there may be differences between the provider's stated preference and their revealed preference (i.e. practice). Preferences may also be shaped by the prevailing institutional and social environment.

Figure 1. Conceptual framework on providers' preference and practice



In summary, the framework shows that the provider's preference depends on financial and non-financial incentives, subject to the information she has available. The provider's financial and non-financial incentives are determined by the contractual relationships the provider has with the patient and also with other principals for whom the provider acts as an agent. These may include her employer, policy makers in the Ministry of Health or suppliers of pharmaceutical products. The multiple principals may also influence the information the provider has about different treatment options. The providers' practice (the treatment supplied) is expected to reflect the provider's stated preference, though may be constrained by information the provider acquires about the patient, explicit demands of their patients, the resources available at the facility, or the patient's ability to pay for treatment. Finally, the framework includes the institutional environment, which recognizes that there may be other factors that influence the provider's preference and her practice.

The empirical literature review showed that most interventions to improve providers' ability to diagnose and treat malaria focused on the information and resources available. For example, the vast majority of the interventions involved training, often using conventional methods to disseminate information about the malaria treatment guidelines, or introduced RDTs. However, there were some interventions where the mechanism of effect would reflect the role of multiple principals. For instance, peer-education or supervision may shape providers' preference through non-financial incentives by appealing to the provider's desire to please or satisfy others.

2.4 Summary

The introduction outlined the changes to the WHO malaria treatment guidelines that have taken place over the past decade: first, the recommendation that ACT became the first-line treatment for uncomplicated malaria, and second, the recommendation that all febrile patients are tested for malaria before treatment is supplied. The introduction also noted that the care received by febrile patients often falls short of the standard set out the in the malaria treatment guidelines: not all febrile patients receive the recommended antimalarial, relatively few febrile patients are tested for malaria, and it was common for patients who tested negative for malaria to be given an antimalarial. As providers are often responsible for the care received, we need a better understanding of what determines their practice, and what interventions could be used to improve providers' adherence to malaria treatment guidelines.

Economic theory offers a perspective from which to explore providers' practice. The review of the conceptual literature indicated how agency theory and thinking from new institutional economics and behavioural economics may help us understand both their preference and their practice, and identify potential mechanisms for changing provider behaviour. The review of the empirical literature on interventions to improve providers' ability to diagnose and treat malaria indicated interventions can have a positive effect. For example, training was widely used and often effective in changing the knowledge, competence and practice of providers treating febrile illness, though the magnitude of effect varied considerably. The review also indicated that introducing RDTs can reduce the over-consumption of antimalarials, though in several studies the proportion of test-negative patients who received an antimalarial remained relatively high.

The evidence summarised in the introduction and literature reviews suggest areas for further research. Studies on the care provided to febrile patients highlighted considerable variation between geographic settings and type of provider, and this suggests that it would be important to understand the environment in which providers work and the prevailing policy context before making decisions on how to expand access to malaria testing, and what interventions could be used to change providers' practice. The review indicated training can be an effective intervention, though it also highlighted several design considerations. These include the content, length and style of the training, the potential for interactive and participatory sessions, the supplementary educational materials required, and also the role for refresher training and supervision. Moreover, if training is to be considered as in intervention, it would be valuable to understand the extent to which providers' preference and practice are consistent with their knowledge of the malaria treatment guidelines. This may indicate where conventional approaches to training, which focus on providers' knowledge of the clinical guidelines, are likely to achieve a change in providers' practice, or whether additional intervention may be needed.

3. Study Setting

This Chapter describes the setting for the research contained in this thesis, which for the purposes of this chapter refers to describes both the geographic context and also the larger project in which the PhD was situated. Section 3.1 introduces the study sites, including the national malaria treatment guidelines and the types of facility from which malaria treatment can be obtained. Section 3.2 provides an overview of the REACT project and its implementation. Section 3.3 is the published trial protocol for the REACT study in Cameroon. It contains a detailed description of the interventions and the study design used to evaluate their effect on the treatment received by febrile patients.

3.1 Study sites in Cameroon and Nigeria

The research was undertaken at public and mission health facilities, pharmacies and medicine retailers in urban and rural areas of Cameroon and Nigeria.

Cameroon

In Cameroon the two sites were Yaoundé in the Centre region, and Bamenda and surrounding areas in the Northwest region. The Yaoundé study site encompasses seven urban health districts and has an estimated population of 2.5 million, who are predominantly French-speaking. The Bamenda study site consists of an urban health district and seven rural health districts that lie within a 21 km radius. The region has a population of approximately 2 million, and English and pidgin-English are widely spoken. Malaria is endemic in both study sites and they both have a long rainy season, which lasts between March and November. In Yaoundé the heaviest rains are in April-May and September-October, while in Bamenda there are heavy rains between June and October.

The health system in Cameroon is divided into three levels: i) central services of the Ministry of Public Health including management of tertiary hospitals, ii) regional delegations who manage the referral hospitals and oversee the distribution of pharmaceutical products and medical supplies to all public facilities within each region, and iii) health districts who are responsible for operational services at the peripheral level, including district hospitals and primary health care centres.

Service delivery in the public health system is adversely affected by a shortage of trained staff in rural health facilities; inadequate staff supervision; insufficient equipment and medical supplies; a weak health management information system; and limited community involvement, which has resulted in low utilization of health services[1].

As Cameroon has one of the highest densities of doctors and nurses in sub-Saharan Africa, the main issue on human resources is not the number of workers, but their distribution [2]. The majority of staff are concentrated in urban areas and it is estimated that almost 40% of the doctors work in the Centre region, which is home to 18% of the population [2]. Absenteeism is also a key issue and signals a lack of motivation. This has been attributed to the working conditions, including the inadequate availability of equipment, drugs and other medical supplies, limited supervision and few opportunities for career progression.

The health system also includes facilities owned and operated by mission organizations, such as the Catholic Church, and private sector providers. There are mission facilities at all three levels of the health system, and they operate in rural as well as urban areas. Like the government system, mission facilities receive supplies from a central pharmaceutical agency and they charge user fees for the services provided. Private sector clinics and private pharmacies operate with the permission of the regional delegation of the Ministry of Public Health and tend to be found in urban and semi-urban areas. Other actors in the health system are not formally recognized, and these include drug stores who retail over-the-counter medicines in the two Anglophone regions of Cameroon; itinerant medicine

vendors; common initiative groups registered under the Ministry of Agriculture who offer some basic health care; traditional healers; and herbalists. Nigeria

The Nigerian study sites were in Enugu State in south-east Nigeria. The two sites were urban communities in Enugu and rural communities in Udi. Enugu State has a population of 3.3 million people, the majority of whom are of Igbo ethnicity and speak the Igbo language. The study sites are similar in terms of language and culture, though as a rural setting, there are fewer public health facilities and pharmacies in Udi. Malaria is endemic in Enugu state, and occurs all year round. The rainy season is between May and October.

In Nigeria, the Federal Ministry of Health is responsible for health policy decisions, though much of the system is decentralized to the State and Local Government Levels. The district health system in Enugu operates with health posts, health dispensaries, and health centres at the primary level, and with cottage and district hospitals at the secondary level [3]. There is also a university teaching hospital in Enugu which provides referral services. The health system is structured so that district hospitals should supervise the primary health centres and cottage hospitals in their district, though in practice supervision is limited and there are weak or non-existent referral mechanisms between health centres and hospitals [3]. There are also major problems with the resources available at the primary care level, and shortages of basic drugs and supplies are relatively common.

Service delivery in the public health system is severely constrained by the availability of trained health workers. Doctors are rare at the primary care level and most health centres are ran by nurses and community health extension workers, who are semi-skilled and have received one or two years of training. In addition, health workers tend to be concentrated in urban areas, while more than 70% of the population in Enugu State resides in rural areas [3]. Supervision and monitoring of health workers is largely ineffective as many health workers lack motivation and are frustrated by resource

constraints absenteeism is common and it is not unusual for health posts and health clinics to be closed [3]. Public sector strikes also interrupt the provision of primary care.

There are, however, also a wide range of private sector providers operating in Enugu State. These include a private hospital and private clinics operating in urban Enugu as well as private sector pharmacies and drug stores, known as patent medicine dealers. Pharmacies tend to be located in urban areas, while drug stores can be found in both urban and rural settings, and these are often the first point of contact for many individuals seeking treatment. In Nigeria, pharmacies and patent medicine dealers are formally recognised in the health care system and are governed by professional organizations, namely the Pharmaceutical Association of Nigeria and the Association of Patent Medicine Dealers. Finally, there are traditional providers of health care, including traditional birth attendants, and herbalists operating in Enugu State.

Malaria diagnosis and treatment in Cameroon and Nigeria

In both countries, malaria treatment guidelines advise malaria should be suspected in all patients presenting with fever or a history of fever in the previous 24 hours [4, 5]. Malaria testing is recommended though not always available, and in the absence of a confirmed diagnosis antimalarials should be taken presumptively, based on symptoms alone. ACT has been the first-line treatment for uncomplicated malaria (in all patients except pregnant women) since 2004 in Cameroon and since 2005 in Nigeria. Antimalarials, including ACT, have over-the-counter status in Cameroon and Nigeria and can be obtained from pharmacies and drug stores as well as public, mission and private facilities. Malaria treatment may also be sought from mobile medicine vendors, herbalists and traditional healers. Patients pay for treatment at all types of facility, though both countries have exemptions for children under five and pregnant women attending public facilities.

In Cameroon, public and mission facilities, and private pharmacies are the main source of treatment for uncomplicated malaria. Most public and mission hospitals and health

centres in the Cameroon sites have a pharmacy and a laboratory for simple diagnostic procedures and are staffed by nurses, pharmacy attendants and laboratory technicians. Some larger facilities also have a medical doctor. In the private sector, pharmacies are legally required to employ a qualified pharmacist and licensed to sell prescription and over-the-counter medicines. In addition, antimalarials are available at drug stores in the North-West region, which are typically owned and staffed by providers with no or few qualifications.

In Enugu State, Nigeria, treatment for uncomplicated malaria is most frequently obtained at public health centres, pharmacies and drug stores (known locally as patent medicine dealers). Malaria diagnostic testing is not widely available at the primary care level and public facilities are staffed by nurses, community health officers and extension workers. For-profit pharmacies and drug stores are formally recognised in the health system and have professional associations. Licensed pharmacies are required to have a qualified pharmacist, while patent medicine dealers are not required to have specific qualifications or training and are formally restricted from selling prescription-only medicine.

3.2 Research on Economics of ACT (REACT) Project

The aim of the REACT project was to improve the diagnosis and treatment of uncomplicated malaria in Cameroon and Nigeria. The project commenced in 2009 and continued until 2013. REACT was financed by the ACT Consortium, which was supported through a grant from the Bill & Melinda Gates Foundation to the London School of Hygiene and Tropical Medicine (www.actconsortium.org).

REACT was founded on the principle that the project should respond to policy priorities in each country and take an evidence-based approach. This required close collaboration with the National Malaria Control Programme in Cameroon and the Enugu State Malaria

Control Programme in Nigeria. Extensive formative research was also critical to identify priorities and design interventions tailored to each study setting.

REACT was implemented in four phases:

1. Formative research to understand how malaria was diagnosed and treated at different types of facility.
2. Design interventions to support the introduction of malaria rapid diagnostic tests and improve providers' adherence to malaria treatment guidelines.
3. Implement interventions and evaluate their effectiveness and cost-effectiveness.
4. Disseminate research findings.

The formative research involved quantitative and qualitative research in all four study sites. Patient exit surveys were conducted at different types of health facility to determine the proportion of febrile patients tested for malaria, and the proportion of febrile patients who received an ACT, the first-line antimalarial. The patient exit surveys were accompanied by provider and facility surveys. Survey results highlighted the limited availability of malaria testing, and treatment practices that did not adhere to the malaria treatment guidelines (Research Papers I and II) [6, 7]. The findings led to additional research:

- Secondary analysis of the survey data to examine the providers' knowledge, preference and practice for treating uncomplicated malaria (Research Papers III and IV) [8, 9].
- Focus group discussions with community members and in-depth interventions with providers in Nigeria to explore the potential for malaria rapid diagnostic testing [10].
- Focus group discussions with health workers at public and mission facilities in Cameroon to explore their perceptions of malaria testing and the reasons why

antimalarials were prescribed to patients who tested negative for malaria (Appendix B) [11].

The findings from the formative research in Cameroon and Nigeria were shared with representatives from their respective Malaria Control Programmes in 2010, shortly after the WHO had published revised malaria treatment guidelines that confirmed RDTs are a valid alternative to malaria microscopy [12]. In these discussions it was agreed REACT should design interventions to support the introduction of malaria RDTs and address problems with providers' practice. However, the interventions needed to be tailored to the country context since the formative research had demonstrated substantial differences between the two countries.

In Nigeria, the State Malaria Control Programme (SMCP) indicated they wanted REACT to intervene in primary health facilities, private sector pharmacies and drug stores, as these types of facilities are often the first point of contact individuals seeking treatment for febrile illness. The formative research showed that malaria treatment was often presumptive since access to malaria testing was extremely limited, and there were major problems with the type of antimalarial supplied, with less than a quarter of febrile patients receiving an ACT. The formative research also highlighted the extent to which patients and caregivers at pharmacies and drug stores asked for a specific medicine.

As a result it was agreed that an intervention in Nigeria would need to address the knowledge and practice of providers, and also the knowledge and preferences of those seeking treatment. Following discussions between the SMCP and the REACT team, it was agreed that RDTs would be introduced in all facilities and medicine retail outlets participating in the trial and the project would evaluate the effectiveness of a provider training intervention that sought to improve the knowledge and practice of providers and the combined effectiveness of a provider and community intervention, with the latter engaging school teachers and school-children to raise awareness about malaria testing

with RDTs and also that ACT is the recommended treatment for confirmed cases of uncomplicated malaria [13]. Interventions were designed and evaluated in Nigeria, though I have not included this research in my thesis.

My thesis does, however, include research undertaken to evaluate the cost-effectiveness of the interventions implemented in Cameroon since the study was closely aligned to my interests on providers' knowledge, preference and practice and I had a lead role in economic evaluation. The remainder of this section explains the rationale and design of the REACT study in Cameroon, and includes a copy of the published trial protocol [14].

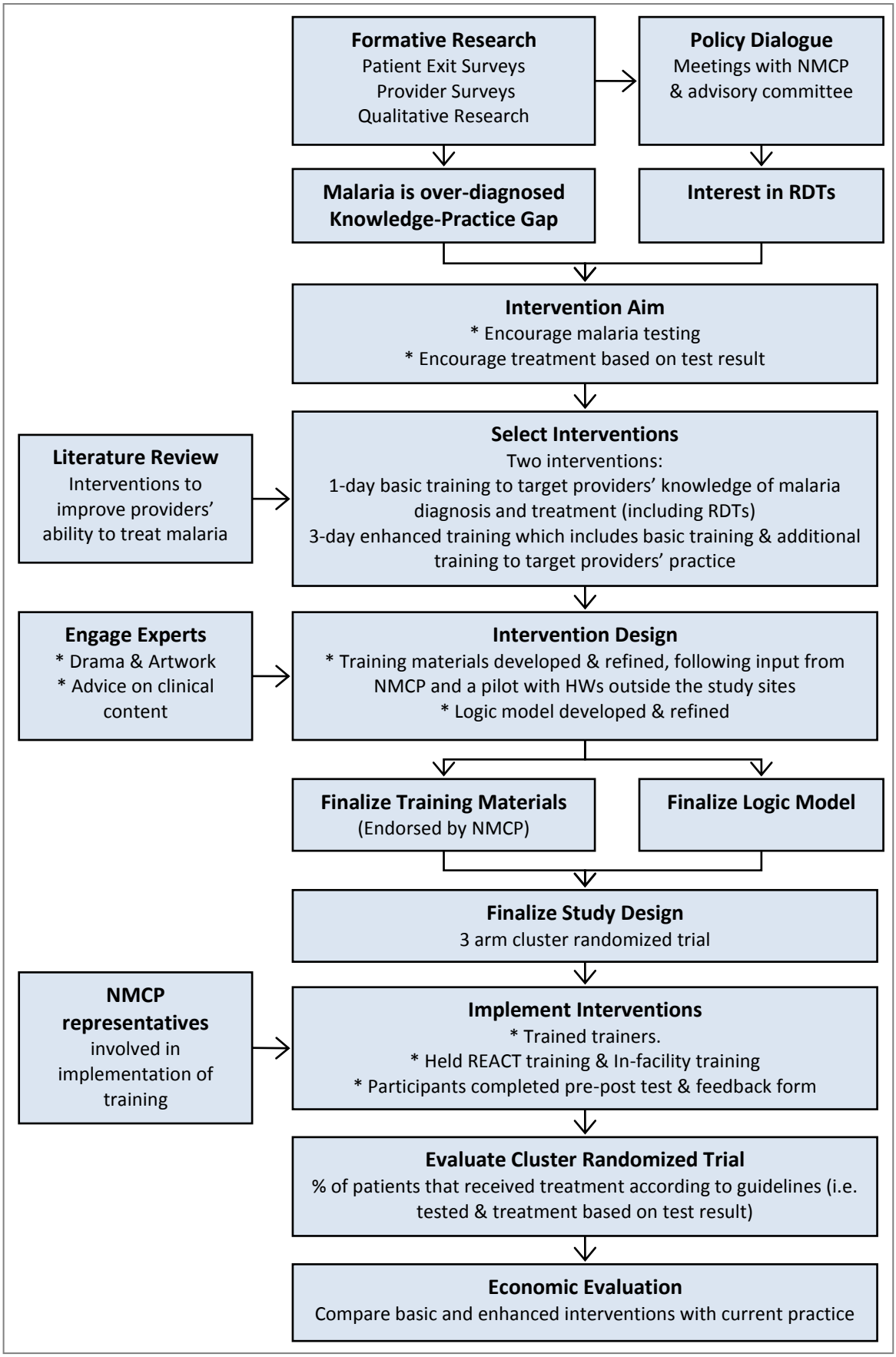
The National Malaria Control Programme (NMCP) in Cameroon indicated they wanted REACT to focus on introducing RDTs at public and mission health facilities. Having found that malaria testing was underused and it was common for febrile patients who tested negative to be prescribed an antimalarial, it was agreed that the intervention would need to encourage providers to test for malaria before prescribing treatment and to ensure that the treatment prescribed should be based on the test result [6]. Also for the intervention to be accepted by the NMCP, it was important for the intervention to be relatively inexpensive, easy to replicate on a larger scale and tested in a setting as close to the 'real-world' as possible. On this basis financial incentives were ruled out since the NMCP had indicated they had concerns about their affordability and sustainability over the longer term. Similarly, it was agreed that the project would not intervene to control the supply of ACT and that the process by which RDTs were supplied to facilities would need to be agreed by the NMCP.

A training intervention was considered since the literature review had shown training can improve providers' practice, though we were also aware training was not identified as a significant predictor in either the primary analysis (Research Paper II) or the secondary analysis on the relationship between providers' knowledge and practice (Research Paper IV). On the other hand, there was evidence that providers' stated preference (Research

Paper III) may depend on the source and method of communication and literature review had emphasized the importance of considering not only the content and length of the training but also the difference between passive and active learning. It was finally agreed two different training interventions would be evaluated.

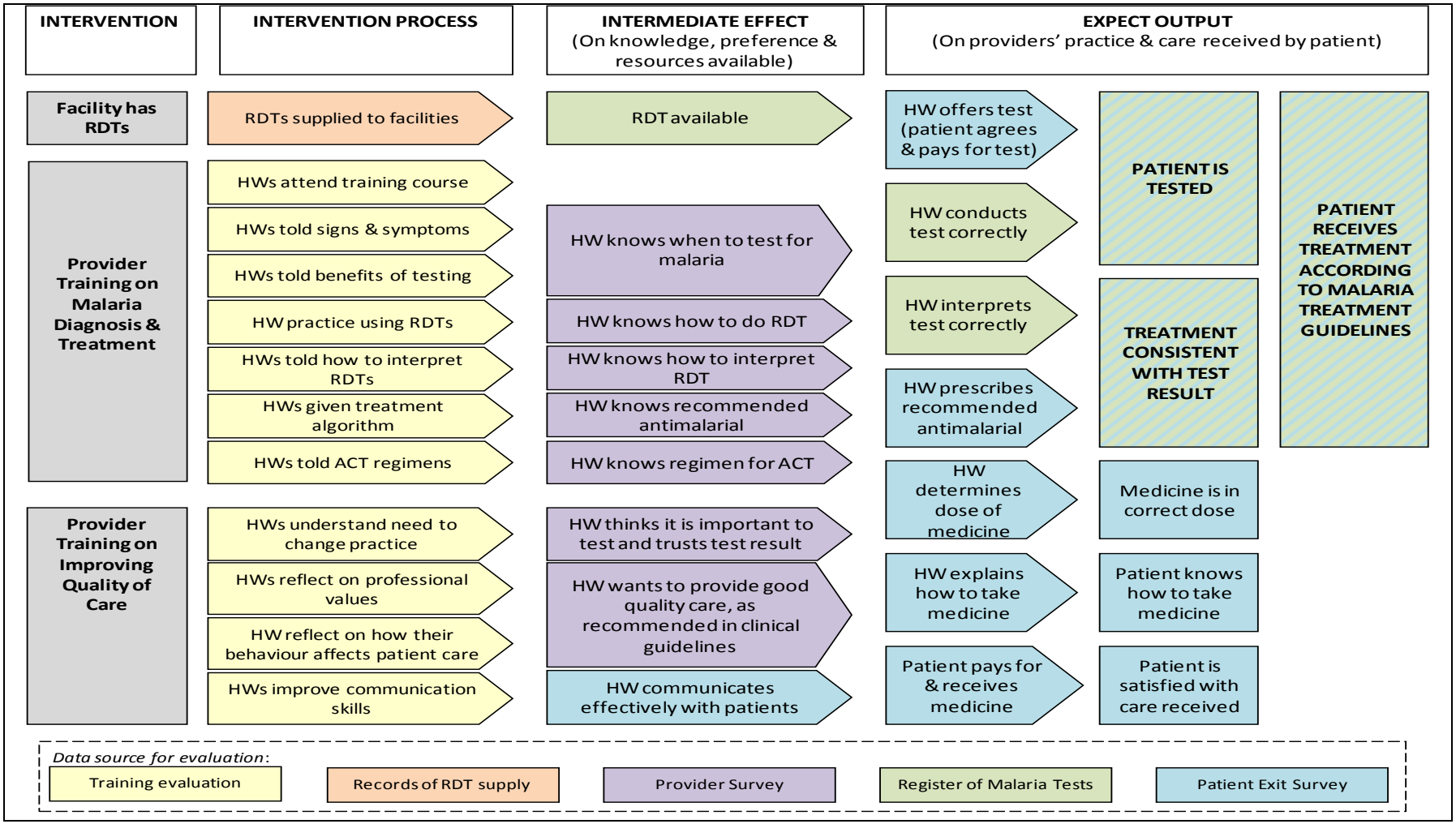
Figure 2 summarizes the development of REACT in Cameroon. It illustrates the key steps that followed formative research, including the selection and design of interventions, implementation and evaluation. For example, it shows how the literature review on interventions to improve providers' ability to diagnose and treat uncomplicated malaria informed the selection of interventions.

Figure 2. Development of REACT in Cameroon



The trial protocol, which contains detail on the interventions designed and evaluated by REACT in Cameroon, has been included in the Section 3.3 [14]. In summary, two types of training interventions were selected: one-day 'basic' training that sought to ensure providers knew the malaria treatment guidelines and were able to use an RDT; and 'enhanced' training over three days that covered the basic training and included additional activities that focused on changing providers' practice. The activities included in the enhanced training were intended to reinforce key messages about malaria diagnosis and treatment, and were based on findings from the formative research. For example, small-group exercises were used, in which providers worked together to discuss challenges and identify possible solutions because we had learnt providers can be influenced by other health workers. A module on communicating with patients was also included because providers were found to be influenced by their patients and role-playing was used to generate ideas and skills for how providers could better manage patient expectations. Training modules and materials were designed and piloted, and the final versions were endorsed by the National Malaria Control Programme. In addition, I developed a logic model to depict how we expected the training interventions to change providers' knowledge and practice, and used the logic model to identify what data would be needed to evaluate their effect (Figure 3).

Figure 3. Logic Model for REACT Cameroon



The final study design was a three-arm cluster-randomized trial and this was used evaluate the effect of the interventions on providers' practice. Clusters were public and mission health facilities in the study sites which had microscopy available. The three arms of the trial were:

- Basic intervention: RDTs supplied monthly to health facilities. One-day training for up to 3 participants per facility. Lectures on malaria diagnosis and treatment and a practical session on using RDTs. Participants received the malaria treatment guidelines, a training manual and job aids. Participants were also encouraged to conduct peer-to-peer 'in-facility' training for their colleagues.

- Enhanced intervention: All aspects of the basic intervention, plus two-days of supplementary training using participatory methods, such as small-group work with problem-solving exercises, games, and drama.

- Control: Current practice (microscopy testing was available)

The effect of the intervention was measured using a composite indicator that required patients to be tested for malaria, receive an ACT if the test result was positive, and receive no antimalarial if the test result was negative. Thus, the primary outcome measures whether the provider adheres to the malaria treatment guidelines, and allows us to assess whether the interventions were effective in changing how they diagnose and treat patients who present with a fever.

While this primary outcome does allow us to evaluate the effect of the intervention, we also recognised it has limitations. The outcome does not capture whether cases of non-malaria febrile illness (i.e. patients who tested negative for malaria and whose fever has other causes) were appropriately treated and does not report the effect of the intervention on the patient's health outcome. Given the uncertainty surrounding the non-malaria causes of febrile illness and the resources available for the REACT project it was agreed

the project should focus on whether providers' adhered to the malaria treatment guidelines rather than the appropriate management of febrile illness. Similarly, the REACT team agreed it was not a priority to evaluate the specificity and sensitivity of malaria tests conducted since requiring all patients to be independently tested for malaria could influence the uptake of malaria testing and make it difficult to assess whether the intervention had any effect on the proportion of patients who were tested during their consultation. The project also lacked the financial resources required to follow up patients and ascertain whether subsequent care was sought for the illness episode and their final health outcome.

The cost-effectiveness of the two training interventions was evaluated compared to current practice and the incremental cost per febrile patient correctly treated (according to the malaria treatment guidelines) was estimated. The analysis uses statistical methods suitable for individual patient data on costs and effects obtained from a cluster randomized trial [15, 16]. This involved taking into account the potential for correlation between costs and effects at the individual-level and cluster-level, intra-cluster correlation, and imbalance in selected baseline characteristics across the study arms. Two scenarios were analysed: a base-case which estimated the cost-effectiveness of the interventions compared to current practice as implemented for the trial, and a 'scale-up scenario' in which the start-up costs were treated as a sunk cost, and it was assumed the training would be held every two years. The estimates from the latter should be useful for policy makers in Cameroon deciding whether to scale-up the introduction of RDTs with health worker training. The economic evaluation focused on the treatment supplied in a single consultation, rather than the health outcome of the illness episode, since it would not have been possible to estimate the number of deaths (or disability-adjusted life-years) averted without making several assumptions about the specificity and sensitivity of each diagnostic methods, causes of non-malaria febrile illness, patient adherence to medication, or the costs and effects of subsequent treatment seeking. This is a limitation, though there

are plans to synthesize findings across multiple cost-effectiveness studies undertaken within the ACT Consortium, which will include data on the accuracy of microscopy and RDTs in routine use and data from following up febrile patients.

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3.3 Trial protocol for REACT study in Cameroon

The trial protocol describes the interventions and the study design used to evaluate their effect on malaria diagnosis and treatment in Cameroon. The trial was designed following extensive formative research (described in Research Papers II, III and IV and Appendix B) and sought to increase the use of malaria testing in public and mission facilities and encourage providers to prescribe treatment based the test result. The trial evaluated the effectiveness and cost-effectiveness of introducing RDTs with either basic or enhanced provider training, where the basic training sought to improve providers' knowledge of the malaria treatment guidelines and the enhanced training focused on changing providers' practice.

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Status: Published in Trials Journal, January 2012. The publication was subject to peer-review

Contribution: VW and WM secured the funding and are responsible for the overall study design and project management. OA and ANN were responsible for coordination and supervision of fieldwork. LM participated in the study design and overall study coordination. WM, OA and LM designed the provider interventions. BC led the statistical design. AMN coordinated data entry and management. CC contributed to study design and supervised the qualitative research component. All authors contributed to the original protocol while VW drafted the manuscript. All authors read and approved the final manuscript.

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TRIALS

STUDY PROTOCOL Open Access

A cost-effectiveness analysis of provider interventions to improve health worker practice in providing treatment for uncomplicated malaria in Cameroon: a study protocol for a randomized controlled trial

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Abstract

Background: Governments and donors all over Africa are searching for sustainable, affordable and cost-effective ways to improve the quality of malaria case management. Widespread deficiencies have been reported in the prescribing and counselling practices of health care providers treating febrile patients in both public and private health facilities. Cameroon is no exception with low levels of adherence to national guidelines, the frequent selection of non-recommended antimalarials and the use of incorrect dosages. This study evaluates the effectiveness and cost-effectiveness of introducing two different provider training packages, alongside rapid diagnostic tests (RDTs), designed to equip providers with the knowledge and practical skills needed to effectively diagnose and treat febrile patients. The overall aim is to target antimalarial treatment better and to facilitate optimal use of malaria treatment guidelines.

Methods/Design: A 3-arm stratified, cluster randomized trial will be conducted to assess whether introducing RDTs with provider training (basic or enhanced) is more cost-effective than current practice without RDTs, and whether there is a difference in the cost effectiveness of the provider training interventions. The primary outcome is the proportion of patients attending facilities that report a fever or suspected malaria and receive treatment according to malaria guidelines. This will be measured by surveying patients (or caregivers) as they exit public and mission health facilities. Cost-effectiveness will be presented in terms of the primary outcome and a range of secondary outcomes, including changes in provider knowledge. Costs will be estimated from a societal and provider perspective using standard economic evaluation methodologies.

Trial Registration: ClinicalTrials.gov: NCT00981877

Keywords: Cost-effectiveness, malaria, Rapid Diagnostics tests (RDTs)

Background

Governments and donors all over Africa are searching for sustainable, affordable and cost-effective ways to improve the quality of malaria case management. Widespread deficiencies have been reported in the prescribing and counselling practices of providers (by which we mean health workers) responsible for treating febrile patients attending public and private facilities [1-8]. Similar problems have been reported in Cameroon where malaria accounts for 35%-40% of all deaths, 50% of morbidity among children under the age of five, 40%-45% of medical consultations and 30% of hospitalizations [9,10].

Despite widespread availability of malaria testing using microscopy in public and private facilities in Cameroon

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and recent guidelines from the World Health Organization (WHO) recommending parasitological confirmation of suspected malaria cases in all patients before treatment where testing facilities are available [11], symptomatic diagnosis of malaria remains routine in more than 50% of consultations [12]. There is, however, increasing interest in scaling up the use of rapid diagnostic tests (RDTs) to expand access to parasitological diagnosis and improving malaria case management. The Government of Cameroon is piloting the introduction of RDTs into communities in 50 health districts in the national territory [13]. This policy initiative is based on the premise that making RDTs available will make it quicker and easier to test and in turn, promote the rational use of artemisinin-based combination therapy (ACT).

The appeal of RDTs lies in their high specificity and sensitivity. They are relatively simple to use compared with microscopy and do not require specialised skills or laboratory equipment and reagents that are often unavailable in rural or resource poor settings [14]. RDTs are also seen as the solution to malaria over-diagnosis, a practice that can be costly [15] and result in poorer health through delays in access to treatment of the correct diagnosis and repeated treatment seeking costs [16]. Misdiagnosis may also contribute to increasing antimalarial drug pressure and thus resistance, thereby speeding up the ineffectiveness of available and affordable drugs [17]. Hence there is both a human and an economic case for introducing RDTs compared with existing presumptive treatment. However, in order for the full benefits of RDTs to be realised, supporting interventions that encourage health workers to deliver treatment that is consistent with malaria guidelines are likely to be needed.

The diagnosis and subsequent treatment of malaria is a complex decision making process [18]. Interventions must be sympathetic to a wide range of issues that providers face including a lack of training in the use of RDTs especially among more junior staff [19], a distrust of test results particularly negative ones [6,20,21], lack of alternative drugs with which to treat fever patients [19,22] and patient demand for inappropriate medicines [8,19,23]. All of these issues have been shown to affect whether a malaria test is done and in turn acted upon.

If diagnostic and prescribing practices of providers are to be improved through the large-scale procurement and deployment of RDTs and ACTs in countries such as Cameroon, some level of supporting interventions are likely to be needed, or the intended benefits of these investments may be seriously undermined. The WHO recommends that a number of conditions are in place before integrating and scaling up the use of RDTs in malaria control and primary health care services including provider training, monitoring how the test is used and the establishment of clear guidelines that incorporate a diagnosis and treatment algorithm that includes RDTs [24]. To date, the most cost-effective composition of training for providers is not known. There are arguments for both a basic introduction to the tests that will require few resources to implement, and for a more comprehensive programme that not only equips providers with the knowledge of the malaria guidelines and skills to use RDTs, but also strives to improve the quality of malaria case management by supporting providers to change their practice and manage patient expectations, especially when the malaria test is negative. This study will use a cluster randomized controlled trial to help identify, in routine health facility scenarios, which of these options is most effective and cost-effective in equipping providers with the knowledge and practical skills needed to effectively diagnose and treat febrile patients. It is important to compare these options for supporting RDT introduction with current practice in the absence of RDTs but where microscopy is widely available, in order to identify whether there is a value to introducing these new tests at all.

A strength of this trial is that the chosen provider interventions target several specific problems identified through our own formative research that undermine the implementation of malaria treatment guidelines in Cameroon. Between May and November 2009, a cross-sectional cluster survey and series of focus group discussions were conducted to understand current practices in delivering malaria treatment in the two sites targeted for the evaluation. It was revealed that all mission and almost 90% of public health facilities have microscopy testing available, though only about a third used it. Quinine, which should be reserved only for cases of severe malaria, was often used for the treatment of uncomplicated malaria. Factors affecting providers' choice of treatment appeared to be broader than simple consideration of the test result, with many patients receiving antimalairals they do not need. Some of the issues identified were unique to the local setting while others reflect problems experienced across the country and elsewhere. A description of the methods and results of the formative research have been published elsewhere [12,25].

Finally, this study also makes an important contribution to the pursuit of efficiency. While evaluations of a wide range of provider training interventions have been reported in the literature [26-28] using an equally wide range of methods, few of these enable the assessment of the relative value for money of these interventions. This study will provide much needed information on the cost-effectiveness of the selected provider training interventions which will aid health care planners in their decisions over how to allocate scarce health care resources.

Wiseman et al. Trials 2012, 13:4
http://www.trialsjournal.com/content/13/1/4

Methods/design

This study is a 3-arm stratified cluster randomised controlled trial across 47 health facilities in two areas of Cameroon. The intervention is being delivered at the facility level and therefore this will be the unit of randomisation with study site as the stratum. Outcomes will be assessed through exit interviews with patients as well as health facility surveys. Economic and financial costs will also be measured to enable the calculation of incremental cost-effectiveness ratios. Ethical approval for this study was obtained from the Cameroon National Ethics Committee and the London School of Hygiene and Tropical Medicine.

Study area and participants

The two study sites are Yaoundé and Bamenda in the Centre and Northwest regions respectively. The Bamenda study site consists of an urban health district and seven rural health districts that lie within a 21 km radius. It is predominantly an English and pidgin-English speaking region with an estimated population of 2 million. The Yaoundé study site encompasses seven urban health districts and has an estimated population of 2.5 million that is predominantly French-speaking.

Although both study sites lie within the forest ecological zone of Cameroon favorable for the development of the *Plasmodium* parasite and Anopheles vector, they have different climatic patterns. The Yaoundé study site has two main seasons: the long wet season that lasts from February to November (with more intense rains between September and November) and a short dry season from December to January. Transmission in this site is perennial with an inoculation rate of over 100 infected bites per person per month. The Bamenda study site is characterized by one long rainy season (March - October) of intense transmission with inoculation rates of 20 infected bites per person per month. In 2004, the forest ecological zone accounted for 40.6% of the total malaria morbidity (40.1%) recorded in the general population [29,30].

All public and mission health facilities have been enumerated and GPS mapped. Health facilities were informed of the proposed study and asked to give verbal consent before GPS coordinates were obtained. They include public district hospitals and health centres, mission hospitals and mission health centres. The health centres are staffed by nurses and sometimes medical doctors. Each of these health facilities has a propharmacy with a pharmacy attendant and a laboratary for simple diagnostic procedures including microscopy testing.

Facilities will be selected at random within each stratum from those that are not included in the Government pilot roll-out of RDTs, do not solely offer specialist services, see 4 or more febrile patients per day, and are accessible by road throughout the wet season. Selected facilities will be asked to give written consent prior to randomisation. If facility-level consent is not provided replacement facilities will be randomly selected from the remaining list of eligible facilities.

Contamination may occur if providers that have received basic or enhanced training meet to discuss their training or if they meet with providers from the control facilities. This may result in information or strategies being shared, the effect of the intervention spreading to control clusters and possible dilution of differences between treatment arms. In order to reduce the risk of contamination, the different intervention and control facilities are separated by a buffer area. Specifically, facilities within the same health area will be selected if they are ≥ 2 km from another facility in Bamenda and ≥ 1 km in Yaoundé.

All patients (or their caregiver) attending the health facilities will be approached on exit for consent to participate in an exit survey and screened for their eligibility. Patients will be eligible if they are present at the facility and they (or their caregiver) report seeking treatment for fever or suspected malaria. Patients will be excluded if they are pregnant, less than 6 months old or have signs and symptoms of severe malaria. All providers that are responsible for diagnosis and treatment of suspected cases of malaria will be eligible to participate in the provider survey.

Interviewers will explain to all participants that involvement in the study is voluntary and they have the right to withdraw at any point in time and ask any questions. Information about the study will be read to all participants and provided in hard copy. All participants will be asked if they give their consent to take part in the study and if so, asked to sign the standard consent form.

Interventions

Health facilities will be randomised to either current practice or one of the two provider interventions. The basic intervention is the introduction of RDTs with basic provider training on malaria diagnosis and treatment while the enhanced intervention will be the introduction of RDTs with enhanced provider training. The enhanced training covers the material in the basic training and also strives to improve the quality of care by supporting providers to adapt their practice by encouraging further discussion of the malaria guidelines, interactive self-awareness, improve their ability to communication with patients and colleagues.

Supply of RDTs

Facilities randomised to either the basic intervention or the enhanced intervention will be supplied with RDTs for use in diagnosing malaria. The RDT that will be

used is SD Bioline Malaria Ag Pf/Pan which is able to detect *P. falciparum, P.vivax, P. malariae or P.ovale*. This test was chosen in conjunction with the National Malaria Control Programme and is reported to have a minimum detection rate of for *P. falciparum* of 97.5% even at low levels of parasitaemia (200 parasites/μl) [31].

The supply of RDTs is intended to be relatively stable in order to assess the impact of the two provider interventions in the context of a reliable supply system. RDTs will be provided by the study team, free of charge, on a four-weekly rotation basis. Estimates of RDTs required will be determined in discussion with the facility head and based on routine records of the number of febrile patients that a facility can expect during a month (taking into account seasonal variations). Members of the research team will deliver RDTs to the facilities at the start of each month with the option for replenishment between delivery dates. Stock management records will be kept by the study team to monitor the distribution of these RDTs.

Facilities will be requested not to charge for the use of an RDT in children <5 years, but will be able to charge a token fee of at most 100CFA (0.2USD) for all patients above 5 years of age. Currently there is no national policy for the cost of RDTs in health facilities. Facilities are routinely supplied with ACTs and we will not alter the current distribution of medicines by the government or mission authorities. Our formative research found that more than 80% of public and mission facilities had ACTs in stock. In the analysis we will take into account that stock-outs of ACTs would prevent patients from receiving ACTs by also considering a secondary outcome which allows either prescription or receipt of an ACT.

Basic Provider Training (BT)

Facilities randomised to the basic intervention will be supplied RDTs and receive basic provider training on malaria diagnosis and treatment. This training is intended to mimic the style of workshop that is routinely implemented as in-service health worker training. The training will be conducted over one day and contain three training modules: 1) Malaria Diagnosis; 2) Rapid Diagnostic Testing; 3) Malaria Treatment. Together these three training modules will provide health workers with the knowledge and skills on why malaria testing is recommended, how to use an RDT, the treatment algorithm and details contained in the malaria guidelines. The malaria guidelines state how confirmed cases of uncomplicated malaria should be treated, including advice on dosing and treatment regimens for different types of ACT. The training also provides advice on other causes of febrile illness which should be investigated if the malaria test is negative. The module on RDTs includes a practical session in which all health workers will get hands-on experience of the steps involved in using an RDT.

The training will be conducted in conference halls of health districts located in both study sites. The following types of providers will be invited to the training: medical doctors, nurses, laboratory technicians and pharmacy attendants. Each facility will be invited to select 3 providers to attend the training. The training will be conducted jointly by medical doctors, representatives of the national malaria control programme and the research team. The trainers will receive extensive briefing by the research team and given a trainer's manual which provides detail of the material for each module and how it should be delivered. The training manual also includes standardized power-point presentations. In addition, the trainers will be trained in presentation and communications skills.

Each basic training workshop will train 25-30 providers. The training primarily takes a didactic seminar style in which the trainer delivers the training material, though there is scope for questions and discussion. A participant's training manual will be given to providers that attend the training course and includes all essential reference material including the malaria treatment guidelines. Participants will also be provided with job aids for RDTs and a treatment algorithm to be placed on their tables while in their health facilities.

All participants of the basic training will be strongly encouraged to train others at their facilities using copies of the training materials including manuals, copies of presentations and table top flip charts. This will not be mandatory or enforced, but as an incentive only those that train their colleagues will be given a certificate of completion.

Enhanced Provider Training (ET)

All facilities randomized to the enhanced intervention will be supplied RDTs and receive enhanced provider training. Enhanced provider training covers all the material contained in the basic provider training but also additional material targeting improvements in quality of care. The enhanced provider training will last for a total of three days (one day on basic training modules and an extra two days for the additional material). This training is more resource-intensive than routine in-service training, but intends to tackle some of the ingrained factors affecting health worker prescribing in relation to malaria, as identified in Cameroon and elsewhere.

The enhanced provider training contains three additional training modules: 4) Adapting to Change; 5) Professionalism; 6) Communicating Effectively. A specific focus of these modules is to address challenges posed by RDTs for interactions between the health workers and patients. The modules take an interactive and supportive approach to training with the majority of the material

Wiseman et al. Trials 2012, 13:4
http://www.trialsjournal.com/content/13/1/4

covered using small-group work. There are several exercises in each module based on games and puzzles, testimonials on the use of RDTs, self-developed participatory drama and role-playing. In these additional modules the role of the trainer is to direct and facilitate the learning process rather than provide technical information. The participants will be given training materials to accompany these modules.

The adapting to change module seeks to provide health workers with the opportunity to reflect and discuss the clinical guidelines, and learn from others. This module includes testimonials on the use of RDTs and participants have the opportunity to reflect on and discuss the recommendations in the malaria guidelines. As well as small group discussions, the module has a card game that 4-6 participants can play. Participants take turn in collecting cards and achieve a point when they present three cards that show a patient has received treatment in line with guidelines. This can be achieved by presenting a 'patient with fever' card accompanied by a 'RDT positive' card and an 'ACT' card, or alternatively by presenting a 'patient with fever' card accompanied with an 'RDT negative' card and a 'further investigation' card. The game ends when a participant has treated five patients in line with the guidelines and scored five points.

The professionalism module appeals to the providers to identify and agree what values and behaviours are important when providing care. It also emphasises the importance of working as a team and supporting each other. The module includes an exercise that considers real-life scenarios that may interrupt the process of care and participants are encouraged to develop strategies for managing these situations.

The final module focuses on improving the providers' skills in communicating with patients. It starts by reflecting on what patients think about malaria and malaria treatment. The module also focuses on managing patient expectations and allows providers to develop skills and techniques for explaining to patients why they should be tested, and also for the situation when the test is negative and an antimalarial should not be prescribed. Dramas are developed and acted out by the participants with the support of the facilitators to help providers understand the consequences for patients when they are not prescribed the recommended medicine and what alternative courses of action may be pursued.

As with the basic training, all participants of the enhanced training will be strongly encouraged to train others at their facilities and will only be given a certificate of completion once this has been undertaken.

Control Arm

The control arm represents current practice. Providers in these facilities will not receive RDTs or training as part of the study and are expected to continue to provide usual medical care for fever patients attending their facility. Our formative research showed that 90% of public health facilities and all mission health facilities in the study sites had microscopy testing, though none had RDTs.

Objectives

The primary objective is to evaluate the effectiveness and cost-effectiveness of:

- Basic intervention (i.e. introducing RDTs with basic provider training) compared to current practice;
- Enhanced Intervention (i.e. introducing RDTs with enhanced provider training) compared to current practice; and
- Enhanced Intervention compared to Basic Intervention.

Secondary objectives include:

- To describe the process of implementing the interventions including participant assessment of the training received;
- To document health worker knowledge and ability to test and appropriately treat patients with suspected malaria;
- To evaluate patient satisfaction with the quality of care received at the health facility;
- To calculate the economic and financial costs of the provider interventions;
- To assess whether the effectiveness and cost-effectiveness of the interventions varies according to urban/rural residence or socioeconomic status of the patient.

Hypotheses

- Basic Intervention is more effective in improving the treatment and diagnosis of malaria (measured by adherence to malaria treatment guidelines) than current practice.
- Enhanced Intervention will be more effective in improving the treatment and diagnosis of malaria compared to current practice and compared to Basic Intervention.
- Basic Intervention is more cost-effective in improving the treatment and diagnosis of malaria compared to current practice.
- Enhanced Intervention is more effective and more costly compared to Basic Intervention.

The relationship between the study hypotheses and outcomes are summarised in Figure 1.

Wiseman *et al. Trials* 2012, **13**:4
http://www.trialsjournal.com/content/13/1/4

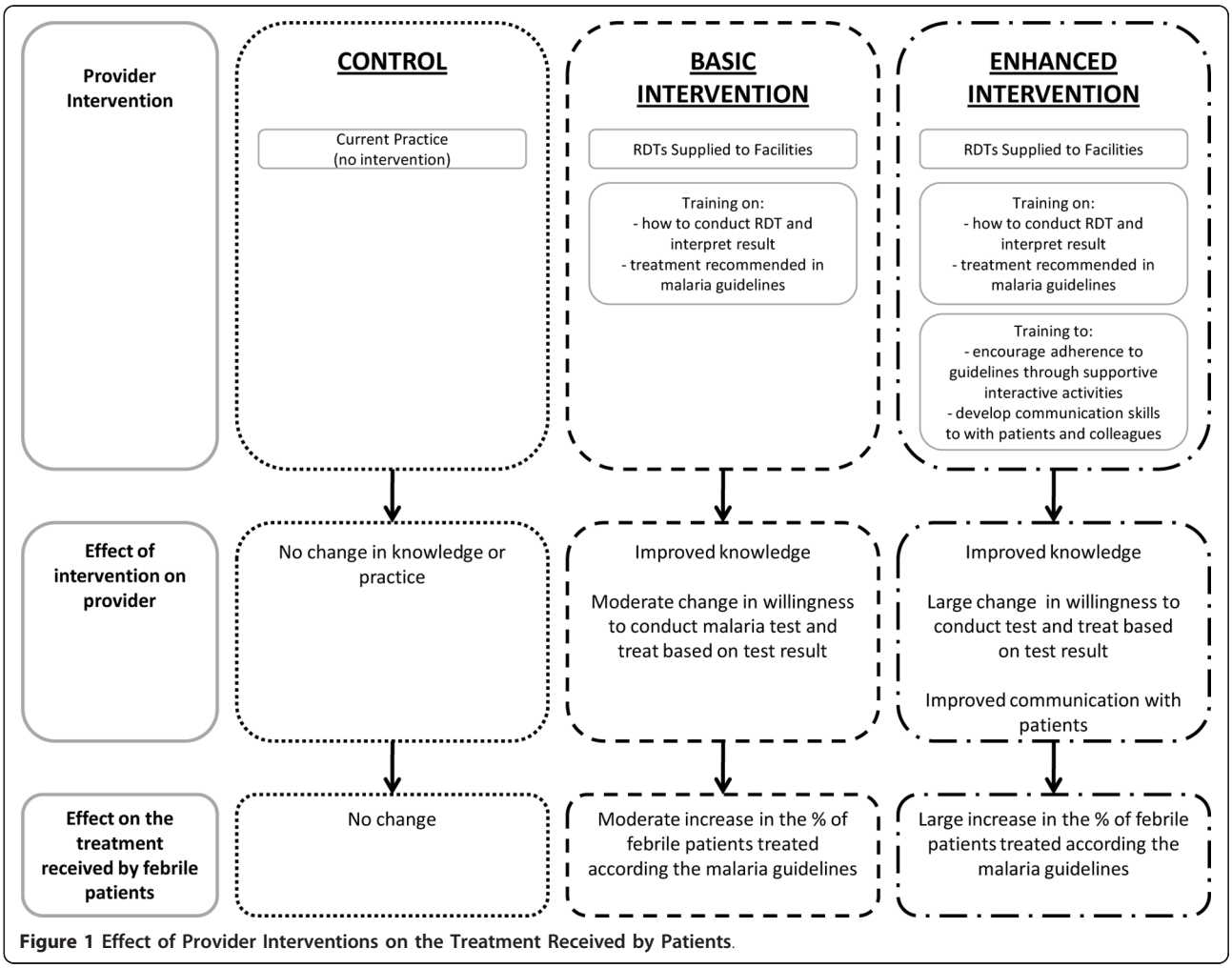

Figure 1 Effect of Provider Interventions on the Treatment Received by Patients.

Outcomes

Primary outcome

The primary outcome is the proportion of patients attending facilities that report a fever or suspected malaria and receive treatment according to malaria guidelines. The corresponding measure of cost-effectiveness is the cost per febrile patient that receives treatment according to the malaria guidelines.

Treatment according to the malaria guidelines is a composite endpoint requiring that:

- Febrile patients should be tested for malaria, using either microscopy or an RDT
- The patient should receive an ACT if he/she has a positive malaria test result
- The patient should not receive an antimalarial if he/she has a negative malaria test result

The outcome measure is summarized in Figure 2.

Secondary outcomes

Secondary outcomes include:

- Proportion of febrile patients that are tested for malaria
- Proportion of febrile patients receiving an antimalarial that receive an ACT
- Proportion of febrile patients receiving an ACT that receive the correct dose for their age
- Proportion of febrile patients receiving an ACT that accurately report how to take the medicine
- Proportion of febrile patients that report they are satisfied with the care received
- Proportion of HWs that report they were satisfied with the training received
- Proportion of HWs that know ACT should be given if the malaria test is positive and that an antimalarial should not be given if the malaria test is negative

Wiseman et al. Trials 2012, 13:4
http://www.trialsjournal.com/content/13/1/4

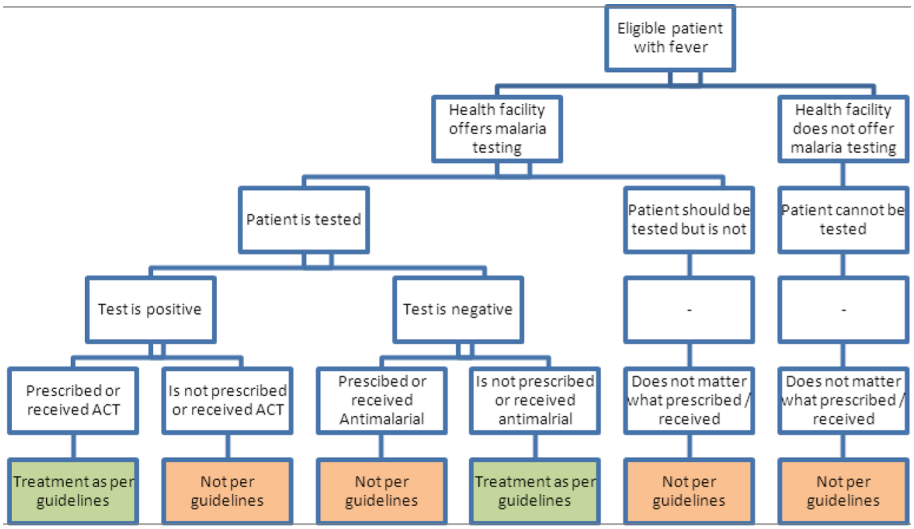

Figure 2 Primary outcome measure.

- Proportion of HWs that report febrile patients should be tested for malaria
- Proportion of HWs that know how to identify positive, negative and invalid malaria RDT results
- Proportion of HWs that know the correct dose of the first-line ACT in an adult and in a child aged 2 years
- Total cost of the provider interventions and the cost per HW attending the BT and ET

Secondary outcomes related to patients will also be reported in terms of their urban/rural residence and socioeconomic status.

Evaluation design

The evaluation of the intervention will use data collected in a patient exit survey, a register of malaria tests conducted by the provider during patient consultations, a provider survey, documentation of the intervention process, costing of the intervention activities and lastly, independent testing of malaria by the study team (see 'quality assurance'). The patient exit survey will be administered before the provider survey to ensure that the treatment received by patients is not influenced by the content of the provider questionnaire. Each of these is described below.

Patient exit survey

The primary outcome will be measured through an interviewer-administered patient exit survey. Data collection will commence three months after the intervention has been implemented. The three-month lag in the data collection is to ensure that the effect measure reflects treatment practices in the medium-term. In the short-term it is recognised that it is possible that the effect is overstated because health workers may change practices initially but revert to past behaviours over time, or that the effect is understated because it takes time for the training to have an effect as some health workers are hesitant and want to learn from the experience of the early-adopters. The survey data collection will take up to two months and will be organized such that the data will show the effect of the intervention over this time period by establishing a maximum number of patients that can be surveyed each week.

The research team will recruit field workers and provide training over a week on all aspects of data collection related to the patient exit survey. The training will include a practical assessment of their ability to provide information to respondents about the survey, obtain consent and administer the questionnaire. The research team will supervise the field workers and will accompany the field worker at the start of data collection to obtain consent from the head of the facility and ensure the fieldworker adheres to the standard operating procedures. Supervisory visits to monitor the performance of the field workers will take place at least once each week during the data collection period.

The patient exit questionnaire is designed to collect information about the patient's experience of seeking treatment and has been piloted a selected facilities in the study site. The questionnaire contains the following ten modules:

A. Background Information, Consent and Screening Questions
B. Details of the Respondent and/or Patient
C. Reasons for attendance
D. Consultation and diagnosis
E. Treatment prescribed and received
F. Patient satisfaction and knowledge of malaria

G. Costs of seeking treatment

H. Household characteristics

I. Malaria test completed by the study team (in subsample of patients)

J. Malaria test completed by health workers (from register of malaria tests at facility)

Register of malaria tests conducted

The patient exit questionnaire will be supplemented by a register of malaria tests at each participating health facility because patients may not always know if they were tested for malaria and the result of the malaria test. With consent from the head of the facility, health workers responsible for conducting malaria tests will be asked to keep a register of all malaria tests undertaken. The following data will be collected: details of the patient, availability of microscopy and RDT, method of test conducted, test result and the provider that conducted the test. At each facility the field workers will collect the register of malaria tests at least once each week and will use the patient's name, gender, age, date of visit to identify the patients that completed the survey and record the details in Section J of the questionnaire.

Provider Survey

The research team will administer a provider survey to all providers responsible for the diagnosis and treatment of suspected cases of malaria. Providers are eligible to participate if their responsibilities include any of the following activities: taking patient signs and symptoms, undertaking diagnostic tests, prescribing or dispensing medication. Written informed consent will be obtained before commencing the survey.

The provider survey has been designed to collect data on the providers' characteristics, knowledge and preferences for diagnosing and treating malaria and details of the resources available at the health facility. The survey will be piloted with providers at facilities that are not participating in the study. The questionnaire contains the following modules (of which A-B are completed by all providers and C-G are completed once for each facility):

A. Background information, consent and screening questions

B. Health worker characteristics and treatment practices

C. Details of the health facility

D. Management and procurement of drugs

E. Availability of RDTs

F. Availability of Antimalarials

G. List of all health workers that are involved in diagnosis or treatment

Documentation of the Intervention Process

The implementation of the malaria training workshops delivered to health workers will be documented. Details of all participants attending the training course will be recorded. Participants will undertake a pre- and post-training test to determine the impact of the training on their knowledge of malaria diagnosis and treatment. All participants will be invited to complete the training evaluation, which assesses the content and delivery of the training course. In addition, the trainers will complete a form to record any challenges faced in running the training workshop. Finally, the process of distributing the RDTs to health facilities will be monitored and any problems with the procedures for replenishing RDT stocks will be documented.

Costing

Direct and indirect costs of each phase of the interventions (i.e. development, implementation, upkeep) will be assessed from both a provider and societal perspective using standard economic evaluation methodologies [32]. Cost data will primarily be estimated from health facility records, project financial accounts and from the provider and patient exit surveys. Any health care savings will also be included and subtracted from costs.

Quality assurance

Data collection and management There is a quality assurance officer responsible for ensuring all implementation and evaluation activities adhere to standard operating procedures. Quality assurance will include monitoring the process of obtaining consent, data collection, transfer of completed survey instruments, data management and the secure storage of study materials. In addition, field supervisors will monitor the survey administration undertaken by field workers and make frequent visits (at least once a week) to assess the quality of data collection and review completed questionnaires.

Only authorised staff with appropriate training will have access to the databases to perform data entry. All databases will be password protected. Each data form will be entered by two data entry clerks in a database of the same structure using two different computers. Entries will be compared for discrepancies using the Epi info 2000 data compare utility. Any discrepancies will be corrected by crosschecking against the corresponding original questionnaire. Checks (validation rules) will be implemented in different fields of the database. Data will also be queried electronically to ensure the correct data is entered under the correct variables for each section of the form/questionnaire. A log of all data changes will be kept. Questionnaires will be kept in a locked filing cabinet.

Independent verification of malaria tests conducted and test results Reliance on providers register of malaria tests conducted and their interpretation of the test result may be a risk for data quality. For example, we are dependent on the providers' skills in conducting and interpreting the test results and the accuracy of their

Wiseman et al. Trials 2012, 13:4
http://www.trialsjournal.com/content/13/1/4

record-keeping. We will examine the accuracy of the register of malaria tests by comparing the patient reported data on whether they had a test with the register. We will also independently conduct RDT tests in a sub-sample of 5% of patients on exit that reported they were tested for malaria to determine the degree of consistency between the test result recorded by the provider and the test result conducted by the fieldworker. In addition, a sample of cases (both positive and negative) will be tested using PCR to check the sensitivity and specificity of both RDT and Microscopy. Quality assurance of the RDTs is beyond the scope of the study.

Sample size

Patient exit survey

Sample size calculations are based on the primary outcome, the proportion of patients that receive treatment according to malaria treatment guidelines. Based on results from the formative research we expect that this will be 15% in the control arm (current practice) with a coefficient of variation (k) within stratum of 0.3.

To evaluate the effect of each of the intervention arms compared to current practice we have powered the study to detect a 15% increase over the control, from 15% to 30%, which was deemed to be the minimum increase for each of the interventions to be worthwhile. Using methods for stratified cluster randomised trials [33] and assuming k = 0.25 in the intervention arms, 7 clusters per arm and 100 patients per facility are required to detect this improvement with 80% power at a 5% significance level. With allowance for drop outs from the trial we propose 9 facilities per arm. A lower coefficient of variation was assumed in the intervention arms due to the shared training.

If both intervention arms prove to be significantly better than the control it is likely that the enhanced intervention will be better than the basic intervention and we expect a further 10% improvement in the primary outcome, to 40%. Therefore to determine whether or not the basic intervention should be recommended we wish to evaluate whether it is just as effective as (i.e. non-inferior to) the enhanced intervention. Assuming that the largest difference between the two intervention arms that would be considered unimportant is 10% (i.e. non-inferiority margin) then using methods for equivalence in cluster randomised trials [33] 17 clusters per intervention arm with 100 patients per cluster are required to have 80% power to demonstrate that the limit of a one-sided 95% confidence interval (CI) will be 10% or less. With allowance for drop outs from the trial we propose 19 clusters per arm.

Provider survey

The sample size calculations for the provider survey gives the anticipated level of precision for calculating the proportion of providers that know the treatment guidelines (i.e. report that parasitological testing is recommended and that ACTs are for confirmed cases of malaria). Based on our formative research we can assume 3-4 providers per facility, an intra-correlation coefficient (ICC) of 0.1, and an estimate of the primary outcome in each arm of 90%. With 9 facilities in the control arm and 19 facilities in each of the intervention arms this allows us to estimate the true primary outcome with ± 11.8% precision in the control arm and ± 7.7% precision in each of the intervention arms.

Randomisation

A total of 47 facilities, 23 in Bamenda and 24 in Yaoundé, will be randomised within stratum to receive current practice, the basic intervention (RDTs and basic training) or the enhanced intervention (RDTs with enhanced training). With cluster randomised trials there is an increased chance that the study arms are unbalanced with respect to known and unknown potential confounders, and therefore undermines the credibility of the trial results. Stratified randomisation will reduce the likely imbalance in factors known to be correlated with the study outcome and the study site. However, the current availability of microscopy and the type of facility (which will also capture variation in health worker and patient characteristics) were assumed to be important correlates and therefore a process of constrained, or restricted, randomisation [34,35] will also be implemented to balance these two factors across the study arms using data collected in the formative research.

Using restricted randomisation schemes increases the risk of producing a design which is biased and not valid. Moulton [35] describes a design as being biased if there is any difference across the clusters in their probability of allocation to any given treatment. A randomised design is said to be valid if every pair of clusters has the same probability of being allocated to the same treatment. If the design is not valid there is a risk that the Type I error changes from its nominal value of 0.05. We will assess the validity of the restricted randomisation by producing a matrix where the rows and columns represent the clusters and the elements of the matrix are the proportion of times each pair of clusters is allocated to the same study arm i.e. the probability that the i^{th} cluster is being allocated to the same intervention group as the j^{th} cluster. The matrix will then be examined for under- and over-represented pairs that would highlight any potential causes for concern in the randomisation.

Randomisation of the facilities will be performed by the study statistician after informed consent has been sought from the head of the facility to avoid selection bias. Patients (or caregivers) and fieldworkers administering the patient exit survey will be blinded to group

Wiseman et al. Trials 2012, 13:4
http://www.trialsjournal.com/content/13/1/4

assignment. The research team involved in implementing the training interventions and supervising data collection will need to be aware of which facilities receive the different interventions.

Figure 3 shows study eligibility, selection, enrolment and methods of data collection.

Data analysis

Initially an overall test of the null hypothesis that there are no differences between either of the intervention arms and the control will be performed to guard against over-interpretation of any significant effects from individual comparisons of each intervention with the control, particularly if there is no evidence of a difference for any of the intervention arms.

The effect of the two interventions compared with control will be analysed with methods appropriate for cluster randomised trials. Point estimates of the primary outcome will be calculated using the unweighted mean of the cluster summaries in each stratum. If the distribution of the summary measures in each study arm is skewed, a logarithmic transformation to the proportions will be considered. An overall estimate of the risk ratio will be obtained by taking a weighted average of the stratum-specific risk ratios where the weights are inversely proportional to the stratum-specific variances. 95% confidence intervals (CI) will be adjusted for observed between-cluster variance and formal hypothesis testing will be conducted using stratified t-tests. Adjustment for covariates, including patient and provider characteristics and knowledge, contextual factors and process factors, will be carried out using a two-stage process. In the first stage, a logistic regression model including stratum as a fixed effect and the covariates of interest, but excluding the intervention effect, will be fitted to calculate cluster-specific expected values. The ratio of observed and expected values will be computed to give the ratio-residual for each cluster. In the second stage, the above methods for estimating the RR and 95% CI and hypothesis testing are carried out with the cluster-level proportions replaced with the covariate-adjusted residuals [35].

Non-inferiority between the two intervention arms will be assessed using the same methods as described above but instead of the risk ratio the risk difference will be estimated. Inference will be based solely on one-sided 95% CIs (or equivalently 2-sided 90% CIs).

Secondary outcomes on treatment received by patients, and provider knowledge and practice, will be analysed using the methods described above. To examine whether secondary outcomes vary according to the urban/rural residence and socioeconomic status of the patients methods appropriate for examining an interaction between the intervention and the individual-level variable will be applied [36]. Differences in coverage

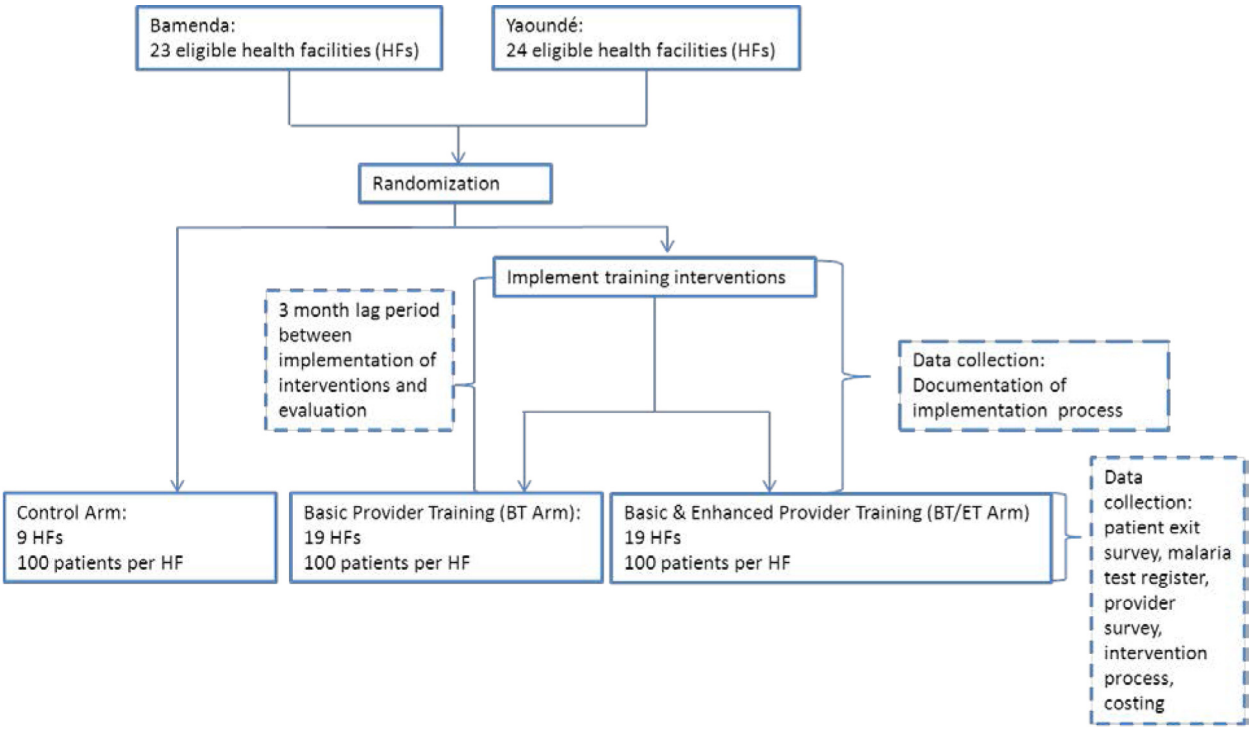

Figure 3 Eligibility, selection, enrolment and methods of data collection.

estimates between the intervention arms will also be estimated by calculating the arithmetic mean of the coverage proportions in each cluster and conducting a two-way analysis of variance, allowing for stratification.

For the economic analysis, cost-effectiveness ratios will be based on the primary outcome (i.e. the cost per case of suspected malaria that received treatment as recommended in the malaria guidelines) as well as a range of secondary outcomes including changes in provider knowledge. Cost-effectiveness will be calculated for each comparison and will be expressed as incremental cost-effectiveness ratios (ICERs). One-way and multi-way sensitivity analysis will be undertaken to examine the effects of varying uncertain variables on study findings. Costs and effects will be presented in both discounted and undiscounted form.

All data will be double entered using Microsoft Access 2007 (Microsoft Inc., Redmond, Washington) and analysed using STATA version 11.0 (STATA Corporation, College Station, Texas). A full analysis plan will be reviewed and agreed before the data are analysed.

Trial status

Patients and providers are currently being recruited into the study for the patient exit survey.

Discussion

Results from the study will be reported at local, national and international levels. At the local and national level, the Research on the Economics of ACTs (REACT) Project (http://www.actconsortium.org/pages/project-5.html) will continue working with the Ministry of Health after the trial is completed to adapt the most cost-effective interventions for national use. At the international level, we also see an opportunity to support the implementation of the 2010 WHO malaria treatment guidelines which acknowledge the need for provider training alongside the large-scale deployment of RDTs and ACTs.

List of abbreviations

RDT: Rapid Diagnostic Test; ACT: Artemisinin-based Combination Therapy

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Authors' contributions

VW and WM secured the funding and are responsible for the overall study design and project management. OA and ANN were responsible for coordination and supervision of fieldwork. LM participated in the study design and overall study coordination. WM, OA and LM designed the provider interventions. BC led the statistical design. AMN coordinated data entry and management. CC contributed to study design and supervised the qualitative research component. All authors contributed to the original protocol while VW drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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PART II – RESULTS PRESENTED

IN SELECTED PAPERS

Introduction to the Research Papers

Part II presents the research undertaken for the thesis in five research papers. These analyse providers' stated and revealed preferences for treating febrile patients, when providers have imperfect information and are agents in multiple agency relationships, and evaluate the cost-effectiveness of interventions that were designed to improve providers' adherence to clinical guidelines. The five papers are:

I. Treatment of uncomplicated malaria at public health facilities and medicine retailers in south-eastern Nigeria.
II. Malaria prevalence and treatment of febrile patients at health facilities and medicine retailers in Cameroon.
III. What determines providers' stated preference for the treatment of uncomplicated malaria?
IV. Mind the gap: knowledge and practice of providers treating uncomplicated malaria at health facilities and medicine retailers in Cameroon and Nigeria.
V. Economic evaluation of a cluster randomized trial of interventions to improve health workers' practice in diagnosing and treating uncomplicated malaria in Cameroon.

Papers I and II describe the treatment received by febrile patients and their caregivers attending health facilities and medicine retail outlets in Nigeria and Cameroon in 2009, before interventions were designed. Exit surveys were conducted to understand how patients with symptoms of malaria were diagnosed and treated and identify priorities for intervention. The results from both countries indicated problems with the choice of antimalarial supplied and a reliance on presumptive treatment based on a symptomatic

diagnosis. Few facilities in Nigeria offered malaria testing. In Cameroon most public, mission and private health facilities had microscopy available, though malaria testing was under-used and the vast majority of patients who tested negative for malaria received an antimalarial. The descriptive results contained in Papers I and II suggest a gap between providers' knowledge of the guidelines and their practice, though no conclusions could be reached on this since the study population included individuals who had requested a specific medicine as well as individuals who had relied on the providers' advice.

Papers III and IV focus on providers' stated and revealed preferences over alternative antimalarials. Paper III investigates providers' stated preference using data from the provider survey conducted at the health facilities where the exit survey was undertaken. The analysis showed providers' preference was influenced by their patients, drug company representatives, colleagues and other providers working in the locality. The findings indicate providers are agents serving multiple principals and constrained by the institutional and social context. This suggested it may be valuable to consider the influence of different actors when designing interventions.

Paper IV investigates the determinants of providers' revealed preference (i.e. their practice) and used exit survey data from the subset of patients who relied on the provider to select treatment and were supplied an antimalarial. Exit survey responses were linked to the individual provider who supplied treatment, and two-level multiple imputation was used to impute missing data that arose when identifying the provider responsible for selecting treatment. A gap between providers' knowledge and practice was identified in both countries, as providers' decision to supply ACT was not significantly associated with their knowledge of the first-line antimalarial. However, providers' stated preference was important, and this suggested interventions should focus on changing providers' preference rather than their knowledge. The results also showed providers' practice may depend on what they perceive their patients prefer or could afford, information about the

patient's symptoms and previous treatment seeking, the type of outlet, and the availability of ACT.

As explained in Chapter 3, the formative research contained in Papers I, II, III and IV was used to select and develop interventions in Cameroon and Nigeria. In Cameroon, two training interventions were designed: one-day 'basic' training that sought to ensure providers knew how to use malaria RDTs and the recommendations in the national malaria treatment guidelines; and three-day 'enhanced' training that explicitly focused on changing providers' practice. The training was implemented in public and mission facilities and accompanied the introduction of RDTs.

Paper V presents the cost-effectiveness of introducing RDTs with training interventions at public and mission facilities in Cameroon. The results demonstrated it was more cost-effective to introduce RDTs with enhanced training than with basic training, when each was compared to current practice. This finding was consistent with our hypothesis that it would be more effective and cost-effective for the intervention to target providers' preference and practice, rather than their knowledge.

Chapter 4

Research Paper I: Treatment of uncomplicated malaria at public health facilities and medicine retailers in south-eastern Nigeria

This research paper describes the treatment received by febrile patients and their caregivers attending public health facilities, pharmacies and drug stores in urban and rural areas of Enugu State in south-eastern Nigeria.

At the time the survey was undertaken, ACT had been the first-line treatment for uncomplicated malaria for four years, and the national malaria treatment guidelines stated that in primary care facilities malaria should be symptomatically diagnosed and treated with an ACT. This was the first study in south-eastern Nigeria to use patient exit survey data to report on the treatment received by patients presenting with malaria symptoms and it highlighted substantial problems: only 23% of febrile patients received an ACT, and instead sulphadoxine-pyrimethamine (SP), the former first-line treatment, was frequently received. While there were problems with health workers' knowledge of the recommended treatment, consumer demand was an important factor and almost two-thirds of the exit survey respondents reported they had asked for a specific medicine.

The findings from this paper showed that interventions to improve malaria diagnosis and treatment in south-eastern Nigeria would need to change consumer preferences as well as improve health service provision. The results also emphasized the importance of distinguishing between retail transactions and interactions that reflect an agency relationship.

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Status: Published in Malaria Journal, June 2011. The publication was subject to peer-review

Contribution: LM designed the survey, undertook the data analysis and drafted the paper with assistance from BC, VW, BU and OO. BC undertook sampling and provided advice on data analysis. OE and EN supervised the survey activities, with oversight from BU and OO. VW and OO provided guidance throughout the entire process. All authors read and approved the final manuscript.

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Treatment of uncomplicated malaria at public health facilities and medicine retailers in south-eastern Nigeria

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Abstract

Background: At primary care facilities in Nigeria, national treatment guidelines state that malaria should be symptomatically diagnosed and treated with artemisinin-based combination therapy (ACT). Evidence from households and health care providers indicates that many patients do not receive the recommended treatment. This study sought to determine the extent of the problem by collecting data as patients and caregivers leave health facilities, and determine what influences the treatment received.

Methods: A cross-sectional cluster survey of 2,039 respondents exiting public health centres, pharmacies and patent medicine dealers was undertaken in urban and rural settings in Enugu State, south-eastern Nigeria.

Results: Although 79% of febrile patients received an anti-malarial, only 23% received an ACT. Many patients (38%) received sulphadoxine-pyrimethamine (SP). A further 13% of patients received an artemisinin-derivative as a monotherapy. An estimated 66% of ACT dispensed was in the correct dose. The odds of a patient receiving an ACT was highly associated with consumer demand (OR: 55.5, $p < 0.001$).

Conclusion: Few febrile patients attending public health facilities, pharmacies and patent medicine dealers received an ACT, and the use of artemisinin-monotherapy and less effective anti-malarials is concerning. The results emphasize the importance of addressing both demand and supply-side influences on malaria treatment and the need for interventions that target consumer preferences as well as seek to improve health service provision.

Background

Malaria remains a major cause of death and illness in children and adults in tropical settings. An integrated strategy is recommended which ensures access to treatment with effective anti-malarials, while also undertaking preventative measures that target vector control [1]. ACT became the recommended treatment for uncomplicated malaria, as resistance emerged to conventional monotherapies, including sulphadoxine-pyrimethamine (SP), chloroquine and amodiaquine, thereby reducing their therapeutic efficacy. Over the last decade, countries have revised their national malaria treatment policies to adopt ACT as the first-line recommended treatment for uncomplicated malaria. Although these policies are now well established, there are persistent problems with their implementation.

Evidence from several settings on malaria case management report problems with the choice of treatment, showing that ACT is often underused and many patients continue to receive less effective anti-malarials, such as SP [2-4]. There are also concerns about the availability and use of artemisinin monotherapy, as drug resistance is more likely to develop if artemisinin derivatives are taken without a partner drug [5,6]. Problems with the dispensing of malaria treatment have also been observed, with patients frequently receiving inadequate doses and without advice on how the medicines should be taken [2,7]. Ensuring accuracy of drug dispensing is particularly challenging for pharmacies and other drug retailers which typically stock a multitude of different

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types of ACT and the accurate dosage depends not only on the patient's age or weight but varies by brand depending on the formulation and composition of the active ingredients [8,9].

In Nigeria, it is estimated that children under five years of age have between two and four episodes of malaria each year, and ensuring prompt access to effective treatment is a key strategy of the Nigerian Federal Ministry of Health [10]. At the level of primary care, the national malaria treatment guidelines state that diagnosis should be based on symptoms using the Integrated Management of Childhood Illnesses (IMCI) classification [10]. Thus, patients presenting with febrile illness at health facilities without diagnostic testing available should be presumptively treated for malaria. ACT became the recommended treatment for uncomplicated malaria in 2005 and at this time new treatment guidelines and training materials were developed [10-12]. The first-line recommended treatment is artemether-lumefantrine (AL), though treatment with artesunate-amodiaquine (ASAQ), artesunate-mefloquine (ASMQ) and dihydroartemisinin-piperaquine (DHAPQ) are also considered acceptable [12]. The policy is also clear that SP is reserved for intermittent preventive treatment in pregnancy, and cases of severe malaria should be treated using quinine injection, artemether injection, or artesunate (either as an injection or suppository); otherwise the use of monotherapies is no longer recommended.

The provision and utilization of malaria treatment in south-eastern Nigeria is well researched, with evidence from household surveys, patient records and from health care providers at a range of health facilities showing that many febrile patients do not receive the recommended anti-malarial [4,13-16]. Much less is known about the quality of care provided at health facilities, and this study explores these concerns directly by collecting data from patients exiting public health facilities and medicine retailers. These types of facilities are the main providers of malaria treatment at the primary care level [14]. This paper describes the characteristics of patients and the health facilities they attend, and their experience of care, including the nature of the consultation, the provision of anti-malarial treatments and the quality of drug dispensing. The paper also investigates whether patient, health worker or facility factors are associated with receiving ACT.

Methods

Study area

The study was undertaken in two study sites in Enugu State in south-eastern Nigeria: Enugu urban (comprising of Enugu East, Enugu South and Enugu North local government areas (LGAs)) and Udi LGA. Enugu urban is the largest predominantly urban area in Enugu State, and Udi LGA is rural. Malaria is endemic in Enugu State, and occurs all year round. The people of Enugu are of Igbo ethnicity and speak the Igbo language. The activities of the majority of the population include farming, fishing, wine tapping, and poultry keeping and rearing of domestic animals; the main agriculture season runs from November to February.

ACT was introduced into the study site in 2005 by the State Malaria Control Programme. The implementation package consisted of training health workers on symptomatic diagnosis, change in antimalarial policy and rational prescription of antimalarials and was accompanied by a community awareness campaign.

Study setting

The study was undertaken at public primary health facilities, private sector pharmacies and patent medicine dealers (PMDs) in Enugu State, south-eastern Nigeria [17]. The term PMD refers to retail outlets that are licensed to sell over the counter pharmaceutical products, though often hold a wider range of stock, and typically have no formal training [18]. Pharmacies and PMDs are a major source of malaria treatment [14,19]. These facilities are medicine retailers and do not routinely offer clinical care or diagnostic services. At the primary care level, presumptive treatment of malaria is recommended in febrile patients, as few public facilities offer malaria microscopy or RDTs. Primary health centres are usually staffed by community health officers and community health extension workers and supported by registered nurses and midwives [20].

Study design

A stratified multistage cluster survey was conducted between July and December 2009. The survey sampling was clustered in 16 randomly selected communities and stratified by type of facility: i) public facilities including primary health centres, dispensaries and health posts, and ii) pharmacies and PMDs. Within each community all public primary health centres were included due to their small number. There are a large number of pharmacies and PMDs, and these were randomly selected with probability proportionate to size assuming that a total of 80 (out of 298) medicine retailers could be visited given the financial resources and time available. All health workers within each facility responsible for prescribing or dispensing medicines were included in the study.

A survey sample of 20 patients per public facility was calculated to estimate the primary outcome, the proportion of febrile patients receiving the recommended treatment for malaria, with a precision of +/- 13%, assuming that the variability (intra-cluster correlation, ICC) in treatment between facilities is 0.3 [21]. For pharmacies

and PMDs, 14 patients per facility allows the primary outcome to be calculated with a precision of +/- 6.6% assuming the same degree of variation. The estimates assume a prevalence of 50% for the primary outcome and give the maximum range for precision (if the observed prevalence by higher or lower than 50% then greater precision would be achieved). The sampling was based on an enumeration of health facilities and their staff conducted in April 2009.

Survey activities

In advance of the survey a field team visited each facility to explain the purpose of the survey to the head of the facility and obtain informed written consent. Informed consent was reconfirmed verbally on the day of the actual survey. The survey questionnaires were developed specifically for the study and pretested on a non-random sample of individuals with characteristics similar to those of the survey population but not chosen for inclusion in the survey. Survey teams were trained on procedures for conducting the survey and involved in the pretesting and revision of the questionnaires. Site supervisors monitored and supervised all aspects of data collection.

Data were collected using three structured approaches; a patient exit questionnaire, a health worker survey and a health facility audit. Written consent from patients and caregivers (who may or may not be accompanied by the patient) exiting the health facility was sought before screening to determine their eligibility to participate in the survey. An individual was considered eligible if s/he reported seeking treatment for a fever or if s/he had received an ACT. Treatment may be sought for themselves, a child or another person who is not present (the latter applies only at medicine retailers). Individuals that were exiting a health facility were assessed in turn until the patient quota was reached. All workers that were involved in prescribing or dispensing malaria treatment and were available at the time of the survey were invited to complete the health worker survey and written consent was obtained from all participants.

The patient exit questionnaire collected data on the patient's prior treatment seeking and use of anti-malarials, reasons for attendance, the consultation and diagnosis, prescriptions and medicines received, the cost of treatment seeking and the demographic characteristics of the patient. The health worker questionnaire captured data on their characteristics, access to in-service training and national malaria treatment guidelines, malaria knowledge and treatment practices. The health worker survey was conducted once all the patient exit questionnaires had been completed to ensure that the treatment received by patients was not influenced by the content of the health worker questionnaire and the patient exit data best reflects current prescribing practices. The health facility audit was conducted following the health worker survey and collected data on the characteristics of the health facility, diagnostic services, management and procurement of medicine, including the availability of ACT.

Definitions

The treatment received by patients was assessed against the national malaria treatment guidelines, which recommends that patients with a fever are presumptively treated with an ACT, with the exception of pregnant women in the first trimester. The accuracy of the ACT dose provided to patients was assessed in accordance with dosage recommendations based on the patient's age and the type and composition of ACT received. Thus, the analysis takes into account that the correct number of tablets (or powder sachets) varies by brand, the amount of active ingredients contained in each tablet and whether they are co-formulated or co-blistered. Suspensions were excluded from the analysis on dosing. As patient age was used as a proxy for weight [11,22] this may cause some error in estimating the accuracy of dosing among children, though this would not apply to adults. Patient knowledge on the dose regimen was ascertained by asking the patient or their caregiver to explain how and when the medicine should be taken. Knowledge was considered accurate if they reported the number of tablets (or powder sachets) which should be taken per day over 3 days that corresponds to the specific brand of ACT received, and the patient's age. Suspensions were excluded from the analysis due to the difficulties in accessing the accuracy of the correct dose.

Statistical analysis

Data were entered and verified using Microsoft Access 2007 (Microsoft Inc., Redmond, Washington) and analysed using STATA version 11.0 (STATA Corporation, College Station, Texas) that allows for complex survey design by identifying different probabilities of selection (sampling weights), clustering and stratification (applying the prefix svy) [23]. Thus, all percentages and odds ratios reported are population-average estimates which have been adjusted to take into account the stratification, clustering and sampling weights of the study design. The weights are equal to the inverse probability of being sampled and took into account the sampling probabilities at the facility, health worker and patient level. At the patient level, number of days it took to recruit patients was used to create a proxy for the volume of patients, with the less time indicative of a larger facility.

Treatment outcomes by strata were compared using the Rao and Scott chi-square correction [24]. Survey logistic regression was used to assess factors associated

with receiving the recommended treatment. The following were investigated for their potential association: characteristics of the patient and health worker, patient consultation, and the resources available at the health facility (all factors are listed in Table six). Factors associated with receiving the recommended treatment were investigated in the multivariable model if the univariable association was statistically significant at the 10 percent level, or the odds ratio was less than 0.5 or greater than 1.5. Factors were retained in this multivariable model if they remained significantly associated at the 10% level of significance or with an adjusted odds ratio less than 0.5 or greater than 1.5. Models were compared using an adjusted Wald test. Pregnant women and children under the age of 6 months were excluded from the analysis because the national malaria treatment guidelines have alternative recommendations for these groups.

Ethical approval

Ethical approval for this study was obtained from the ethics committees of University of Nigeria and London School of Hygiene and Tropical Medicine.

Results

Patient characteristics

Data were collected from 100 health facilities and the analysis is based on exit data collected from 1,642 febrile patients attending public facilities and medicine retailers and 149 health workers (Figure 1). There was notable variation in the characteristics of patients attending the different types of health facility (Table 1). More than half (57%) of the patients treated at public health facilities were children, while 80% of the cases presenting at pharmacies and PMDs were adults. Treatment-seeking also varied by education levels and socioeconomic status (SES), with respondents surveyed at medicine retailers more likely to have tertiary education and be of a higher wealth quintile. At medicine retailers81% of patients reported it was the first time that they had sought treatment for this illness episode, and 43% had sought treatment on the same or day following the onset of symptoms. While at public facilities 61% of patients at public facilities were seeking treatment for the first time and the time before treatment was much longer, with only 16% seeking treatment on the same or day

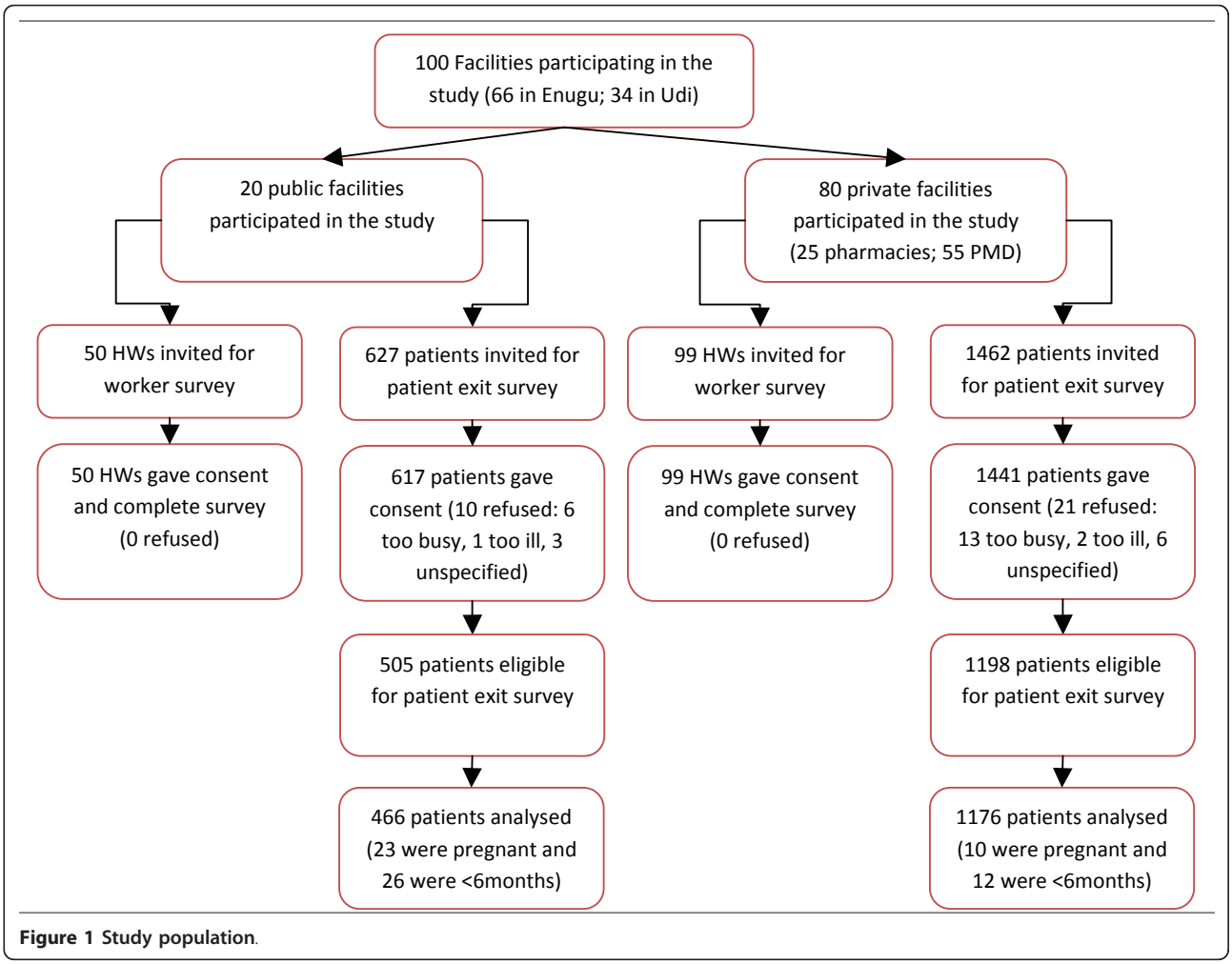

Figure 1 Study population.

Table 1 Patient Characteristics by type of facility*

	Public		Medicine retailer		Total		
	N = 466	%	N = 1176	%	N = 1642	%	P value
Patient gender[i]							
Male	218	45.4	624	56.4	842	55.5	0.006
Female	242	54.6	536	43.6	778	44.5	
Patient age							
>15 years (adult)	185	42.8	913	79.6	1098	76.7	<0.001
10-15 years	27	6.6	85	7.3	112	7.3	
5-9 years	61	12.6	71	4.6	132	5.3	
<5 years	193	38.0	107	8.4	300	10.7	
Patient socioeconomic status[ii]							
Poorest quintile	223	46.4	343	15.7	566	18.1	<0.001
Second quintile	97	20.4	219	20.0	316	20.1	
Third quintile	55	11.8	219	21.3	274	20.6	
Fourth quintile	56	13.5	189	21.2	245	20.6	
Richest quintile	35	8.0	206	21.8	241	20.7	
Education level of patient (or caregiver)[iii]							
No formal education	25	5.8	41	1.3	66	1.6	<0.001
Primary education	116	28.0	198	12.5	314	13.7	
Secondary education	213	46.1	469	39.7	682	40.2	
Tertiary education	93	20.0	445	46.6	538	44.5	
Was first time sought treatment[iv]							
Yes	269	61.4	896	81.7	1165	81.1	<0.001
No	196	38.7	273	18.3	469	19.9	
Number of days since start of symptoms[v]							
None (same day)	14	3.3	234	22.1	248	20.6	<0.001
1 day	71	12.6	259	21.2	330	20.5	
2 days	93	19.3	228	21.2	321	21.1	
3-5 days	202	45.4	284	23.5	486	25.3	
6+ days	85	19.4	169	12.0	254	12.6	
Reasons given for choice of health facility[vi]							
Convenient	229	49.2	617	55.9	846	55.4	0.284
Used previously	243	48.6	732	54.7	975	54.2	0.346
Good reputation	145	30.1	529	49.6	674	48.1	0.002
Availability of drugs	127	23.3	548	48.7	675	46.7	0.001
Inexpensive	206	46.2	178	13.3	384	15.9	<0.001
Qualification of staff	132	24.7	174	12.9	306	13.9	0.011

i missing 22 responses: 6 from public and 16 from medicine retailer

ii Principal components analysis was undertaken to generate a SES index based on household asset ownership [33]. The SES index was disaggregated into wealth quintiles.

iii missing 42 responses: 19 from public and 23 from medicine retailer

iv missing 8 responses: 1 from public and 7 from medicine retailer

v missing 3 responses: 1 from public and 2 from medicine retailer

vi more than one reason could be given

following the onset of symptoms. When asked about their choice of health facility, many respondents said that they had sought treatment at this facility for past illnesses (54%) and it was convenient (55%). In addition, patients at public health facilities often mentioned the lower cost of treatment, while the reputation of the provider and the availability of drugs were more often cited at medicine retailers.

Health facility and health worker characteristics

The provision of basic equipment, such as weighing scales and thermometers was good in public health facilities, though more mixed in pharmacies and PMDs (Table 2). Very few health facilities offered malaria microscopy testing and none of the health facilities surveyed used RDTs. At the time of the survey, all health facilities reported that they had anti-malarials in stock, and field staff verified that ACT was in stock in 80% of health facilities. There was some variation by facility type, with 71% of public health centres and 89% of pharmacies and PMDs stocking at least one ACT. Two-thirds of health facilities had artemether-lumefantrine (AL) available, though other types of ACT were common in medicine retailers. Artemisinin monotherapy was available in 96% of medicine retailers while the vast majority (90%) of facilities also had SP as well as other types of anti-malarials available; these included less

Table 2 Facility Characteristics

	Public		Medicine retailer		Total		
HEALTH FACILITIES	**N = 20**	**%**	**N = 80**	**%**	**N = 100**	**%**	**P value**
Equipment and services available							
Weighing scale†	19	94.1	36	50.0	55	53.1	<0.001
Thermometer	19	94.2	35	46.5	54	49.8	<0.001
Microscopy services†	3	12.8	0	-	3	0.9	<0.001
RDT	0	-	0	-	0	-	-
Availability of anti-malarials							
Any anti-malarial	20	100.0	80	100.0	100	100.0	-
Artesunate monotherapy	5	24.6	76	96.1	81	91.1	<0.001
Sulphadoxine Pyrimethamine (SP) †	18	89.8	71	89.9	89	89.9	0.982
Chloroquine	14	71.1	77	96.8	91	95.0	<0.001
Quinine	4	20.3	70	89.1	74	84.3	<0.001
Amodiaquine	3	14.4	60	85.3	63	80.3	<0.001
Any type of ACT	14	71.1	66	89.6	80	88.3	<0.001
Artemether Lumefantrine (AL)	12	65.6	64	79.6	66	78.4	<0.001
Artesunate Amodiaquine (ASAQ)	2	8.6	57	78.8	59	73.9	<0.001
Artesunate Mefloquine (ASMQ)	0	-	35	52.9	35	49.2	<0.001
Artesunate Sulphadoxine-Pyrimethamine (ASSP)	0	-	18	28.4	18	26.4	<0.001
Dihydroartemisinin-Piperaquine (DHAPQ)	0	-	55	78.0	55	72.6	<0.001
Median cost of ACT (& IQ range)							
Adult dose of any ACT	-		600 (350, 750)		600 (350, 750)		-
Child dose of any ACT	-		350 (260, 600)		350 (250, 600)		-
Adult dose of AL	-		750 (650, 835)		750 (650, 820)		-
Child dose of AL	-		650 (580, 750)		650 (520, 700)		-
HEALTH WORKERS	N = 50	%	N = 99	%	N = 149	%	P value
Doctor	7	14.0	0		9	1.7	<0.001
Nurse or Midwife	7	14.0	7	7.3	14	8.1	
Community Health Officer	14	28.0	1	1.3	15	4.5	
Community Health Extension Worker	22	44.0	3	4.1	25	8.9	
Pharmacist‡	-		3	3.9	3	3.4	
PMD or pharmacy attendant‡	-		85	83.4	85	73.5	
HW has attended malaria training in past 3 years	13	24.6	31	33.0	44	31.9	0.011
HW has access to malaria treatment guidelines	15	30.9	4	5.2	19	8.5	<0.001
HW accurately reported ACTs are the recommended treatment for uncomplicated malaria	38	77.2	44	62.2	82	65.4	<0.001

† missing response from one pharmacy

‡ not applicable in public facilities

effective conventional treatments such as chloroquine and amodiaquine.

All the public facilities reported that ACT was available to patients free of charge. In pharmacies and PMDs the median price of an ACT was 600 Naira for an adult dose and 350 Naira for a child dose (which is approximately equivalent to USD $4.00 and USD $2.30). The median price of AL was higher at 750 Naira for an adult dose and 650 Naira for a child dose (equivalent to USD $6.00 and USD $4.30).

Just under half (44%) of workers in public facilities were community health extension workers, semi-skilled health workers trained in primary care, and while junior to the other cadres listed in Table 2 may prescribe treatment or undertake minor procedures [20]. In the medicine retailers the majority (83%) described themselves as patent medicine dealers or pharmacy attendants.

Knowledge of malaria treatment was variable, though better in public facilities, as 80% of workers in public facilities reported that ACT is the recommended treatment for uncomplicated malaria, compared to 62% of workers in pharmacies and PMDs. Moreover, less than one in three health workers surveyed had attended an in-service malaria training workshop over the past three years and relatively few (9%) had access to the malaria treatment guidelines (31% of public health workers and 5% of health workers at pharmacies and PMDs).

Patient consultation, prescription and requests for medicine

The nature of the patient's consultation differed by type of health facility (Table 3). In public health facilities 95% of respondents reported the health workers were told of the patient's symptoms, and 90% reported that they had told the health worker about the patient's fever. Patients reported to have been physically examined in 65% of cases, 50% had their temperature taken, though just 6% of patients were tested for malaria. At public facilities with microscopy testing available 21% of patients were tested for malaria. In pharmacies and PMDs patients were rarely examined (6%) or tested (<1%), though in 32% of cases health workers were told about the patient's symptoms and asked further questions.

The majority of patients attending public facilities had medicines prescribed and in 78% of cases the prescription was for an anti-malarial. ACT was prescribed to 34% of patients seeking treatment, though as many patients were prescribed SP, which is no longer recommended for treating malaria.

At pharmacies and PMDs, 15% of patients had a prescription and patients often asked for a specific medicine. At these facilities, 58% of patients attending asked for an anti-malarial. Patients often asked for SP (26%), though also requested ACT (16%) and artemisinin-monotherapy (12%). Almost all (96%) of those patients that asked for an anti-malarial also received the medicine they had requested.

Malaria treatment received by patients

Overall, the majority of patients received an anti-malarial, though ACT was received by only 22% of all patients attending health facilities and by 29% of children under five years of age (Table 4). SP is no longer recommended, though still frequently used, and 38% of patients had received this medicine. At public facilities, differences were observed between the proportion of patients that were prescribed and received antimalarials at facilities which had ACT in stock. The proportion of patients that received an antimalarial at public facilities was also low compared to the medicine retailers. There were, however, few differences between the proportions of patients receiving ACT and SP at public health facilities and medicine retailers, though patients were more likely to receive oral artemisinin monotherapy at medicine retailers than public facilities (14% compared to 2%, $p < 0.001$). Other anti-malarials, such as chloroquine, amodiaquine and quinine were rarely received by patients. By type of ACT, AL (44%) was most often dispensed and was widely used in the public sector. In medicine retailers, AL was regularly dispensed, though patients also received ASAQ and DHAPQ.

Quality of dispensing of ACT

Two-thirds (66%) of all types of ACT dispensed were estimated to be in the correct dose, while 58% of ACT dispensed were in the correct dose and the patient (or their caregiver) accurately reported how the medicine should be taken (Table 5). Given the challenges in estimating the accuracy of ACT dosage in children, the results are also presented for febrile adults receiving ACT. Overall the results are reasonably similar, with 56% of ACT received in the correct dose and by patients that had accurate knowledge of how to take the medicine. Very few patients receiving an ACT were told of any side effects associated with the medicine.

Factors influencing treatment received by patients

The odds of a febrile patient receiving an ACT were significantly associated with whether the patient had a prescription, asked for an ACT, the patient's gender, and the education level of the patient (or their caregiver) (Table 6). Patients were also significantly more likely to receive an ACT at health facilities that were better equipped, and had one or more health workers that knew ACT was recommended for uncomplicated malaria. Patients that chose the health facility because it was convenient or relatively inexpensive were significantly less likely to receive an ACT. Of all the variables considered in the univariable analysis, patients

Table 3 Patient consultation

	Public	Medicine retailer	Total	
	N = 466	N = 1176	N = 1642	
	% (95% CI)	% (95% CI)	% (95% CI)	P value
Patient reported consultation				
Told HW about patient symptoms	94.9 (94.4-95.4)	44.3 (36.9-52.0)	48.3 (41.3-55.4)	<0.001
Told HW that had a fever	89.8 (87.2-91.9)	40.3 (33.0-48.2)	44.3 (37.1-51.4)	<0.001
HW asked follow up questions about patient's symptoms	79.9 (76.3-83.0)	32.0 (25.0-39.9)	35.7 (29.1-43.1)	<0.001
Patient was physically examined	65.1 (48.8-78.5)	6.2 (3.5-10.5)	10.8 (7.8-14.5)	<0.001
Patient had temperature taken	49.7 (38.6-60.9)	1.7 (0.6-4.9)	5.5 (3.9-7.8)	<0.001
Patient tested for malaria at this facility	5.8 (3.6-9.3)	0.2 (0.0-1.4)	0.7 (0.3-1.3)	<0.001
Patient requests for medicine				
% of patients that asked for:				
any type of medicine	2.8 (1.9-4.2)	65.4 (57.9-72.3)	60.5 (53.7-66.9)	<0.001
an anti-malarial	1.2 (0.7-2.1)	58.3 (51.1-65.2)	53.8 (47.3-60.2)	<0.001
any ACT	0.9 (0.4-1.9)	16.0 (11.1-22.5)	14.8 (10.3-20.9)	<0.001
Artemisinin monotherapy	0	11.5 (8.6-15.3)	10.6 (8.0-14.1)	0.162
Amodiaquine	0	1.6 (0.8-3.4)	1.5 (0.7-3.2)	0.402
Chloroquine	0.1 (0.0-0.4)	1.3 (0.6-2.7)	1.2 (0.6-2.5)	<0.001
Quinine	0	0.7 (0.2-2.6)	0.7 (0.2-2.4)	0.631
SP	0.1 (0.1-0.1)	26.2 (21.5-31.5)	24.1 (19.8-29.1)	<0.001
Anti-malarial prescriptions				
% patients prescription (from any facility)	94.2 (92.4-95.6)	15.4 (10.7-21.5)	21.6 (17.1-26.9)	<0.001
% patients that received prescription from this facility	94.2 (92.4-95.6)	1.8 (0.7-4.0)	8.8 (7.3-11.0)	<0.001
% patients that were prescribed*:		-	-	-
an anti-malarial†	78.4 (72.6-83.3)	-	-	-
any ACT‡	34.0 (21.9-48.7)	-	-	-
Artemisinin monotherapy	4.7 (3.1-7.1)	-	-	-
Amodiaquine	1.1 (0.9-1.5)	-	-	-
Chloroquine	3.3 (0.8-11.6)	-	-	-
Quinine	0.2 (0.0-3.1)	-	-	-
SP	34.7 (21.7-50.6)	-	-	-

* Reported only for public health facilities

† At public facilities 73.4% of children under five years were prescribed an antimalarial.

‡ At public facilities 51.5% of children under five years were prescribed an ACT. At public health facilities with ACTs in stock 43.8% of patients (all ages) and 57.9% of children under five years were prescribed an ACT.

asking for ACT had by far the highest odds ratio of 53.3 (15.9-179.1, p < 0.001). This variable remained highly significant in the multivariable model with an odds ratio of 55.5 (15.0-205.6, p < 0.001), though the other significant variables were the patient's gender, the education level of the patient (or caregiver), whether the facility had a thermometer available, and whether the facility had health workers that knew ACT was recommended.

Discussion

There is great need to improve the quality of care for uncomplicated malaria in south-eastern Nigeria. Parasitological diagnosis was available in only 3% of facilities and while the national malaria treatment guidelines recommend presumptive treatment of a fever with ACT when malaria tests are not available, less than a quarter (22%) of febrile patients attending facilities received the recommended treatment. Moreover, the estimates show that only 58% of patients that received ACT were given the correct dose and knew how the medicine should be taken. Inadequate dosing and poor compliance to treatment regimens will reduce the efficacy of the treatment taken and may contribute to the development of drug resistance [25].

After four years with ACT as the recommended first-line antimalarial, these results at public health facilities are extremely concerning. In Kenya and Zambia poor

Table 4 Anti-malarials received

	Public	Medicine retailer	Total	
	% (95% CI)	% (95% CI)	% (95% CI)	P value
Anti-malarials received (all ages)	N = 466	N = 1176	N = 1642	
% of patients (of all ages) that received:				
an anti-malarial	54.2 (44.1-63.9)	81.5 (76.2-85.8)	79.3 (74.5-83.4)	<0.001
any ACT†	17.3 (9.0-30.5)	22.8 (17.2-29.7)	22.4 (17.0-28.8)	0.378
Artemisinin monotherapy*	2.0 (0.8-5.2)	14.4 (11.4-18.0)	13.4 (10.6-16.7)	<0.001
Amodiaquine	0.1 (0.00-1.0)	2.0 (0.9-4.6)	1.9 (0.8-4.2)	0.002
Chloroquine	2.4 (0.5-10.6)	3.3 (2.0-5.4)	3.2 (2.0-5.2)	0.673
Quinine	0	0.9 (0.3-2.2)	0.8 (0.3-2.0)	0.501
SP	33.6 (20.9-49.1)	38.2 (31.8-45.1)	37.9 (31.8-44.3)	0.546
Anti-malarials received (children < 5 yrs only)	N = 193	N = 107	N = 300	
% of children <5 years that received:				
an anti-malarial	33.2 (20.0-49.7)	80.2 (63.6-90.4)	67.1 (53.7-78.1)	0.001
any ACT‡	21.3 (9.9-39.9)	31.6 (18.2-49.0)	28.7 (18.0-42.6)	0.329
Artemisinin monotherapy*	2.0 (0.2-14.5)	10.2 (3.4-26.8)	7.9 (2.9-20.2)	0.110
Amodiaquine	0.2 (0.0-3.0)	9.3 (2.3-30.6)	6.7 (1.6-23.8)	0.001
Chloroquine	1.5 (0.7-3.2)	12.6 (4.2-32.1)	9.5 (3.5-23.5)	0.001
Quinine	0	4.5 (0.6-26.8)	3.23 (0.5-20.2)	0.497
SP	9.2 (3.7-21.0)	19.9 (8.5-40.0)	16.9 (8.1-32.0)	0.176
Type of ACT received	N = 105	N = 210	N = 315	
% AL	96.5 (92.5-98.4)	40.2 (26.9-55.1)	43.6 (31.0-57.2)	<0.001
% ASAQ	3.0 (1.4-6.2)	28.5 (16.1-45.2)	26.9 (15.3-42.8)	<0.001
% DHAPQ	0	24.3 (15.1-36.5)	22.8 (14.3-34.3)	0.074
% ASMQ	0.5 (0.1-1.9)	4.1 (0.9-16.6)	3.9 (0.9-15.5)	0.019
% ASSP	0	2.9 (0.7-11.5)	2.8 (0.7-10.8)	0.648

† At facilities with ACTs in stock 27.0% (20.4-34.7%) of patients at public facilities and 24.2% (17.9-31.9%) of patients at medicine retailers received an ACT

‡ At facilities with ACTs in stock 31.7% (22.0-43.4%) of children under five years at public facilities and 32.5% (18.0-51.3%) of children under five years at medicine retailers received an ACT

* This was in tablet form at medicine retailers.

quality treatment practices were observed at public and mission facilities soon after ACT was introduced as first-line, though subsequent studies up to five years later show improvements in the proportion of patients that are prescribed and receive ACT [3,7,26]. As found elsewhere, the proportion of patients that were prescribed or received an ACT seems low given the availability of ACT at health facilities and the proportion of health workers that knew ACT was recommended [3,7,27,28]. It was also interesting to note that only half of patients at public facilities that were prescribed an ACT also received one, though it is not clear why this occurred: 34% of patients at public facilities were prescribed an ACT, while 17% received an ACT. The discrepancy is only partially explained by the availability of ACT and is unlikely to reflect the cost of treatment, as ACT is provided to patients in public facilities without charge.

There were some problems with the availability of ACT: 70% of public facilities and 83% of pharmacies and PMDs had at least one ACT in stock at the time of the survey. While the availability of ACT in the public sector was not as high as has been reported in Angola, Kenya, or Uganda [7,9,28-30], the availability of ACT in the study sites was much higher than the Nigerian national average from 2008, when it was found that 38% of public health facilities had ACT in stock. The availability of ACT at private sector outlets was found to be higher than the Nigerian national average from 2008, which reported 78% of pharmacies and 19% of PMDs had ACT in stock [9]. It is concerning to find that artemisinin monotherapy is widely available in medicine

Table 5 Quality of dispensing for patients that received an ACT

	Public	Medicine retailer	Total	
	% (95% CI)	% (95% CI)	% (95% CI)	P value
All febrile patients that received an ACT*	N = 100	N = 176	N = 276	
% accurate dose†	75.8 (70.6-80.2)	65.5 (50.1-78.1)	66.2 (51.8-78.0)	0.135
% patient has accurate knowledge of treatment regimen‡ [i]	68.3 (63.7-72.6)	58.5 (41.6-73.6)	59.2 (43.4-73.3)	0.218
% patients with accurate dose and knowledge of treatment regimen[ii]	66.8 (61.3-71.9)	57.2 (40.3-72.5)	57.8 (41.7-72.4)	0.236
% patients that reported were told of side effects[iii]	1.5 (1.2-1.9)	3.0 (0.6-14.0)	3.0 (0.6-12.9)	0.357
Febrile adults that received an ACT*	N = 21	N = 125	N = 146	
% in accurate dose†	72.8 (68.6-76.6)	62.0 (43.5-77.5)	62.2 (44.2-77.4)	0.165
% patient has accurate knowledge of treatment regimen‡ [iv]	72.8 (68.6-76.6)	55.4 (36.3-73.0)	55.8 (37.1-73.0)	0.051
% patients with accurate dose and knowledge of treatment regimen[iv]	72.8 (68.6-76.6)	55.4 (36.3-73.0)	55.8 (37.1-73.0)	0.051
% patients that reported were told of side effects[v]	6.2 (5.0-7.7)	4.2 (0.8-18.5)	4.2 (0.9-17.8)	0.570

* excludes suspensions and syrups and limited to cases for which have data on dosage

† defined as dose that is consistent guidance on dosage by patient age.

‡ defined as patient reports treatment regimen is consistent with guidance on dosage by patient age

i missing 10 observations (2 from public and 8 from medicine retailers)

ii missing 12 observations (4 from public and 8 from medicine retailers)

iii missing 6 observations (2 from public and 4 from medicine retailers)

iv missing 2 observations (from medicine retailers)

v missing 3 observations (from medicine retailers)

retailers and that many patients request this medicine. The use of oral artemisinin monotherapy in 13.4% of patients is also a major concern, since its use without a combination therapy can lead to the development of drug resistance [5,6].

Differences observed between the characteristics of patients by type of health facility are broadly consistent with evidence from household surveys conducted in Nigeria on malaria treatment seeking. For example, rural-urban differences, the education of caregivers, and socioeconomic status have been found to be important determinants of where treatment is sought [14,15,31-33]. Other studies have also shown that urban residents were more likely to obtain ACT [15] and individuals of higher levels of education and socioeconomic status were more likely to have correct knowledge of malaria treatment [31].

Differences between the facility types in the resources available and the patient's consultation were much as expected, with patients attending public health facilities more likely to discuss symptoms and be examined. Similarly, as pharmacies and PMDs are retail outlets it is not surprising that many lacked weighing scales and thermometers and that patients often asked for specific medicines. Moreover, it was expected that health workers in public facilities would have better access to the malaria treatment guidelines and be more likely to know that ACT is recommended for uncomplicated malaria.

The odds of a febrile patient receiving an ACT were positively associated with the health workers knowledge of the treatment guidelines, though there is no evidence of an association between access to treatment guidelines and attendance at malaria training. It should be noted that these variables were defined at the facility-level because in many cases it was not possible to link patients to the health worker that prescribed or recommended treatment, either because the health worker was absent at the time of the survey or because several health workers attended to the patient.

The treatment received by patients from medicine retailers was often driven by consumer requests for a specific medicine, and the odds of a febrile patient receiving an ACT were extremely high if the patient or their caregiver had asked for one. Previous studies from Nigeria have also highlighted the importance of patient demand. For example, Onwujekwe *et al* reports that 40% of providers across a range of primary health facilities said requests by patients influenced the type of drug provided [4]. Qualitative research with patent medicine dealers undertaken by Okeke *et al* also highlighted that patients often ask for specific medicines and the doses of anti-malarial drugs can be determined by patient's ability to pay [18]. Patients' requests for specific medicine at medicine retailers were likely to include cases for which treatment had been prescribed elsewhere, though as only 15% of patients had a prescription other factors are likely to be relevant and there

Mangham et al. Malaria Journal 2011, 10:155
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Table 6 Factors influencing whether a patient received an ACT

Variable				Univariable Analysis			Multivariable Analysis		
		n/N	%	OR	95% CI	P value	OR	95% CI	P value
Study Site	Enugu	211/989	22.7	1.71	(0.81-3.61)	0.148			
	Udi	71/531	14.7	1.0					
Patient characteristics									
Gender	Male	173/795	25.3	1.63	(1.00-2.65)	0.051	1.91	(1.02-3.55)	0.045
	Female	109/725	17.2	1.0			1.0		
Age Group	>15 yrs	157/1023	19.8	1.0		0.336			
	10-15 yrs	16/104	20.7	1.06	(0.44-2.53)				
	5-9 yrs	38/124	37.8	2.46	(0.90-6.74)				
	<5 yrs	71/269	29.0	1.65	(0.88-3.09)				
Quintile	Richest	57/230	28.8	2.35	(1.12-4.96)	0.201			
	Fourth	48/217	26.2	2.07	(0.99-4.35)				
	Third	48/257	18.7	1.34	(0.58-3.12)				
	Second	61/297	19.8	1.44	(0.64-3.25)				
	Poorest	68/519	14.6	1.0					
Education Level	No formal	3/61	2.1	0.09	(0.02-0.31)	0.001	0.13	(0.03-0.50)	0.045
	Primary	45/297	19.9	1.0			1.0		
	Secondary	113/651	19.1	0.95	(0.47-1.95)		0.81	(0.35-1.85)	
	Tertiary	121/511	25.4	1.37	(0.70-2.70)		0.84	(0.41-1.73)	
First-time go for treatment	Yes	207/1091	21.5	0.93	(0.50-1.73)	0.811			
	No	75/429	22.7	1.0					
Time before treatment	Same day	30/229	15.5	1.0		0.368			
	1 day	58/302	17.8	1.17	(0.49-2.83)				
	2 days	60/307	23.0	1.62	(0.78-3.38)				
	3-5 days	95/446	28.0	2.11	(0.97-4.58)				
	6+ days	39/236	23.4	1.66	(0.64-4.29)				
Consultation with health worker (HW)									
HW told of symptoms	Yes	170/1030	18.0	0.65	(0.34-1.22)	0.162			
	No	112/490	25.4	1.0					
HW is told of patient's fever	Yes	165/961	19.2	0.76	(0.41-1.43)	0.373			
	No	117/559	23.8	1.0					
HW asks follow up Qs	Yes	139/700	23.6	1.33	(0.68-2.61)	0.376			
	No	143/819	18.5	1.0					
Patient is examined	Yes	83/370	19.5	0.88	(0.42-1.87)	0.724			
	No	199/1150	22.0	1.0					
Takes patient temperature	Yes	53/251	19.1	0.90	(0.44-1.85)	0.755			
	No	229/1269	21.9	1.0					
Patient has a prescription	Yes	99/327	42.1	3.51	(1.77-6.95)	0.001			
	No	183/1193	17.1	1.0					
Asked for ACT	Yes	114/138	86.2	53.28	(15.9-179.1)	<0.001	55.47	(15.0-205.6)	<0.001
	No	168/1382	10.6	1.0			1.0		
Health facility characteristics									
Type of facility	Public	94/430	16.6	0.70	(0.29-1.67)	0.385			
	Retailer	188/1090	22.2	1.0					
Weighing scale available	Yes	216/892	27.2	2.13	(1.05-4.32)	0.037			
	No	66/628	14.6	1.0					
Thermometer available	Yes	198/872	27.5	1.94	(1.01-3.71)	0.046	1.99	(0.94-4.18)	0.068
	No	84/648	16.2	1.0			1.0		
Offer malaria microscopy	Yes	17/70	24.0	1.12	(0.77-1.63)	0.519			

Table 6 Factors influencing whether a patient received an ACT *(Continued)*

	No	265/1430	21.7	1.0					
Facility has one or more HWs that...									
... have attended malaria training	Yes	137/660	22.0	1.03	(0.52-2.02)	0.927			
	No	145/860	21.6	1.0					
... have access to guidelines	Yes	66/236	19.2	0.83	(0.51-1.34)	0.413			
	No	216/1284	22.0	1.0					
... know ACT is recommended	Yes	251/1136	24.8	2.40	(1.03-5.57)	0.043	2.47	(0.91-6.73)	0.073
	No	31/384	11.5	1.0					

would be merit in further examining the role of patient demand in influencing the choice of treatment for uncomplicated malaria in private sector facilities.

Conclusions

ACT became the recommended treatment for uncomplicated malaria in 2005, though they remain underused, and less than a quarter of febrile patients attending health facilities in this study received ACT. Although there is increasing emphasis on the parasitological rather than symptomatic diagnosis of malaria, the study suggests that there is a need for interventions that also focus on choice of treatment to ensure that patients with malaria receive the recommended anti-malarial, irrespective of the diagnostic method. Improving the provision of health services should also address the quality of dispensing, and ensure that health workers can accurately determine the correct dose across a range of different brands and types of ACT. Concurrently attention needs to be given to the high availability and use of artemisinin monotherapy, as well as the continued use of less effective treatments, particularly SP. Consideration should also be given to the role of patient demand in influencing the treatment received, especially in medicine retailers, since this was found to be a major determinant of whether patients received an ACT. Thus, in developing interventions to improve malaria case management the results demonstrate the importance of addressing both demand and supply-side influences on malaria treatment.

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Authors' contributions

LM designed the survey, undertook the data analysis and drafted the paper with assistance from BC, VW, BU and OO. BC undertook sampling and provided advice on data analysis. OE and EN supervised the survey activities, with oversight from BU and OO. VW and OO provided guidance throughout the entire process. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Chapter 5

Research Paper II: Malaria prevalence and treatment of febrile patients and medicine retailers in Cameroon

This research paper describes the prevalence of malaria among febrile patients attending health facilities and medicine retailers in Cameroon, and the quality of malaria case management. The study was undertaken five years after ACT had been adopted as the first-line treatment, and made an important contribution to the literature on malaria in Cameroon.

ACT was the type of antimalarial most frequently prescribed or received; it was supplied to 51% of febrile patients, though other antimalarials, including quinine, were also used. Malaria was confirmed in 29% of febrile patients seeking treatment, and this highlighted the importance of testing for malaria before treatment is prescribed. Microscopy was available in most public, mission and private health facilities, though less than half of the patients at these facilities were tested. Moreover, when patients were tested for malaria the findings suggest the test result was ignored: more than 80% of patients who were tested during the consultation and found to be malaria negative were prescribed or received an antimalarial.

The findings from this study raised several questions about providers' knowledge of the national malaria treatment guidelines, and their preferences on malaria testing and on the type of antimalarial to supply for uncomplicated malaria. This paper was the starting point for the subsequent research included in this thesis (Papers III, IV, and V, and Appendices B and C).

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VOLUME 17 NO 3 PP 330–342 MARCH 2012

Malaria prevalence and treatment of febrile patients at health facilities and medicine retailers in Cameroon

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Abstract

OBJECTIVE To investigate the quality of malaria case management in Cameroon 5 years after the adoption of artemisinin-based combination therapy (ACT). Treatment patterns were examined in different types of facility, and the factors associated with being prescribed or receiving an ACT were investigated.

METHODS A cross-sectional cluster survey was conducted among individuals of all ages who left public and private health facilities and medicine retailers in Cameroon and who reported seeking treatment for a fever. Prevalence of malaria was determined by rapid diagnostic tests (RDTs) in consenting patients attending the facilities and medicine retailers.

RESULTS Among the patients, 73% were prescribed or received an antimalarial, and 51% were prescribed or received an ACT. Treatment provided to patients significantly differed by type of facility: 65% of patients at public facilities, 55% of patients at private facilities and 45% of patients at medicine retailers were prescribed or received an ACT ($P = 0.023$). The odds of a febrile patient being prescribed or receiving an ACT were significantly higher for patients who asked for an ACT (OR = 24.1, $P < 0.001$), were examined by the health worker (OR = 1.88, $P = 0.021$), had not previously sought an antimalarial for the illness (OR = 2.29, $P = 0.001$) and sought treatment at a public (OR = 3.55) or private facility (OR = 1.99, $P = 0.003$). Malaria was confirmed in 29% of patients and 70% of patients with a negative result were prescribed or received an antimalarial.

CONCLUSIONS Malaria case management could be improved. Symptomatic diagnosis is inefficient because two-thirds of febrile patients do not have malaria. Government plans to extend malaria testing should promote rational use of ACT; though, the introduction of rapid diagnostic testing needs to be accompanied by updated clinical guidelines that provide clear guidance for the treatment of patients with negative test results.

keywords fever, malaria, prevalence, treatment, Cameroon

Background

Malaria is a major cause of morbidity and mortality and places considerable burden on health services in countries across sub-Saharan Africa. Symptomatic diagnosis of malaria is a routine practice in malaria endemic settings; though, recent guidelines from the World Health Organization recommend parasitological confirmation of suspected malaria cases in all patients before treatment, where testing facilities are available (WHO 2010a). Rapid diagnostic tests (RDTs) have attracted interest in recent years because of their high specificity and sensitivity and are suitable for resource-constrained settings as they require minimal infrastructure and training. Moreover, there is an economic case for introducing RDTs, compared with presumptive treatment, given the comparatively high cost of unnecessary treatment with antimalarials, such as artemisinin-based combination therapy (ACT), among those with non-malarial febrile illness (Lubell *et al.* 2007; Shillcutt *et al.* 2008).

The Cameroon government adopted the ACT, artesunate-amodiaquine (ASAQ), as the first-line treatment for uncomplicated malaria in 2004 and endorsed artemether lumefantrine (AL) as an alternative ACT in 2006 (Sayang *et al.*2009a). The National Malaria Control Programme (NMCP) organised workshops across all regions in Cameroon to inform health workers at public, mission and private health facilities of the policy change. Quinine

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

and artemether injection are reserved for cases of severe malaria, and sulfadoxine-pyrimethamine for intermittent preventive treatment during pregnancy. The 2008 treatment guidelines for suspected cases of uncomplicated malaria lack coherence: confirmation using microscopy was advised in patients over 5 years; though, the treatment algorithm did not incorporate parasitological diagnosis and there was no advice on what action should be taken if the microscopy was negative. Moreover, while the guidelines noted that microscopy is necessary to reveal the presence of *Plasmodium*, they also stated that 'a negative blood film or smear does not rule out the presence of malaria' (Ministry of Public Health 2008). The guidelines note that pregnant women presenting with signs of malaria should be treated for severe malaria using quinine (Ministry of Public Health of the Republic of Cameroon 2008).

In August 2009, the Cameroon government announced their intention to promote the rational use of ACT using RDTs or microscopy in all cases of fever in patients over 5 years before treatment (Ministry of Public Health 2009).The NMCP is currently developing plans to pilot the introduction of RDTs in public health facilities in selected health districts across Cameroon.

Patterns of malaria treatment have been researched elsewhere in Africa and shown the extent to which malaria is over-diagnosed (Reyburn *et al.* 2007; Rowe *et al.* 2009; Juma & Zurovac 2011). Intervention studies have investigated the effect of improving microscopy and introducing RDTs on treatment (Ngasala *et al.* 2008; Skarbinski *et al.* 2009; Kyabayinze *et al.* 2010). Much less is known about malaria treatment practices in Cameroon. In the year following the introduction of ACT, Sayang *et al.* (2009b,c) found that few health workers were aware of the change in antimalarial drug policy, and facility records indicated that quinine was usually prescribed for adults and amodiaquine for children <5 years.

This study describes malaria case management in Cameroon 5 years after the adoption of ACT. Diagnosis and treatment patterns were examined in different types of facility, and the factors associated with being prescribed or receiving an ACT were investigated.

Methods

Study setting

The study was conducted in two sites in Cameroon: Yaoundé in the Centre region and Bamenda in the North-West region. In Yaoundé, the capital and predominately Francophone population, all five health districts were included. The Bamenda site encompassed urban Bamenda and five rural health districts within 21 km radius, which serve an Anglophone population. Facilities included public district hospitals and primary health centres; private health care facilities (including mission hospitals, mission health centres and private clinics); and medicine retailers (either pharmacies or drug stores). Many public and private facilities include a laboratory; though, malaria microscopy may be limited by the availability of reagents or trained staff. Pharmacies are present in both study sites and are licensed to sell prescription and over-the-counter medicines, although not to provide patient consultations or malaria testing. Drug stores are informal providers that typically sell over-the-counter medicines and are peculiar to the North-West and South-West regions (R. Hughes, C. I. R. Chandler, L. Mangham, W. Mbacham, unpublished data). Malaria is endemic in both study sites. Transmission in Yaoundé is perennial, and in the North-West region, peak transmission is between March and October.

Study design

A stratified multistage cluster survey was conducted between July and November 2009. The survey sampling was clustered in 20 randomly selected communities, defined as a natural grouping of health areas, stratified by site. Facilities were then selected, stratifying by type of facility: i) public facilities, ii) private facilities and iii) medicine retailers. Private facilities grouped both mission and for-profit facilities, which operate with considerable independence from the government. Within each community, all public and private facilities were included, while medicine retailers were randomly selected with probability proportionate to size assuming that a total of 100 medicine retailers could be visited.

The primary outcome was the proportion of individuals reporting seeking treatment for a fever that were prescribed or received an ACT. A survey sample of 12 patients per public facility and eight patients per private facility and medicine retailer was calculated to estimate the primary outcome with a precision of ±6.2% (private facility or medicine retailer) and ±8.6% (public facility), assuming that the intra-cluster correlation in treatment between facilities is 0.3 (Bennett *et al.* 1991). These precision estimates differ given the different sample sizes per type of facility and assume a prevalence of 50% for the primary outcome to give the least amount of precision. The sampling was based on an enumeration of health facilities conducted in February–May 2009.

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

Survey activities

A field team visited each facility to explain the purpose of the survey to the head of the facility or medicine retailer and obtain informed consent. Data were collected using four structured approaches: 1) patient exit questionnaire, 2) malaria testing, 3) health worker survey and 4) facility audit. The survey questionnaires were developed specifically for the study and pretested on a non-random sample of individuals at facilities not selected for inclusion in the study. Field teams were trained on procedures for conducting survey activities, including administering RDTs, and were involved in the pretesting and revision of the questionnaires. The field team comprised of researchers without a medical background but with laboratory expertise and masters' degrees in public health or microbiology. A quality assurance officer supervised all aspects of data collection.

The primary outcome was measured through the exit questionnaire which collected data on the patient's previous treatment seeking, their consultation and diagnosis, prescriptions and medicines received, the cost of treatment seeking, and demographic characteristics. Individuals exiting the facility or medicine retailer were invited to participate, asked to give written consent and were considered eligible if s/he reported seeking treatment for a fever (for themselves, a child or a patient not present) or if s/he had received an ACT. Patients with signs of severe malaria were excluded by the field teams. Patients who were present at the facility or medicine retailer were also asked whether they were willing to be tested for malaria using a RDT (SD Bioline Malaria Ag Pf/pan) to determine the prevalence of malaria and the proportion of patients receiving appropriate treatment. Treatment was considered appropriate if the patient's test result was positive and s/he had been prescribed or had received an ACT, or if the test result was negative and s/he had not been prescribed and had not received an antimalarial. Patients were told the test result, and anyone with a positive result was advised that ACT is the recommended antimalarial.

The health worker questionnaire asked about access to in-service training, guidelines, and recommended practices for treating uncomplicated malaria. The facility audit recorded data on diagnostic services and antimalarials available. The health worker and facility data were collected once the patient exit survey was complete. All health workers within each facility (including medicine retailers) responsible for prescribing or dispensing medicines and available at the time of the health worker and facility audit were included in the survey. Written consent was obtained from all individuals that participated in the study.

Statistical analysis

Data were double-entered and verified using Microsoft Access 2007 (Microsoft Inc., Redmond, Washington) and analysed using STATA version 11.0 (STATA Corporation, College Station, Texas) that allows for complex survey design by identifying different probabilities of selection (sampling weights), clustering and stratification (StataCorp 2009). Thus, the percentages, 95% confidence intervals and odds ratios reported are population-average estimates which have been adjusted to take into account the stratification, clustering and sampling weights of the study design.

Treatment outcomes by strata were estimated using the Rao and Scott chi-square correction (Rao & Scott 1981). Survey logistic regression was used to assess factors associated with being provided an ACT (which is defined as either being prescribed or receiving an ACT). Patient characteristics, health worker characteristics, details of the consultation and type of facility were investigated for their potential association with being provided an ACT (as listed in Table 4). Factors whose univariable association with being provided an ACT reached statistical significance at the 10 per cent level or which were strongly associated with the outcome (with an odds ratio <0.5 or >1.5) were included a multivariable model. The multivariable model was developed using stepwise regression, and all factors were retained if they remained significantly associated at the 10% level or with an adjusted odds ratio of <0.5 or >1.5. Models were compared using an adjusted Wald test. Pregnant women and children under the age of 6 months were excluded from the analysis because the guidelines recommend alternative treatments.

Ethical approval

Ethical approval was obtained from the ethics committees of the London School of Hygiene and Tropical Medicine and Cameroon National Ethics Committee. Administrative clearance was obtained from the Directorate of Operational Research in Health from the Ministry of Public Health.

Results

Patient characteristics

In total, 964 eligible patients (or their caregivers) consented to participate in the exit survey. Of these, 16 pregnant women and 10 children under 6 months were excluded from the analysis. Thus, the analysis is based on exit data collected from 938 febrile patients attending 174 facilities (Figure 1). The characteristics of patients surveyed at each

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

type of facility varied by age, socioeconomic status (SES) and level of education, with those attending public facilities of a slightly lower SES and education level (Table 1). In total 544 (59%) patients reported, it was the first time treatment was sought for this illness episode and 182 (19%) were seeking treatment on the same day or the day following onset of symptoms. Of those that had previously sought treatment, 154 of 386 (43%) recalled receiving an

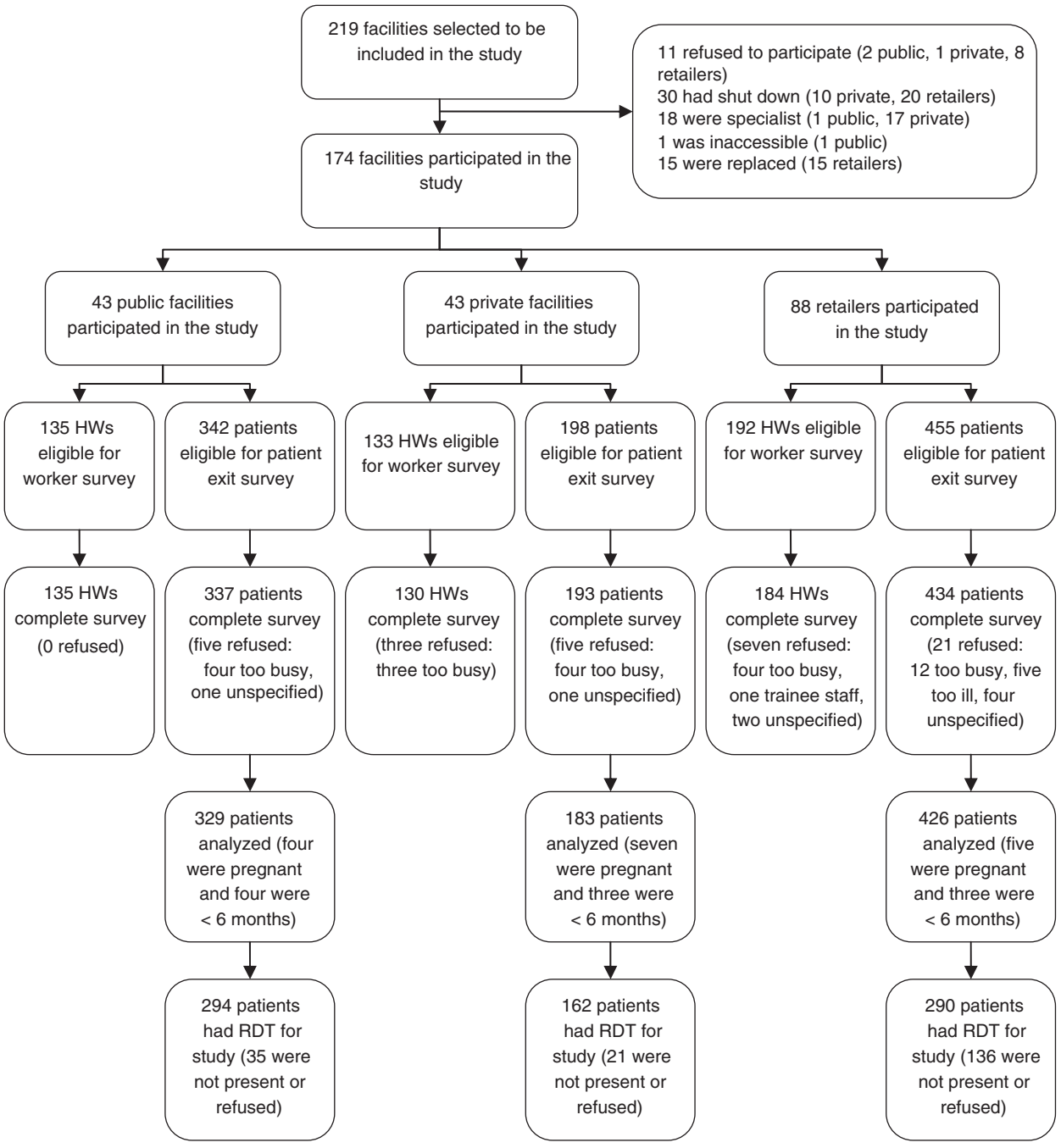

Figure 1 Survey population in Cameroon.

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

Table 1 Patient characteristics

	Public		Private		Medicine retailer		Total		
	N = 329	%	*N* = 183	%	*N* = 426	%	*N* = 938	%	*P*-value
Study site									
Bamenda	225	69.1	83	39.2	226	58.6	534	57.5	0.148
Yaoundé	104	30.9	100	60.8	200	41.5	404	42.6	
Gender*									
Male	157	46.2	81	43.2	228	52.7	466	49.4	0.149
Female	169	53.8	99	56.8	195	47.3	463	50.6	
Age									
>15 years (adult)	191	57.6	111	59.1	294	69.1	596	64.6	0.090
5–15 years	53	15.2	28	16.3	37	7.6	118	11.0	
<5 years	85	27.2	44	24.6	95	23.3	224	24.4	
Socioeconomic status (by wealth quintile)†									
Poorest	104	31.4	30	16.8	55	16.7	189	20.1	0.025
Second	70	21.2	24	11.9	92	22.0	187	20.0	
Third	63	19.6	44	26.5	80	18.5	187	20.2	
Fourth	51	15.8	48	28.4	89	18.5	188	19.7	
Richest	40	12.0	37	16.5	110	24.3	187	20.0	
Education (or caregiver education)‡									
None or primary education	143	42.2	69	42.2	129	35.5	341	38.3	0.142
Secondary education	144	46.7	84	41.4	190	42.9	418	43.5	
Tertiary education	37	11.1	29	16.4	98	21.6	164	18.2	
Number of days since start of symptoms (*n* = 938)									
≤1 day	54	15.0	32	16.4	96	20.7	182	18.6	0.453
2 days	60	18.3	24	13.4	92	21.0	176	19.0	
3–5 days	116	35.8	70	38.0	138	33.2	34	34.7	
6 days or longer	99	30.9	57	32.2	100	25.1	256	27.8	
Was first time sought treatment§									
Yes	184	53.5	93	47.6	267	65.4	544	59.3	0.055
No	143	46.5	90	52.4	153	34.7	386	40.7	
Recall of treatment received at last place sought treatment	*N* = 143	%	*N* = 90	%	*N* = 153	%	*N* = 386	%	
Any AM	45	30.6	34	42.6	74	49.8	154	42.9	0.048
ACT	14	9.3	10	9.4	38	26.3	62	17.7	0.002
Antibiotic	22	14.7	9	7.3	14	10.3	45	10.8	0.450
Antipyretic	87	61.5	54	54.2	63	41.2	204	49.8	0.025

ACT, artemisinin-based combination therapy; SES, socioeconomic status.
*Missing nine observations (three from public, three from private and three from medicine retailers).
†Principal components analysis was undertaken to generate a SES index based on household asset ownership (Filmer & Pritchett 2001) The SES index was disaggregated into quintiles.
‡Missing 15 observations (five from public, one from private and nine from medicine retailers).
§Missing eight observations (two from public and six from medicine retailers).

antimalarial at the last place they sought treatment and 62 of 386 (18%) recalled receiving an ACT.

Health facility and health worker characteristics

Public and private facilities were well equipped, with microscopy testing available in 36 (91%) public facilities and 43 (100%) private facilities (Table 2). ACT was available in 121 (70%) facilities. Public facilities tended to stock artesunate-amodiaquine; though, other types of ACT including artemether-lumefantrine and dihydroartemisinin-piperaquine were available at private facilities and medicine retailers. Most facilities reported quinine and sulfadoxine-pyrimethamine were available, while artemisinin-monotherapy was available in 54 (40%) facilities.

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

Table 2 Health facility and health worker characteristics

	Public		Private		Medicine retailer		Total		
Health facilities	*N* = 43	%	*N* = 43	%	*N* = 88	%	*N* = 174	%	*P*-value
Study site									
Bamenda	32	58.3	20	28.6	59	57.1	111	51.5	0.005
Yaoundé	11	41.7	23	71.4	29	43.0	63	48.5	
Equipment and services available									
Weighing scale*	40	93.9	43	100	39	49.0	122	66.5	<0.001
Thermometer*	39	94.6	42	95.4	57	61.2	138	73.4	<0.001
Microscopy services*	36	90.5	43	100	3	3.3	82	36.7	<0.001
RDT in stock*	0	0	5	10.9	1	1.1	6	2.9	<0.001
Availability of antimalarials									
Any antimalarial	42	98.2	42	98.0	88	100	172	99.3	0.023
Artesunate monotherapy†	9	32.2	15	35.4	30	42.7	54	39.6	0.237
Amodiaquine†	3	9.7	7	12.5	36	35.0	46	26.5	<0.001
Quinine†	38	91.8	39	95.6	84	96.2	161	95.4	0.774
Sulfadoxine-pyrimethamine (SP)†	35	86.2	34	82.8	80	92.5	149	89.6	0.028
Any ACT‡	34	82.8	27	65.2	60	71.8	121	72.2	0.039
Artemether lumefantrine	5	9.9	18	49.5	37	47.8	60	42.1	<0.001
Artesunate amodiaquine	33	77.0	14	33.7	50	62.6	97	59.0	0.002
Artesunate mefloquine	2	8.5	4	11.7	21	32.9	27	24.7	<0.001
Artesunate sulfadoxine-pyrimethamine	0	0	1	2.0	18	25.9	19	16.9	0.003
Dihydroartemisinin-piperaquine	3	14.3	8	17.5	23	34.9	34	28.1	0.004
Health workers	*N* = 134	%	*N* = 129	%	*N* = 184	%	*N* = 447	%	*P*-value
HW has attended malaria training in past 3 years	74	49.2	40	33.9	48	29.5	162	34.5	<0.001
HW has access to malaria treatment guidelines	88	54.8	54	42.2	8	4.6	150	24.1	<0.001
HW accurately reported ACTs are the recommended treatment for uncomplicated malaria	108	80.1	83	60.4	93	54.3	284	60.9	<0.001

ACT, artemisinin-based combination therapy.
*Missing one observation (from pharmacy).
†Missing two observations (one from public & one from private).
‡The availability of ACTs was verified by the field staff.

Across all facilities, 284 (61%) health workers reported that ACT is the recommended treatment for uncomplicated malaria, 150 (24%) had access to guidelines and 162 (35%) had attended malaria training in the past 3 years. The knowledge of health workers at public facilities was higher, with 108 (80%) health workers aware that ACT is the recommended treatment compared with 83 (60%) at private facilities and 93 (54%) at medicine retailers.

Prescribed treatment for malaria

Patient-reported consultations differed by type of facility, with health workers at public and private facilities more likely to ask about symptoms, examine and test the patient than health workers at medicine retailers (Table 3). Patients were more likely to request antimalarials, including ACT, at medicine retailers, whilst those attending private facilities were more likely to be tested for malaria.

Almost three-quarters (73%, 95% CI: 65–80%) of all patients were prescribed or received an antimalarial. Antibiotics were prescribed or received by 24% of febrile patients, and antipyretics were prescribed or received by 56% of febrile patients. Approximately half (51%, 95% CI: 44–59%) of all patients were prescribed or received an ACT, the recommended treatment for uncomplicated malaria; 65% (95% CI: 55–72%) of patients at public facilities, 55% (95% CI: 40–69%) at private facilities and 45% (95% CI: 35–56%) at medicine retailers ($P = 0.023$). This includes 17% (95% CI: 12–23%) of patients who reported they were tested for malaria during their consultation; though, the results are similar if the sample is

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

Table 3 Recommended treatment of malaria

	Health facility type				
	Public	Private	Medicine retailer	Total	
	N = 329	*N* = 183	*N* = 426	*N* = 938	
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	*P*-value
Patient reported consultation					
Told HW about patient symptoms	95.6 (90.8–97.9)	97.6 (90.6–99.4)	62.1 (52.5–70.8)	76.6 (68.6–83.0)	<0.001
Told HW that had a fever	66.9 (58.9–74.0)	64.3 (49.2–77.0)	49.5 (39.9–59.2)	56.4 (49.1–63.4)	0.024
HW asked follow up questions about patient's symptoms	75.8 (65.8–83.6)	66.9 (53.7–77.8)	32.7 (24.0–42.7)	49.1 (41.2–56.9)	<0.001
Patient was examined	60.0 (48.8–70.3)	75.3 (54.7–88.6)	12.3 (7.9–18.7)	35.2 (26.5–44.9)	<0.001
Patient had temperature taken	67.9 (54.3–79.0)	55.9 (26.1–82.0)	9.0 (5.0–15.7)	31.4 (23.6–40.4)	<0.001
Patient tested for malaria at this facility	35.1 (25.7–45.7)	44.4 (30.0–59.7)	1.0 (0.2–6.1)	17.0 (12.3–23.1)	<0.001
% Of patients who requested					
Any type of medicine	8.6 (5.0–14.6)	2.2 (0.7–6.3)	53.7 (42.2–64.8)	33.8 (25.3–43.4)	<0.001
Antimalarial (any type)	7.5 (4.1–13.4)	1.5 (0.4–5.0)	37.3 (26.8–49.2)	23.8 (16.7–32.7)	<0.001
Any ACT	3.7 (1.8–7.3)	1.0 (0.3–3.8)	25.2 (17.2–35.2)	15.7 (10.6–22.6)	<0.001
Artemisinin monotherapy	0	0	0.3 (0.0–1.5)	0.1 (0.0–0.9)	0.814
Quinine	3.3 (1.1–9.5)	0.4 (0.1–2.0)	6.7 (3.3–13.0)	4.8 (2.6–8.7)	0.033
SP	0.5 (0.0–6.2)	0	4.4 (2.1–8.8)	2.7 (1.3–5.5)	0.084
% of all patients who were prescribed or received					
Antimalarial (any type)	78.3 (71.9–83.6)	84.5 (70.5–92.6)	66.9 (55.5–76.7)	72.8 (64.7–79.7)	0.016
ACT*	64.8 (55.3–72.3)	54.5 (39.5–68.8)	44.9 (34.5–55.7)	51.3 (44.0–58.6)	0.023
Artemisinin monotherapy	1.1 (0.3–4.1)	3.1 (0.3–24.4)	0.1 (0.0–1.1)	0.9 (0.2–3.5)	0.031
Quinine	13.4 (7.6–22.4)	21.1 (11.0–36.8)	15.2 (8.7–25.2)	15.9 (10.9–22.5)	0.477
SP	0.2 (0.0–3.9)	10.7 (4.5–23.2)	4.5 (2.1–9.3)	4.7 (2.6–8.2)	0.008
Antibiotic	41.9 (32.8–51.7)	41.1 (33.3–49.2)	12.0 (8.0–17.5)	24.4 (19.6–29.9)	<0.001
Antipyretic	69.4 (60.8–76.8)	71.4 (53.0–84.7)	44.9 (35.0–55.3)	55.6 (46.5–64.2)	0.002
% Of patients who were not tested for malaria and were prescribed or received					
Antimalarial (any type)	78.4 (71.1–84.2)	85.1 (67.4–94.0)	67.3 (56.0–76.9)	71.5 (62.6–79.0)	0.046
ACT*	67.6 (56.4–77.1)	63.8 (50.6–75.1)	45.0 (34.7–55.7)	51.4 (43.5–59.3)	0.005
Artemisinin monotherapy	0.8 (0.2–3.0)	0	0.1 (0.0–1.1)	0.2 (0.1–0.7)	0.120
Quinine	10.7 (5.4–20.1)	15.7 (8.5–27.1)	15.3 (8.9–25.0)	14.5 (9.6–21.4)	0.597
SP	0	7.3 (2.2–21.3)	4.6 (2.2–9.2)	4.1 (2.1–7.6)	0.203
Antibiotic	41.2 (31.4–51.6)	45.3 (35.9–55.1)	11.8 (8.0–16.9)	21.3 (16.8–26.6)	<0.001
Antipyretic	71.3 (62.3–78.9)	72.1 (50.6–86.7)	45.4 (35.8–55.3)	53.4 (44.3–62.3)	0.002
Dosage and advice given for ACT dispensed					
% Of ACTs dispensed that were an accurate dose†	92.4 (84.0–96.6)	98.5 (93.5–99.7)	97.5 (92.3–99.2)	96.5 (93.3–98.1)	0.065
% Patient that has accurate knowledge of treatment regimen‡	83.9 (70.7–91.8)	89.0 (74.3–95.7)	85.8 (74.7–92.5)	86.1 (79.8–90.6)	0.781

ACT, artemisinin-based combination therapy.
*61.4% (49.4–72.2%) of children under 5 years that were prescribed or received an ACT. By facility type the percentage of children under 5 years that were prescribed or received an ACT was 79.4% (69.0–87.0%) at public facilities; 50.6% (26.2–74.8%) at private facilities; and 56.6% (39.7–72.1%) at medicine retailers ($P = 0.080$).
†Defined as dose that is consistent guidance on dosage by patient age (and excludes suspensions and syrups). Based on 306 observations (112 from public, 68 from private and 126 from medicine retailers).
‡Defined as patient reports treatment regimen is consistent with guidance on dosage by patient age (and excludes suspensions and syrups). Based on 283 observations (111 from public, 64 from private and 108 from medicine retailers).

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

Table 4 Factors influencing whether a patient is prescribed or received an ACT

Variable		*n/N*	%	Univariable analysis		Multivariable analysis	
				OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Study site	Bamenda	194/355	55.0	1.20 (0.69–2.10)	0.502		
	Yaoundé	282/489	50.5	1.0			
Patient characteristics							
Gender	Male	234/418	52.9	1.04 (0.65–1.66)	0.850		
	Female	242/426	51.9	1.0			
Age Group	>15 years	291/539	49.6	1.0	0.173		
	5–15 years	55/105	47.9	1.02 (0.45–1.90)			
	<5 years	130/200	62.0	1.65 (0.95–2.89)			
Quintile	Richest	97/159	64.4	2.06 (0.98–4.34)	0.371		
	Fourth	102/172	55.4	1.41 (0.68–2.94)			
	Third	88/171	50.1	1.14 (0.59–2.21)			
	Second	93/173	46.4	0.99 (0.56–1.75)			
	Poorest	96/169	46.7	1.0			
Education level of patient (or caregiver)	Tertiary	90/147	60.3	1.68 (0.93–3.02)	0.221		
	Secondary	214/387	53.4	1.27 (0.77–2.07)			
	None/Primary	172/310	47.6	1.0			
Time before treatment sought	≤1 day	98/164	53.7	1.0	0.203		
	2 days	102/162	61.6	1.38 (0.71–2.67)			
	3–5 days	143/289	45.0	0.70 (0.39–1.26)			
	6+ days	133/229	54.1	1.01 (0.53–1.93)			
First time sought treatment	Yes	293/495	54.7	1.26 (0.84–1.89)	0.245		
	No	183/349	48.9	1.0			
Had not previously sought an antimalarial	Yes	416/704	55.0	1.81 (1.03–3.17)	0.039	2.29 (1.46–3.59)	0.001
	No	60/140	40.3	1.0		1.0	
Had not previously sought an ACT	Yes	447/786	52.9	1.34 (0.50–3.61)	0.537		
	No	29/58	45.5	1.0			
Patient-reported consultation							
Health worker (HW) is told patient has fever	Yes	275/458	52.1	0.97 (0.58–1.62)	0.917		
	No	201/359	52.7	1.0			
HW asks follow up questions	Yes	280/476	54.8	1.21 (0.77–1.91)	0.390		
	No	196/368	50.1	1.0			
Patient is examined by HW	Yes	222/357	61.5	1.77 (1.11–2.83)	0.020	1.88 (1.11–3.18)	0.021
	No	254/487	47.4	1.0		1.0	
Patient has temperature taken	Yes	207/336	58.7	1.45 (0.85–2.49)	0.162		
	No	269/508	49.5	1.0			
HW tests patient for malaria	Yes	102/184	51.1	0.94 (0.53–1.67)	0.832		
	No	373/660	52.6	1.0			
Patient is tested and RDT negative	Yes	61/107	59.1	1.35 (0.78–2.36)	0.269		
	No	415/737	51.7	1.0			

Table 4 *(Continued)*

Variable		*n/N*	%	Univariable analysis OR (95% CI)	*P*-value	Multivariable analysis OR (95% CI)	*P*-value
Asked for ACT	Yes	115/129	90.1	11.11 (4.90–25.15)	<0.001	24.14 (9.40–62.04)	<0.001
	No	361/715	45.1	1.0		1.0	
Health facility characteristics							
Type of facility	Public	193/290	67.5	2.46 (1.35–4.48)	0.023	3.55 (1.87–6.74)	0.003
	Private	96/174	54.1	1.39 (0.72–2.71)		1.99 (0.91–4.39)	
	Medicine retailer	187/380	45.8	1.0		1.0	
One or more HWs at facility attended malaria training	Yes	346/560	61.6	2.46 (1.44–4.49)	0.002		
	No	130/284	39.4	1.0			
One or more HWs at facility have access to guidelines	Yes	273/427	60.6	1.77 (0.89–3.55)	0.100		
	No	203/417	46.4	1.0			
One or more HWs at facility know ACT is recommended	Yes	431/731	56.0	2.44 (0.84–7.14)	0.097		
	No	45/113	34.3	1.0			

ACT, artemisinin-based combination therapy.

restricted to those that were diagnosed based on symptoms alone: 51% (95% CI: 44–59%) of patients were presumptively prescribed or received an ACT.

The odds of a febrile patient being prescribed or receiving an ACT were significantly higher for patients who asked for an ACT (OR = 24.1, $P < 0.001$), were examined by the health worker (OR = 1.88, $P = 0.021$), had not previously sought an antimalarial for the illness (OR = 2.29, $P = 0.001$) and sought treatment at a public (OR = 3.55) or private facility (OR = 1.99, $P = 0.003$) (Table 4). There was no evidence that the treatment prescribed or received was significantly associated with the patient's demographic characteristics or being tested for malaria. In the univariable analysis, the odds that febrile patients were prescribed or receiving an ACT were significantly associated with facilities that had one or more health workers who had i) attended malaria training and ii) knew ACT is recommended; though, these factors did not remain significant in the multivariable model.

Quinine was prescribed or received by 16% (95% CI: 11–22%) of patients and a further 5% (95% CI: 3–9%) of patients were prescribed or received sulfadoxine-pyrimethamine (Table 3). Almost all ACTs dispensed were estimated to be dispensed in the correct dose for the patient's age, and 86% (95% CI: 80–91%) of patients receiving an ACT accurately reported how the medicine should be taken.

Appropriate treatment for malaria

RDTs were used by the study team to test for malaria in 746 (79%) patients, and malaria was confirmed using RDTs in 29% (95% CI: 22–36%) of patients tested (Table 5). Based on these findings, 39% (95% CI: 33–45%) of patients received appropriate treatment; 43% (95% CI: 34–52%) in public facilities, 29% (95% CI: 21–39%) in private facilities and 41% (95% CI: 33–49%) in medicine retailers ($P = 0.08$). Of those who were positive for malaria, 59% (95% CI: 50–66%) received an ACT, while of those negative for malaria, 48% (95% CI: 40–57%) received an ACT. Almost three-quarters of patients (70%, 95% CI: 60–78%) received an antimalarial despite not having malaria.

Health workers' choice of treatment was investigated using patient-reported information on whether a test was conducted during the consultation, the test result (determined by the field team) and the treatment prescribed or received. The test result of the RDT conducted by the field team was used because patient-reported results were unreliable as many patients did not know their test result and routine test data were not accessed. Treatment does

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

Table 5 Appropriate treatment of malaria

			% Prescribed or received an antimalarial		% Prescribed or received ACT		% Received appropriate treatment
		RDT result	Yes	No	Yes	No	
	N	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
All facilities	746						38.7 (32.9–45.0)
Malaria positive	222	28.6 (22.3–35.9)	82.8 (73.4–89.3)	17.3 (10.7–26.6)	58.8 (50.7–66.4)	41.2 (33.6–49.3)	
Malaria negative	524	71.4 (64.1–77.7)	69.5 (60.1–77.4)	30.7 (22.7–40.0)	48.4 (40.0–56.9)	51.7 (43.2–60.1)	
Public facilities	294						42.6 (33.9–51.6)
Malaria positive	102	33.0 (22.9–45.0)	89.5 (81.7–94.3)	10.5 (5.7–18.3)	75.6 (64.1–84.3)	24.4 (15.7–35.9)	
Malaria negative	192	67.0 (55.0–77.1)	73.8 (65.8–80.6)	26.2 (19.4–34.3)	61.5 (49.7–72.1)	38.9 (28.2–50.7)	
Private facilities	162						29.0 (20.5–39.3)
Malaria positive	47	33.6 (18.0–53.9)	79.4 (64.1–89.3)	20.6 (10.7–35.9)	56.7 (39.5–72.4)	43.3 (27.7–60.5)	
Malaria negative	115	66.4 (46.1–82.0)	85.0 (69.1–93.5)	15.0 (6.5–30.9)	57.4 (44.6–69.3)	42.6 (30.8–55.5)	
Medicine retailers	290						40.8 (33.3–48.8)
Malaria positive	73	24.3 (17.9–32.0)	79.7 (59.8–91.3)	20.3 (8.7–40.2)	47.8 (33.5–62.5)	52.2 (37.5–66.5)	
Malaria negative	217	75.7 (68.0–82.1)	61.5 (50.0–71.8)	38.5 (28.2–50.0)	39.0 (28.5–50.7)	61.0 (49.3–71.5)	

ACT, artemisinin-based combination therapy.

Table 6 Treatment prescribed to patients tested/not tested during patient consultation

		Prescribed or received an antimalarial	Prescribed or received an ACT	Prescribed or received quinine	Prescribed or received an antibiotic
	N	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Patient tested during consultation and malaria positive*	56	77.5 (66.1–85.9)	52.3 (35.3–68.9)	15.8 (61.2–34.8)	38.9 (22.1–58.8)
Patient tested during consultation and malaria negative*	121	81.9 (71.2–89.2)	56.3 (39.8–71.5)	22.1 (11.2–33.0)	37.9 (25.7–51.9)
Patient was not tested during consultation	730	71.5 (62.5–79.1)	51.5 (43.4–59.5)	14.5 (9.5–21.6)	21.3 (16.7–26.8)
All patients	938	72.8 (64.7–79.7)	51.3 (44.0–58.6)	15.9 (10.9–22.5)	24.3 (19.5–29.9)

ACT, artemisinin-based combination therapy.
*Patient reported data on test results was considered unreliable as more than half of respondents reported that they did not know the result of the test that was conducted and routine test data was not available to the field team. The malaria test result used here is that from the RDT conducted by the field team.

not significantly differ for patients who were tested during their consultation; 78% (95% CI: 66–86%) of patients who were tested positive, 82% (95% CI: 71–89%) of patients who were tested negative and 72% (95% CI: 62–79%) of patients not tested were prescribed or received an antimalarial (Table 6).

Discussion

Almost three-quarters (73%) of all patients who reported seeking treatment for a fever were prescribed or received an antimalarial, and approximately half (51%) were prescribed or received an ACT. These estimates include patients who were tested for malaria; though, the prescribing patterns were similar for presumptive treatment (based only on a symptomatic diagnosis). Sixty-one per cent of children under 5 years with a fever were prescribed or received an ACT. Studies undertaken in East and Southern Africa reported similar results: 50% of febrile children under 5 years were prescribed an ACT in Zambia in 2006 and 66% in Uganda in 2007 (Zurovac *et al.* 2007, 2008a).

The results of this study show an improvement of the situation in Cameroon in 2005, when prescribing records indicated that less than 15% of antimalarials prescribed were an ACT (Sayang *et al.* 2009b,c). The use of quinine in

Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

non-severe cases has fallen substantially since 2005 (Sayang *et al.* 2009b,c); though, it remains a concern: 16% of patients with symptoms of uncomplicated malaria were prescribed or received quinine. These improvements over time may reflect efforts to disseminate the policy change, as observed in Kenya where the percentage of febrile children under 5 years that were prescribed an ACT at government facilities with AL in stock increased from 28% in 2006 to 69% in 2010 (Zurovac *et al.* 2008b; Juma & Zurovac 2011). In this study, attendance at malaria training and health worker knowledge of malaria guidelines were no longer significant in the multivariable model; though, the association between patients provided an ACT and health worker attributes may be an underestimate because these factors were investigated at the facility level.

The odds of a febrile patient being prescribed or receiving an ACT were significantly associated with patients who asked for an ACT, were examined, had not previously obtained an antimalarial and the type of facility at which treatment was sought. Treatment practices at medicine retailers were significantly worse than at public and private facilities, although it is encouraging that patients asking for an antimalarial most often requested an ACT. Moreover, the percentage of patients receiving an ACT (45%) was better than was observed at pharmacies and patent medicine stores in neighbouring Nigeria, where 23% of febrile patients received an ACT (Mangham *et al.* 2011).

Reliance on presumptive treatment has led to considerable over-diagnosis of malaria. In this survey, malaria was confirmed in less than a third of suspected cases using RDTs. The RDTs used have high specificity and sensitivity (WHO 2010b); though, it is a limitation that their results were not validated using gold standard microscopy. It was also beyond the scope of this study to investigate the cause of non-malarial febrile illness, and we are unable to comment on the suitability of other medicines received. Based on the RDT results, the majority of patients (61%) were prescribed or received antimalarials they did not need, and thus, many patients received ineffective medicines and incurred unnecessary costs obtaining treatment. Over-diagnosis also has adverse cost implications for the Cameroon government, which subsidises ACT at public facilities.

Microscopy was widely available in public and private facilities, but underused, with less than half of patients tested for malaria during their consultation. Similar findings were reported in an Angolan study, in which 40% of the patients were tested despite the widespread availability of microscopy and RDTs (Rowe *et al.* 2009). Moreover, we observed no significant differences in the treatment prescribed or received by patients between those that were tested positive, tested negative and not tested during their consultation with the health worker. Poor adherence to test results has been observed in Ghana and Tanzania, with 50% of patients with negative RDT test results being prescribed an antimalarial in Ghana (Ansah *et al.* 2010) and 54% in Tanzania (Reyburn *et al.* 2007). Inferences about health workers' use of the test result in selecting treatment in this study are limited because there is some uncertainty whether the RDT result used for the analysis was consistent with the result of routine microscopy undertaken at the facility. Health worker perspectives on malaria testing were subsequently explored using qualitative methods (C. I. R. Chandler, L. Mangham, A. N. Njei, O. Achonduh, W. F. Mbacham, V. Wiseman, unpublished data).

Increasing the use of malaria testing has the potential to promote the rational use of ACT and appropriate treatment of non-malarial febrile illness (Sayang *et al.* 2009a). The government's plans to introduce RDTs should increase the proportion of patients tested because RDTs are simple to use and provide quick results. The study also highlights the potential benefits of extending the availability of RDTs to private facilities and medicine retailers. However, the findings suggest that attention needs to be given to the role of testing within the therapeutic process to ensure uptake of RDTs and prescriptions that adhere to the test result.

On a related point, the lack of clear guidance in the malaria guidelines, which advises confirmation using microscopy but does not explain what actions to take if the test is negative, may lead to over-treatment of malaria in patients with negative test results. The uncertainty over how to manage febrile patients with a negative malaria test result is not confined to the Cameroon setting, and there is currently no consensus on how these cases should be managed (Björkman & Mårtensson 2010). Needless to say, if the introduction of RDTs is to be cost-effective, it will be important to revise clinical guidelines and provide health workers with advice on how to undertake diagnosis and provide treatment for patients presenting with a fever in situations when the test is positive *and* when the test is negative for malaria.

Conclusion

This study provides timely insight into the quality of malaria case management at health facilities and medicine retailers in Cameroon. ACT was prescribed or received by 51% of patients; though, quinine was also provided for uncomplicated malaria. Symptomatic diagnosis is inefficient because two-thirds of febrile patients do not have malaria. Government plans to extend malaria testing should promote rational use of ACT; though, the introduction of rapid diagnostic testing needs to be

accompanied by updated clinical guidelines that provide clear guidance on the treatment of patients with negative test results. Based on these findings and with the support of the NMCP, the REACT Project has developed provider training interventions that should improve malaria case management in public and mission health facilities and these are currently being evaluated.

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Tropical Medicine and International Health VOLUME 17 NO 3 PP 330–342 MARCH 2012

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Chapter 6

Research Paper III: What determines providers' stated preference for the treatment of uncomplicated

Chapters 4 and 5 described the problems with the treatment received by febrile patients attending health facilities and medicine retail outlets in Nigeria and Cameroon. This research paper sets out to explore why, and reports on providers' knowledge of the national malaria treatment guidelines and the determinants of providers' stated preference for treating uncomplicated malaria. The findings from this paper were used to select and design interventions to improve the diagnosis and treatment of uncomplicated malaria.

A primary motivation for this analysis was to assess whether an intervention targeting providers' knowledge would be effective, or whether additional effort would be needed to ensure providers' preference over alternative antimalarials was aligned to the national guidelines. The paper focuses on providers' stated preference, since their revealed preference (i.e. their practice) may be constrained by the resources and information available. The analysis is underpinned by agency theory, and recognises that providers are not only agents for their patients, but may also act on behalf of other health sector actors, such as their employer, the Ministry of Health and pharmaceutical suppliers.

Providers' stated preference was elicited by asking each provider "which antimalarial do you think is the best for treating patients with uncomplicated malaria?". The brand and generic names stated were subsequently coded and the analysis was undertaken using a binary outcome: whether or not the provider had stated an ACT. As discussed in the paper, there is some uncertainty in how providers understood the question used and we

acknowledge this is a limitation. The questionnaires were piloted before the full survey was administered and no problems were reported. However, this particular question was not given specific attention in the piloting since this analysis was not planned a priori and the provider questionnaire contained more than a hundred questions.

The econometric analysis uses a discrete choice model based on random utility theory [1-2]. Although utility cannot be directly observed, individuals are assumed to be economically rational and make choices that maximize their utility. In this application I examine whether providers prefer an ACT and use an multilevel logit regression to assess the extent to which providers' stated preference depends on financial and non-financial incentives, subject to information they have available on different antimalarials and the underlying institutional environment.

The analysis uses pooled data from provider surveys conducted at different types of facility in Cameroon and Nigeria. This resulted in a heterogeneous study population and the opportunity to explore the extent to which providers' preference reflected their institutional and social context. It was straightforward to merge the data from the two countries since a standardized questionnaire had been used. Using pooled data also increased the sample size, which was restricted because the provider survey was part of a larger study that had been designed to examine the treatment supplied to febrile patients. As pooled data were used, country-specific effects were examined in the multilevel analysis. This included an explanatory variable for the country, and interactions to investigate whether any of the provider, facility and area attributes had a country-specific effect. Interactions were added to the random-intercept model one at a time and their statistical significance was assessed using the Wald test and the likelihood ratio test at a 10% level of significance. As noted in the paper, model specification was assessed using various methods, and none of the interactions were found to significantly improve the fit of the model.

The findings confirmed that providers' stated preference may be influenced by their patients, drug company representatives, and other providers who work at the same facility or in the same locality. The findings also contributed to a theory-based approach to intervention design. Based on these findings, the enhanced training incorporated interactive small-group work and sessions on communicating with patients. In addition, the enhanced training was intended to build consensus within a facility and all providers attending the training workshops were encouraged to hold training and share what they had learnt with their colleagues.

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What determines providers' stated preference for the treatment of uncomplicated malaria?☆

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ABSTRACT

As agents for their patients, providers often make treatment decisions on behalf of patients, and their choices can affect health outcomes. However, providers operate within a network of relationships and are agents not only for their patients, but also other health sector actors, such as their employer, the Ministry of Health, and pharmaceutical suppliers. Providers' stated preferences for the treatment of uncomplicated malaria were examined to determine what factors predict their choice of treatment in the absence of information and institutional constraints, such as the stock of medicines or the patient's ability to pay.

518 providers working at non-profit health facilities and for-profit pharmacies and drug stores in Yaoundé and Bamenda in Cameroon and in Enugu State in Nigeria were surveyed between July and December 2009 to elicit the antimalarial they prefer to supply for uncomplicated malaria. Multilevel modelling was used to determine the effect of financial and non-financial incentives on their preference, while controlling for information and institutional constraints, and accounting for the clustering of providers within facilities and geographic areas.

69% of providers stated a preference for artemisinin-combination therapy (ACT), which is the recommended treatment for uncomplicated malaria in Cameroon and Nigeria. A preference for ACT was significantly associated with working at a for-profit facility, reporting that patients prefer ACT, and working at facilities that obtain antimalarials from drug company representatives. Preferences were similar among colleagues within a facility, and among providers working in the same locality. Knowing the government recommends ACT was a significant predictor, though having access to clinical guidelines was not sufficient.

Providers are agents serving multiple principals and their preferences over alternative antimalarials were influenced by patients, drug company representatives, and other providers working at the same facility and in the local area. Efforts to disseminate drug policy should target the full range of actors involved in supplying drugs, including providers, employers, suppliers and local communities.

Introduction

The market for health care is characterized by information asymmetry, as patients delegate decision-making and rely on providers to select as well as administer treatment (Arrow, 1963). The performance of providers in low-and-middle-income countries continues to be scrutinized and there is widespread interest in strategies to improve their practice (Rowe, de Savigny, Lanata, & Victora, 2005). In designing interventions to improve the quality of care it is important to understand what or who influences providers' treatment decisions. Structural factors are often emphasized, and providers' practice may be constrained by the availability of essential equipment, supplies and medicines (Peabody, Taguiwalo, Robalino, & Frenk, 2006), and by shortages of health professionals, as existing staff care for large volumes of patients and substitute for more senior cadres (Chen et al., 2004). There is,

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however, evidence on providers' knowledge, competence and practice demonstrating that poor resource availability and knowledge of clinical guidelines are not the only reasons why patients receive poor quality care (Das, Hammer, & Leonard, 2008; Willis-Shattuck et al., 2008).

The literature on medical practice variation examines the extent to which individual providers affect the quality of patient care. The notion of 'practice style' was introduced to describe the variation attributed to providers' preference over alternative forms of care (Wennberg, Barnes, & Zubkoff, 1982). Early studies focused on geographic variation, and showed that variations in medical practice were not fully explained by patients' health care needs and demographic characteristics (McPherson, Wennberg, Hovind, & Clifford, 1982). As the literature grew, studies investigated differences between facilities and between individual providers (Scott & Shiell, 1997a, 1997b). For example, Davis et al. examined decision-making in primary care facilities and found considerable variation between doctors in prescribing, referral for diagnostic tests and follow up having accounted for case-mix, patient, and practitioner attributes (Davis, Gribben, Scott, & Lay-Yee, 2000). Although the literature on medical practice variation is reasonably extensive, it offers limited insight into the extent to which providers' preference varies by type of organization. Moreover, most studies come from high-income countries where facilities are well-resourced and institutions monitor and regulate the quality of health care.

Providers' preference over alternative treatments is said to be revealed by their actual practice, though the choice of treatment may be constrained by other factors, such as the stock of medicines, specific information about the patient's condition or the patient's ability to pay. Stated preferences are usually used in economic studies to substitute for revealed preferences under conditions where it is not possible to capture revealed preferences (because, for example, the product in question is not available in the market). However, in some cases it may be useful to focus on stated preferences in their own right, as distinct from revealed preferences. For instance, focussing on what providers' state they prefer, rather than what they know or do, will help to determine whether an intervention that targets providers' knowledge is likely to be effective or whether additional effort is needed to change what they prefer. In other words, it is acknowledged that changing what providers prefer may not be sufficient to change actual practice, but any gap between stated and revealed preference would require supplementary interventions, such as those that address resource constraints or reduce the patients' cost of accessing care.

Providers' stated preferences for the treatment of uncomplicated malaria were examined as part of the formative stages of a study undertaken to test supply-side interventions to improve malaria diagnosis and treatment in Cameroon and Nigeria (Wiseman, Ezeoke, et al., 2012; Wiseman, Mangham, et al., 2012). Malaria places a considerable burden on the health system in sub-Saharan Africa, and is treated by providers working at a range of facilities, including private-sector pharmacies and drug stores. The clinical guidelines for malaria treatment are unambiguous, and can be used by providers with limited clinical knowledge or expertise. Artemisinin-combination therapy (ACT) is the recommended antimalarial for uncomplicated malaria and should be supplied to all patients presenting with a fever or history of fever, unless they have a negative test result or are in the first trimester of pregnancy. ACT has been the first-line antimalarial in Cameroon since 2004 and in Nigeria since 2005. In each country, the Malaria Control Programme of the Ministry of Health, at either national or state level, is responsible for disseminating malaria policy (Ministry of Health of the Federal Republic of Nigeria, 2005; Ministry of Public Health of the Republic of Cameroon, 2008). Their efforts include distributing clinical guidelines and holding training workshops. Providers in public and mission facilities have greater access to information and training, though professional associations may conduct training for staff at private-sector pharmacies and drug stores.

In this paper, we report the type of antimalarial that providers in Cameroon and Nigeria state they prefer to use to treat uncomplicated malaria. We assess whether their stated preference is consistent with their knowledge of the recommended antimalarial, and investigate who or what influences their preference over alternative antimalarials. Previous epidemiological studies from Cameroon and Nigeria have investigated the factors associated with patients receiving an ACT, though these studies do not focus on providers' preference or practice as they include patients at pharmacies and drug stores that requested specific treatment (Mangham et al., 2012, 2011). Studies from elsewhere in sub-Saharan Africa have examined providers' actual practice in treating febrile patients, though these were limited to care provided at public and mission facilities (Osterholt et al., 2006; Rowe et al., 2000; Zurovac et al., 2004). This paper complements the existing literature by investigating providers' preference using stated preference data obtained from providers working at non-profit health facilities and for-profit pharmacies and drug stores in Cameroon and Nigeria.

Theoretical considerations

Providers' preference over different types of antimalarials was examined from an economic perspective founded in agency theory. An agency relationship occurs when one individual acts on behalf of another (Shapiro, 2005), and this arises in health care interactions, including those at pharmacies and drug stores, when the patient relies on the provider to determine their health care needs (Coast, 2001). It is conventional to focus on the principal-agent relationship between patients and providers, though providers may be party to multiple agency relationships (Blomqvist, 1991). In this study, we acknowledge that providers operate within a network of relationships, and may be an agent not only for their patients but also for other actors in the health system, such as their employer, the Ministry of Health, or antimalarial supplier (Jan, 2005). Agency relationships may have a formal contract, though will often be an unwritten understanding in which the provider perceives a responsibility to act on behalf of another.

The economics literature assumes agents are rational and make choices to maximize their own utility. In standard agency theory it is assumed that agents are financially motivated and would act to obtain an optimal combination of income and leisure time, or at least achieve a threshold level of income, irrespective of the principal's preference (Evans, 1974). The provider's preferred treatment could, therefore, reflect the method of remuneration, whether the organization has a profit motive, or income from additional sources, such as secondary employment, sales commission, or ownership of private businesses (Chaix-Couturier, Durand-Zaleski, Jolly, & Durieux, 2000; Ferrinho, Van Lerberghe, Fronteria, Hipolito, & Biscaia, 2004). These influences can be considered from a static or dynamic perspective, with the latter taking into account reputation effects, in which future income depends on the amount of competition and the principal's satisfaction with the agent's current practice (Mooney & Ryan, 1993). The theory has also been extended to recognize that providers have a professional responsibility to act in the interests of the patient and may derive satisfaction from their work (Mooney & Ryan, 1993). Thus, providers' choice of treatment may reflect an intrinsic motivation not only to fulfil patients' expectations and improve patients' health, but also to satisfy their

employer, the Ministry of Health or other principals (Leonard & Masatu, 2010).

Agents' choice, and therefore their ability to obtain utility, will be constrained by the information they have available. Providers may vary in their access to information from pre- or in-service training, clinical guidelines, public health campaigns, marketing materials, and observing colleagues. Institutional, social and psychological factors may also constrain preferences. Formal institutions, such as regulation, can limit behaviour, though informal institutions can also have an important effect, as preferences are embedded within social structures, cultures, values and behavioural norms (Burke, Fournier, & Prasad, 2010; Charles, Gafni, Whelan, & O'Brien, 2006; Rabin, 1998). For instance, providers may be influenced by their colleagues, as social networks not only affect the flow of information but can be a source of reward and punishment (Granovetter, 2005).

Methods

Econometric model

The econometric analysis is based on random utility theory. Although utility cannot be directly observed, individuals are assumed to be economically rational and make choices that maximize their utility. The provider's choice of preferred treatment can be described as:

$$U = f(Y, S)$$

where U is the utility of the provider's preferred treatment, Y is income (and other financial incentives), S is the satisfaction (and non-financial incentives). Utility is maximized subject to the information about the treatment options and the underlying institutional environment. It is assumed that the utility yielded by mutually exclusive treatment options depends on the observable factors contained in the provider's utility function and unobserved or unknown influences on individual behaviour. In its simplest form, the observed sources of utility are defined as a linear expression in which each explanatory variable is weighted by a parameter that accounts for that variable's marginal utility.

A multilevel model was used to estimate a three-level random effects model (Hox, 2010). This approach accounts for the clustering of providers, since some correlation between providers within a facility or area is possible if they have similar incentives, share information, and face a common institutional environment (Rice & Jones, 1997). For a three-level logistic regression the dependent variable π_{ijk} is defined as the probability that the preferred treatment was an ACT for provider i from facility j in area k, where $(\pi_{ijk}/(1\text{-}\pi_{ijk}))$ is the log odds that the preferred treatment is an ACT. The model for provider's preferred treatment is specified as:

$$\text{logit}\left(\pi_{ijk}\right) = \alpha + \beta Y_{ijk} + \lambda S_{ijk} + \theta I_{ijk} + \gamma F_{jk} + \phi A_k + \varepsilon_{ijk} + u_{jk} + v_k$$

$$\varepsilon_{ijk} \sim N\left(0, \sigma^2\right) \rightarrow u_{jk} \sim N\left(0, \tau^2\right), v_k \sim N\left(0, \varphi^2\right),$$

where:

α is the intercept;
Y_{ijk} is the income of provider i at facility j in area k;
S_{ijk} is satisfaction of provider i at facility j in area k;
I_{ijk} are information constraints for provider i at facility j in area k;
F_{jk} are institutional constraints common to all providers at facility j in area k;
A_k are institutional constraints common to all providers in area k;
β, λ, θ, γ and ϕ are the parameters associated with the explanatory variables;

ε_{ijk}, u_{jk} and v_k, are the residuals at the level of the provider, facility and geographical area, respectively, and capture unobserved variation, measurement and specification errors.

Study setting

The study was undertaken in four sites in Cameroon and Nigeria that had been selected for cluster randomized trials of interventions to support the introduction of malaria rapid diagnostic testing (Wiseman, Ezeoke, et al., 2012; Wiseman, Mangham, et al., 2012). This paper analyses provider survey data that were collected as part of a larger study on malaria diagnosis and treatment at different types of facility and undertaken to guide the design of interventions that would accompany the roll-out of malaria rapid diagnostic tests.

The four sites were Yaoundé and Bamenda in Cameroon, and Enugu and Udi in Enugu State, south-east Nigeria. Yaoundé is the capital of Cameroon and has an urban, predominately French-speaking population. The Bamenda site consisted of one urban and seven rural districts in the North-West region, where the main language is English or pidgin-English. The urban sites in Nigeria were drawn from Enugu town, and the rural areas were located in Udi local government area. Igbo is the dominant ethnic group and language in Enugu State. Malaria is endemic and occurs throughout the year in all four sites, though there is seasonal variation in the Bamenda site, with peak transmission occurring between March and November.

Antimalarials, including ACT, have over-the-counter status in Cameroon and Nigeria and can be obtained from pharmacies and drug stores as well as public, mission and private facilities. Malaria treatment may also be sought from mobile medicine vendors, herbalists and traditional healers. The government supplies public facilities, and mission facilities receive medicines from a central agency. Pharmacies and drug stores obtain medicines through formal and informal channels, including drug company representatives, wholesalers and the main market in the local area.

In Cameroon, public and mission facilities, and private pharmacies are the main source of treatment for uncomplicated malaria (Ongolo-Zogo & Bonono, 2010). Most public and mission hospitals and health centres in the Cameroon sites have a pharmacy and a laboratory for simple diagnostic procedures and are staffed by nurses, pharmacy attendants and laboratory technicians. Some larger facilities also have a medical doctor. In the private-sector, pharmacies are legally required to employ a qualified pharmacist and licensed to sell prescription and over-the-counter medicines. In addition, antimalarials are available at drug stores in the North-West region, which are typically owned and staffed by providers with no or few qualifications (Reynolds Whyte, van der Geest, & Hardon, 2002). In Enugu State, Nigeria, treatment for uncomplicated malaria is most frequently obtained at public health centres, pharmacies and drug stores (known as patent medicine stores) (Onwujekwe et al., 2005). Malaria diagnostic testing is not widely available at the primary care level and public facilities are staffed by nurses, community health officers and extension workers. For-profit pharmacies and drug stores are formally recognised in the health system and have professional associations. Licensed pharmacies are required to have a qualified pharmacist, while patent medicine dealers are not required to have specific qualifications or

training (Okeke, Uzochukwu, & Okafor, 2006) and are formally restricted from selling prescription-only medicine.

Survey data

Data on providers' stated preference for treating uncomplicated malaria were obtained in stratified multi-stage cluster surveys conducted at selected facilities in the study sites between July and December 2009 (Mangham et al., 2012, 2011). The sampling of geographic areas and facilities was undertaken separately for each country, based on an enumeration of facilities conducted in March–May 2009. At selected facilities a patient exit survey, a provider survey and a facility audit were conducted. Sample size calculations were undertaken for the patient exit survey and sought to determine the proportion of patients supplied ACT, with a given level of precision (Mangham et al., 2012, 2011). The primary outcome was the proportion of individuals reporting seeking treatment for a fever that were supplied (prescribed or received) an ACT. In Cameroon a survey sample of 12 patients per public facility was calculated to estimate the primary outcome with a prevision of +/−8.6%, and eight patients per mission facility and medicine retailer was calculated to estimate the primary outcome with a precision of +/− 6.2% (Mangham et al. 2012). In Nigeria, a survey sample of 20 patients per public facility was calculated to estimate the primary outcome with a precision of +/− 13%, while 14 patients per medicine retailer allows the primary outcome to be calculated with a precision of +/− 6.6% (Mangham et al. 2011). All of these calculations assume the intra-cluster correlation in treatment between facilities was 0.3. These precision estimates differ given the different sample sizes per type of facility and assume a prevalence of 50% for the primary outcome.

Table 1
Dependent and explanatory variables.

Variable	Coding	Proportion
Dependent		
Stated Preference: ACT is best type of AM for uncomplicated malaria	Yes (1) No (0)	0.69
Explanatory		
Level 1: Provider ($N = 518$)		
Remuneration method:	Fixed Salary employee (1) Sales-related as owns facility (0)	0.81
Works at other facilities:	Yes (1) No (0)	0.03
Reports patients usually ask for ACT:	Yes (1) No (0)	0.52
Knows ACT is recommended:	Yes (1) No (0)	0.61
Has access to guidelines:	Yes (1) No (0)	0.28
Attended malaria training in past 3 years:	Yes (1) No (0)	0.36
Cadre:	Doctor (1)	0.06
	Nurse or Midwife (2)	0.16
	Nurse Assistant (3)	0.05
	Health Extension Worker (4)	0.16
	Pharmacy or laboratory technician (5)	0.18
	No formal qualifications (PMD or attendant) (0)	0.37
Years worked at facility:	<1year (0)	0.18
	1–4 years (1)	0.34
	5–10 years (2)	0.32
	11 + years (3)	0.16
Level 2: Facility ($N = 245$)		
Facility Ownership:	Non-profit Public/ Mission (1) Private-for-profit Drug Retailer (0)	0.46
AM supplied by drug company representative	Yes (1) No (0)	0.10
Level 3: Area ($N = 36$)		
Density of facilities:	Low (<10 per area) (0)	0.22
	Medium (10–19 per area) (1)	0.37
	High (20 + per area) (2)	0.41
Residence	Urban (1) Rural (0)	0.72
Country:	Cameroon (1) Nigeria (0)	0.71

In each country, geographic areas were randomly selected, stratified by site. Facilities dispensing antimalarials were then selected based on the number and distribution of facilities in each area. In both countries, all public primary care facilities were included and pharmacies and drug stores were randomly selected with probability proportionate to their number in the local area. In Cameroon, all district hospitals and mission facilities in the selected areas were also included since they were an important source of treatment in Yaoundé and Bamenda (though not a major source of treatment in the Nigerian study sites). The provider survey was undertaken at all facilities selected for the patient exit survey and individually administered by trained fieldworkers to all providers that prescribe or dispense medicines, were available at the time of the survey and gave informed consent. Most facilities had two or three providers who prescribed or dispensed treatment, though the number ranged from one to twelve. In addition, one provider in each facility completed the facility survey.

Provider and facility questionnaires were administered to obtain data on provider and facility characteristics, and the health care available for febrile illness. Providers were asked about their pre-service and in-service training, access to guidelines, knowledge of recommended treatment, and preference over different antimalarials. Providers were asked to state their preference over alternative antimalarials prior to questions on training, guidelines and malaria treatment policy to avoid framing bias that could arise by referring first to the recommended antimalarial. The questionnaires were developed specifically for the study and pre-tested at facilities not selected for the survey. Site co-ordinators monitored and supervised data collection. Data were independently double-entered and verified using Microsoft Access 2007 (Microsoft Inc., Redmond, Washington). Data entry errors were corrected to ensure consistency with the original form.

Dependent and explanatory variables

The dependent variable was a binary outcome derived from the question "which antimalarial do you think is the best for treating patients with uncomplicated malaria?". Providers could respond by stating a generic or brand name. Each response was recorded and subsequently coded: ACT, artemisinin-monotherapy, chloroquine, sulphadoxine-pyrimethamine, quinine, other, and don't know. No provider refused to answer this question. The dependent variable was 1 if the provider responded ACT and 0 otherwise.

Explanatory variables occurred at three levels (Table 1). Provider attributes were at level-1, and included the method of remuneration, based on whether the individual was the owner or an employee. As providers may yield income from patients obtaining treatment at a private facility, a variable was included for whether providers work elsewhere, though we recognized providers may be unwilling to disclose information relating to their financial interests. A binary variable was used to identify providers who reported their patients usually ask for an ACT since providers may derive satisfaction from fulfilling patient expectations. Several variables indicated providers' information about ACT, including whether or not the provider knew ACT was recommended by the

government, had access to a copy of the malaria treatment guidelines, and attended malaria training in the past three years. Providers' cadre was included since pre-service training may have affected the information they had available, and we controlled for the number of years worked at a facility.

At the facility level (level-2), a variable indicated whether providers work in a non-profit organization (owned by the government or mission) or in a private-for-profit organization. Facility ownership may affect the income incentive of providers, or their employers, though may also reflect differences in the information available and the institutional environment. Whether a facility received antimalarials from drug company representatives was also included since they may use financial incentives, such as discounts or commission, to encourage the sale of specific products, as well as share information and promotional materials on their products. It was expected that drug company representatives would promote ACT over other types of antimalarials.

Area-level (level-3) variables included whether the provider worked in an urban or rural setting, the density of health facilities in the locality, and the country. Random effects were used to capture the degree to which providers' preference were clustered since it was hypothesized that providers working within the same facility may have similar preferences because they operate within the same institutional context, share information, learn from others and conform to social norms. Providers' social network may also extend to others working in the local area, and for the same reasons may have similar preferences over different treatments.

Empirical strategy

The first step was to analyze stated preference using an intercept-only model in order to determine the suitability of a multilevel model over a single-level model and whether to adopt two or three levels (Hox, 2010). Likelihood ratio tests were used to compare model fit. The proportion of the total variance that was attributable to each level of the model was estimated using the variance partition coefficient (VPC). The VPC is similar to the intra-cluster correlation, though used when the dependent variable is discrete. The VPC was calculated as:

$$\mathrm{VPC}_{\mathrm{facility}} = \left(\sigma^2_{\mathrm{facility}}/\sigma^2_{\mathrm{facility}} + \sigma^2_{\mathrm{area}} + 3.29\right)$$

and

$$\mathrm{VPC}_{\mathrm{area}} = \left(\sigma^2_{\mathrm{area}}/\sigma^2_{\mathrm{facility}} + \sigma^2_{\mathrm{area}} + 3.29\right)$$

where the variance at level 1 was the variance of the standard logistic distribution ($\pi^2/3 = 3.29$) (Hox, 2010). Larger values of the VPC ($0 < \mathrm{VPC} < 1$) indicate greater potential for a level to influence the value of the dependent variable.

The second step was to estimate a random-intercept model with all explanatory variables at provider, facility and area levels that were hypothesized may influence providers' preference over alternative antimalarials. The VPC showed the proportion of the total variance attributable to each level that remained having incorporated explanatory variables. The third step was to examine the random-intercept model with interaction terms. Interactions were investigated for combinations of explanatory variables for which it was hypothesized there may be a joint effect. Interactions between facility ownership and information variables were examined since access to guidelines and training may depend on the type of facility. Access to guidelines, attendance at training, cadre, and whether supplies were received from drug company representatives were each interacted with knowledge that ACT was the recommended treatment. Finally, interactions were used to investigate whether provider, facility and area characteristics have a country-specific effect. Interactions were added to the random-intercept model one at a time. The statistical significance was assessed using the Wald test and the likelihood ratio test. Interaction terms were retained in the model if they were significant at the 10% level.

Multilevel models were estimated using adaptive quadrature to approximate the marginal likelihood by numerical integration in Stata 11.2 (StataCorp, 2009). Although computationally demanding, estimation with numerical integration was the preferred method as there were small cluster sizes at level-2 and quasi-likelihood methods would be susceptible to bias (Hox, 2010; Rodriguez & Goldman, 1995). Bootstrap and Bayesian methods are also recommended for small cluster sizes (Hox, 2010), though numerical integration was used as it is well-suited for relatively simple models with binary outcomes (Steele, 2009). Model stability was assessed by comparing the model estimates from adaptive quadrature with seven integration points, with those generated by a model using a higher number of integration points.

Several methods were used to assess model specification. The assumption of normally distributed residuals was examined using normal plots of standardized level-2 and level-3 residuals. Multicollinearity was assessed using the variance inflation factor, since large inflation factors show evidence of correlation among explanatory variables. The deviance, which equals minus two times the log likelihood, was reported and is an indication of goodness of fit. The Ramsey RESET test was also used as this is a general test for problems associated with the functional form (Jones, 2007). It involves taking the square of the predicted value and re-estimating the model with this as an additional explanatory variable. If the model is well specified the new variable will not be significant (Rice, 2000). The RESET test can, therefore, identity specification errors associated with omitted variable bias, simultaneity bias or measurement error if they lead to nonlinearity in the relationship between the dependent and explanatory variables. Finally, the model was estimated with and without the explanatory variable for knowing ACT was recommended to investigate the simultaneity bias that would arise if providers' preference over alternative antimalarials was determined at the same time they acquired knowledge of the recommended treatment.

The final results were validated by re-analysing the final model using Bayesian Markov Chain Monte Carlo (MCMC) estimation methods in MLwiN 2.25 (Rasbash, Charlton, Browne, Healy, & Cameron, 2012). The MCMC estimation used uninformative priors and starting values based on second-order penalized quasi-likelihood (PQL2) generated using restricted iterative generalized least-squares (RIGLS) (Browne, 2012). Convergence of the Markov chain was assessed graphically and by checking that similar posterior distribution summaries were achieved with different starting values. Again, goodness of fit was assessed using the RESET Test.

Results

The study was based on a population of 518 providers working at 245 facilities in 36 geographic areas in Cameroon and Nigeria. Of the 540 providers invited to participate in the survey, 9 refused to give consent, and 13 had missing data for at least one of the model variables. The analysis was conducted on complete cases as bias from missing responses was expected to be small.

The study population included 240 providers from public and mission facilities and 278 providers from pharmacies and drug stores, with providers in Cameroon representing 71% of the study population (Table 1). The majority (81%) of providers were employees and less than 3% reported working at other facilities. Just

over half (52%) of the providers reported ACT was the antimalarial most often requested by patients. Almost two-thirds (61%) of providers stated ACT was the antimalarial recommended by the government, though only 36% of providers attended malaria training in the past 3 years, and 28% of providers had access to a copy of the national malaria treatment guidelines. The providers spanned a range of cadres, though the largest group (37%) were patent medicine dealers and sales attendants without formal health qualifications. The length of time providers had worked at the current facility ranged from less than one year to more than 11 years.

Overall 69% (359/518) of providers stated ACT was the best treatment for uncomplicated malaria. Other responses included quinine and artemisinin-monotherapy, which are recommended for severe cases of malaria, and sulphadoxine-pyrimethamine, which was the former first-line therapy (Table 2).

Table 3 presents the two-way relationship between providers' stated preference and their knowledge of the antimalarial recommended by the government for uncomplicated malaria. Overall, 46% (236/518) of all providers surveyed reported ACT was their preferred treatment and knew it was recommended. There were 24% (123/518) of providers who stated a preference for ACT and did not know it was the recommended treatment, but also 16% (82/518) of providers who knew ACT was the recommended treatment and did not report this was the best treatment.

The degree of variability in providers' preference that can be attributed to facility and area levels was examined using intercept-only models to determine whether to use a two-level and three-level logistic regression. Significant random effects were found at both levels, and the deviance and likelihood ratio tests indicate that the three-level model (Model 1 in Table 4) was superior to the two-level models (Appendix A).

The odds ratios generated by the three-level logistic regression containing explanatory variables are presented in Table 4. Model 2 included all explanatory variables except the variable "Knows ACT is the recommended treatment", while Model 3 included all explanatory variables. As expected, the introduction of the explanatory variables reduced the residual variability within facilities and areas (compared to Model 1). Model estimates were stable to three decimal places. The RESET test indicated Models 2 and 3 were well specified and there was no evidence of multicollinearity or simultaneity bias. Model 3 was preferred, based on model diagnostics, and was used to investigate interaction terms, though none were found to significantly improve the fit of the model.

The final model (Model 3) showed that providers' stated preference for an ACT was not significantly associated with income incentives, as measured by the method of remuneration and whether they worked elsewhere. Providers were, however, twice as likely to state a preference for ACT if this was the type of antimalarial most often requested by their patients. Knowing ACT was the recommended treatment was also a significant determinant, with the odds of stating a preference for ACT 2.5 times greater amongst providers who reported ACT was recommended by the government. The results also showed the effect of malaria training was of borderline significance, and access to malaria treatment guidelines did not significantly predict a preference for ACT. Providers' preference for ACT was significantly lower at non-profit facilities, and the odds of preferring an ACT was 4 times greater if the facility obtained antimalarials from drug company representatives. Random effects remained relatively large after the inclusion of explanatory variables indicating there was unexplained variability attributable to the facility and local area.

The sensitivity of the results to the estimation method was investigated by reanalysing the final model in MLwiN 2.25 using PQL2 generated using RIGLS and then by running Bayesian MCMC using non-informative priors. The results were similar and are provided in Appendix B.

Table 3
Two-way relationship between knowledge of guidelines and preference for ACT.

		Stated ACT was the best treatment for uncomplicated malaria					
		Yes		No		Total	
		N	%	*N*	%	*N*	%
Knows ACT is recommended for uncomplicated malaria	Yes	236	45.6	82	15.8	318	61.4
	No	123	23.8	77	14.9	200	38.6
	Total	359	69.3	159	30.7	518	100.0

Discussion

The majority of providers stated a preference over different types of antimalarials, with just 8% unable or unwilling to state which antimalarial they prefer for treating uncomplicated malaria. 69% of providers had a preference for ACT, though alternatives included quinine and artemisinin-monotherapy, which should be reserved for cases of severe malaria, and sulphadoxine-pyrimethamine, which was the former first-line treatment.

Method of remuneration, access to additional employment income, and facility ownership were used as proxies to investigate the effect of financial incentives on providers' preference. Of these variables, facility ownership had a significant effect, with providers at for-profit facilities more likely to prefer an ACT over other antimalarials. Further research would be required, however, to ascertain whether the effect of facility ownership reflects income incentives or other institutional characteristics.

We found a positive association between providers who stated a preference for ACT and providers who reported ACT was the antimalarial their patients most often request. This suggests that providers were more likely to prefer ACT if their patients prefer (or perceive their patients prefer) ACT, though the interpretation is

Table 2
Providers' stated preference for treatment of uncomplicated malaria.

	Country				Type of facility				All	
	Cameroon		Nigeria		Public/Mission		Medicine retailer			
	N = 369	%	*N* = 149	%	*N* = 240	%	*N* = 278	%	*N* = 518	%
ACT	266	72.1	93	62.4	156	65.0	203	73.0	359	69.3
Artemisinin monotherapy	2	0.5	23	15.4	7	2.9	18	6.5	25	4.8
Chloroquine	0	0.0	10	6.7	8	3.3	2	0.7	10	1.9
Quinine	63	17.1	0	0	44	18.3	19	6.9	63	12.2
Sulphadoxine-pyrimethamine	1	0.3	17	11.4	7	2.9	11	4.0	18	3.5
Other AM	0	0.0	4	2.7	2	0.8	2	0.7	4	0.8
No preference	37	10.0	2	1.4	16	6.7	23	8.3	39	7.5

Table 4
Factors predicting providers' stated preference for ACT.

Fixed effects		MODEL 1: Intercept-only model		MODEL 2: With all explanatory variables except knowledge			MODEL 3: With all explanatory variables		
				OR	SE	*P*-value	OR	SE	*P*-value
Level 1: Provider									
Remuneration method:	Fixed salary			1.46	0.712	0.434	1.63	0.794	0.320
	Sales related			Ref			Ref		
Additional employment:	Yes			1.94	1.928	0.507	2.04	2.054	0.477
	No			Ref			Ref		
Reports patients usually ask for ACT:	Yes			2.17	0.737	0.023	2.08	0.710	0.033
	No			Ref			Ref		
Has access to guidelines:	Yes			2.06	0.901	0.100	2.04	0.900	0.106
	No			Ref			Ref		
Has attended malaria training:	Yes			1.96	0.662	0.047	1.88	0.638	0.061
	No			Ref			Ref		
Knows ACT is recommended:	Yes			–	–	–	2.54	0.824	0.004
	No						Ref		
Cadre:	Doctor			1.18	0.907	0.127	0.79	0.613	0.147
	Nurse or Midwife			2.21	1.308		1.96	1.160	
	Nurse Assistant			1.37	1.047		1.16	0.888	
	Extension Worker			0.72	0.392		0.61	0.336	
	Pharmacist/technician			0.58	0.296		0.55	0.281	
	No qualifications			Ref			Ref		
Years worked at facility:	<1 year			Ref		0.440	Ref		0.406
	1–4 years			0.81	0.373		0.74	0.346	
	5–10 years			0.53	0.257		0.50	0.241	
	11 + years			0.95	0.555		0.88	0.517	
Level 2: Facility									
Ownership:	Public/Mission			0.40	0.248	0.140	0.33	0.205	0.075
	Drug Retailer			Ref			Ref		
AM supplied by drug company rep	Yes			5.77	4.858	0.037	4.83	4.048	0.060
	No			Ref			Ref		
Level 3: Area									
Density of facilities:	Low			Ref		0.809	Ref		0.872
	Medium			0.99	0.800		0.97	0.798	
	High			1.58	1.514		1.43	1.397	
Residence	Urban			1.24	1.030	0.793	1.44	1.225	0.666
	Rural			Ref			Ref		
Country	Cameroon			1.99	1.281	0.283	1.81	1.188	0.366
	Nigeria			Ref			Ref		
Random Effects		Estimate	SE	Estimate	SE		Estimate	SE	
Residual variance	Level-2: σ^2 (u_j)	2.94	1.224	2.64	1.206		2.486	1.170	
	Level-3: σ^2 (v_{jk})	1.66	0.862	1.29	0.768		1.427	0.817	
VPC:	Level-2: facility	0.377		0.366			0.345		
	Level-3: area	0.209		0.179			0.198		
Diagnostics									
Deviance (−2*llh)		577.074		536.568			527.868		
RESET		–		0.249			0.278		

uncertain. For example, providers may derive utility from selecting ACT, either because they have an intrinsic motivation to satisfy their patients, or because they want to maintain a good reputation and secure future income. Local competition would also be expected to affect the latter, though there was no evidence that the density of facilities within an area had an effect on providers' preference. Alternatively, it could be argued that the association reflects an omitted exogenous factor, such as a public health campaign, that had an influence on both providers' and patients' preference. Either way, knowing that preferences were positively associated may be useful for designing strategies to improve providers' practice or influence patients' demand.

It was encouraging, and not unexpected, to find providers who knew ACT was the recommended treatment for uncomplicated malaria were significantly more likely to state a preference for ACT. Moreover, providers that had attended malaria training in the past three years were more likely to state a preference for ACT (at the 10% level of significance) having controlled for their knowledge. This suggests training can have an effect that goes beyond informing providers about treatment policy and can influence their preferences over different treatments. Access to malaria treatment guidelines had no significant effect on providers' preference, even in the model which did not control for their knowledge. This suggests having access to guidelines is not a good predictor that providers will supply the recommended treatment. The results imply, therefore, that the nature of communication can have an important influence on providers' preference and further research on this may help to identify effective strategies for educating providers about changes in health policy and clinical guidelines.

The results suggest an agency relationship in which drug company representatives (drug reps) influence providers' preference over antimalarials, though it is also possible that obtaining medicines from drug reps may proxy for unobserved organizational attributes. If there is a direct effect, then this could reflect explicit incentives, such as sales commission, or an information effect from marketing strategies that promote the use of ACT. The interaction between knowledge that ACT is recommended by the government and use of drug reps did not significantly improve the model, which suggests drug reps have an effect that is independent of providers' knowledge of the recommended treatment, though the sample from which to detect interaction effects was limited. In any case, there may be merit in exploring the potential to engage drugs reps

in strategies to change providers' preference and improve their practice. There are few examples in the empirical literature, though a vendor-to-vendor education programme in Kenya, in which wholesalers were trained to supply providers at drug shops and kiosks with information and job aids on malaria treatment, was found to have a moderate effect (Tavrow, Shabahang, & Makama, 2003).

There is evidence that providers' preference for ACT was similar among colleagues within a facility and among providers within a local area. Although the level-2 and level-3 residual variance was reduced by the inclusion of explanatory variables, it remained significant in the final model and the VPC indicated that a substantial proportion of the unexplained heterogeneity can be attributed to facility and area factors. This may reflect the influence of institutional and behavioural factors, such as networks and social norms, though we are cautious in drawing conclusions since average cluster size was small and the size of the random effect depends on the estimation method. Further research would be beneficial to explore how preferences may be shaped or constrained by colleagues, and how strategies to improve providers' practice could utilize networks or promote social norms.

There are some methodological limitations to our work. First, there is uncertainty in how providers understood the question used to elicit their preference over alternative antimalarials. The question "which antimalarial do you think is best for treating uncomplicated malaria?" followed questions on the type of antimalarial usually supplied and type of antimalarial patients' prefer. It is possible, however, that some providers understood the question to be asking about the efficacy of different antimalarials, or aspects of the treatment regimen, such as the number of tablets, or potential side effects. If this were the case, then we would expect the effect of income and satisfaction on their choice of treatment to be reduced as providers focus on other attributes. Qualitative methods may be useful to probe what providers understand by 'best' in this context. Moreover, it is possible that our direct method of eliciting stated preference encouraged providers to give a socially acceptable response and report what they know is recommended. More sophisticated methods, such as discrete choice experiments, are often used and designed to overcome this framing bias. The direct method was, however, practical given that the formative research sought to examine multiple questions about the treatment of uncomplicated malaria, and was also feasible since ACT was not a new product.

Second, the sample size was restricted because the provider survey was conducted as part of a larger study principally designed to examine the treatment supplied to febrile patients. None of the interactions included in the model were found to have a significant effect, and this may be due to the limited number of observations. Furthermore, the average cluster size at level-2 was small since the survey involved many primary care facilities and medicine retailers that operate with few, sometimes lone, providers. In this setting, the small cluster sizes could not have been overcome and they were an important consideration for the statistical analysis. Correlation between providers within a facility was empirically investigated to determine whether facility should be included as a level in the model. There remained evidence of clustering at the facility-level (as well as the area-level) once explanatory variables were added to the model. In addition, the robustness of the study results to the estimation method was investigated because of the small cluster sizes at the facility-level. The alternative methods generated comparable results, though the small cluster sizes may have explained the differences in the magnitude of estimated coefficients. This is consistent with findings from a recent study which showed how the choice of estimation method and software can affect the results of multilevel logistic regression when the data are limited and the average cluster size is small (Li, Lingsma, Steyerberg, & Lesaffre, 2011).

Conclusions

Ensuring providers prefer to supply the recommended type of antimalarial is an important prerequisite for ensuring patients with uncomplicated malaria receive the most effective treatment. Providers were asked which antimalarial they think is the best for treating patients with uncomplicated malaria to elicit which antimalarial providers prefer to supply when not constrained by the resources available or patients' ability to pay, and we investigated who or what influences their preference. The type of antimalarial providers prefer not only depended on their knowledge of the clinical guidelines, but also reflected their perceptions of what patients prefer, and the influence of drug company representatives, their colleagues and other providers in the locality. These findings support the premise that providers are agents serving multiple principals. Understanding who and what influences providers' stated preference over alternative antimalarials is useful for identifying strategies to encourage providers to supply effective malaria treatment. The influence of multiple actors on the providers' choice of treatment emphasizes the need to communicate changes in drug policy not only to providers but also to suppliers and local communities. Moreover, our findings suggest that public health interventions would be more effective if they target groups of providers, rather than individuals, and promote a supportive environment since providers working within a facility or local area have similar preferences.

Ethical approval

Ethical approval was obtained from the ethics committees of the London School of Hygiene and Tropical Medicine (5429), University of Nigeria (03.11.08) and Cameroon National Ethics Committee (030/CNE/DNM/09).

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Appendix. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.socscimed.2013.12.024

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Appendix

Appendix A: Comparing two-level and three-level intercept-only models

		Two-level intercept-only model: facility		**Two-level intercept-only model: area**		**Three-level intercept-only model: facility + area *(Model 1)***	
		Estimate	SE	Estimate	SE	Estimate	SE
Random Effects							
Residual variance	Level-2: σ^2 (u_j)	4.304***	1.550	-		2.944***	1.224
	Level-3: σ^2 (v_{jk})	-		1.173**	0.476	1.657**	0.862
VPC:	Level 2: facility	0.567		-		0.377	
	Level 3: area	-		0.263		0.209	
Diagnostics							
Deviance (-2*llh)		589.212		599.626		577.074	

*** significant at 1% level, ** significant at 5% level, * significant at 10% level

Appendix B: Final model using different estimation methods

Estimation Method		Numerical Integration ***(Model 3)***		PQL2 (RIGLS)†		MCMC‡	
Fixed Effects		OR	SE	OR	SE	OR	SE
Level 1: Provider							
Remuneration method:	Fixed salary	1.625	0.794	1.607	0.801	1.915	1.182
	Sales related	Ref		Ref		Ref	
Additional employment:	Yes	2.044	2.054	1.938	2.076	5.052	11.260
	No	Ref		Ref		Ref	
Reports patients usually ask for ACT:	Yes	2.075**	0.710	2.079**	0.749	2.472**	0.985
	No	Ref		Ref		Ref	
Has access to guidelines:	Yes	2.041	0.900	2.096	0.983	2.596	1.566
	No	Ref		Ref		Ref	
Has attended malaria training:	Yes	1.884*	0.638	1.881*	0.679	2.116*	0.843
	No	Ref		Ref		Ref	
Knows ACT is recommended:	Yes	2.543***	0.824	2.569***	0.896	3.176***	1.240
	No	Ref		Ref		Ref	
Cadre:	Doctor	0.787	0.613	0.742	0.593	0.860	0.785
	Nurse or Midwife	1.958	1.160	1.901	1.199	2.465	1.731
	Nurse Assistant	1.160	0.888	1.207	0.971	1.647	1.673
	Extension Worker	0.612	0.336	0.579	0.335	0.619	0.423
	Pharmacist / technician	0.548	0.281	0.506	0.270	0.504	0.291
	No qualifications	Ref		Ref		Ref	
Years worked at facility:	<1 year	Ref		Ref		Ref	
	1 – 4 years	0.740	0.346	0.652	0.293	0.655	0.334
	5 – 10 years	0.495	0.241	0.459	0.216	0.467	0.251
	11+ years	0.879	0.517	0.884	0.495	1.083	0.721
Level 2: Facility							
Ownership:	Public/Mission	0.329*	0.205	0.314*	0.213	0.349*	0.240
	Drug Retailer	Ref		Ref		Ref	
AM supplied by drug company rep	Yes	4.833*	4.048	4.614*	4.394	17.346**	33.293
	No	Ref		Ref		Ref	
Level 3: Area							
Density of facilities:	Low	Ref		Ref		Ref	
	Medium	0.969	0.798	0.875	0.814	1.956	2.413
	High	1.429	1.397	1.156	1.272	2.398	2.925
Residence	Urban	1.443	1.225	1.390	1.373	1.945	1.729
	Rural	Ref		Ref		Ref	
Country	Cameroon	1.809	1.188	1.570	1.157	2.354	2.052
	Nigeria	Ref		Ref		Ref	
Random Effects		Estimate	SE	Estimate	SE	Estimate	SE
Residual variance	Level-2: σ^2 (u_j)	2.486**	1.170	3.060***	0.818	5.346**	2.507
	Level-3: σ^2 (v_{jk})	1.427*	0.817	2.136**	0.903	3.048*	1.779
VPC:	Level 2: facility	0.345		0.361		0.471	
	Level 3: area	0.198		0.252		0.284	
Diagnostics							
RESET		0.278		0.259		0.357	

*** significant at 1% level, ** significant at 5% level, * significant at 10% level

† Burn-in length=2000, Monitoring chain length=200000, thinning=10

‡ Difference in random effects is likely to be caused by the estimation technique – MCMC can have a positive bias because does not allow negative variances

Chapter 7

Research Paper IV: Mind the Gap: knowledge and practice of providers treating uncomplicated malaria at public and mission health facilities, pharmacies and drug stores in Cameroon and Nigeria

The previous chapters have described the problems with malaria diagnosis and treatment in Cameroon, and the influences on providers' stated preferences for treating uncomplicated malaria. This research paper examines the determinants of providers' revealed preference (i.e. their practice) for treating patients with symptoms of uncomplicated malaria, and focuses on whether providers' choice of antimalarial adheres to the malaria treatment guidelines.

This paper is one of the first to focus on knowledge-practice gap in the context of malaria treatment. The analysis used exit survey data from the subset of patients who relied on the provider to select treatment and were supplied an antimalarial. Exit survey responses then were linked to the individual provider who supplied treatment. The findings demonstrated providers' decision to supply ACT was not significantly associated with their knowledge of the first-line antimalarial in either Cameroon or Nigeria. However, stated preferences were important, and I concluded it would be important to design interventions that focus on changing providers' preference in addition to their knowledge. Thus, the findings from this study informed the development of interventions in Cameroon and resulted in a trial which allowed us to test the hypothesis that interactive training targeting providers' practice would be more cost-effective than conventional approaches to training.

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Contribution: I was the lead author and responsible for the conception, analysis and preparation of the manuscript. Co-authors commented on a full draft of the research paper, and read and approved the final draft.

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Mind the Gap: knowledge and practice of providers treating uncomplicated malaria at public and mission health facilities, pharmacies and drug stores in Cameroon and Nigeria

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Abbreviated title

Providers' practice and malaria guidelines

Keywords

Provider practice; malaria; Cameroon; Nigeria; multilevel analysis; multiple imputation

Key messages

- Providers' choice of antimalarial was not determined by their knowledge of the malaria treatment guidelines
- Providers make treatment decisions based on their preference, attributes of the patient and resources available
- Strategies to disseminate clinical guidelines need to identify mechanisms that change preference and practice in the local setting

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Word count

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Abstract

Background:

Artemisinin Combination Therapy (ACT) has been the first-line treatment for uncomplicated malaria in Cameroon since 2004 and Nigeria since 2005, though many febrile patients receive less effective antimalarials. Patients often rely on providers to select treatment, and interventions are needed to improve providers' practice and encourage them to adhere to clinical guidelines.

Methods

Providers' adherence to malaria treatment guidelines was examined using data collected in Cameroon and Nigeria at public and mission facilities, pharmacies and drug stores. Providers' choice of antimalarial was investigated separately for each country. Multilevel logistic regression was used to determine whether providers were more likely to choose ACT if they knew it was the first-line antimalarial. Multiple imputation was used to impute missing data that arose when linking exit survey responses to details of the provider responsible for selecting treatment.

Results

There was a gap between providers' knowledge and their practice in both countries, as providers' decision to supply ACT was not significantly associated with knowledge of the first-line antimalarial. Providers were, however, more likely to supply ACT if it was the type of antimalarial they prefer. Other factors were country-specific, and indicated providers can be influenced by what they perceived their patients prefer or could afford, as well as information about their symptoms, previous treatment, the type of outlet, and availability of ACT.

Conclusions

Public health interventions to improve the treatment of uncomplicated malaria should strive to change what providers prefer, rather than focus on what they know. Interventions to

improve adherence to malaria treatment guidelines should emphasize that ACT is the recommended antimalarial, and it should be used for all patients with uncomplicated malaria. Interventions should also be tailored to the local setting, as there were differences between the two countries in providers' choice of antimalarial, and who or what influenced their practice.

Introduction

Clinical guidelines are systematically developed statements to assist providers' decision-making on the appropriate care for specific clinical conditions (Field et al. 1992). By establishing common standards for diagnosis and treatment, they are central to efforts to improve the quality of health care and can expedite the introduction of new health technologies (Cabana et al. 1999; Woolf et al. 2012). Each year governments invest considerable resources in the development and distribution of clinical guidelines to ensure providers have access to the latest scientific evidence. Despite these efforts, there are challenges translating evidence into practice and patients often receive substandard care (Grol & Grimshaw 2003). Moreover, several studies on the performance of health care providers have identified a knowledge-practice gap, which suggests that public health interventions to disseminate clinical guidelines may not be sufficient to change providers' practice (Das et al. 2008; Leonard & Masatu 2010).

Over the past decade, national malaria treatment policies have been revised in all African countries to establish artemisinin combination therapy (ACT) as the first-line treatment for uncomplicated malaria. However, uptake of ACT has been slow in some countries and studies undertaken in Cameroon and Nigeria in 2009, four years after ACT became the recommended first-line treatment, showed that many patients treated for malaria did not receive an ACT (Mangham et al. 2012; Mangham et al. 2011). The situation in southeast Nigeria was of particular concern as only 22% of febrile patients seeking treatment at primary health centres, pharmacies and drugs stores received an ACT (Mangham et al. 2011). These studies also showed that providers were routinely responsible for the choice of treatment at the public and mission facilities and advised on treatment in more than a third of cases at pharmacies and drug stores (Mangham et al. 2012; Mangham et al. 2011).

Interventions to improve malaria diagnosis and treatment have traditionally focused on ensuring providers are informed about policy changes and have used training and job aids to

improve their knowledge of the clinical guidelines (Smith et al. 2009). However, evidence from intervention and cross-sectional studies show access to in-service training, guidelines and job aids often have a limited effect in changing providers' practice (Osterholt et al. 2006; Rowe et al. 2000; Rowe et al. 2003; Smith et al. 2009; Zurovac et al. 2005; Zurovac et al. 2008a; Zurovac et al. 2004; Zurovac et al. 2008b).

It is timely to explore the relationship between providers' practice in treating uncomplicated malaria and their knowledge of the clinical guidelines, as malaria treatment guidelines undergo further revision to advise on the use of malaria rapid diagnostic tests (RDTs) and dissemination strategies are being developed. Moreover, early evidence suggests that malaria RDTs will only be cost-effective if providers adhere to the malaria treatment guidelines: testing before treatment should reduce the number of febrile patients consuming antimalarials that they do not need, but this requires providers to adhere to the test results when making treatment decisions (Lubell et al. 2008).

In this paper, we examine providers' adherence to malaria treatment guidelines at public and mission facilities, pharmacies and drug stores in urban and rural areas of Cameroon and Nigeria prior to the introduction of malaria RDTs. We investigate what influences providers' choice of antimalarial, and assess whether providers were more likely to select an ACT if they knew it was the first-line treatment for uncomplicated malaria. This analysis was undertaken to guide the design of interventions to support the roll out of malaria RDTs and the dissemination of updated clinical guidelines. The effectiveness and cost-effectiveness of the interventions are being evaluated in cluster-randomized trials at selected sites in Cameroon and Nigeria (Wiseman et al. 2012a; Wiseman et al. 2012b).

Methods

Study Setting

The study was conducted at public and mission health facilities, pharmacies and drug stores in urban and rural areas of Cameroon and Nigeria, where cluster-randomized trials would be conducted to evaluate interventions to support the introduction of malaria RDTs. In Cameroon, the two sites were Yaoundé in the Centre region, which is urban and predominately French-speaking, and Bamenda and seven rural districts in the Northwest region where English and pidgin-English are widely spoken (Mangham et al. 2012). In Nigeria, both sites were in Enugu State and included urban communities in Enugu, and rural communities in Udi (Mangham et al. 2011).

Malaria is endemic in all four sites and occurs throughout the year. At the time the study was conducted, the national malaria treatment guidelines in both countries advised that malaria should be suspected in all patients presenting with a fever or history of fever, patients should be tested prior to treatment where malaria testing was available, but in the absence of a confirmed diagnosis presumptive treatment for uncomplicated malaria was recommended (Ministry of Health of the Federal Republic of Nigeria 2005; Ministry of Public Health of the Republic of Cameroon 2008). ACT was the first-line treatment for uncomplicated malaria (in all patients except pregnant women), and was typically more expensive than other types of antimalarial. In all outlets patients pay for the treatment they receive, though there were exemptions for children under five and pregnant women attending public facilities.

In Cameroon and Nigeria, malaria is routinely treated using antimalarials obtained at primary care facilities, outpatient departments, pharmacies, and drug stores. In the public and mission facilities in Cameroon, malaria cases are treated by doctors, nurses and pharmacists, and some facilities have a laboratory technician able to conduct malaria microscopy. In Enugu State, malaria is often treated in primary health centres and health posts that do not offer malaria

testing and are staffed by nurses, and health extension workers. Medicine retailers were present in all study sites. In both countries, pharmacies are legally required to have a trained pharmacist in order to sell prescription-only and over-the-counter medicines, and they are more prevalent in urban areas. Drug stores, also known as patent medicine dealers, are formally recognized in the Nigerian health system and staff are eligible to sell over-the-counter medicines (including antimalarials) without any specific qualifications or training. In Cameroon, drug stores operate under a business licence in the Anglophone regions (which includes the Northwest region) and are staffed by providers with no or few health qualifications (Hughes et al. 2013).

Survey sampling and activities

Stratified cluster surveys were conducted with patients and caregivers exiting health facilities, pharmacies and drug stores and with providers working at these outlets between July and December 2009. Sample size calculations were undertaken separately for each country and sought to determine the proportion of febrile patients seeking treatment that were supplied an ACT, with a given level of precision (Mangham et al. 2012; Mangham et al. 2011). The sampling, conducted in March-May 2009, was based on an enumeration of outlets that regularly dispense antimalarials. In each country, geographic areas were randomly selected, stratified by site. Outlets dispensing antimalarials were then selected based on the number and distribution of outlets in each area. In both countries, all public primary care facilities were included and pharmacies and drug stores were randomly selected with probability proportionate to their number in the local area. In Cameroon, all district hospitals and mission facilities in the selected areas were also included because they were also an important source of treatment in Yaoundé and Bamenda.

Questionnaires were developed and pre-tested at outlets that were not included in the survey. The exit questionnaire collected data about the patient, previous treatment seeking, the consultation or interaction with the health care provider, and the treatment prescribed and

received. Individuals were eligible to complete the exit survey if they reported seeking treatment for a fever, either for themselves or another (who may or may not be present), the patient had no signs of severe malaria, and they gave informed written consent. Providers were surveyed to collect data on pre-service and in-service training, their knowledge of the national treatment guidelines, and their preference for treating patients with symptoms of uncomplicated malaria. All providers that prescribed or dispensed antimalarials, were available at the time of the survey, and gave informed written consent were eligible to participate. In addition, one provider at each outlet completed a questionnaire which asked about the services and medicines available, and the procurement of antimalarials. All questionnaires were individually-administered by trained fieldworkers working under the supervision of site coordinators. Data were double-entered and verified using Microsoft Access 2007 (Microsoft Inc., Redmond Washington) and data entry errors were corrected to ensure consistency with the original form.

Ethical Approval

Ethical approval was obtained from the ethics committees of the London School of Hygiene and Tropical Medicine (5429), Cameroon National Ethics Committee (030/CNE/DNM/09) and University of Nigeria (03.11.08).

Data Sources

Providers' choice of antimalarial was investigated using patient exit and provider survey data from Cameroon and Nigeria. Data analysis was undertaken separately for each country. Exit survey responses that fulfilled the following criteria were included: i) the patient or caregiver reported seeking treatment for a fever; ii) the patient was not pregnant or under six months of age; iii) the patient or caregiver did not request a specific medicine; iv) the patient had a presumptive or confirmed malaria diagnosis (i.e. patients with a negative malaria test result were excluded); and v) an antimalarial was prescribed or received (as shown in Figure 1).

Multilevel logistic regressions were used to investigate what factors influenced providers' choice of antimalarial. The dependent variable was a binary outcome that indicates whether or not the provider supplied an ACT (coded 1 if an ACT was prescribed or received, and 0 otherwise). This variable was derived from several questions about all medicines that were prescribed or received whilst at the health facility, pharmacy or drug store.

Explanatory variables include attributes of the provider, the patient, their interaction, and also the outlet in which the interaction took place (Table 1). To investigate the relationship between providers' knowledge and practice, the following provider attributes were included: whether providers knew an ACT was the recommended first-line treatment for uncomplicated malaria; their access to national malaria treatment guidelines; whether they had attended in-service training on malaria in the past three years; their highest level of pre-service health training; whether they state ACT to be best treatment for uncomplicated malaria; and whether they report ACT is the type of antimalarial their patients most often request. The last two were included because there may be a difference between providers' knowledge of the malaria treatment guidelines, the type of antimalarial they state they prefer, and the type of antimalarial they perceive their patients prefer.

It was also assumed that providers may select treatment based on the attributes of the patient or information obtained during the interaction. The explanatory variables included the following patient attributes: gender; age; household wealth (relative to others who sought treatment); the education of the patient or caregiver; whether treatment was sought within two days of the onset of fever; and whether previous treatment had been sought for this illness episode, including whether an antimalarial had been taken. In addition, relevant aspects of the provider-patient interaction were: whether the patient was examined; had a presumptive or confirmed malaria diagnosis; and whether the provider was told that the patient had diarrhoea or had been vomiting (as these symptoms may affect the suitability of different medicines).

Attributes of the outlet may also have some bearing on the treatment supplied, as contextual factors may constrain the providers' choice of treatment. Outlet attributes included in the model were: outlet type; availability of ACT; whether antimalarials were received from a drug company representative (whose promotional activities may be a source of information or influence); and whether the outlet was in an urban or rural area.

Relational Databases

To investigate the relationship between providers' knowledge and practice it was necessary to prepare a database that linked patient exit responses i) to information about the outlet and ii) to the individual provider who was responsible for selecting treatment. The outlet at which the exit survey was conducted was known for all patients. Patients and caregivers were asked to describe all the providers that were involved in supplying care, and fieldworkers recorded the unique code that identified each provider. When care was supplied by a single provider then it was straightforward to link the patient and provider data if the provider had completed the survey. When care was supplied by two or more providers and the cadre of all providers was known, then it was assumed the more senior provider decided which treatment to supply. For example, if care was supplied by a registered nurse and a pharmacy attendant, we assume the pharmacy attendant dispensed the type of antimalarial prescribed by the registered nurse. In the remaining cases, it was not possible to identify the individual provider, and therefore data on provider attributes were missing.

Statistical Analysis

The statistical analysis involved multiple imputation and multilevel logistic regression (Carpenter & Kenward 2013; van Buuren 2010). There were almost complete data on patient, and outlet attributes, though up to 26% of cases were missing provider attributes due to challenges linking the databases (Table 1). The missing data were binary or categorical responses and were non-monotone. The proportion of missing provider data was disproportionately greater at public and mission facilities in Cameroon, where ACT was

available, and at outlets located in urban areas. Thus, the missing data were presumed to be conditional on attributes of the outlet, which is known as 'missing at random' in the statistical literature (Sterne et al. 2009).

Given the scale of missing data and suggested missingness mechanism, multiple imputation using chained equations was appropriate since analysis using only complete-cases may be biased (White & Carlin 2010). Multiple imputation is a statistical technique for dealing with data 'missing at random' and is recommended when more than 10% of observations would be excluded in a complete-case analysis (Burton & Altman 2004). Multiple imputation allows for uncertainty about the missing data by generating multiple copies of datasets in which missing values are replaced by imputed values, and then uses standard statistical methods to estimate the model of interest using the imputed datasets (Sterne et al. 2009). Rubin's rules are used to take into account of the variability in the results between the imputed datasets, and valid inferences are obtained by averaging over the distribution of missing data given the observed data (Sterne et al. 2009 White et al. 2011).

Multiple imputation methods should respect the data structure; ignoring the data hierarchy can lead to bias because the variance of the imputation distribution would be underestimated (Goldstein et al. 2009). REALCOM-IMPUTE is statistical software that enables multiple imputation for a two-level model and fits the specified imputation model using Markov Chain Monte Carlo methods (Carpenter et al. 2011). Two-level multiple imputation was used because this is the maximum that is possible with currently available software.

The linked patient-provider data have a hierarchical structure, as patients may be clustered by provider and by outlet. For computational reasons it was not possible to take into account all possible levels, and a two-level model was specified with patients and provider attributes at level-1, and outlet attributes at level-2. Outlet was defined as the level-2 identifier to reflect the sampling strategy, the amount of clustering expected at this level, and because it was

known for every observation (while it was not always possible to identify which provider supplied treatment).

For a two-level logistic regression the dependent variable ω_{ij} is defined as the probability that the antimalarial supplied is an ACT for patient *i* from outlet *j*, and $(\omega_{ij}/(1-\omega_{ij}))$ is the log odds that the antimalarial supplied is an ACT. The model for the providers' choice of antimalarial was specified as:

$$\text{logit}(\omega_{ij}) = \alpha + \beta V_{ij} + \lambda P_{ij} + \theta F_j + \varepsilon_{ij} + u_j \qquad \varepsilon_{ij} \sim N(0,\sigma^2) \qquad u_j \sim N(0,\tau^2)$$

where: α was the intercept; V_{ij} were attributes of the provider supplying an antimalarial to patient *i* at outlet *j*; P_{ij} were attributes of patient *i* receiving an antimalarial at outlet *j*; F_j were attributes of outlet *j*; β, λ, and θ were the parameters associated with the explanatory variables; ε_{ij} and u_j were the residuals at level-1 and level-2 respectively, and capture unobserved variation, measurement and specification errors. The statistical significance was measured using the Wald test, and assessed at the 10% level. Multicollinearity amongst the explanatory variables was assessed in the complete cases using the variance inflation factor. We used the Ramsey RESET test to check for misspecification of the regression model (Rice 2000). This is a general test for problems associated with functional form and can identify errors associated with omitted variable bias, measurement error and simultaneity bias if they lead to nonlinearity in the relationship between the dependent and explanatory variables (Jones 2007). The models were also estimated without the explanatory variable for providers' stated preference to investigate simultaneity bias that would arise if providers' preference over alternative antimalarials was determined at the same time they acquired knowledge of the recommended treatment. The proportion of the total variance that was attributable to the outlet-level of the model was estimated using the variance partition coefficient (VPC) (Hox 2010). The VPC is similar to the intra-cluster correlation, though used when the dependent variable is discrete, and calculated as:

$$VPC = \tau^2 / (\tau^2 + 3.29)$$

where τ^2 is the variance at level-2 and the variance at level-1 is the variance of the standard logistic distribution ($\pi^2/3=3.29$) . Larger values of the VPC ($0<VPC<1$) indicate that the level has greater potential to influence the value of the dependent variable (Hox 2010).

Two-level logistic regressions were estimated using adaptive quadrature to approximate the marginal likelihood by numerical integration in Stata 12.1 (StataCorp 2009). The model was initially estimated with data from each country using listwise deletion, and therefore used only those cases that were complete and have no missing data (also known as complete cases). The model was subsequently estimated using data from 50 imputations generated by two-level multiple imputation using chained equations completed using Stata 12.1 and REALCOM-IMPUTE with a burn-in of 2000 and 500 further updates between each imputation (White et al. 2011). To avoid bias the imputation model used all variables that were included the analysis model (White et al. 2011). Fifty imputations were used since the number of imputations should be at least equal to the percentage of incomplete cases, and also confirmed the obtained results were not sensitive to the number of imputations used (White et al. 2011).

Results

Description of the Sample

The linked patient-provider database contained data on 2451 cases of febrile illness that sought treatment at public and mission health facilities and medicine retailers, with 871 cases from Cameroon and 1634 from Nigeria (Figure 1). The provider was presumed to be responsible for diagnosis and treatment when the patient or caregiver reported that they did not ask for a specific medicine. There were 516 patients in Cameroon and 942 patients in Nigeria eligible for malaria treatment, based on either a symptomatic or confirmed diagnosis (having excluded cases which requested a specific medicine and 45 patients from Cameroon

that tested negative for malaria). Of the eligible patients, 405 (79%) patients in Cameroon and 641 (68%) patients in Nigeria were supplied an antimalarial. In Cameroon, providers often chose to supply ACT, (74% of antimalarials supplied), though quinine either as a tablet or injection was also common (21%) (Table 2). While in Nigeria, providers regularly supplied sulphadoxine-pyrimethamine (40%) as well as ACT (37%), and other alternatives included artesunate-monotherapy (11%) and chloroquine (10%).

Linking patients to the provider that supplied treatment

Across the two countries 1046 patients were supplied an antimalarial (Figure 2). Almost all patients and caregivers were able to describe the providers they interacted with whilst at the public or mission health facility, pharmacy or drug store (396/405 in Cameroon and 634/641 in Nigeria). In Nigeria most cases (527/641) involved interactions with a single provider, while in Cameroon the majority of cases (291/405) involved interaction with two or more providers. It was possible to link the patient to details about the provider in 75% of cases (304/405) in Cameroon and 80% of cases (512/641) in Nigeria (Table 1). In the remaining cases, the provider's details were unknown because the respondent was unable to recall one or more of the providers who supplied care (9 in Cameroon and 7 in Nigeria); care was supplied by one or more providers who did not complete the survey (74 in Cameroon and 102 in Nigeria); or patients received care from multiple providers of the same cadre (18 in Cameroon and 20 in Nigeria).

Provider, outlet and patient attributes

The febrile patients were linked to 119 providers working at 105 outlets in Cameroon and 107 providers working at 93 outlets in Nigeria (Table 3). Approximately two-thirds of these providers accurately reported ACT was the first-line treatment for uncomplicated malaria, with better knowledge of the recommended treatment reported among providers working at public facilities. In Cameroon, 90% of providers at public facilities knew ACT was recommended compared to 65% at mission facilities, 50% at pharmacies and 45% at drug stores; while in

Nigeria, 79% of providers at public facilities, 73% at pharmacies, and 36% at drug stores accurately reported ACT was the recommended first-line treatment. Providers' access to malaria treatment guidelines and training also differed by country and type of outlet, with providers at public and mission health facilities more likely to report having access to the national malaria treatment guidelines than those working at pharmacies and drug stores. Providers' responses to survey questions on which type of antimalarial their patients usually ask for and which antimalarial is best for uncomplicated malaria also varied by setting. It was also interesting to note there were 20 providers in Cameroon and 21 providers in Nigeria who knew ACT was recommended but did not state it was their preferred treatment for uncomplicated malaria. The majority of outlets had ACT available at the time of the survey, and almost all pharmacies were located in urban areas.

The characteristics of febrile patients who relied on the provider to select treatment and were supplied an antimalarial are shown in Table 4. The proportions by gender and age group were similar across the different types of outlet in Cameroon, though in Nigeria proportionately more children under five were treated at public facilities than at pharmacies and drug stores. In both countries, there was some variation in the education level of the person seeking treatment and household wealth, with individuals at pharmacies having higher levels of education and from wealthier quintiles. There were also notable differences in the patient-provider interaction, as patients at public and mission health facilities were more frequently examined. Presumptive diagnosis of malaria was the norm in all outlets, though 23% of patients at public and mission facilities in Cameroon had their malaria diagnosis confirmed by microscopy.

Factors influencing the providers' decision to supply ACT

The relationship between providers' knowledge of the malaria treatment guidelines and their decision to supply ACT was examined in Cameroon and in Nigeria using univariable and multivariable models (Tables 5 and 6). Analysis was conducted using complete cases and once

missing data had been imputed. The specification of the multivariable models was assessed: the results for Ramsey RESET tests were not significant and there was no evidence of multicollinearity. The variable for providers' stated preference was included in the final model since there was no evidence of simultaneity bias. Also likelihood ratio tests indicated model fit was significantly better when providers' stated preference was included. Multivariable models without the variable for providers' stated preference are available as an appendix (web tables A and B).

There was no evidence of a relationship between providers' knowledge and practice in the univariable analysis in neither Cameroon nor Nigeria. However, the multivariable models identified several attributes of providers, patients and outlets that were significant predictors of providers supplying an ACT (at the 10% level of significance). Providers in both countries were more than twice as likely to supply ACT if they reported ACT was the best type of antimalarial for uncomplicated malaria (OR=2.80, p=0.025 in Cameroon and OR=2.54, p=0.044 in Nigeria). In Nigeria this was the only provider attribute that had a significant effect. In Cameroon, however, there was also evidence that providers were more likely to select ACT if they had reported it was the type of antimalarial that their patients most often request (OR=2.36, p=0.075). In addition, once missing data had been imputed the results suggest that pre-service training may have some bearing on their choice (p=0.092), and knowledge of the malaria treatment guidelines may be negatively associated with the decision to supply an ACT (OR=0.39, p=0.070).

Providers' choice of antimalarial was related to several patient attributes, though there were notable differences between the two countries. In Cameroon, providers were less likely to supply an ACT if the patient had previously taken an antimalarial (OR=0.22, p=0.005) or had their diagnosis confirmed using microscopy (OR=0.031, p=0.008). Also, once missing data had been imputed there was also some evidence that those from wealthier quintiles were more likely to receive an ACT (p=0.048). In Nigeria, there was strong evidence that providers were

more likely to supply ACT to patients under five years of age (OR=2.67, p=<0.001) and to male patients (OR=1.85, p=0.007), though wealth was not significant. The results also indicate that providers in Nigeria were more likely to supply ACT when told the patient had diarrhoea or had been vomiting (OR=2.36, p=0.002), though less likely to supply an ACT if it was the first time treatment was sought for the illness episode (OR=0.49, p=0.023). As in Cameroon, patients with a confirmed malaria diagnosis were less likely to receive an ACT (OR=0.23, p=0.057), however it is important to recognise that only 2% of all patients in Nigeria had their diagnosis confirmed by a malaria test.

In both countries, providers' decision to supply an ACT was correlated with attributes of the outlet. In Cameroon, patients were more likely to receive an ACT if treatment was sought at a pharmacy or public facility (p<0.001), while in Nigeria providers were three times more likely to supply ACT if it was in stock (OR=3.25, p=0.012). Finally, having controlled for a wide range of provider, outlet and patient attributes, the variance partition coefficient (VPC) indicates that a substantial proportion of the remaining heterogeneity can be attributed to unobserved outlet-level factors.

Discussion

The analysis focused on the relationship between providers' knowledge and practice, and was motivated by a need to design interventions to support the introduction of malaria RDTs in Cameroon and Nigeria. There was no evidence from either country that a provider's decision to supply ACT was determined by their knowledge of the national malaria treatment guidelines. There was, however, significant evidence from both countries that providers were more likely to supply ACT if they reported it was the best treatment for uncomplicated malaria. This positive association between providers' stated and revealed preferences highlights the importance of designing interventions that strive to change what providers' think and believe to be appropriate, not only enhance what they know.

The results also showed that having access to a copy of the clinical guidelines and access to malaria training was not sufficient to ensure appropriate treatment. Evidence from similar studies at public and mission facilities elsewhere in Africa have mixed results: prescribing practices were predicted by the providers' access to in-service training, guidelines or wall charts in Benin and Kenya (Rowe et al. 2003; Zurovac et al. 2008a; Zurovac et al. 2004), though not in Central African Republic, Malawi, Uganda and Zambia, (Osterholt et al. 2006; Rowe et al. 2000; Rowe et al. 2003; Zurovac et al. 2005; Zurovac et al. 2008b).

There was evidence from both countries that providers' choice of treatment can depend on their patients, though which factors were statistically significant differed by setting. It was interesting to find providers in Cameroon who reported their patients prefer ACT were more likely to supply it and the relative wealth of the patient was also a significant predictor of receiving an ACT. These findings were consistent with views expressed during focus group discussions, in which providers from public and mission facilities in the Cameroon study sites explained how their practice would depend on what they perceive their patients want from the consultation and can afford (Chandler et al. 2012).

Patient attributes were also relevant in Nigeria, where providers' decision to supply ACT was significantly associated with the patient's age and gender. Age was also found to be a significant predictor in other studies, with providers more likely to supply ACT to children than adults (Zurovac et al. 2008a; Zurovac et al. 2008b). In-depth interviews conducted at public health centres in Kenya described how providers who were concerned about stock outs would reserve ACT for young children and patients with more severe symptoms (Wasunna et al. 2008). Although we cannot comment on the relative severity of febrile illness among the patients in our sample, it was intriguing to find providers were less likely to supply ACT to patients seeking treatment for the first time or with a confirmed diagnosis. Given the small number of patients that reported having a positive malaria test, we are cautious about drawing conclusions on the choice of antimalarial following a confirmed diagnosis, though

note that the test-positive patients not supplied ACT were treated with an antimalarial recommended for severe malaria, and these cases were clustered in 14 public and mission facilities in Cameroon and 3 public facilities in Nigeria. We were also unable to investigate whether timing or length of the consultation were important, which were significant predictors some studies (Osterholt et al. 2006; Rowe et al. 2003; Zurovac et al. 2005; Zurovac et al. 2004).

Contextual factors were also associated with providers' practice, and as there were substantial differences between the two countries, the findings highlight the importance of understanding the local context when designing public health interventions. It was not surprising that providers were more likely to supply ACT if it was in stock, though having ACT available was not a prerequisite and providers could prescribe ACT and advise it should be obtained elsewhere. It should also be noted that the exit survey would not have captured any cases where the provider recommended ACT and the patient or caregiver opted for an alternative.

Before concluding some limitations are acknowledged. While several factors significantly predicted whether a provider supplied an ACT, it is possible others were not identified because the sample size was restricted to a subset of exit survey respondents who did not request a specific medicine, had a presumptive or confirmed malaria diagnosis, and were supplied an antimalarial. Also, two assumptions were made to prepare the data for analysis: the more senior cadre selected treatment if patients were seen by more than one provider, and data were missing at random. The first assumption was based on the process of care that we observed at many health outlets: junior staff record signs and symptoms and direct patients to the relevant senior health worker for a consultation, treatment is prescribed during the consultation, and prescribed medicines are obtained from a pharmacy attendant. At pharmacies and drug stores the process is less structured, though where a pharmacist and a sales attendant were involved we observed the pharmacist giving advice and recommending medicines, while the attendant administered the retail transaction. The second assumption that data were missing at random (MAR) was critical to the multiple imputation. The observed

pattern of missingness was consistent with our expectation that provider attributes were more likely to be missing at larger outlets and in urban areas. We acknowledge, however, that it is not possible to determine whether data were MAR, as defined in the statistical literature (White et al. 2011). Similarly, since the missing data can never be known, we cannot ascertain whether differences between the complete case and multiple imputation results, such as those observed in Cameroon for the effect of pre-service training and knowledge, arise because the complete cases are biased, because multiple imputation depends on the MAR assumption, or because of the specification of the imputation model (White et al. 2011).

Conclusions

As governments prepare to introduce malaria RDTs in public and private sectors, clinical guidelines will be updated to include guidance on the new type of diagnostic test and dissemination strategies will be developed. The introduction of RDTs, with revised guidelines, presents an opportunity to improve providers' practice, not only by increasing the proportion of patients that are tested prior to treatment, but also the proportion of patients that receive the recommended treatment. The results of this investigation suggest that ensuring providers have access to the guidelines, and know the treatment algorithm will not be enough to change providers' practice. The findings highlight that public health interventions to improve the treatment of uncomplicated malaria should strive to change what providers prefer, rather than focus on what they know. In developing interventions, the differences between the two countries highlight the need to understand the local context, as providers' treatment decisions may depend on what they perceive their patients' prefer or can afford as well as information about their symptoms or previous treatment seeking. In addition, the findings suggest it will be important to emphasize that the treatment algorithm should not depend on patient attributes, such as age or wealth, and that ACT is suitable for patients with a confirmed malaria diagnosis, unless they have symptoms of severe malaria or are pregnant. Finally, it should be recognized

that working environment can constrain providers' practice, and providers can only adhere to clinical guidelines if essential medicines and supplies are available.

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Figure 1: Flow chart of patients and caregivers that sought for febrile illness at public and mission facilities, pharmacies and drug stores in Cameroon and Nigeria

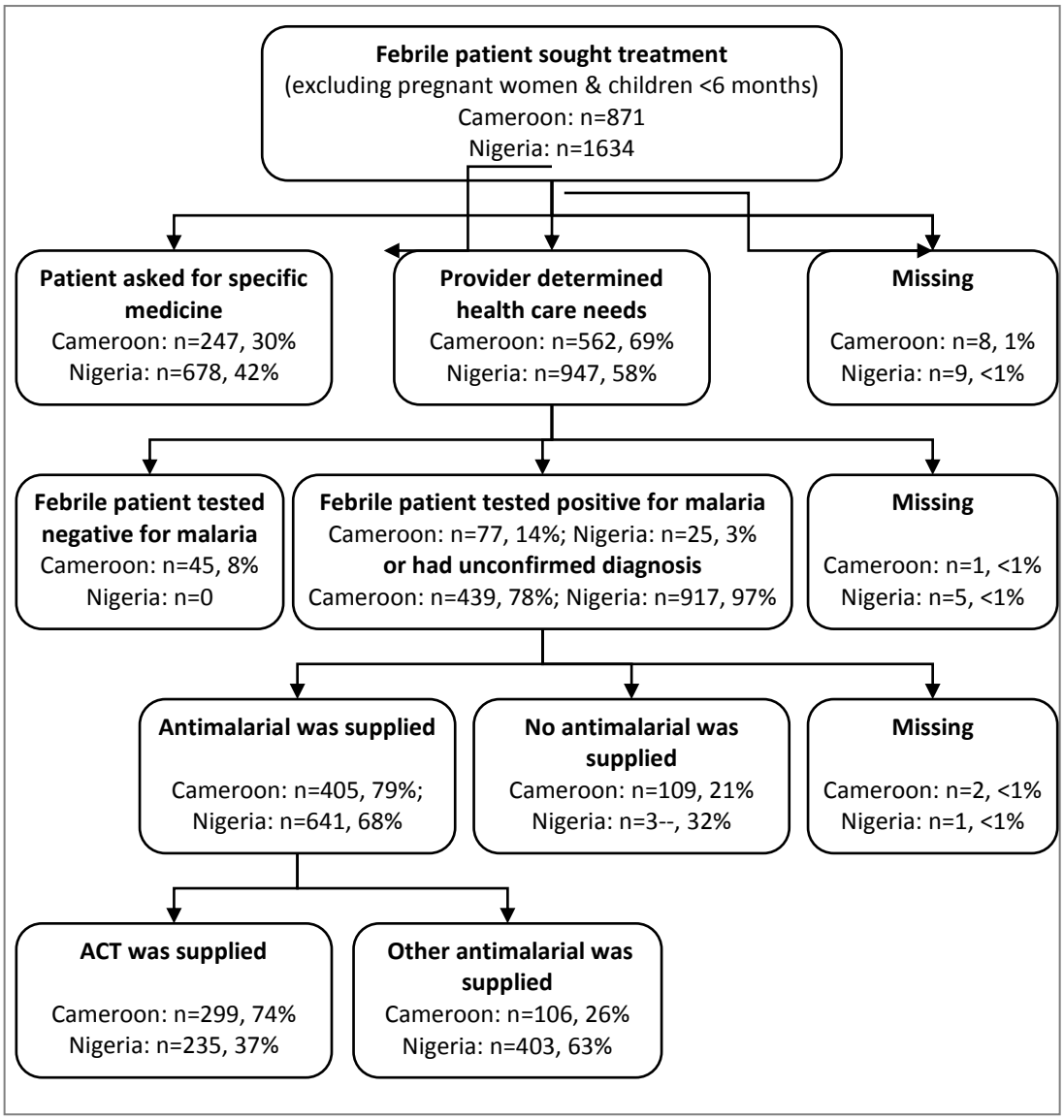

Figure 2: Flow chart showing how patients were linked to providers

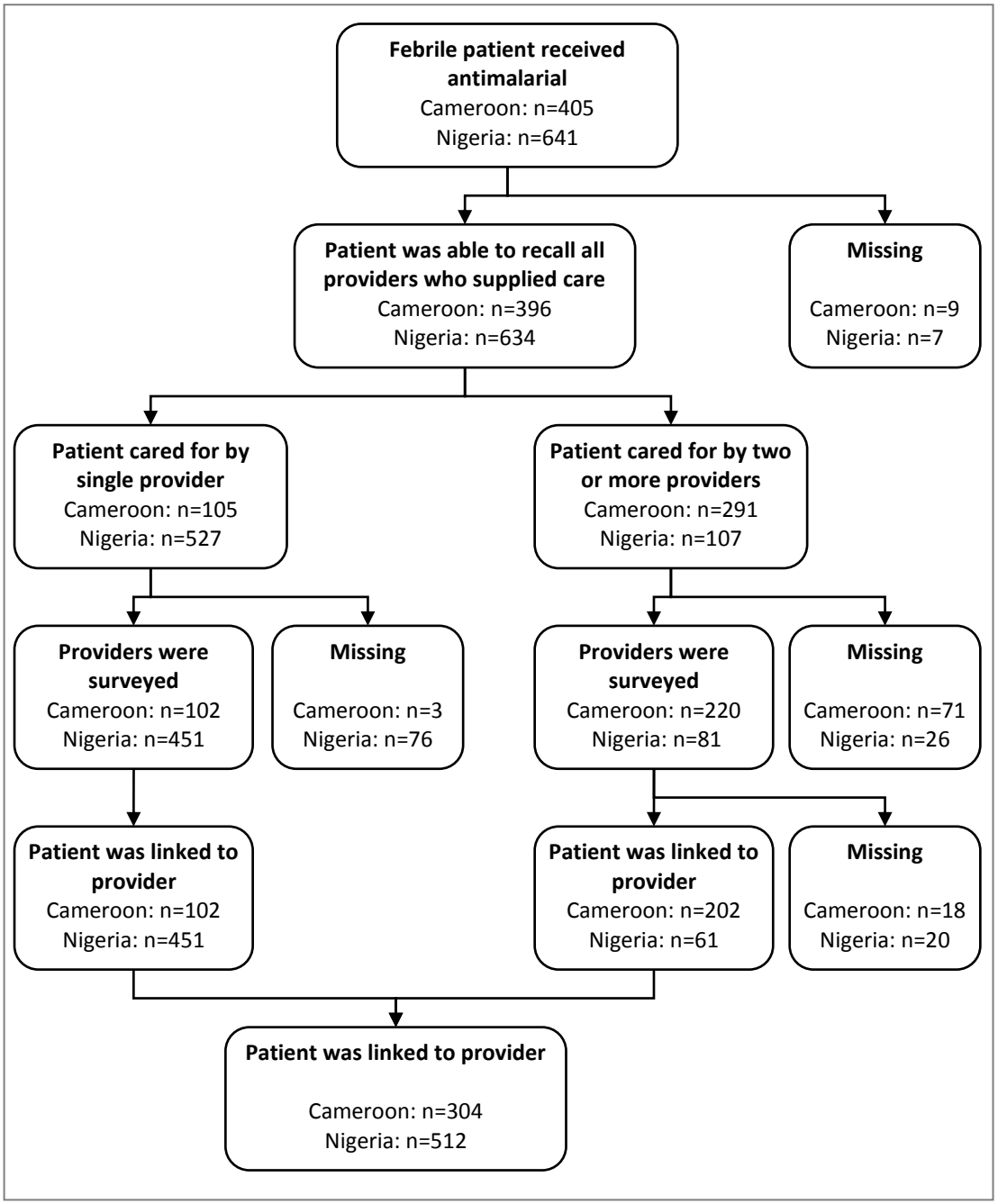

Table 1: Number of observations with missing data for each explanatory variable, by country and type of outlet

VARIABLE	CAMEROON (N=405)				NIGERIA (N=641)		
	Public	**Mission**	**Pharmacy**	**Drug Store**	**Public**	**Pharmacy**	**Drug Store**
Number of patients	N=202	N=80	N=52	N=71	N=323	N=60	N=258
Number of patients that were linked to provider	N=165	N=39	N=32	N=68	N=258	N=43	N=211
Level 1: Patient-Provider Interaction							
Provider knew ACT was first-line antimalarial for uncomplicated malaria	37	41	20	3	83	22	63
Provider reported having access to malaria treatment guidelines	37	41	20	3	66	18	47
Provider had attended malaria training in past 3 years	37	41	20	3	65	18	47
Provider's pre-service training	37	41	20	3	65	17	47
Provider stated ACT was best type of antimalarial for uncomplicated malaria	37	41	20	3	65	17	47
Provider reported the antimalarial that patients' usually ask for is ACT	37	41	20	3	100	17	47
Patient's gender	2	2	-	1	3	1	3
Patient's age group (<5years; 5+years)	5	-	-	-	2	-	3
Education of person that sought treatment	3	-	1	1	13	1	5
Wealth quintile of patient (relative to other patients)	-	-	-	-	-	-	-
Treatment was sought within 2 days following onset of fever	-	-	-	-	-	-	-
First time treatment was sought (for this illness episode)	-	-	-	-	-	-	-
Patient had previously taken antimalarial (for this illness episode)	-	-	-	-	-	-	-
Provider was told patient has diarrhoea or been vomiting	-	-	-	-	-	-	-
Patient was examined by provider	-	-	-	-	-	-	-
Patient reported malaria was confirmed using microscopy	-	-	-	-	-	-	-
Level 2: Outlet							
Outlet had ACT in stock	-	-	-	-	-	-	-
Outlet receives antimalarials from drug company representative	-	-	5	9	-	13	-
Urban / rural area	-	-	-	-	-	-	-

Table 2: Providers' choice of antimalarial, by country and type of outlet

TYPE OF ANTIMALARIAL	CAMEROON (N=405)								NIGERIA (N=641)					
	Public		Mission		Pharmacy		Drug Store		Public		Pharmacy		Drug Store	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	N=202		N=80		N=52		N=71		N=123		N=323		N=318	
Artemisinin Combination Therapy (ACT)	164	81.2	52	65.0	51	98.1	32	45.1	158	48.9	24	40.0	53	20.5
Amodiaquine	-	-	-	-	-	-	5	7.0	4	1.2	1	1.7	1	0.4
Artesunate monotherapy	3	1.5	2	2.5	-	-	-	-	30	9.3	10	16.7	29	11.2
Chloroquine	-	-	-	-	-	-	1	1.4	16	5.0	-	-	51	19.8
Halofantrine	-	-	-	-	-	-	-	-	3	1.2	1	1.7	1	0.4
Quinine	35	17.3	22	27.5	-	-	28	39.4	1	0.3	1	1.7	-	-
Sulphadoxine-pyrimethamine (SP)	-	-	4	5.0	1	1.9	5	7.0	111	34.4	23	38.3	123	47.7

Table 3: Provider and Outlet Attributes, by country and type of outlet

ATTRIBUTES	CAMEROON (N=405)								NIGERIA (N=641)					
	Public		Mission		Pharmacy		Drug Store		Public		Pharmacy		Drug Store	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Provider	**N=48**		**N=20**		**N=22**		**N=29**		**N=38**		**N=22**		**N=47**	
Knew ACT was first-line antimalarial†	43	89.6	13	65.0	11	50.0	13	44.8	30	78.9	16	72.7	17	36.2
Reports has access to malaria guidelines†	35	72.9	12	60.0	2	9.1	1	3.4	12	31.6	1	4.5	1	2.1
Has attended malaria training†	23	47.9	5	25.0	6	27.3	1	3.4	12	31.6	4	18.2	14	29.8
Pre-service training‡														
Doctor	10	20.8	6	30.0	-	-	-	-	6	15.8	-	-	-	-
Nurse or Midwife	25	52.1	5	25.0	3	13.6	3	10.3	5	13.2	2	9.1	-	-
Pharmacist	1	2.1	0	0.0	10	45.5	2	6.9	-	-	3	13.6	-	-
Nurse Assistant	7	14.6	6	30.0	2	9.1	15	51.7	-	-	-		-	-
CHO or CHEW	-		-		-		-		26	68.4	2	9.1	3	6.4
None (Attendant or Drug Seller)	5	10.4	3	15.0	7	31.8	9	31.0	1	2.6	15	68.2	44	93.6
Reported patients usually ask for ACT†	22	45.8	8	40.0	18	81.8	9	31.0	11	28.9	12	54.5	8	17.0
Stated ACT was best antimalarial for uncomplicated malaria†	38	79.2	9	45.0	15	68.2	23	79.3	22	57.9	19	86.4	24	51.1
Knew ACT was the first-line antimalarial but did not state it was the best antimalarial	9	18.8	6	30.0	4	18.2	1	3.4	11	28.9	3	13.6	7	14.9
Outlet	**N=35**		**N=15**		**N=25**		**N=30**		**N=20**		**N=21**		**N=52**	
Outlet had ACT in stock	28	80.0	13	86.7	23	92.0	17	56.7	14	70.0	21	100.0	38	73.1
Outlet receives antimalarials from drug company representative†	-		-		1	4.0	2	6.7	-		12	57.1	9	17.3
Urban / rural area														
Urban	13	37.1	9	60.0	24	96.0	17	56.7	12	60.0	20	95.2	31	59.6
Rural	22	62.9	6	40.0	1	4.0	13	43.3	8	40.0	1	4.8	21	40.4

† Some observations were missing (see Table 1)

‡ Categories differ by country. In Cameroon: Doctor; Nurse or Midwife; Pharmacist; Nurse Assistant; None (includes attendants). In Nigeria: Doctor; Nurse or Midwife; Pharmacist; Community Health Officer (CHO) or Community Health Extension Worker (CHEW); None (includes patent medicine dealers))

Table 4: Patient Attributes by country and type of outlet

PATIENT ATTRIBUTES	CAMEROON (N=405)								NIGERIA (N=641)					
	Public		Mission		Pharmacy		Drug Store		Public		Pharmacy		Drug Store	
	N		N		N		N		N		N		N	
	N=202		N=80		N=52		N=71		N=323		N=60		N=258	
Patient's gender†														
Male	100	49.5	33	41.3	27	51.9	32	45.1	141	43.7	32	53.3	129	50.0
Female	100	49.5	45	56.3	25	48.1	38	53.5	179	55.4	27	45.0	126	48.8
Patient's age group†														
Under 5 years	61	30.2	19	23.8	15	28.8	16	22.5	122	37.8	7	11.7	32	12.4
5 years and over	136	67.3	61	76.3	37	71.2	55	77.5	199	61.6	53	88.3	223	86.4
Education of person who sought treatment†														
Tertiary	15	7.4	14	17.5	18	34.6	8	11.3	67	20.7	28	46.7	54	20.9
Secondary	86	42.6	29	36.3	22	42.3	29	40.8	150	46.4	26	43.3	119	46.1
None or Primary	98	48.5	37	46.3	11	21.2	33	46.5	93	28.8	5	8.3	80	31.0
Patients' wealth quintile (relative to other patients)														
Least poor	21	10.4	9	11.3	19	36.5	5	7.0	46	14.2	19	31.7	25	9.7
Fourth	24	11.9	21	26.3	12	23.1	9	12.7	48	14.9	18	30.0	50	19.4
Third	40	19.8	18	22.5	11	21.2	13	18.3	72	22.3	9	15.0	55	21.3
Second	44	21.8	13	16.3	7	13.5	26	36.6	82	25.4	11	18.3	56	21.7
Poorest	73	36.1	19	23.8	3	5.8	18	25.4	75	23.2	3	5.0	72	27.9
Treatment was sought within 2 days	69	34.2	24	30.0	32	61.5	36	50.7	131	40.6	40	66.7	164	63.6
First time treatment was sought	125	61.9	39	48.8	39	75.0	57	80.3	220	68.1	48	80.0	194	75.2
Patient had previously taken antimalarial	19	9.4	20	25.0	6	11.5	4	5.6	34	10.5	4	6.7	14	5.4
Provider was told patient had diarrhoea or been vomiting	27	13.4	14	17.5	4	7.7	3	4.2	70	21.7	13	21.7	41	15.9
Patient was examined by provider	175	86.6	73	91.3	14	26.9	21	29.6	228	70.6	7	11.7	39	15.1
Patient reported malaria was confirmed	47	23.3	18	22.5	2	3.8	-	-	16	5.0	-	-	-	-

† Some observations were missing (see Table 1)

Table 5: Factors associated with providers' decision to supply ACT in Cameroon

	COMPLETE CASES				MULTIPLE IMPUTATION			
Number of patients	304		281		405		405	
Number of outlets	91		84		105		105	
FIXED EFFECTS	**OR (95 CI)**	**P-value**	**OR (95 CI)**	**P-value**	**OR (95 CI)**	**P-value**	**OR (95 CI)**	**P-value**
Level 1: Patient-Provider Interaction								
Provider knew ACT is first-line antimalarial for uncomplicated malaria	0.84 (0.33-2.13)	0.709	0.39 (0.11-1.35)	0.138	0.61 (0.28-1.33)	0.216	0.39 (0.14-1.08)	0.070
Provider had access to malaria guidelines			0.59 (0.20-1.80)	0.354			1.00 (0.37-2.70)	0.992
Provider had attended malaria training in past 3yrs			1.31 (0.46-3.74)	0.608			1.73 (0.63-4.76)	0.289
Provider's pre-service								
Doctor			0.91 (0.17-5.02)	0.458			2.78 (0.53-14.46)	0.092
Nurse / Midwife			0.41 (0.10-1.72)				1.06 (0.26-4.36)	
Pharmacist			0.53 (0.03-9.36)				0.21 (0.03-1.65)	
Nurse Assistant			1.32 (0.33-5.28)				2.90 (0.70-11.98)	
None (Attendant/drug seller)			1.0				1.0	
Provider stated patients usually ask for ACT			2.60 (0.92-7.31)	0.070			2.36 (0.92-6.06)	0.075
Provider stated ACT was best antimalarial for uncomplicated malaria			3.55 (1.28-9.88)	0.015			2.80 (1.14-6.89)	0.025
Patient was male			1.00 (0.47-2.12)	0.996			1.06 (0.56-1.99)	0.856
Patient was under 5 years of age			1.87 (0.72-4.77)	0.191			1.45 (0.67-3.13)	0.345
Education of person seeking treatment								
Tertiary			0.42 (0.10-1.87)	0.490			0.67 (0.21-2.19)	0.733
Secondary			0.68 (0.27-1.70)				0.77 (0.36-1.65)	
None or Primary			1.0				1.0	

Patient's wealth quintile								
Least Poor			3.63 (0.68-19.51)	0.279			2.62 (0.64-10.71)	0.048
Fourth			6.31 (1.23-32.20)				6.46 (1.73-24.13)	
Third			1.77 (0.53-5.86)				1.63 (0.58-4.60)	
Second			1.68 (0.63-4.50)				1.10 (0.45-2.69)	
Poorest			1.0				1.0	
Treatment was sought within 2 days			1.22 (0.53-2.82)	0.635			1.02 (0.51-2.05)	0.956
First time treatment was sought			0.24 (0.07-0.79)	0.019			0.41 (0.17-1.02)	0.056
Patient had previously taken an antimalarial			0.08 (0.02-0.39)	0.002			0.22 (0.07-0.64)	0.005
Provider was told patient has diarrhoea or been vomiting			1.07 (0.33-3.47)	0.908			0.77 (0.28-2.08)	0.603
Patient was examined by provider			0.90 (0.33-2.45)	0.839			1.08 (0.43-2.72)	0.872
Patient had a confirmed malaria diagnosis			0.33 (0.12-0.91)	0.032			0.31 (0.13-0.74)	0.008
Level 2: Outlet								
Type of outlet								
Public			22.46 (3.86-130.69)	0.002			7.38 (1.53-35.57)	<0.001
Mission			7.69 (1.16-50.80)				2.23 (0.45-11.08)	
Pharmacy			72.63 (3.84-1372.3)				203.38 (13.10-3156.3)	
Drug Store			1.0				1.0	
Outlet had ACT in stock			1.85 (0.67-5.13)	0.238			2.15 (0.74-6.26)	0.160
Outlet usually receives antimalarial from drug company representative			1.75 (0.15-19.81)	0.650			1.43 (0.10-20.52)	0.791
Outlet was in an urban area			0.69 (0.25-1.88)	0.470			0.70 (0.26-1.87)	0.481
Constant	4.16 (1.76-9.87)	0.001	0.73 (0.10-5.18)	0.753	5.47 (2.63-11.37)	<0.001	0.38 (0.06-2.32)	0.296
RANDOM EFFECTS								
Residual SD	1.42 (0.91-2.21)		0.77 (0.23-2.58)		1.37 (0.92-2.04)		1.12 (0.67-1.86)	
VPC	0.38		0.15		0.36		0.28	

Table 6: Factors associated with providers' decision to supply ACT in Nigeria

	COMPLETE CASES				MULTIPLE IMPUTATION			
Number of patients	473		423		641		641	
Number of outlets	73		71		93		93	
FIXED EFFECTS	**OR (95 CI)**	**P-value**	**OR (95 CI)**	**P-value**	**OR (95 CI)**	**P-value**	**OR (95 CI)**	**P-value**
Level 1: Patient-Provider Interaction								
Provider knew ACT is first-line antimalarial for uncomplicated malaria	1.66 (0.70-3.90)	0.247	1.08 (0.44-2.66)	0.869	1.69 (0.76-3.75)	0.196	1.08 (0.50-2.33)	0.851
Provider had access to malaria guidelines			0.83 (0.25-2.76)	0.761			1.54 (0.57-4.18)	0.392
Provider had attended malaria training in past 3yrs			0.66 (0.29-1.49)	0.316			0.69 (0.33-1.46)	0.332
Provider's pre-service training								
Doctor or Nurse/Midwife or Pharmacist‡			2.18 (0.39-12.22)	0.453			1.75 (0.41-7.48)	0.717
CHO or CHEW			2.66 (0.58-12.16				1.62 (0.41-6.34)	
None (Attendant/drug seller)			1.0				1.0	
Provider stated patients usually ask for ACT			1.41 (0.29-1.49)	0.458			1.38 (0.62-3.07)	0.429
Provider stated ACT was best antimalarial for uncomplicated malaria			2.54 (0.92-7.00)	0.071			2.54 (1.02-6.32)	0.044
Patient was male			1.61 (0.92-2.82)	0.093			1.85 (1.19-2.89)	0.007
Patient was under 5 years of age			3.84 (1.91-7.73)	<0.001			2.67 (1.54-4.63)	<0.001
Education of person seeking treatment								
Tertiary			0.91 (0.37-2.26)	0.903			1.37 (0.67-2.78)	0.643
Secondary			0.84 (0.39-1.80)				1.08 (0.60-1.96)	
None or Primary			1.0				1.0	
Patient's wealth quintile								
Least Poor			1.35 (0.40-4.62)	0.951			1.39 (0.54-3.60)	0.962
Fourth			1.40 (0.43-4.58)				1.32 (0.54-3.25)	
Third			1.57 (0.52-4.80)				1.30 (0.55-3.09)	
Second			1.36 (0.64-3.45)				1.30 (0.62-2.73)	
Poorest			1.0				1.0	
Treatment was sought within 2 days			1.75 (0.91-3.39)	0.095			1.45 (0.87-2.40)	0.151

First time treatment was sought			0.56 (0.25-1.25)	0.155			0.49 (0.26-0.90)	0.023
Patient had previously taken an antimalarial			1.80 (0.59-5.51)	0.300			1.01 (0.43-2.41)	0.976
Provider was told patient has diarrhoea or been vomiting			2.39 (1.18-4.82)	0.015			2.36 (1.38-4.04)	0.002
Patient was examined by provider			1.06 (0.49-2.27)	0.885			1.29 (0.71-2.35)	0.408
Patient had a confirmed malaria diagnosis			0.06 (0.00-0.79)	0.033			0.23 (0.05-1.04)	0.057
Level 2: Outlet								
Type of outlet								
Public			2.83 (0.51-15.80)	0.380			2.22 (0.50-9.94)	0.558
Pharmacy			0.78 (0.13-4.51)				1.25 (0.36-4.33)	
Drug Store			1.0				1.0	
Outlet had ACT in stock			3.24 (1.05-9.96)	0.040			3.25 (1.30-8.14)	0.012
Outlet usually receives antimalarial from drug company representative			1.93 (0.44-8.55)	0.386			1.04 (0.34-3.14)	0.947
Outlet was in an urban area			1.70 (0.50-5.72)	0.393			1.49 (0.54-4.09)	0.442
Constant	0.21 (0.10-0.46)	<0.001	0.01 (0.00-0.06)	<0.001	0.23 (0.12-0.45)	<0.001	0.02 (0.00-0.06)	<0.001
RANDOM EFFECTS								
Residual SD	1.73 (1.23-2.42)		1.06 (0.65-1.73)		1.68 (1.25-2.25)		0.99 (0.66-1.48)	
VPC	0.48		0.26		0.46		0.23	

‡ Categories

Appendix A: Factors associated with providers' decision to supply ACT in Cameroon (model does not include providers' stated preference for ACT)

	COMPLETE CASES		MULTIPLE IMPUTATION	
Number of patients	281		405	
Number of outlets	84		105	
FIXED EFFECTS	**OR (95 CI)**	**P-value**	**OR (95 CI)**	**P-value**
Level 1: Patient-Provider Interaction				
Provider knew ACT is first-line antimalarial for uncomplicated malaria	0.47 (0.13-1.70)	0.252	0.46 (0.17-1.27)	0.135
Provider had access to malaria guidelines	0.56 (0.17-1.79)	0.327	0.98 (0.35-2.70)	0.961
Provider had attended malaria training in past 3yrs	1.40 (0.47-4.23)	0.546	1.75 (0.63-4.90)	0.279
Provider's pre-service				
Doctor	1.22 (0.21-7.15)	0.763	3.07 (0.58-16.22)	0.097
Nurse / Midwife	0.61 (0.14-2.66)		1.39 (0.34-5.79)	
Pharmacist	0.72 (0.03-15.06)		0.20 (0.03-1.60)	
Nurse Assistant	1.39 (0.32-6.01)		2.85 (0.68-11.97)	
None (Attendant/drug seller)	1.0		1.0	
Provider stated patients usually ask for ACT	3.02 (1.00-9.12)	0.051	2.56 (0.98-6.69)	0.054
Patient was male	0.96 (0.44-2.07)	0.912	1.06 (0.57-2.00)	0.845
Patient was under 5 years of age	2.07 (0.79-5.44)	0.141	1.50 (0.70-3.24)	0.301
Education of person seeking treatment	0.45 (0.10-2.04)	0.522	0.74 (0.23-2.38)	0.818
Tertiary	0.66 (0.26-1.68)		0.81 (0.38-1.72)	
Secondary	1.0		1.0	
None or Primary				
Patient's wealth quintile				
Least Poor	4.02 (0.71-22.58)	0.238	2.72 (0.67-11.17)	0.061
Fourth	7.03 (1.34-36.88)		6.34 (1.68-23.89)	
Third	2.33 (0.69-7.90)		1.77 (0.63-5.00)	
Second	1.83 (0.66-5.02)		1.15 (0.47-2.83)	
Poorest	1.0		1.0	
Treatment was sought within 2 days	1.39 (0.59-3.25)	0.448	1.10 (0.55-2.21)	0.781
First time treatment was sought	0.28 (0.08-0.93)	0.037	0.46 (0.19-1.13)	0.089
Patient had previously taken an antimalarial	0.09 (0.02-0.42)	0.002	0.23 (0.08-0.66)	0.007
Provider was told patient has diarrhoea or been vomiting	1.07 (0.32-3.62)	0.907	0.78 (0.29-2.13)	0.630
Patient was examined by provider	0.88 (0.32-2.43)	0.809	1.11 (0.44-2.79)	0.826
Patient had a confirmed malaria diagnosis	0.28 (0.10-0.79)	0.017	0.30 (0.12-0.70)	0.006
Level 2: Outlet				
Type of outlet				
Public	17.08 (2.68-108.73)	0.006	148.44 (9.59-2297.3)	0.001
Mission	4.21 (0.62-28.82)		1.48 (0.30-7.35)	
Pharmacy	42.41 (2.22-808.51)		6.09 (1.24-29.69)	
Drug Store	1.0		1.0	
Outlet had ACT in stock	2.24 (0.74-6.79)	0.155	2.45 (0.82-7.35)	0.109
Outlet usually receives antimalarial from drug company representative	1.79 (0.12-25.91)	0.668	1.51 (0.10-23.38)	0.767
Outlet was in an urban area	0.74 (0.25-2.18)	0.586	0.73 (0.26-1.98)	0.536
Constant	1.12 (0.14-8.69)	0.914	0.55 (0.09-3.31)	0.514
RANDOM EFFECTS				
Residual SD	1.02 (0.45-2.29)		1.20 (0.74-1.96)	
VPC	0.24		0.30	

Appendix B: Factors associated with providers' decision to supply ACT in Nigeria (model does not include providers' stated preference for ACT)

	COMPLETE CASES		MULTIPLE IMPUTATION	
Number of patients	423		641	
Number of outlets	71		93	
FIXED EFFECTS	**OR (95 CI)**	**P-value**	**OR (95 CI)**	**P-value**
Level 1: Patient-Provider Interaction				
Provider knew ACT is first-line antimalarial for uncomplicated malaria	0.98 (0.40-2.43)	0.970	0.94 (0.46-2.20)	0.985
Provider had access to malaria guidelines	0.91 (0.27-3.09)	0.882	1.73 (0.62-4.76)	0.288
Provider had attended malaria training in past 3yrs	0.63 (0.27-1.42)	0.264	0.65 (0.31-1.38)	0.264
Provider's pre-service training				
Doctor or Nurse/Midwife or Pharmacist‡	2.47 (0.45-13.66)	0.417	1.97 (0.45-8.58)	0.646
CHO or CHEW	2.79 (0.60-12.87)		1.63 (0.41-6.57)	
None (Attendant/drug seller)	1.0		1.0	
Provider stated patients usually ask for ACT	1.30 (0.52-3.26)	0.576	1.34 (0.60-3.00)	0.476
Patient was male	1.64 (0.94-2.86)	0.084	1.87 (1.20-2.93)	0.006
Patient was under 5 years of age	3.98 (1.97-8.04)	<0.001	2.77 (1.59-4.82)	<0.001
Education of person seeking treatment	0.97 (0.39-2.39)	0.842	1.43 (0.71-2.90)	0.539
Tertiary	0.82 (0.38-1.76)		1.07 (0.59-1.94)	
Secondary	1.0		1.0	
None or Primary				
Patient's wealth quintile				
Least Poor	1.37 (0.40-4.68)	0.960	1.41 (0.55-3.65)	0.963
Fourth	1.43 (0.44-4.64)		1.33 (0.54-3.27)	
Third	1.56 (0.51-4.77)		1.30 (0.55-3.09)	
Second	1.29 (0.51-3.29)		1.27 (0.61-2.68)	
Poorest	1.0		1.0	
Treatment was sought within 2 days	1.76 (0.91-3.40)	0.091	1.43 (0.87-2.37)	0.162
First time treatment was sought	0.54 (0.24-1.21)	0.136	0.48 (0.26-0.89)	0.020
Patient had previously taken an antimalarial	1.86 (0.61-5.65)	0.273	1.04 (0.44-2.46)	0.936
Provider was told patient has diarrhoea or been vomiting	2.36 (1.17-4.75)	0.016	2.36 (1.38-4.05)	0.002
Patient was examined by provider	1.13 (0.53-2.40)	0.754	1.35 (0.74-2.45)	0.323
Patient had a confirmed malaria diagnosis	0.06 (0.00-0.87)	0.039	0.24 (0.05-1.10)	0.066
Level 2: Outlet				
Type of outlet				
Public	2.50 (0.44-14.29)	0.414	1.22 (0.35-4.28)	0.655
Pharmacy	0.68 (0.12-3.85)		2.00 (0.43-9.22)	
Drug Store	1.0		1.0	
Outlet had ACT in stock	3.54 (1.14-10.95)	0.029	3.67 (1.45-9.25)	0.006
Outlet usually receives antimalarial from drug company representative	2.44 (0.56-10.62)	0.234	1.21 (0.40-3.65)	0.733
Outlet was in an urban area	2.50 (0.78-8.00)	0.122	2.18 (0.84-5.64)	0.110
Constant	0.01 (0.00-0.08)	<0.001	0.02 (0.00-0.08)	<0.001
RANDOM EFFECTS				
Residual SD	1.09 (0.66-1.79)		1.03 (0.68-1.54)	
VPC	0.26		0.24	

Chapter 8

Research Paper V: Economic evaluation of a cluster-randomized trial of interventions to improve health workers' practice in diagnosing and treating uncomplicated malaria in Cameroon

In Chapter 5 I described problems with malaria diagnosis and treatment in Cameroon. Although microscopy was available in most public and mission facilities it was often under-used, and many febrile patients who were tested and found to be negative received an antimalarial they did not need.

The economic argument for introducing RDTs critically depends on providers' practice, and whether the treatment prescribed is consistent with the malaria test result. Having identified a gap between providers' knowledge and their practice, I hypothesized that interventions would be needed to support the introduction of RDTs and that training would be more effective and cost-effective if it focused on providers' practice, not only their knowledge of the malaria treatment guidelines.

This research paper reports the economic evaluation of a trial, developed on the basis of work the work reported in Chapters 5 through 7, which introduced of RDTs with either basic or enhanced health worker training at public and mission health facilities in Cameroon. While the basic training took a conventional approach, with lectures on the revised malaria treatment guidelines and a practical session on how to use RDTs, the enhanced training incorporated participatory methods that sought to change providers' preference and encourage them to adapt their practice and adhere to the treatment guidelines.

The results from this paper demonstrated it was more cost-effective to introduce RDTs with enhanced training, when each intervention was compared to current practice. The paper may also be useful for other researchers, as it is one of the first examples to apply the recent methodological guidance on analysing individual patient level data on costs and effects from a cluster randomized trial.

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Contribution: VW, OO & WM conceptualised the study and secured funding for the trial. VW, WM, BC & LMJ designed the trial. WM, LMJ, OA & VW designed the interventions. WM, LMJ, BC, OA & VW were involved in the evaluation activities. TD & LMJ estimated the cost of the intervention. TD & OA undertook the facility costing. LMJ undertook the analysis and drafted the manuscript. All authors read and approved the final manuscript.

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Economic evaluation of a cluster-randomized trial of interventions to improve health workers' practice in diagnosing and treating uncomplicated malaria in Cameroon

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Competing interests

The authors declare that they have no competing interests

Author's contribution

VW, OO & WM conceptualised the study and secured funding for the trial. VW, WM, BC & LMJ designed the trial. WM, LMJ, OA & VW designed the interventions. WM, LMJ, BC, OA & VW were involved in the evaluation activities. TD & LMJ estimated the cost of the intervention. TD & OA undertook the facility costing. LMJ undertook the analysis and drafted the manuscript. All authors read and approved the final manuscript.

Key words

Cost-effectiveness analysis; health worker knowledge, attitudes, practice; malaria; Cameroon

Running title

Improve health worker's practice of malaria

ABSTRACT

Background

Malaria rapid diagnostic tests (RDTs) are a valid alternative to malaria testing with microscopy and are recommended for testing of febrile patients before prescribing an antimalarial. There is the need for interventions to support the uptake of RDTs by health workers.

Objective

To evaluate the cost-effectiveness of introducing RDTs with basic or enhanced training in health facilities where microscopy was available, compared to current practice.

Methods

A three-arm cluster randomized trial was conducted in 46 facilities in Centre and North-west Cameroon. Basic training had a practical session on RDTs and lectures on malaria treatment guidelines. Enhanced training included small-group activities designed to change health workers' practice and reduce consumption of antimalarials among test-negative patients. The primary outcome was the proportion of febrile patients correctly treated: febrile patients should be tested for malaria, artemisinin combination therapy should be prescribed for confirmed cases, and no antimalarial should be prescribed for patients who are test-negative. Individual patient data were obtained from facility records and an exit survey. Costs were estimated from a societal perspective using project reports and patient exit data. The analysis used bivariate multilevel modelling and adjusted for imbalance in baseline covariates.

Results

Incremental cost per febrile patient correctly treated was $8.40 for basic and $3.71 for enhanced arms. Upon scale-up it was estimated RDTs with enhanced training would save $0.75 per additional febrile patient correctly treated.

Conclusion

Introducing RDTs with enhanced training was more cost-effective than RDTs with basic training, when each was compared to current practice.

INTRODUCTION

In 2010 the World Health Organization (WHO) updated malaria treatment guidelines to confirm that rapid diagnostic tests (RDTs) are a valid alternative to testing using microscopy and to recommend parasitological testing in all patients before prescribing an antimalarial (1). Interest in RDTs has intensified and governments across sub-Saharan Africa are now deciding how to expand access to malaria testing, and whether to introduce RDTs in health facilities that already offer malaria testing using microscopy. These policy decisions will require revisions to national malaria treatment guidelines and supporting interventions that ensure the policy change is accompanied by a change in health workers' practice.

In malaria endemic areas, cases of uncomplicated malaria are routinely treated in primary health facilities and hospital outpatient departments, and clinical guidelines advise that in high transmission settings malaria should be suspected in patients who present with a fever or report having a fever in the past 24 hours (1). Malaria testing is advised, since malaria symptoms are non-specific and the fever may have other causes. However, microscopy requires a laboratory and technicians able to prepare and read blood slides and these are often limited in low-income settings. Consequently, it has become common for health workers to make treatment decisions based on symptoms alone and for antimalarials to be presumptively prescribed to febrile patients.

RDTs offer considerable potential to transform malaria diagnosis and treatment since they do not require a laboratory and can be used with minimal training. However, this potential will only be realized if health workers' prescribe treatment based on the test result. Evidence from several countries, including Cameroon, suggests the reliance on a presumptive malaria diagnosis has created a mindset among health workers and patients that febrile illness should be treated with an antimalarial and it is not uncommon for antimalarials to be prescribed to patients who tested negative for malaria (2-6).

The economic argument for introducing RDTs critically depends on health workers' practice (7, 8). This assumption has been emphasized in several studies (7, 9, 10) and the sensitivity of the cost-effectiveness results to health workers' practice has been illustrated using trial data from Tanzania (8). Results were also sensitive to the prevalence of malaria in febrile patients, specificity and sensitivity of the test, cost of testing and medicines, whether non-malaria febrile

illness were bacterial or self-resolving viral infections, the efficacy of antimalarials and antibiotics taken, and whether patients take medicines as advised (9). The literature shows that RDTs tend to be more cost-effective than microscopy, when each are compared to a presumptive diagnosis (7, 11, 12), while the cost-effectiveness of RDTs compared to microscopy depends on the relative cost of the tests, as well as their specificity and sensitivity in routine use (10, 13-15).

In order to improve malaria diagnosis and treatment using RDTs in Cameroon, interventions were designed following formative research with patients and health workers in two regions of Cameroon (3, 6, 16). The formative research showed microscopy was available in the majority of public and mission facilities, but was under-used and less than 50% of febrile patients were tested for malaria (6).Malaria was over-diagnosed: 73% of febrile patients received an antimalarial yet malaria was present in only 30% of febrile patients tested by the study team (6). Moreover, patients often received an antimalarial regardless of the test result: 82% of patients who reported they tested negative for malaria were prescribed an antimalarial (6). Qualitative research also provided insight on health workers' practice and highlighted both a mistrust of malaria test results and challenges in managing patient expectations (3).

In collaboration with the National Malaria Control Programme (NMCP) of Cameroon, training modules were developed to support the introduction of RDTs in public and mission facilities. The basic training was intended to equip health workers with the knowledge and practical skills needed to diagnose and treat uncomplicated malaria, including how to conduct a RDT. As improving health workers' adherence to the malaria treatment guidelines was a key objective, additional training was designed that used interactive methods and sought to address the gap between health workers' knowledge and practice, and change prescribing behaviour.

This paper reports the incremental cost per febrile patient correctly treated (according to the malaria treatment guidelines) of each intervention compared to current practice. Cost-effectiveness was assessed from both a provider and a societal perspective. The analysis uses statistical methods suitable for individual patient data on costs and effects obtained from a cluster-randomized trial (17, 18).

METHODS

Trial Design & Intervention

A cluster randomized trial was designed to evaluate effectiveness and cost-effectiveness of introducing RDTs with basic or enhanced training in facilities where microscopy was available, compared to current practice. The three-arm cluster randomized trial was conducted at 46 public and mission health facilities, which offered malaria microscopy testing, and were located in Centre and Northwest regions of Cameroon where malaria is endemic. The trial design and interventions are summarized here, and further details are available elsewhere (19, 20). The trial was registered (clinicaltrials.gov: NCT01350752), the study protocol is available (19), and the main trial paper has been published (20). The effect of the interventions on the proportion of febrile patients correctly treated according to the malaria treatment guidelines was measured by surveying febrile patients exiting health facilities.

Facilities were stratified by site, randomly selected and allocated to one of three arms: control, basic and enhanced. There was no intervention at facilities in the control arm. Each facility in the two intervention arms was supplied 100 RDTs (SD Bioline Malaria Ag Pf/Pan, Standard Diagnostics, Yongin, South Korea) per month without charge. The brand and number of RDTs supplied was selected based on advice from the NMCP, and the test is reported to have a minimum detection rate of 97.5% for *P. falciparum* malaria, even at low levels of parasitemia (200 parasites/µl) (21).

Each facility in the basic arm was invited to send three health workers to the one-day training course that was organised by the study team in each study site. The one-day training had three lectures on the revised malaria clinical guidelines and a practical session on how to use RDTs. In addition, three-day enhanced training workshops were held in each study site. The enhanced intervention replicated the basic intervention, but also contained an additional two days of training. The additional training used participatory methods to reinforce material covered in the basic training, whist also encouraging health workers to adapt to change, communicate effectively and support each other. For instance, trainers facilitated small-group work, and used problem-solving exercises, a treatment algorithm game, self-developed participatory drama and role-playing. The training courses were delivered by representatives from the NMCP and members of the study team. Copies of the training materials can be downloaded from the ACT

Consortium website (http://www.actconsortium.org/resources.php/82/training-manuals-from-react-study-in-cameroon).

Health workers that attended the basic and enhanced training courses were encouraged to hold training sessions at their facility (hereafter referred to as in-facility training) and inform their colleagues about RDTs and the revised malaria treatment guidelines. Members of the REACT team were invited to attend the in-facility training but they did not have a role in leading or facilitating the training. The trial was designed to approximate 'real-world' rather than controlled conditions, and it was possible, for example, that a facility encountered stock-outs of RDTs and artemisinin combination therapies (ACTs) during the evaluation.

Effectiveness of Interventions

The effect of the interventions was measured by the proportion of the febrile patients attending facilities who were correctly treated according to the revised malaria treatment guidelines. This was a composite measure which required all febrile patients to be tested for malaria using microscopy or RDT, patients to receive an ACT if they have a positive malaria test result, and patients not to receive an antimalarial if they have a negative malaria test result. Patients were invited to participate in an exit survey if they sought treatment for a fever at one of the facilities participating in the trial, were over six months old, not pregnant and did not have symptoms of severe malaria. With informed consent, the exit survey was administered by trained fieldworkers to the patient or their caregiver. A copy of the malaria test register in each facility was also obtained. Data collection took place between October and December 2011 and commenced three months after interventions were implemented. The effectiveness results have been submitted for peer-reviewed publication in an academic journal (20).

Cost Measurement and Valuation

The health care costs for each patient in the exit survey was estimated taking into account the direct and indirect costs incurred by the patient and caregivers to obtain care, net costs to the facility (adjusting for user fees) and the intervention cost. All costs were estimated in 2011 in Central African Francs (CFA) and converted to US dollars (USD) at 2011 prices, using a conversion rate of USD1 = CFA 471.87 (the official exchange rate for 2011, http://wdi.worldbank.org/table/4.16 accessed on 23 August 2013).

Intervention cost

Financial and economic costs of the training interventions were estimated from project reports and interviews with staff, using an ingredients-based approach (Table 3 and Appendix A). For the costing, the intervention was separated into the following activities: i) development of the training materials; ii) engaging with stakeholders; iii) training facilitators; iv) administration and implementation of the basic training; v) administration and implementation of the enhanced training; vi) in-facility training in which health workers train colleagues with support from project staff. For each of these activities, the amount of resources uses and their unit cost of was determined by referring to time sheets completed by staff members or project reports that documented either the number of items procured (e.g. stationery or refreshments) or the number of participants (e.g. per diems). Cost of transport and communications were also logged. The cost categories were: personnel, venue; intervention materials; stationery, refreshments; transport; communications; per diems, equipment and overheads. The cost of the equipment used was estimated based on the useful life of the equipment, a 3% discount rate, and the number of days the equipment was used. Overheads were estimated based on the cost of running the REACT office, taking into account rent and utilities.

Start-up costs were incurred to develop the training materials and to engage national and local stakeholders on the training programme and revisions to the malaria treatment guidelines. One-off implementation costs were incurred to train the trainers, administer and implement the training workshops, and hold in-facility training. The base-case scenario assumed one-off implementation costs would be incurred annually. Many activities to prepare for the basic and enhanced training were conducted simultaneously, and the cost that corresponds to each arm has been determined by estimating which costs would have been incurred if the interventions were independent (Appendix A). For example, the time spent developing training materials for the basic training workshop was assumed to be one third of the total cost since the basic training last a third of the length of the enhanced training. The cost of the in-facility training was estimated separately for each facility, based on the length of the training and number of health workers attending. RDTs were not included in the cost of the intervention, but were captured elsewhere.

The total annual economic cost of the intervention was estimated for each facility. Start-up costs of the training interventions were annualized over 4 years using a 3% discount rate, based on the assumption that the training materials would remain relevant for a minimum of 4 years (22). The economic costing also incorporated the time health workers spent at the in-facility training, for which there was no financial cost. The cost of the intervention per febrile patient was estimated by apportioning the total annual economic cost across all febrile patients who attend the facility each year, based on an estimate obtained from facility records.

Cost of febrile illness

Costs incurred by patients to diagnose and treat febrile illness were estimated for each individual participating in the exit survey and the mean cost per febrile patient was calculated. Exit survey respondents described the care received during the facility visit; and reported direct costs incurred for the consultation, tests undertaken and medicines received; direct cost of travel and other out-of-pocket expenses; and the time spent at the facility and for travel. The time of patients and caregivers was valued at the wage of an unskilled worker (CFA 1200 per day).

The costs incurred by facilities to diagnose and treat each febrile patient were also estimated. The facility cost was estimated for each febrile patient using patient-reported information on the consultation, such as the cadre of health worker, malaria tests conducted (by microscopy or RDT), and medicines prescribed and dispensed. These data were combined with detailed unit cost data collected at selected facilities on the average health worker time and resource use per activity plus portion of overhead costs. The net facility cost per febrile patient was estimated by deducting the amount paid by the patient. In some cases the amount paid by the patient exceeded the cost to the facility (i.e. net facility cost was zero) though in other cases (often when the patient was under five years of age) the cost to the facility exceeded the fees paid.

Cost-Effectiveness Analysis

Incremental cost-effectiveness ratios (ICERs) for the basic and enhanced interventions, with each intervention compared to control, were calculated for the primary outcome (correctly treated according to guidelines) in an intention-to-treat analysis from both a provider and a

societal perspective. The ICERs represent the incremental cost for each additional febrile patient correctly treated.

The cost-effectiveness analysis used individual patient-level data on costs and effects from the cluster-randomized trial, according to the latest methods (17, 18, 23). An initial examination of the data found correlation between costs and effects at the individual-level and cluster-level; and intra-cluster correlation in both costs and effects. In addition, although randomization of clusters to trial arms should negate the need to include individual-level and cluster-level covariates, there was imbalance in selected patient and facility characteristics across the three arms. For instance, there was a larger percentage of public facilities in the control arm (85.3%) than in basic (61.3%) and enhanced (56.7%) arms, and the control arm (36.7%) contained a larger percentage of patients and caregivers who had asked for a blood test than the basic (22.4%) and enhanced (21.3%) (Table 1). The incremental costs and effects were estimated using a bivariate multilevel model with covariates. This method simultaneously estimates the multilevel model for cost, c_{ij}, and the multilevel model for effect, e_{ij}:

$$c_{ij} = \beta_0^c + \beta_1^c a_j + \beta_2^c x_{ij} + \beta_3^c z_j + u_j^c + \varepsilon_{ij}^c \qquad \begin{pmatrix} \varepsilon_{ij}^c \\ \varepsilon_{ij}^e \end{pmatrix} \sim BVN \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{matrix} \sigma_c^2 & \rho\sigma_c\sigma_e \\ & \sigma_e^2 \end{matrix} \right)$$

$$e_{ij} = \beta_0^e + \beta_1^e a_j + \beta_2^e x_{ij} + \beta_3^e z_j + u_j^e + \varepsilon_{ij}^e \qquad \begin{pmatrix} u_{ij}^c \\ u_{ij}^e \end{pmatrix} \sim BVN \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{matrix} \tau_c^2 & \varphi\tau_c\tau_e \\ & \tau_e^2 \end{matrix} \right)$$

where a_j is the arm of the trial, x_{ij} are the individual-level covariates, z_j are the cluster-level covariates, β_1, β_2, and β_3 are the corresponding parameter for these variables, β_0 is the constant, and e_{ij} and u_j capture the individual-level and cluster-level variation. The individual-level covariates were: the patient's age; whether previous treatment had been sought for the illness episode, and whether the patient (or their caregiver) requested a blood test. The cluster-level covariates were: study site; type of facility; the average number of patients that attend the facility per day; whether the facility had any stock outs of ACT in the past 4 weeks and the cluster size. By including covariates in the model (and thereby controlling for differences in individual and cluster characteristics by arm) the results report the incremental costs and effects that are associated with the arm of the trial. The assumption of normality was investigated for

costs and effects. The distribution of the costs was close to a normal distribution. We assumed a normal distribution for effects having considered the alternative specifications, and having confirmed the predicted probabilities from the linear probability model lay within the 0 to 1 interval, and were similar to those from a logit model (24, 25). Statistical analysis was completed by running MLwiN 2.28 from Stata 12.1 (26).

Confidence intervals for the ICERs cannot be interpreted because there were some observations with worse outcomes and higher costs and some with better outcomes and lower costs, and hence not reported. This is shown on a cost-effectiveness plane when bootstrap replications occurring in more than one quadrant.

Cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) were generated by bootstrapping the residuals from the bivariate multilevel models (17, 27). Bootstrapping is a well-established method for estimating uncertainty of parameter estimates in statistical models (27). For each costing perspective (provider and societal) and scenario (base-case and scale-up), incremental costs and effects were obtained for 5000 bootstrap replications, both with and without adjustment for imbalance in patient and facility characteristics across the study arms (Figures 1-4). CEACs were generated to illustrate the probability that each intervention was optimal for a range of willingness-to-pay values, where the willingness to pay is the value placed on an additional person treated according to the malaria treatment guidelines (28). CEACs were obtained using the bootstrap replications of cost and effect (with adjustment for imbalance in patient and facility characteristics across the study arms). For each willingness to pay value (λ) the percentage of bootstrap replications for which the net monetary benefit (NMB = λ * effect – cost) is less than the willingness to pay value was estimated. This determines the probability that the intervention is cost-effective at a given willingness to pay threshold. CEACs have been presented in Figure 5, and this shows the incremental cost effectiveness of the two interventions compared to current practice for a given costing perspective and scenario.

The base-case analysis estimated the cost-effectiveness of the interventions compared to current practice as implemented for the trial. The base-case included all start-up costs and implementation costs, assuming the training materials would remain useful for four years and the training would be held annually. The cost-effectiveness of the interventions were also considered in a ‘scale-up scenario’ in which the start-up costs were excluded because they

were a sunk cost, and it was assumed the training would be held every two years. These estimates should be useful for the Government of Cameroon in deciding whether to scale-up the introduction of RDTs with health worker training.

Ethics Statement

Ethical approval was obtained from the ethics committees of the London School of Hygiene and Tropical Medicine (No.5429) and Cameroon National Ethics Committee (No 030/CNE/DNM/09). Administrative clearance was obtained from the Ministry of Public Health (No. D30-343/AAR/MINSANTE/SG/DROS/CRC/JA). The trial is registered with clinicaltrials.gov NCT01350752.

RESULTS

The study took place between June and December 2011 and 46 facilities participated in the study. The basic and enhanced training was successfully delivered to 37 facilities in the intervention arms, and in-facility training was held in 34 facilities (15 of 18 in the basic arm, and all 19 in the enhanced arm) (Appendix A). Each month 100 RDTs were supplied to all facilities in the intervention groups for a period six months, which commenced at the end of the training and continued until all data collection was complete. Although facilities were asked not to charge more than 100 CFA ($0.20) per test, most facilities charged substantially more, with a mean charge of $3.10 in the basic arm and $2.43 in the enhanced arm. ACT was supplied by the government or mission central medical stores and availability was reasonably good through the study period. One of the 9 facilities in the control arm reported they offered rapid diagnostic testing, but they also reported stock outs of RDTs in the past month. We were told they had received RDTs as a donation and not part of the intervention and they did not receive any training in the use of RDTs. Additional information on the implementation and fidelity of the interventions has been described elsewhere (20).

Study Population

The effectiveness and cost-effectiveness of the basic and enhanced interventions were evaluated using 3982 eligible patients that completed the exit survey (Table 1). Patient

characteristics across the three arms of the trial show some differences in the age distribution of patients, and in the proportion that had previously sought treatment and asked for a blood test. Similarly, while facilities were randomly allocated to the trial arm, there were also some differences across the arms in the type of facility, the average number of febrile patients per day and percent of facilities that encountered stock-outs of ACT in the past 4 weeks. In other respects the facilities were comparable (Appendix B).

Effects

The proportion of febrile patients who were correctly treated according to the clinical guidelines was 42% in the basic arm and 55% in the enhanced arm, compared to 37% in the control arm (Table 2). This is a composite indicator, which requires febrile patients to be tested for malaria and for their treatment to be consistent with the malaria test result. Breaking down this indicator shows that the difference between the arms is largely in the treatment prescribed and received by patients who tested negative for malaria: 47% of patients in the basic arm and 68% in the enhanced arm were correctly treated compared to 14% in the control arm. There were also some differences in the malaria positivity rates across the arms, and the percent of patients with a positive result was higher when patients were tested using microscopy rather than RDT. It should be noted that all these results are unadjusted, and do not take into account the clustering or the imbalance in the baseline covariates, and more detailed analyses are presented elsewhere (20).

Costs

The financial cost of the basic training was $28,392 and the enhanced training was $63,127. A description of the resources used is provided in Appendix A. The start-up costs constitute a large proportion of the total financial costs (73% and 74% of the basic and enhanced interventions, respectively), which largely reflects the amount of time staff spent designing, piloting and refining the training materials.

On the assumption that the training materials would remain useful for four years, the total annual economic cost was $14,481 for the basic training and $30,976 for the enhanced training (Table 3). The annual economic cost of the training workshops held by the NMCP and study team (including the training of facilitators) was $5,497 for two basic workshops that trained 50

health workers from 18 facilities, and was $12,100 for two enhanced workshops that trained 48 health workers from 19 facilities. The economic cost of the in-facility training was on average $190 per facility in the basic arm and $328 per facility in the enhanced arm, and included the value of in-kind items and time of participating health workers. It was estimated that the total annual economic cost of the training interventions in a 'scale-up' scenario would be $4,662 for basic and $9,585 for enhanced training.

The mean cost per febrile patient was estimated from a provider and societal perspective, and presented by study arm for both the base-case and scale-up scenarios (Table 4). The mean cost of the training per febrile patient in the base-case scenario was $0.52 in the basic and $1.12 in the enhanced arm (and falls to $0.16 and $0.35 respectively for the scale-up scenario). In the base-case scenario, the total cost per febrile patient in the base-case scenario was $1.28 in the basic and $1.88 in the enhanced arm from a provider perspective and $13.47 in the basic and $13.69 from a societal perspective. The substantial difference between the provider and societal costs arises because patients pay user fees to access health care, which vary by facility and depend on the care received. The average out-of-pocket costs relating to the consultation, tests conducted and treatment received was reported to be $8-10 per febrile patient.

Cost-Effectiveness

In the base-case scenario, the interventions were more costly but also more effective than current practice. From a provider perspective, the incremental cost per patient correctly treated was $10.13 for the basic and $6.70 for the enhanced intervention (Table 5). From a societal perspective, which includes any costs incurred by patients, the incremental cost per patient correctly treated was $8.40 for the basic and $3.71 for the enhanced intervention. Thus, it was more cost-effective to introduce RDTs with enhanced training, than basic training, when each intervention was compared to current practice.

The cost of the intervention is reduced in the scale-up scenario, and the interventions become more cost-effective. From a provider perspective, incremental cost per patient correctly treated was $4.39 for the basic and $2.45 for the enhanced arm. From a societal perspective, incremental cost was $2.46 per patient correctly treated in the basic arm, while the enhanced had a net saving of $0.75 per additional patient correctly treated.

It is not appropriate to report confidence intervals for these incremental cost-effectiveness ratios because there are some instances were some observations with worse outcomes and higher costs and others with higher costs and worse outcomes. This is shown on the cost-effectiveness planes with bootstrap estimates in all multiple quadrants. The cost-effectiveness planes are useful for illustrating the degree of uncertainty around the point estimate.

An alternative approach is to estimate the net benefit of an intervention, though this depends on the willingness to pay threshold and there is no agreed willingness to pay threshold in Cameroon. Instead, CEACs are often used to illustrate the probability than an intervention is cost-effective at a range of willingness to pay thresholds. The probabilities that each intervention was cost-effective at different levels of the cost-effectiveness threshold, compared to current practice, are illustrated using CEACs (Figure 5). These graphs show that the basic intervention has the lowest probability of being cost-effective at all values from both a provider perspective and a societal perspective. Current practice has the highest probability of being cost-effective at very low threshold levels (less than $5), though as the threshold increases so does the probability that the enhanced intervention is cost-effective. The CEACs for the scale-up scenario lie to the left of the base-case scenario, and in the scale-up scenario from a societal perspective the enhanced intervention has the highest probability of being cost-effective at all threshold values. The CEACs in the scale-up scenario lie to the left of the CEACs in the base-case because the start-up costs associated with developing the intervention were treated as a sunk cost leading to a lower incremental cost in the scale-up scenario. As a result for each willingness to pay value the probability that the intervention is cost-effective is higher in the scale-up scenario than it is in the base-case.

DISCUSSION

The cluster randomized trial evaluated the introduction of RDTs at health facilities where microscopy was available with either basic or enhanced training. The interventions had a positive effect on health workers' practice in the diagnosis and treatment of febrile illness, though were also more costly than current practice. The enhanced intervention was more cost-effective than the basic intervention, when each intervention was compared to current practice, which indicates the additional two days of training represent good value for money. However,

since there is no established cost-effectiveness threshold in Cameroon, the question of whether it is cost-effective to introduce RDTs (with training) in health facilities where microscopy is already available will depend on the government's willingness to pay for improvements in the diagnosis and treatment of febrile patients. The incremental cost of introducing RDTs with enhanced training for the trial was $3.71 per patient correctly treated from a societal perspective (2011 prices). Similar ICERs have been reported elsewhere (7, 10, 11, 13, 29). For instance, the incremental cost per patient correctly treated of replacing microscopy with RDTs in public health facilities was $3.6 in Ghana (2009 prices) (13), and in Uganda was $1.78 in low and $8.9 in high malaria transmission areas (2011 prices) (11).

Differences in study design should be noted, however, when comparing results, and our study was distinctive for several reasons. First, RDTs were introduced to complement rather than replace malaria microscopy, since existing laboratory services were expected to continue in Cameroon. Second, we included the costs of training health workers and distributing revised guidelines since the NMCP indicated changes in policy would need to be disseminated. The need for interventions that improve health workers' adherence clinical guidelines was also identified in formative research and highlighted in the cost-effectiveness literature (3, 6, 8). Third, the study used individual patient-level data collected in a 'real-world' setting which meant the availability, use and quality of malaria testing was not controlled and there was variation among febrile patients in whether they were tested for malaria, the type of test used, the treatment prescribed and the prices charged. Finally, the analysis applied statistical methods that took into account the cluster randomized design, correlation between costs and effects, and imbalance between arms in baseline characteristics (17, 18). Several aspects of the study design should be noted when interpreting the effectiveness and cost-effectiveness results. The NMCP considered training as integral to the introduction of RDTs, and the evaluation was designed to focus on whether health workers' adhered to the malaria treatment guidelines. As a result, it is not possible to distinguish the effect of introducing RDTs from the effect of the training, though the observed differences between the basic and enhanced arms suggest training alone can change health workers' practice.

Moreover, the study was not designed to assess specificity and sensitivity of the tests conducted and the primary outcome was measured using the test result recorded by health

workers. Disaggregating this outcome indicated there were similar results across the study arms in the proportion of febrile patients tested for malaria. This countered our expectations, as we had expected the interventions would encourage malaria testing but we also noted there had been a substantial increase in the use of testing since 2009 (6).

The decision to focus on the treatment supplied in a single consultation, rather than the health outcome of the illness episode, also has limitations for the cost-effectiveness analysis and it would not have been possible to estimate the number of deaths (or disability-adjusted life-years) averted without making several assumptions about the specificity and sensitivity of each diagnostic methods, causes of non-malaria febrile illness, patient adherence to medication, or the costs and effects of subsequent treatment seeking. There are, however, plans to synthesize findings from this and other cost-effectiveness studies undertaken within the ACT Consortium (www.actconsortium.org), and the synthesis will include data on the accuracy of microscopy and RDT in routine use and data from following up febrile patients.

The study was designed to approximate the 'real world', though the extent to which this can be achieved in the context of a trial could be questioned. For example, while the number and distribution of RDTs supplied was based on advice from the NMCP and sought to replicate the existing supply management systems, some modifications may be needed for nationwide implementation. The timing of the evaluation is a further consideration. The results reflect the situation three months post-implementation, but we do not know whether the effect of the interventions on health workers' practice will be sustained.

We considered a scale-up scenario to facilitate the governments' decision on whether to roll out RDTs beyond the study sites. In this analysis the start-up costs incurred to develop the training were considered a sunk cost. Excluding start-up costs not only substantially reduces the cost of the intervention, but also increases the probability interventions were cost-effective. Moreover, from a societal perspective the results indicate it would be net saving to introduce RDTs with enhanced training, though there is uncertainty surrounding the point estimates.

Finally, the findings highlight two areas for further research. First, differences in the malaria positivity rates by type of test should be explored as data from a limited sample of patients re-tested by the study team indicated there were more false positives with microscopy than RDT. The observed differences are unlikely to affect the findings of this study, which assesses

whether the treatment prescribed was consistent with the test result recorded by the provider, however it would be valuable to understand the implications for health outcomes and the incremental cost-effectiveness of each diagnostic method in routine use. If there are more false positives when malaria is diagnosed using microscopy then the case for introducing RDTs with provider training may be strengthened, though the economic analysis would need to take into account the costs of treating non-malaria febrile illness as well as the cost savings from the overuse of ACT.

Second, the patient cost of testing and treatment warrants further investigation. There was considerable variation in the cost of malaria diagnosis and treatment and the cost reported by patients was often high compared to the amount we estimated it cost health facilities to provide these services. It will be important to understand the extent to which cost is a barrier to treatment seeking.

CONCLUSION

It was more cost-effective to introduce RDTs with enhanced training than RDTs with basic training, when each was compared to current practice. The supplementary training improved health workers practice, especially in terms of reducing the consumption of antimalarials among test-negative patients. Since the trial concluded, the Government of Cameroon has revised the national malaria treatment guidelines to support the use of RDT and recommend all febrile patients are tested for malaria using microscopy or RDT. The NMCP has incorporated the enhanced training in their efforts to disseminate the policy change and health worker training is due to commence in January 2014.

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Table 1: Patient and facility characteristics

	CURRENT PRACTICE	BASIC	ENHANCED
	N=681	N=1632	N=1669
PATIENT CHARACTERISTICS			
Patient's gender			
Male	45.8%	45.0%	44.0%
Female	54.2%	55.0%	56.0%
Patient's age			
6-12 month	5.7%	7.7%	6.8%
1-4 years	28.9%	29.1%	29.8%
5-19 years	28.5%	22.7%	22.1%
20-39 years	19.2%	26.4%	26.2%
40+ years	17.3%	14.2%	15.2%
Previously sought treatment for this illness episode			
Yes	73.1%	59.5%	64.8%
No	26.9%	40.5%	35.2%
Patient or caregiver asked for a blood test			
Yes	36.7%	22.4%	21.3%
No	63.3%	77.7%	78.7%
FACILITY CHARACTERISTICS			
Type of facility			
Public	85.3%	61.3%	56.7%
Mission	14.7%	38.7%	43.3%
Average number of patients at facility per day			
Mean (Range)	20.5 (5-80)	45.1 (6-300)	51.3 (4-200)
Facility had stock outs of artemisinin combination therapy (ACT) in past 4 weeks			
Yes	14.8%	12.3%	6.0%
No	85.2%	87.7%	94.0%
Study Site			
Bamenda, Northwest region	58.7%	42.8%	46.6%
Yaoundé, Centre region	41.3%	57.2%	53.4%

Table 2: Summary of effects*

	CURRENT PRACTICE	BASIC	ENHANCED
	N=681	N=1632	N=1669
PRIMARY OUTCOME			
% of febrile patients who were correctly treated according to malaria guidelines	36.8%	42.0%	55.0%
Components of Primary Outcome:			
% tested for malaria	79.2%	76.6%	78.6%
If malaria test-positive, % with ACT	75.6%	74.3%	75.8%
If malaria test-negative, % without an antimalarial	13.7%	46.6%	68.2%
MALARIA TEST TYPE AND RESULT†			
If tested for malaria, % tested using microscopy	100%	63.4%	57.3%
% positive if tested using microscopy	53.2%	39.7%	46.0%
% negative if tested using microscopy	45.9%	60.3%	54.0%
If tested for malaria, % tested using RDT	-	36.6%	42.7%
% positive if tested using RDT	-	23.2%	30.6%
% negative if tested using RDT	-	76.9%	69.4%
TREATMENT PRESCRIBED OR RECEIVED			
Of those not tested:	N=274	N=385	N=479
% with any antimalarial	90.4%	62.1%	55.3%
% with an ACT	75.6%	48.3%	47.8%
% with an antibiotic	69.6%	56.4%	52.8%
Of those who tested positive for malaria:	N=235	N=773	N=730
% with any antimalarial	96.7%	92.5%	94.4%
% with an ACT	75.6%	74.3%	75.8%
% with an antibiotic	39.1%	44.9%	42.6%
Of those who tested negative for malaria:	N=135	N=351	N=320
% with any antimalarial	86.3%	53.4%	31.8%
% with an ACT	81.3%	41.9%	22.9%
% with an antibiotic	71.5%	62.5%	63.4%

RDT = rapid diagnostic test; ACT = artemisinin combination therapy

* The results are unadjusted and do not take into account the clustering or the imbalance in the baseline covariates across the study arms.

† From facility records. Across the three arms 144 patients were retested by the study team, with 92 patients previously tested using microscopy and 52 tested using RDT. Of the 92 patients previously tested using microscopy, we found 18 (20%) were true positive, 51 (55%) were true negative, 22 (24%) were false positives and 1 (1%) was false negative. Of the 52 patients previously tested using RDT, we found 10 (19%) were true positive, 37 (71%) were true negative, 4 (8%) were false positives and 1 (2%) was false negative.

Table 3: Financial and economic costs of the basic and enhanced training (USD, 2011 prices)

	FINANCIAL COST*		ANNUAL ECONOMIC COST			
			BASE-CASE†		SCALE UP‡	
	BASIC	ENHANCED	BASIC	ENHANCED	BASIC	ENHANCED
START-UP						
Develop training (including stakeholder engagement)	20,670	46,970	5,561	12,636	0	0
TRAINING WORKSHOP						
Train facilitators & hold workshops	5,497	12,100	5,497	12,100	2,873	6,324
IN-FACILITY TRAINING						
Health workers' train colleagues	2,225	4,057	3,423	6,240	1,789	3,261
TOTAL COST	**28,392**	**63,127**	**14,481**	**30,976**	**4,662**	**9,585**

* Financial costs incurred to design and implement training.
† Start-up costs are treated as investment & annualized over 4 years. Assumes health workers are trained annually. Cost of in-facility training takes into account in-kind items and health workers' time
‡ Excludes start-up costs. Assumes health workers are trained every two years, thus implementation costs treated as investment & annualized over 2 years. Cost of in-facility training takes into account in-kind items and health workers' time

Table 4: Mean cost per febrile patient (USD 2011 prices)

	CURRENT PRACTICE N=681		BASIC N=1632		ENHANCED N=1669	
	Mean	(Min, Max)	Mean	(Min, Max)	Mean	(Min, Max)
COST OF TRAINING [a]						
Base case	-	-	0.52	(0.04, 1.57)	1.12	(0.11, 5.44)
Scale-up scenario	-	-	0.16	(0.01, 0.50)	0.35	(0.04, 1.73)
COST OF FEBRILE ILLNESS INCURRED BY PATIENTS AND CAREGIVERS [b]						
Consultation [b]	1.10	(0.00, 16.11)	1.14	(0.00, 12.72)	1.55	(0.00, 8.48)
Microscopy [b]	3.97	(0.00, 20.13)	4.11	(0.00, 19.50)	3.42	(0.00, 20.13)
Rapid Diagnostic Test (RDT) [b]	-		3.10	(0.00, 19.50)	2.43	(0.00, 18.65)
Treatment [b]	3.77	(0.00, 20.66)	4.70	(0.00, 20.98)	4.16	(0.00, 20.98)
Travel [b]	0.34	(0.00, 12.72)	0.51	(0.00, 10.60)	0.56	(0.00, 10.60)
Other *(including food)* [b]	0.20	(0.00, 14.83)	0.32	(0.00, 17.17)	0.23	(0.00, 11.23)
Travel Time *(return journey)* [c]	0.35	(0.00, 2.80)	0.30	(0.00, 4.77)	0.36	(0.00, 9.66)
Time at Facility [c]	1.48	(0.04, 11.44)	2.07	(0.00, 6.48)	2.13	(0.00, 36.62)
Total Costs to Patient	10.49	(0.51, 41.96	12.18	(0.17, 45.99	11.80	(0.08, 41.07)
COST OF FEBRILE ILLNESS INCURRED BY THE FACILITY [d]						
Consultation	1.51	(0.78, 2.48)	1.60	(0.78, 2.48)	1.56	(0.78, 2.48)
Microscopy *(if applicable)*	1.38	(1.38, 1.38)	1.38	(1.38, 1.38)	1.38	(1.38, 1.38)
RDT *(if applicable)*	-		1.71	(1.71, 1.71)	1.71	(1.71, 1.71)
Treatment *(if received)*	2.58	(0.38, 9.92)	2.22	(0.38, 16.91)	2.37	(0.38, 16.17)
Total Cost to Facility	4.82	(0.88, 12.61)	4.85	(0.78, 21.10)	4.88	(0.78, 19.19)
Net Cost to Facility [e]	0.77	(0.00, 9.11)	0.77	(0.00, 19.65)	0.76	(0.00, 16.86)
TOTAL COST: PROVIDER PERSPECTIVE [f]						
Base case	0.77	(0.00, 9.11)	1.28	(0.04, 20.62)	1.88	(0.11, 18.68)
Scale-up scenario	0.77	(0.00, 9.11)	0.93	(0.01, 19.96)	1.11	(0.04, 17.36)
TOTAL COST: SOCIETAL PERSPECTIVE [g]						
Base case	11.27	(1.89, 41.96)	13.47	(2.32, 46.40)	13.69	(2.01, 44.21)
Scale-up scenario	11.27	(1.89, 41.96)	13.11	(1.78, 46.12)	12.91	(1.81, 43.05)

a) Total cost of intervention per facility (obtained from project reports, interviews with staff) divided by the number of febrile patients per facility per year (estimated from facility records)
b) From patient exit survey. Patients reported the amount, including zero costs if the category was applicable.
c) Time of patient (& caregiver if applicable). Amount of time, as reported in exit survey. Time valued at wage of an unskilled worker (Central African Franc, CFA 1200 per day or US $2.54).
d) From facility costing undertaken at 9 facilities. Facility unit cost per activity was estimated taking into account use of HW time, equipment and supplies. Cost to facility per febrile patient was estimated exit survey data on resource use (e.g. if tested, type of test, medicines received) and average unit costs from facility costing. Cost per-patient takes into account the cadre of HW (as reported by the patient) for each activity, where possible.
e) Total cost to facility less amount patient reported for consultation, test and treatment.
f) Sum of Training Cost & Net Cost to Facility
g) Sum of Training Cost, Patient Cost & Net Cost to Facility

Table 5: Total and incremental costs and effects*

	TOTAL COSTS AND EFFECTS			INCREMENTAL COSTS AND EFFECTS	
	Current Practice	**Basic**	**Enhanced**	**Basic vs. Current Practice**	**Enhanced vs. Current Practice**
Effect (proportion of patients correctly treated)	0.25	0.35	0.50	0.10 (0.03, 0.32)	0.25 (0.17, 0.47)
PROVIDER PERSPECTIVE					
Cost (USD 2011)					
Base-case	0.56	1.62	2.24	1.06 (0.67, 2.08)	1.67 (1.24, 2.74)
Scale-up	0.08	0.55	0.65	0.46 (0.10, 1.36)	0.56 (0.22, 1.43)
Incremental cost per febrile patient correctly treated †					
Base-case	-	-	-	10.13	6.70
Scale-up	-	-	-	4.39	2.25
SOCIETAL PERSPECTIVE					
Cost (USD 2011)					
Base-case	9.83	10.68	10.76	0.85 (-0.12, 3.62)	0.92 (0.17-3.89)
Scale-up	10.30	10.55	10.12	0.25 (0.77, 2.90)	-0.19 (-1.31, 2.40)
Incremental cost per febrile patient correctly treated †					
Base-case	-	-	-	8.40	3.71
Scale-up	-	-	-	2.46	-0.75

* Estimates from bivariate multilevel model, having adjusted for clustering, correlation between costs and effects and imbalance in patient and facility characteristics. The following covariates were included: patient's age; whether previous treatment had been sought for the illness episode, and whether the patient (or their caregiver) requested a blood test; study site; type of facility; the average number of patients that attend the facility per day; whether the facility had any stock outs of ACT in the past 4 weeks and the cluster size. Full regression results are reported in Appendices C and D.

† Confidence intervals for the ICERs were not reported because there were some observations with worse outcomes and higher costs and some with better outcomes and lower costs and they cannot be interpreted.

Figure 1: Cost-effectiveness Planes for the base-case from a provider perspective (with and without covariates to adjust for imbalance in patient and facility characteristics)

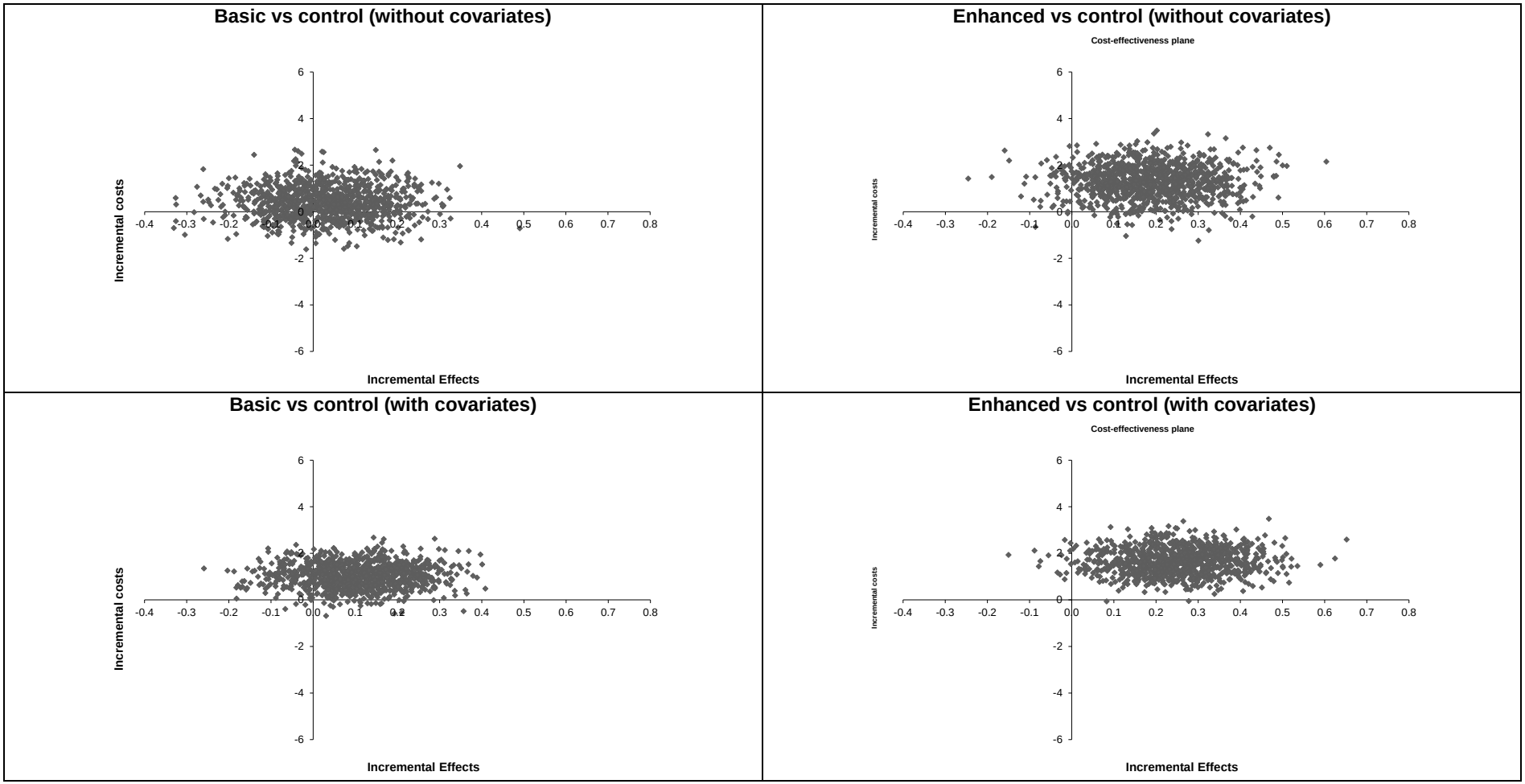


Figure 2: Cost-effectiveness Planes for the base-case from a societal perspective (with and without covariates to adjust for imbalance in patient and facility characteristics)

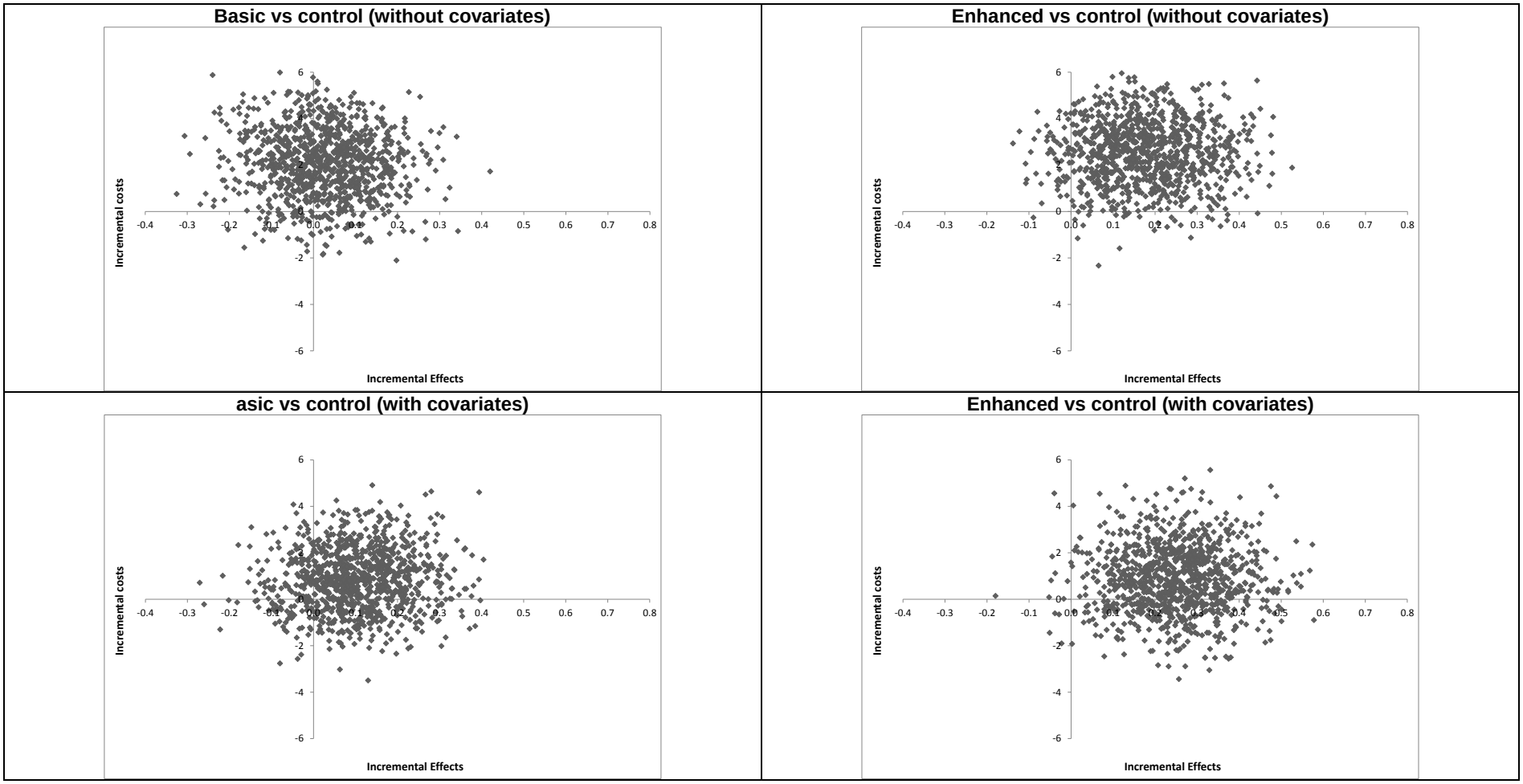


Figure 3: Cost-effectiveness Planes for the scale-up scenario from a provider perspective (with and without covariates to adjust for imbalance in patient and facility characteristics)

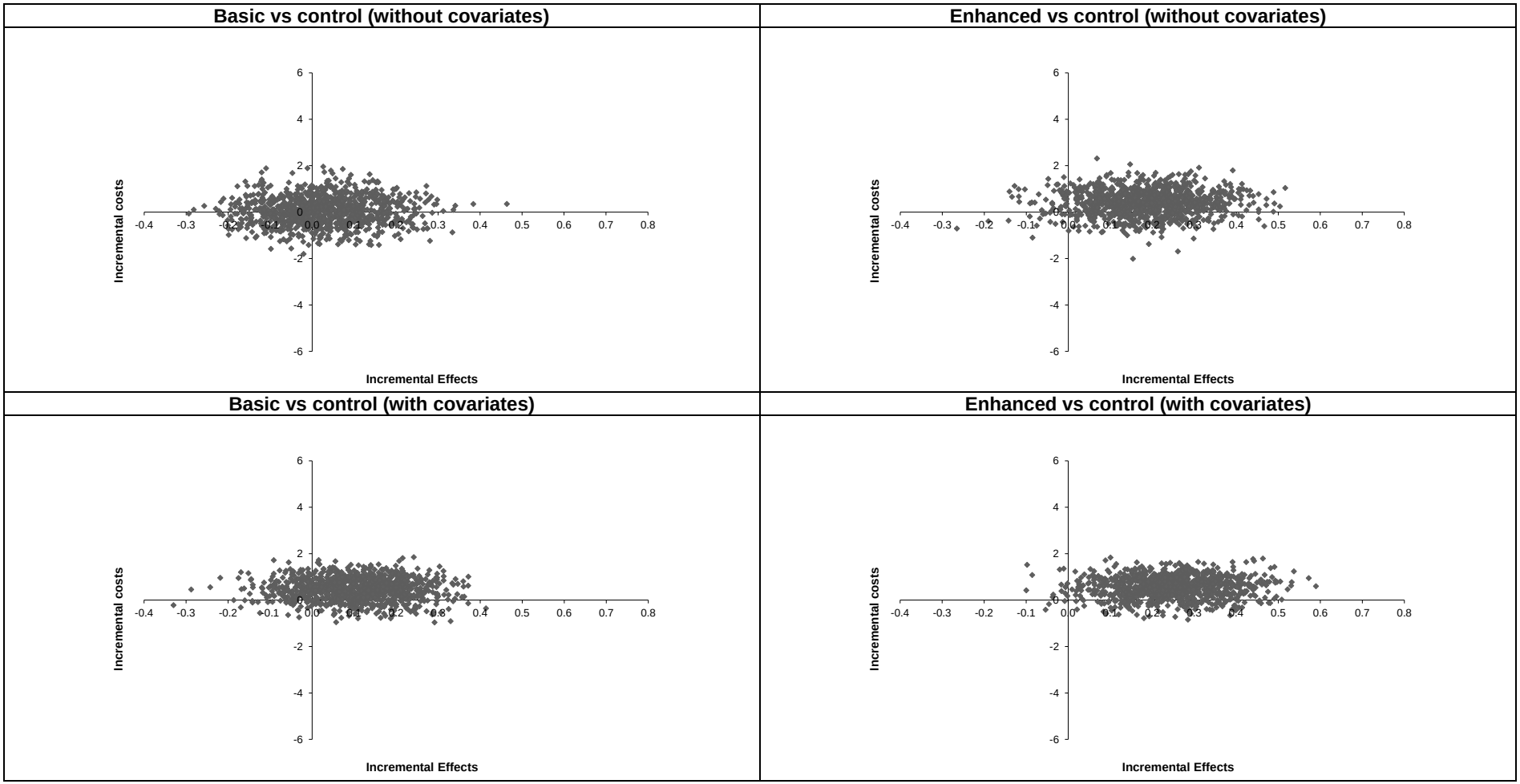


Figure 4: Cost-effectiveness Planes for the scale-up scenario from a societal perspective (with and without covariates to adjust for imbalance in patient and facility characteristics)

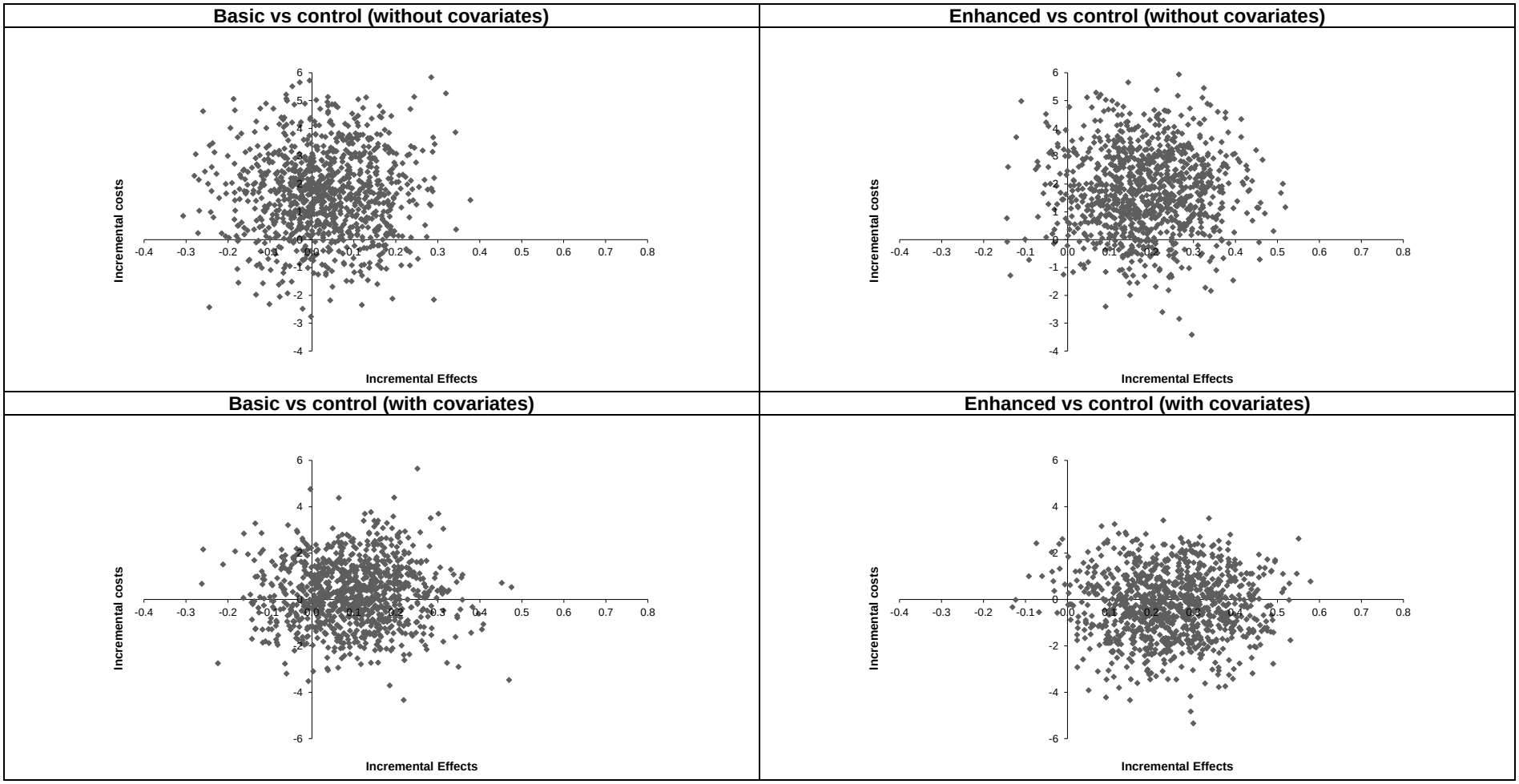
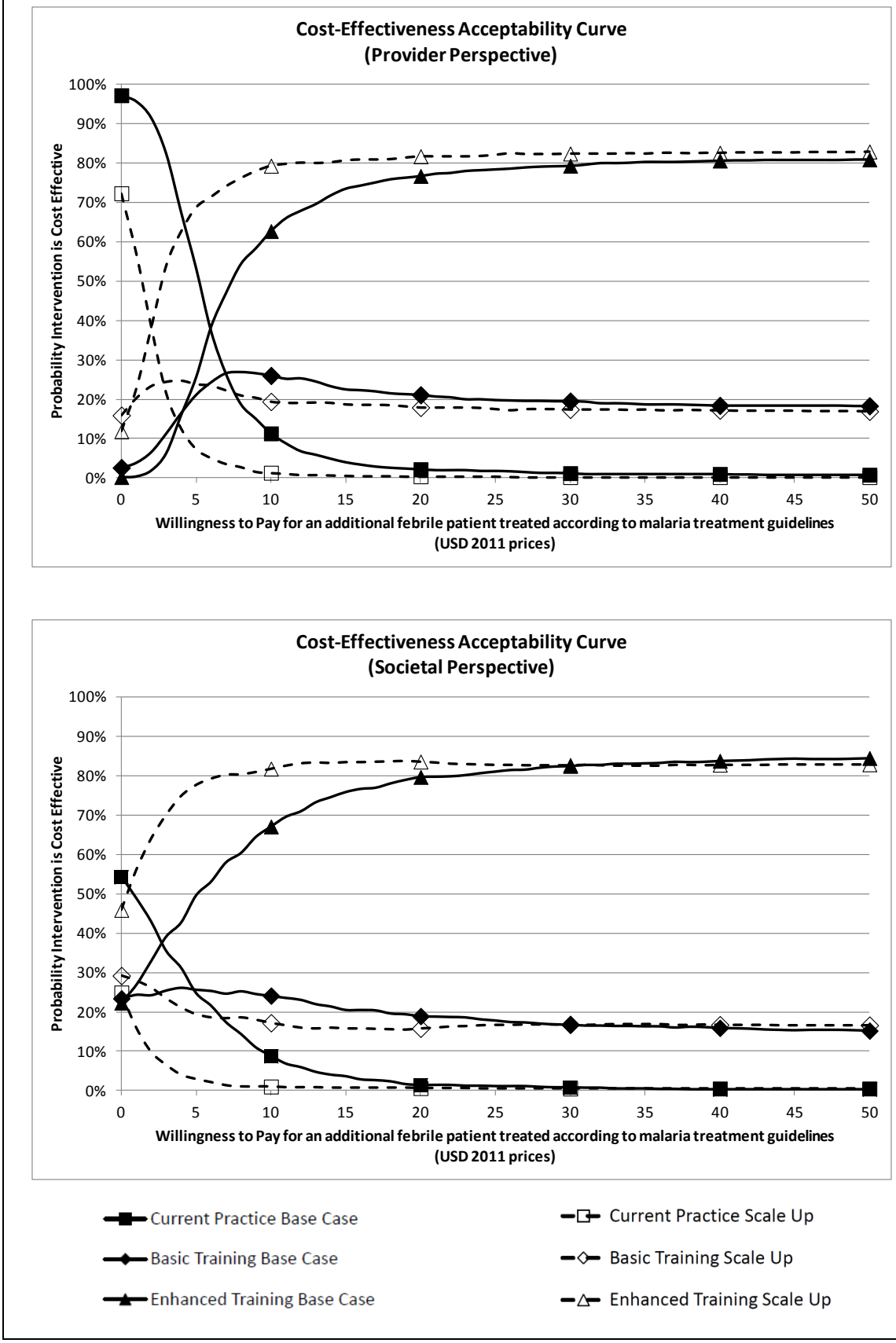


Figure 5: Cost Effectiveness Acceptability Curves



Appendix A: Financial Cost of Training Interventions (USD, 2011 prices)

CATEGORY	RESOURCES USED	TOTAL COST	ALLOCATION BY ARM	
			BASIC	ENHANCED
START UP		**46,970**	**20,670**	**46,970**
Development of training (including all materials) *	Development and piloting of training materials took place over 6 months. In total used 2 months of senior staff; 38 months of project staff & 45 days of health worker (HW) time. Costs incurred for 3 design workshops, commissioned artwork, travel and accommodation for pilot in Buea, intervention materials, stationery, office equipment and overheads	39,450	13,150	39,450
Engaging with stakeholders *	Two workshops with 33 stakeholders were held in Yaoundé and Bamenda. To prepare and hold workshops used 3 days of senior staff time, 100 days of junior staff time & 33 days of stakeholder time. Costs incurred to invite participants, venue hire, intervention materials, refreshments, travel, stationery, office equipment and overheads	7,520	7,520	7,520
TRAINING WORKSHOP		**16,461**	**5,497**	**12,100**
Training of Facilitators *	Training workshop held with National Malaria Control Programme (NMCP) staff who would deliver training alongside project staff. In total used 2 days of senior staff; 78 days of project staff time & 4 days of NMCP staff time. Costs incurred for venue hire, intervention materials, refreshments, travel, stationery, office equipment and overheads	3,409	1,136	3,409
Administration and Implementation of Basic Training	Two 1-day workshops were held in Yaoundé and Bamenda. 57 HWs from 19 facilities were invited and 50 attended. To prepare and hold training used 50 days of project staff & 2 days of NMCP staff time. Costs also incurred for venue, intervention materials, refreshments, travel, stationery, office equipment and overheads. HWs received per diems to cover transport costs.	4,361	4,361	-
Administration and Implementation of Enhanced Training	Two 3-day workshops were held in Yaoundé and Bamenda. 57 HWs from 19 facilities were invited and 48 attended. To prepare and hold training used 66 days of project staff & 6 days of NMCP staff time. Costs incurred for venue, intervention materials, refreshments, travel, stationery, office equipment and overheads. HWs received per diems to cover transport costs.	8,691	-	8,691
IN-FACILITY TRAINING		**6,282**	**2,225**	**4,057**
Health workers train their colleagues (with support from project staff) ‡	In-facility training occurred in15 of 18 (84%) facilities in the basic arm (totalling 8.5 days) and in all 19 (100%) facilities in the enhanced arm (totalling 15.5 days). Resources used varied by facility with each training lasting between 0.5 and 2 days. 2 project staff attended each in-facility training. On average 20 HWs attended each in-facility training. Costs were incurred for intervention materials, refreshments, stationery and travel.	6,282	2,225	4,057
TOTAL FINANCIAL COST		**69,713**	**28,392**	**63,127**

* Joint costs were incurred for these activities as they were undertaken simultaneously. For these activities, costs have been apportioned to the basic and enhanced arm on the basis of what costs would have been incurred if the interventions were independently developed and implemented. One-third of the costs incurred to i) develop the training materials and ii) train facilitators has been allocated to the basic arm since the training was one-third of the length of the enhanced training; while the total cost of these activities have been allocated to the enhanced arm. The total cost of engaging with stakeholders has been allocated to each arm since this cost would have been incurred if the training programmes were developed separately.
‡ Estimated per facility based on uptake and length of in-facility training

Appendix B: Characteristics of facilities (clusters) across the study arms

Characteristics	Control N_c=9†	Basic N_c=18	Enhanced N_c=19
Stratum			
Bamenda	5 (56%)	8 (44%)	9 (47%)
Yaoundé	4 (44%)	10 (56%)	10 (53%)
Type of facility			
Public District Hospital	1 (11%)	6 (33%)	4 (21%)
Public Health Centre	7 (78%)	5 (28%)	6 (32%)
Mission Hospital	0 (0%)	0 (0%)	1 (5%)
Mission Health Centre	1 (11%)	7 (39%)	8 (42%)
Time established‡			
≤5 years	1 (11%)	2 (12%)	2 (12%)
> 5 years	8 (89%)	15 (88%)	15 (88%)
Number of patients per day			
Median (Inter-quartile range)	8 (5 – 10)	20 (15 – 30)	30 (10 – 75)
Number of clinicians (median, range)			
Who regularly work at the facility	17 (4, 32)	16 (4, 35)	11 (4, 61)
Who are involved in treatment of malaria#	8 (2, 14)	8 (4, 18)	9 (4, 20)
Cadre of clinician#			
Doctor	4 (44%)	9 (50%)	9 (47%)
Nurse or midwife	8 (89%)	16 (89%)	14 (74%)
Nurse or midwife assistant	5 (56%)	11 (61%)	12 (63%)
Lab technician or assistant	8 (89%)	16 (89%)	19 (100%)
Pharmacist	2 (22%)	1 (6%)	3 (16%)
Pharmacy technician or assistant	7 (78%)	15 (83%)	14 (74%)
Services available			
Weighing scale	8 (89%)	18 (100%)	18 (95%)
Functioning thermometer	8 (89%)	17 (94%)	15 (79%)
Functioning microscope##	9 (100%)	18 (100%)	18 (95%)
Malaria microscopy testing##	9 (100%)	18 (100%)	19 (100%)
RDT, ACT & antibiotic availability			
ACTs currently in stock	8 (89%)	18 (100%)	19 (100%)
Stock-outs of ACTs in past 4 weeks	1 (11%)	2 (11%)	1 (5%)
ACT supply problems in past year	2 (22%)	3 (17%)	3 (17%)
RDTs currently in stock§	1 (13%)	8 (47%)	13 (72%)
Stock-outs of RDTs in past 4 weeks§	1 (13%)	10 (59%)	10 (56%)
Antibiotics currently in stock	8 (89%)	16 (89%)	18 (95%)

Notes: Numbers and percentages are presented unless stated otherwise. Percentages may not add to 100 due to rounding.

† N_c represents the number of clusters (facilities).

‡ All facilities had been established for a minimum of 3 years. The number of years ago the facility was established was not known for one facility in the basic arm and two facilities in the enhanced arm.

Clinicians who diagnose, prescribe or dispense malaria treatment at the facility.

One facility noted that they provided microscopy testing but they did not have a functioning microscope. All facilities that offered malaria microscopy testing had at least one laboratory technician or assistant who regularly worked at the facility, except four facilities in the enhanced arm for whom this information is not known.

§ The facility/provider questionnaire (PQ) was conducted after the last delivery of RDTs by the research team. Information missing for one facility in the basic and one facility in the enhanced arm. One facility in the control arm received RDTs as a donation and not as part of the REACT intervention. They did not receive any training associated with using the RDTs.

Appendix C: Bivariate multilevel regression results for the base-case

		Base-case from provider perspective			Base-case from societal perspective		
		coefficient	standard error	p-value	coefficient	standard error	p-value
COSTS (USD)							
Arm	Basic	1.06	0.53	0.048	0.85	1.38	0.539
	Enhanced	1.67	0.54	0.002	0.92	1.40	0.510
Age group	6-12 month	0.24	0.11	0.029	-0.33	0.37	0.374
	1-4 years	0.42	0.11	0.000	0.78	0.38	0.040
	5-19 years	0.21	0.11	0.068	0.77	0.38	0.042
	20-30 years	0.12	0.12	0.327	1.40	0.41	0.001
First time sought treatment	Yes	0.04	0.06	0.491	0.00	0.21	0.988
Asked for blood test	Yes	0.04	0.07	0.617	0.73	0.25	0.003
Study site	Bamenda	0.35	0.40	0.381	0.76	1.04	0.465
Facility type	Public	0.59	0.45	0.183	2.95	1.15	0.010
Stock outs of ACT in past 4 weeks	Yes	-0.13	0.68	0.849	-0.07	1.76	0.967
Patients per facility	Mean	-0.01	0.00	0.011	0.01	0.01	0.582
Cluster size	Cluster size	0.00	0.02	0.844	0.11	0.05	0.045
	Cluster size squared	0.00	0.00	0.022	0.00	0.00	0.047
Constant	constant	0.56	0.52	0.279	9.83	1.37	0.000
EFFECTS							
Arm	Basic	0.10	0.11	0.345	0.10	0.11	0.361
	Enhanced	0.25	0.11	0.026	0.25	0.11	0.027
Age group	6-12 month	0.06	0.03	0.049	0.06	0.03	0.050
	1-4 years	0.04	0.03	0.174	0.04	0.03	0.178
	5-19 years	0.04	0.03	0.193	0.04	0.03	0.196
	20-30 years	0.00	0.03	0.910	0.00	0.03	0.981
First time sought treatment	Yes	0.04	0.02	0.040	0.04	0.02	0.041
Asked for blood test	Yes	0.07	0.02	0.001	0.07	0.02	0.001
Study site	Bamenda	-0.09	0.08	0.307	-0.09	0.08	0.305
Facility type	Public	-0.03	0.09	0.782	-0.03	0.09	0.742
Stock outs of ACT in past 4 weeks	Yes	0.12	0.14	0.399	0.12	0.14	0.398
Patients per facility	Mean	0.00	0.00	0.068	0.00	0.00	0.072
Cluster size	Cluster size	0.00	0.00	0.548	0.00	0.00	0.549
	Cluster size squared	0.00	0.00	0.100	0.00	0.00	0.102
Constant	constant	0.24	0.11	0.026	0.25	0.11	0.025

Appendix D: Bivariate multilevel regression results for the scale-up scenario

		Scale-up scenario from provider perspective			Scale-up scenario from societal perspective		
		coefficient	standard error	p-value	coefficient	standard error	p-value
COSTS (USD)							
Arm	Basic	0.46	0.48	0.340	0.25	1.39	0.858
	Enhanced	0.56	0.49	0.250	-0.19	1.41	0.894
Age group	6-12 month	0.24	0.11	0.030	-0.33	0.37	0.374
	1-4 years	0.42	0.11	0.000	0.78	0.38	0.040
	5-19 years	0.21	0.11	0.068	0.77	0.38	0.041
	20-30 years	0.12	0.12	0.325	1.41	0.41	0.001
First time sought treatment	Yes	0.05	0.06	0.468	0.01	0.21	0.969
Asked for blood test	Yes	0.04	0.07	0.597	0.74	0.25	0.003
Study site	Bamenda	-0.03	0.36	0.944	0.38	1.05	0.713
Facility type	Public	0.51	0.40	0.200	2.88	1.16	0.013
Stock outs of ACT in past 4 weeks	Yes	-0.16	0.61	0.795	-0.10	1.77	0.955
Patients per facility	Mean	-0.01	0.00	0.085	0.01	0.01	0.350
Cluster size	Cluster size	0.00	0.02	0.959	0.11	0.05	0.037
	Cluster size squared	0.00	0.00	0.023	0.00	0.00	0.059
Constant	constant	0.09	0.47	0.853	10.30	1.38	0.000
EFFECTS							
Arm	Basic	0.10	0.11	0.346	0.10	0.11	0.360
	Enhanced	0.25	0.11	0.026	0.25	0.11	0.027
Age group	6-12 month	0.06	0.03	0.050	0.06	0.03	0.050
	1-4 years	0.04	0.03	0.175	0.04	0.03	0.178
	5-19 years	0.04	0.03	0.195	0.04	0.03	0.196
	20-30 years	0.00	0.03	0.916	0.00	0.03	0.979
First time sought treatment	Yes	0.04	0.02	0.041	0.04	0.02	0.041
Asked for blood test	Yes	0.07	0.02	0.001	0.07	0.02	0.001
Study site	Bamenda	-0.09	0.08	0.306	-0.09	0.08	0.305
Facility type	Public	-0.03	0.09	0.778	-0.03	0.09	0.742
Stock outs of ACT in past 4 weeks	Yes	0.12	0.14	0.400	0.12	0.14	0.398
Patients per facility	Mean	0.00	0.00	0.068	0.00	0.00	0.072
Cluster size	Cluster size	0.00	0.00	0.548	0.00	0.00	0.548
	Cluster size squared	0.00	0.00	0.101	0.00	0.00	0.102
Constant	constant	0.24	0.11	0.026	0.25	0.11	0.025

PART III - DISCUSSION

9. Discussion and Conclusion

This Chapter summarises the overall findings of the thesis and describes the contribution of the research. The limitations of the thesis are acknowledged and areas for further research are outlined. The Chapter concludes by considering the implications of the research for the design and evaluation of interventions to encourage providers to adhere to malaria treatment guidelines and on malaria treatment policy in Cameroon and the generalizability of the findings to other settings.

9.1. Introduction

Working as agents for their patients, health care providers are often responsible for diagnosing the illness and selecting treatment. Clinical guidelines establish standards for patient care and can expedite the introduction of new technologies or changes in policy. Conventional public health interventions typically focus on ensuring providers are informed about changes to clinical guidelines, though studies that have evaluated their effect suggest they may have a limited impact in changing providers' practice and patient care often falls short of the required standard.

The thesis is on the knowledge, preference and practice of providers treating febrile patients with suspected malaria in Cameroon and Nigeria. In this setting uncomplicated malaria is routinely diagnosed and treated by health workers in outpatient departments and primary health centres, or treated using antimalarials purchased from pharmacies and drug stores. Drawing on economic theory, research was undertaken to design and evaluate interventions to support the roll out malaria RDTs and train providers on revised malaria treatment guidelines. Providers' stated and revealed preferences were analysed,

when providers have imperfect information and are agents in multiple agency relationships. The cost-effectiveness of interventions designed to improve providers' adherence to clinical guidelines was evaluated.

The specific objectives were:

- To describe the treatment supplied to febrile patients at health facilities and medicine retailers in Cameroon and Nigeria.
- To assess providers' knowledge of the national malaria treatment guidelines and investigate the determinants of providers' stated preference for treating uncomplicated malaria.
- To examine the determinants of providers' revealed preference (i.e. their practice) for treating patients with malaria symptoms.
- To evaluate the cost-effectiveness of interventions to improve providers' practice in diagnosing and treating uncomplicated malaria at public and mission facilities in Cameroon.

9.2 Summary of the research findings

Research Papers I and II report the main findings from exit surveys with febrile patients and their caregivers conducted at different types of facility in Nigeria and Cameroon [1, 2]. These papers highlight considerable problems with the treatment supplied. Although ACT had been the first-line treatment for uncomplicated malaria for more than four years, ACT was under-used in both settings. In Nigeria less than a quarter of febrile patients were presumptively supplied an ACT and most patients received sulphadoxine-pyrimethamine (SP), which is much less effective. The situation was more favourable in Cameroon and ACT was the dominant choice, though only 51% of febrile patients eligible for malaria treatment were supplied ACT. Malaria testing had limited availability in Nigeria, and while microscopy testing was available at most public, mission and private health facilities in

Cameroon, it was under-used. Moreover, when patients were tested there appeared to be no relationship between the test result and the treatment prescribed. Independent malaria testing conducted by the Cameroon study team indicated malaria was prevalent in less than one in three febrile patients, yet 82% of patients who were tested during their consultation and did not have malaria, received an antimalarial.

As patients often rely on providers to select as well as dispense treatment, I was interested in the relationship between providers' knowledge of the malaria treatment guidelines, their preference over alternative antimalarials, and their actual practice. The descriptive statistics suggested a knowledge-practice gap, since the proportion of patients receiving an ACT appeared low when compared to the proportion of providers who correctly identified ACT as the recommended treatment for uncomplicated malaria. However, no conclusions could be drawn from these initial analyses because the study population included individuals who requested a specific medicine, as well as individuals who relied on the providers' advice. Also, exit survey responses had not been linked to the details of the specific provider who selected treatment and provider attributes were aggregated at the facility level in the regression analysis.

To explore providers' stated and revealed preferences over alternative antimalarials, secondary analyses of the provider and exit survey data were undertaken (Research Papers III and IV) [3, 4]. I wanted to understand what treatment providers' prefer to supply when they are not constrained by the resources available or patient-specific factors. This would indicate whether an intervention targeting providers' knowledge would be likely to achieve a change in providers' practice, or whether additional intervention would be needed to first change what they prefer. Hence, I decided to focus on their stated preference over alternative antimalarials as well as the treatment actually supplied. Research Paper III presents multilevel analysis on influences over providers' stated preferences, and showed that the type of antimalarial they prefer not only depended on their knowledge of clinical guidelines, but also their perceptions of what

patients' prefer, and on drug company representatives, colleagues and other providers working in the locality [3]. These findings suggested interventions to disseminate changes in drug policy should acknowledge that providers are agents serving multiple principals and involve a wide range of actors, including employers, suppliers and local communities.

Research Paper IV focused on the relationship between providers' knowledge and practice in Cameroon and Nigeria [4]. Providers' adherence to malaria treatment guidelines was examined using exit survey data from the subset of patients who relied on the provider to select treatment and were supplied an antimalarial. For this analysis exit survey responses were linked to the individual provider who supplied treatment, and two-level multiple imputation was used to impute missing data that arose when identifying the provider responsible for selecting treatment. In both countries, there was a gap between providers' knowledge and practice, since providers' decision to supply ACT was not significantly associated with their knowledge of the first-line antimalarial. Providers were, however, more likely to supply an ACT if they stated a preference for treating uncomplicated malaria with ACT (rather than other antimalarials). Other factors were country-specific, and indicated that providers can be influenced by what they perceived their patients' prefer or can afford, as well as information about their symptoms, previous treatment seeking, the type of outlet, and the availability of ACT.

Interventions were developed to improve providers' practice in diagnosing and treating uncomplicated malaria in both countries, though the remainder of the thesis focused on developments in Cameroon. Policy-makers in Cameroon were interested in malaria RDTs, and it was agreed interventions should be developed to support their introduction at public and mission health facilities. The interventions for Cameroon were selected and designed based on formative research, which included Research Papers II, III and IV, qualitative research (Appendix B) and a literature review (Section 2.2) [1, 3-5]. The findings emphasized the need to improve providers' practice when diagnosing and treating uncomplicated malaria, and suggested that conventional approaches, such as a

training workshop to inform providers of the change in malaria treatment guidelines may have a limited effect on the treatment prescribed following a negative malaria test result.

The interventions developed to improve providers' practice in diagnosing and treating malaria were evaluated using a cluster-randomized trial (Appendix C). Public and mission health facilities in the study sites were randomly allocated to one of three arms: basic, enhanced and control. Facilities in the basic and enhanced arms were supplied RDTs each month and up to three providers per facility were trained on the basic knowledge and practical skills needed to effectively diagnose and treat malaria. Providers in the enhanced arm also received two-days of supplementary training using participatory methods that explicitly sought to change providers' practice. The proportion of patients who were tested for malaria and the proportion of patients with a positive test result who were prescribed or received an ACT were similar across the study arms. However, the proportion of patients with a negative test result who were prescribed or received an antimalarial was significantly reduced in the enhanced arm, and non-significantly reduced in the basic arm. Stratum-specific relative risk results indicate the interventions were more effective in Bamenda than in Yaoundé in reducing over-treatment with antimalarials among those who tested negative for malaria (as shown in Table 3 of Appendix C), though as the sample size in some clusters was too small to do an adjusted analysis we are cautious about drawing conclusions.

The economic evaluation of interventions to improve providers' practice in diagnosing and treating patients with malaria symptoms presenting at public and mission health facilities in Cameroon was presented in Research Paper V [6]. This paper considers the economic argument for introducing RDTs with training in a setting where microscopy testing was already available. The analysis used individual patient data on costs and effects and took into account the cluster-randomized study design. The incremental cost per febrile patient correctly treated was US$ 8.40 for the basic arm and US$ 3.71 for the enhanced arm (in 2011 prices), which demonstrated that introducing RDTs with enhanced training was

more cost-effective than RDTs with basic training, when each was compared to current practice. Moreover, in a 'scale-up' scenario, which excluded the costs of intervention design, it was estimated the enhanced intervention would save US$ 0.75 per additional febrile patient correctly treated if the government adopted and implemented the training in Cameroon.

9.3 Overall contribution of the thesis

9.3.1 Economics perspective on a public health problem

This thesis approached a common public health problem, how to improve providers' performance and encourage adherence to malaria treatment guidelines, from an economics perspective. Approaching the problem from this perspective led me to question whether providers would always act in the patient's interest and supply the treatment recommended in the clinical guidelines, which is an assumption that underpins many public health interventions. Agency theory was the starting point for examining the knowledge-practice gap, as the theory emphasizes how provider behaviour may depend on financial incentives and intrinsic motivation as well as information and structural constraints, such as access to clinical guidelines or the medicines available. Thinking from behavioural economics and new institutional economics was also valuable, as it indicates that individuals may be bounded in their ability to make rational utility-maximizing decisions and constrained by the institutional and social context. Although the extent to which these theories could be tested was limited by the data available, I was able to demonstrate that there was no significant relationship between providers' knowledge and their practice, and that preferences were similar among providers working in the same facility or locality.

These findings complement the existing literature on the behaviour of providers diagnosing and treating uncomplicated malaria. Existing studies focused on the treatment prescribed at public and mission facilities, and investigated the effect of pre-service

training, in-service training, and access to clinical guidelines rather than directly assessing whether knowledge predicts practice [7-18]. In addition, most studies used generalised estimating equations to account for the hierarchical data structure and potential correlation among patients treated by the same provider. This method generates population-averaged estimates, rather than subject-specific effects, and so the extent to which unexplained variation reflected differences between providers or facilities was unknown.

Variation in providers' practice has, however, been studied in the context of other illnesses and health conditions. Wennberg coined the term 'practice style' to describe the variation in prescribing practices attributed to providers' preference over alternative forms of care [19], and economists have previously used multilevel modelling to assess, among other things, the effect of competition and remuneration systems on doctors' behaviour [20-22]. Moreover, the distinction between providers' competence and practice has been highlighted in work undertaken on quality of care in low-income settings by Das, Leonard and others [23-25]. I also recognise that this thesis contributes to a much larger body of work on patient-provider interactions, which has a long history and has been approached from many different disciplines. For example, there are anthropological models of behaviour change, such as social learning theory in which behaviour change results from observing and imitating others [26], and literature on the role of social expectations and trust within patient-provider relationships [27-29].

9.3.2 Theory-based intervention design

The research undertaken for this thesis made a substantial contribution to the selection and design of interventions to improve the diagnosis and treatment of uncomplicated malaria in both countries, though especially in Cameroon. The analysis of providers' revealed preference showed that an intervention should focus on ensuring that providers' preferences are consistent with the treatment guidelines, rather than simply informing them about recommended practice. The analysis of providers' stated preference over

alternative antimalarials highlighted the influence of multiple principals, including patients, suppliers and other providers. These findings led me to hypothesize that conventional educational interventions, which typically involve training providers to inform them about revisions to the malaria treatment guidelines, would have a limited effect on prescribing practice in Cameroon.

In early discussions, representatives from the National Malaria Control Programme in Cameroon indicated they were considering introducing malaria RDTs in public and mission facilities. It was agreed this could be explored by REACT, and that the intervention should train providers in how to use the new type of test and interpret the result, and should be easy to replicate and suitable for implementation on a national scale.

Given the findings from the formative research, a three-arm cluster randomized trial was proposed, in which two interventions: i) supplying RDTs with 'basic' training, and ii) supplying RDTs with 'enhanced' training, would be compared to current practice in health facilities where microscopy was available. The proposal to evaluate two types of training interventions arose from the hypothesis that the intervention would be more effective, and more cost-effective, if it sought to change providers' preference, rather than enhance their knowledge.

The activities included in the two supplementary days of enhanced training were chosen to reinforce the key messages about malaria diagnosis and treatment, but also based on the insights on who or what influenced providers' preference. For example, a testimonial on rapid diagnostic testing from a senior medical doctor was included since providers may be influenced by other health workers. Similarly, many of the activities used small-group exercises in which providers worked together to discuss challenges and identify possible solutions, while a module on communicating effectively with patients was included as providers can be influenced by their perception of what their patients prefer. The communications module included an activity in which providers had the opportunity to reflect and discuss patient perceptions about malaria, and also a series of role-playing

activities to generate ideas on how they could better manage patient expectations, especially when the patient tested negative for malaria.

Providers who had attended the training were encouraged to conduct 'in-facility' training and run training workshops with their colleagues using the knowledge and skills they had obtained and the training materials provided by REACT. This peer-to-peer learning was a relatively inexpensive method of extending the dissemination efforts, but also sought to build consensus within a facility on appropriate treatment of malaria. This was thought to be important because stated and revealed preferences were similar among providers within a facility, and the economics literature emphasized the importance on behavioural norms within an institutional environment.

Finally, having interventions founded on economic theory and extensive empirical analysis was important for generating specific hypotheses for how the intervention would lead to a change in providers' practice. These hypotheses were illustrated in a logic model (Section 3.2, Figure 3). This depicts the mechanisms by which the training interventions were expected to change providers' knowledge, preference and practice. The logic model proved to be a powerful communication tool, and was used within the research team, with colleagues in the ACT Consortium, and stakeholders at the NMCP. The logic model also facilitated a theory-based approach to the evaluation. It was used to map the evaluation data that would be needed to assess the intermediate as well as output indicators, and in the development of research instruments.

9.3.3 Demonstrating the explanatory potential of multilevel modelling

Multilevel modelling was used in three research papers: to analyse providers' stated preferences, to assess the knowledge-practice gap, and to determine the cost-effectiveness of training interventions in improving providers' practice. Multilevel modelling readily applies to economic and social research in which individual behaviour may depend on the influence of social groups or the social context in which they belong [30]. This can be conceptualized as a hierarchical system of individuals nested within groups, and

multilevel analysis examines the relationship between variables that characterize individuals and variables that characterize groups. Thus, multilevel models are suitable for examining variations in medical practice since they account for correlation between providers within a facility or area that may arise because they have similar incentives, share information and face a common institutional environment [31]. The intra-class correlation coefficients from Research Papers I-V are summarized in Appendix D.

Alternative statistical methods can be used to account for data that have a hierarchical structure, and to ensure the point estimates and standard errors reflect the sampling design. If the hierarchical structure was ignored, then standard errors are likely to be under-estimated, which may lead to results that appear statistically significant when in fact they are not. The first two research papers used the survey prefix (svy) in Stata 11.0 to account for the multistage sampling. This approach allowed me to obtain population-representative estimates using survey data collected from a sample of the population. In each paper results were generated having specified the geographic areas that constituted the primary sampling unit, indicated that stratification was by study site, and using sampling weights to correct for unequal probability of selection. While this approach is widely used for analysing survey data and provides unbiased esimates of standard errors, it has limitations when compared to multilevel modelling. For example, multilevel models allow the analyst to ascertain the extent to which observed variation is attributable to different levels of the data hierarchy [30]. Multilevel models also explicitly model dependencies and cope well with unbalanced data structures [30, 31]. Moreover, multilevel models have been shown to generate robust estimates for cost-effectiveness analysis of cluster randomized trials in a wide range of simulated scenarios when compared to alternative methods, including seemingly unrelated regressions and generalized estimating equations [32].

Multilevel modelling was used for the secondary analyses contained in Research Papers III and IV because I wanted to investigate subject-specific effects, between-group variability,

and the effects of group-level characteristics on individual outcomes. For example, multilevel modelling enabled me to determine the extent to which the variation in providers' practice was explained by facility-level and patient-level factors, and the extent to which unexplained variation was partitioned among different levels of the hierarchy [33]. Thus, using a multilevel model allowed me to gain additional insights that were of relevance to the research questions in those chapters. In addition to the differences in the modelling approach adopted, the results from Research Papers III and IV cannot be directly compared to Research Papers I and II because of differences in the study sample.

Each application of multilevel modelling raised different methodological considerations. Small cluster size was an important consideration in the analysis of providers' stated preferences because some facilities were staffed by sole or very few providers. In building the model the degree of variability attributed to facility and area levels was assessed using the variance partition coefficient. In addition, the deviance and the likelihood ratio tests indicated that the three-level model was superior and the results were not sensitive to the estimation method. This analysis highlighted the value in estimating the variance partition coefficient and the importance of taking into account clustering, even when the average cluster size is small.

Missing data was a feature of the analysis on providers' knowledge and practice, since it was not possible to identify the individual provider who selected treatment for all exit survey responses. The missing data were presumed to be conditional on attributes of the facility or outlet, which is known as 'missing at random' in the statistical literature. Multiple imputation is recommended when data are missing at random, and it allows for uncertainty by generating multiple copies of datasets in which missing values are imputed. Multiple imputation methods are well established, though only relatively recently has statistical software become available that allows the multiple imputation to respect the data structure. Consequently, there are relatively few empirical examples demonstrating the use of two-level multiple imputation, and Research Paper IV should be a useful case

study for others facing similar challenges. It is also relatively unusual to use multiple imputation for missing survey data, and this application demonstrates the role for multiple imputation alongside multilevel modelling in the context of relational databases.

The final application of multilevel modelling was for the cost-effectiveness analysis of the cluster randomized trial. This is also an area where there have been recent methodological developments, and there are relatively few empirical examples. Bivariate multilevel modelling is recommended for cost-effectiveness analysis when individual patient data are available and there may be intra-cluster correlation, correlation between individual-level and cluster-level effects, and imbalance between the trial arms [32, 34]. Other considerations include the distribution of costs and effects, the number of clusters, cluster size, and imbalance in the number of observations per cluster. As an initial analysis of the data indicated intra-cluster correlation, correlation between costs and effects and imbalance in selected baseline characteristics across the three arms of the trial, the incremental costs and effects were estimated using a bivariate model with individual-level and cluster-level covariates. Given the paucity of examples using individual patient data from cluster randomized trials, particularly from low-income settings, Research Paper V may prove to be a useful example for other researchers.

9.3.4 Evidence-based policy-making in Cameroon

The REACT project worked closely with the National Malaria Control Programme (NMCP) throughout the project, and the research presented in this thesis has had a direct effect on malaria treatment policy in Cameroon.

The interest in rapid diagnostic testing arose in early discussions with policy makers, as representatives of the NMCP explained they were considering whether to introduce RDTs in public and mission health facilities where microscopy testing was already available. Economic modelling studies had suggested it would be cost-effective to introduce RDTs where microscopy was already available in areas of low-to-medium malaria transmission, though also highlighted that the results required providers adhere to the test result when

prescribing treatment [35, 36]. The formative research was instrumental in highlighting the need for interventions to support the roll-out of RDTs that focused on changing providers' practice, and as already discussed, the research findings contributed to the selection and design of the training interventions.

NMCP representatives participated in intervention design and endorsed the training materials. NMCP representatives also worked hand-in-hand with the REACT research team to facilitate the basic and enhanced provider training workshops held in Yaoundé and Bamenda. This close collaboration with the NMCP helped to ensure the training interventions would be suitable for implementation on a large scale.

Since the trial concluded in 2013, the Government of Cameroon has revised malaria treatment guidelines to recommend that all febrile patients are tested for malaria using either microscopy or RDTs. The evaluation demonstrated that the enhanced intervention was both more effective and more cost-effective than the basic intervention, when each was compared to the control arm (Research Paper V). Based on these findings, the Government of Cameroon has incorporated the enhanced training in their plans to roll out RDTs and disseminate the policy change. Nationwide training of providers at public health facilities commenced in January 2014.

9.3.5 Generalizability

While the research undertaken for this thesis was focused on improving malaria diagnosis and treatment in Cameroon and Nigeria, many of the findings have implications that will be relevant elsewhere. Taking a theory-based approach to intervention design had a number of advantages, as discussed earlier, and these would readily applicable to other settings. I would encourage researchers to ensure interventions are selected and developed based on a comprehensive understanding of the prevailing context, particularly when the intervention involves some aspect of behaviour change. Similarly, I believe it is good practice to clearly articulate the rationale for intervention and ensure assumptions about the causal mechanisms are explicit.

The problems identified in the diagnosis and treatment of malaria are not unique to Cameroon and Nigeria, and the lessons from this study should be useful for researchers and policy makers in other countries who want to expand access to malaria testing and improve patient care. The findings highlight the value of understanding the relationship between providers' knowledge, preference and practice, and they demonstrate the economic rationale for introducing RDTs together with interventions that focus on changing prescribing behaviour.

Finally, many of the ideas incorporated in the development of the enhanced training could be adapted in other geographic settings, or for training on other health topics. For instance, it would be conceivable to use participatory methods to reinforce the clinical guidelines in other applications. Similarly, the small-group sessions that encourage providers to adapt to change, communicate effectively and support each other could be tailored to another setting. In fact, some of the ideas developed in Cameroon were adapted and used in Nigeria to train providers from pharmacies and drug stores. The examples included the treatment algorithm game, and the exercises that used drama and role-playing to improve providers' communication with their clients.

9.4 Limitations

The research for the thesis was undertaken in the context of the REACT project. This had a number of benefits, not least an ability to undertake policy-orientated research and contribute to improvements in malaria diagnosis and treatment in Cameroon, though it also had some constraints. From the outset I knew I wanted to study for a PhD and that my research interests related to the behaviour and actions of health care providers, and the institutional environment in which they work. However, the focus on providers' knowledge and preferences for treating uncomplicated malaria emerged following the primary analysis of the survey data from each country. While the findings suggested there may be a gap between providers' knowledge of the guidelines and their practice, inference

was limited by the study population, which included patients and caregivers who requested a specific medicine, and because exit survey responses were not linked to the individual provider that supplied treatment.

Secondary analysis of the survey data was undertaken to investigate some of the limitations of the primary analyses, however there were also some challenges with the data available. For example, it was necessary to use a subset of the exit survey responses for the analysis conducted on the knowledge-practice gap, and the sample size was limited to individuals who did not ask for a specific medicine and received an antimalarial. There were also challenges linking exit survey responses to individual providers since it was common for patients to interact with multiple providers during their visit, and the survey did not ask respondents to specify which provider had prescribed or recommended the treatment they received. Similarly, the analysis on providers' stated preferences used the sample of providers surveyed at facilities where the exit survey was conducted, but the sample size was limited by the number of providers available at the time of the survey. In addition, their preference over alternative antimalarials was obtained from the single question "which antimalarial do you think is best for treating uncomplicated malaria?" rather than elicited using more extensive stated preference techniques, such as a discrete choice experiment.

There were also challenges in examining whether providers' practice was motivated by financial incentives. Individual providers at public and mission facilities and employees in medicine retail outlets should not, in principle, derive any financial benefit from the health care interaction beyond their salary, however in practice it is not uncommon for providers to receive 'under-the-counter' payments, or for providers to encourage patients to obtain medicines from retail outlets in which they have an ownership interest [37-39]. We sought to collect data from providers on alternative sources of income and employment, though we recognise that providers may not disclose this information. Similarly we were unable to ascertain whether under-the-counter payments were received. Thus, questions remain

about the extent to which the over-treatment of antimalarials in test-negative patients that was observed in both the formative research and during the evaluation reflects providers' financial incentives.

Other limitations reflect the evaluation design. A cluster-randomized trial was a rigorous study design for determining whether the basic and enhanced interventions were effective and cost-effective. However, within each arm of the trial it was not possible to identify the relative contribution of specific activities within the training package or 'in-facility' training. Moreover, given the resources available for the study, it was not feasible to follow up patients and ascertain whether they recovered or whether additional treatment was sought. Nor was it possible to independently verify for all cases whether the cause of the fever was malaria and there are also outstanding research questions about non-malaria causes of febrile illness. A decision was made not to independently re-test all patients due to ethical concerns about testing patients twice and because we wanted minimize any Hawthorne effect associated with the data collection activities. Consequently, the primary outcome for the trial was an output indicator: the proportion of patients who received the correct treatment according to the malaria treatment guidelines. This measure was also used for the economic evaluation, which reported the incremental cost per patient correctly treated. This measure has been used in several studies to report the cost-effectiveness of RDTs, relative to presumptive treatment and microscopy [35, 40-43], though otherwise has limited comparability. Extrapolating to health outcomes was considered but not undertaken because there was substantial uncertainty relating to patient adherence to treatment, non-malaria causes of febrile illness, and the extent to which subsequent treatment would be sought.

9.5 Future research

The research demonstrated the advantages of examining providers' practice from an economics perspective, and there is a rich body of theory from which to draw when

considering provider behaviour. The extent to which some of these theories could be tested in this thesis was, however, limited by the data available, and further research would be beneficial. In recent years there has been a growth in studies exploring the effect of financial incentives on provider performance and the quality of care, either using pay-for-performance or results-based financing schemes [44-46]. In comparison, non-monetary incentives have received much less attention, though they were highlighted in selected studies and I found them to be important in previous work on the employment preferences of registered nurses in Malawi [47, 48]. There is also considerable scope to undertake empirical work to further investigate the role of the institutional and social context on providers' practice and concepts from behavioural economics.

Behavioural economics is a relatively new area of economic thinking, though there is growing interest in how it can be applied to public health problems. There are some empirical examples that focus on lifestyle choices of individuals, such as healthy eating or smoking cessation [49], though as yet few examples that focus on provider behaviour. For instance, it would be interesting to use experimental methods to explore concepts such as status quo bias and risk aversion in the context of malaria diagnosis and treatment, to understand why many providers continue to knowingly supply non-recommended antimalarials and supply antimalarials to patients who test negative for malaria.

The study was not designed to assess the specificity and sensitivity of microscopy and RDTs, and the primary outcome measure assesses whether the treatment prescribed was consistent with the test result recorded by providers in the malaria test register. A sub-sample of patients, approximately 5%, were independently re-tested using RDTs by the study team and these results suggested there may be some false positive results among those tested using microscopy. Further research on the accuracy of the microscopy and RDTs in routine use would be beneficial and the case for introducing RDTs would be strengthened if diagnostic testing with RDT was found to be more accurate than with microscopy.

Further research on the cost-effectiveness of malaria RDTs would also be useful. The arguments for testing febrile patients for malaria before prescribing treatment are primarily economic. Knowing whether the fever was malaria or had other causes should reduce the unnecessary consumption of antimalarials, assuming providers use the test result when selecting treatment [35, 50]. Guidance from the World Health Organization (WHO) was predominately based on studies that applied the specificity and sensitivity of RDTs in trial conditions [51] and on economic modelling studies that incorporated assumptions about the relative cost of testing and treatment, the extent to which non-malaria febrile illnesses were bacterial or self-resolving viral infections, the efficacy of antimalarials and antibiotics taken, and whether patients take medicines as advised [35, 50]. Since these first economic evaluations were undertaken the market for RDTs and ACT has developed and competition between different brands has reduced prices. There have also been negotiations with pharmaceutical manufacturers for the Affordable Medicines Facility – malaria (AMFm) led by the Clinton Health Access Initiative (CHAI) and these have also reduced the price of ACT purchased by first-line buyers (www.theglobalfund.org/en/amfm). Moreover, there is also growing clinical research on the causes of non-malaria febrile illness which could replace assumptions based on expert opinion. It would be valuable, therefore, to update the economic modelling studies with the latest information.

I would also like to evaluate the cost-effectiveness of RDTs with respect to health outcomes. This was a limitation of the REACT study, and having data on the specificity and sensitivity of both microscopy and RDTs in routine settings, subsequent treatment seeking behaviour and final health outcomes would strengthen the work I have undertaken. In addition, I would like to extend the economic modelling studies to take into account the cost of interventions that support the introduction of RDTs. The cost of these interventions will be particularly important for policy decisions in settings where uptake of malaria testing is low, or where providers persist in supplying antimalarials to test-negative

patients. This includes policy questions about the potential for making RDTs available in the private sector, where medicine retailers are a major source of malaria treatment.

9.6 Conclusion

The research in this thesis examined providers' knowledge, preference and practice in treating febrile patients with suspected malaria in Cameroon and Nigeria. Drawing on economic theory, research was undertaken to inform the design and evaluation of interventions to support the roll out of malaria RDTs and train providers on revised malaria treatment guidelines.

In formative research, findings from exit surveys undertaken at public health facilities and private retail outlets indicated considerable problems with malaria diagnosis and treatment. Malaria testing had limited availability in Nigeria, and while microscopy testing was available at most public, mission and private health facilities in Cameroon, it was under-used. There were also problems with the choice of treatment. Many febrile patients did not receive the recommended antimalarial, and when patients were tested for malaria, the test result was often ignored when providers were prescribing treatment.

By approaching these public health problems from an economics perspective I questioned the conventional assumption that providers prefer to act in the best interest of their patients, and I analysed their stated and revealed preferences over different antimalarials. The research recognized that providers make decisions in an institutional and social context and often act as agents in multiple agency relationships. I was able to demonstrate that there was no significant relationship between providers' knowledge and their practice, and that preferences over alternative antimalarials were similar among providers working in the same facility or locality, and therefore constrained by institutional and social factors.

The research contributed to the selection and design of interventions to improve the diagnosis and treatment of uncomplicated malaria in Cameroon. Specifically, we hypothesized that informing providers about revisions to the malaria treatment guidelines would have a limited effect on prescribing practice unless the intervention also sought to change how providers' prefer to diagnose and treat uncomplicated malaria.

Evidence on the effectiveness and cost-effectiveness of the enhanced intervention, which introduced RDTs with training that explicitly sought to change providers' practice, has contributed to malaria treatment policy in Cameroon. Since the trial concluded, the Ministry of Health has incorporated the enhanced training in the roll out of RDTs and nationwide training of providers at public health facilities commenced in January 2014. The findings also have relevance for policy makers in other settings, and highlight the value in developing strategies to improve providers' adherence to malaria treatment guidelines when expanding access to malaria testing.

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APPENDIX

Introduction to the Appendix

The thesis has three appendices:

A. A review of interventions to improve providers' ability to diagnose and treat uncomplicated malaria: Appendix

B. Research Paper VI: 'As a clinician you are not managing lab results, you are managing the patient': How enactment of malaria at health facilities in Cameroon compares with new WHO guidelines for the use of malaria tests.

C. Research Paper VII: What does it take to improve diagnosis and treatment for uncomplicated malaria? A three-arm cluster randomised trial in two areas of Cameroon.

Appendix A is the appendix to the Empircal Literature Review from Section 2.2.

Appendix B is a qualitiative study on the preferences of providers' at public and mission health facilities in Cameroon. It explores the role of malaria testing in the therpeutic process and reasons why providers prescribe an antimalarial when the malaria test was negative.

Appendix C is the main trial paper and contains information about the implementation and effectiveness of the introducing RDTs with basic and enhanced training at public and mission facilities in Cameroon. This paper complements Research Paper V, which reports the cost-effectiveness analysis.

Appendix A

A review of interventions to improve providers' ability to diagnose and treat uncomplicated malaria: Appendix

The appendix to the empirical literature review in Section 2.2 has been included as Appendix A. This contains information on publications that were rejected following the full text review, and detail of the different types of intervention that were included in the review.

Appendix A. Reasons for rejection of publications based on full text review

Country	Intervention	Reference
Intervention did not seek to improve the ability of health workers: involves introduction of community agent		
Ghana, Nigeria, Uganda	Recruit & train community medicine distributors	Ajayi IO, Browne EN, Garshong B, et al. 2008. Feasibility and acceptability of artemisinin-based combination therapy for the home management of malaria in four African sites. *Malaria Journal* 7:6.
Nigeria	Recruit & train community medicine distributors to sell pre-packaged drugs	Brieger WR, Salako LA, Umeh RE, et al. 2002-2003. Promoting prepackaged drugs for prompt and appropriate treatment of febrile illnesses in rural Nigerian communities. *International Quarterly of Community Health Education* 21(1):19-40.
Ghana	Recruit & train community medicine distributors	Chinbuah AM, Gyapong JO, Pagnoni F, et al. 2006. Feasibility and acceptability of the use of artemether-lumefantrine in the home management of uncomplicated malaria in children 6-59 months old in Ghana. *Tropical Medicine and International Health* 11(7):1003-1006.
Zaire	Recruit & train community health workers	Delacollette C, Van der Stuyfy, P, Molima K. 1996. Using community health workers for malaria control in Zaire. *Bulletin of the World Health Organization* 74(4):423-430
Sudan	Recruit & train malaria control assistants to use RDTs and treat malaria	Elmardi KA, Malik EM, Abdelgadir T, et al. 2009. Feasibility and acceptability of home-based management of malaria strategy adapted to Sudan's conditions using artemisinin-based combination therapy and rapid diagnostic test. *Malaria Journal* 8:39.
Sri Lanka (refugee camp)	Compares treatment by community health workers to Field Laboratory	Hoek WVD, Premasiri DAR, Wickremasinghe AR. 1997. Early diagnosis and treatment of malaria in a refugee population in Sri Lanka. *Southeast Asian Journal of Tropical Medicine and Public Health*. 28(1):12-17.
Nigeria	Introduction of community health workers to provide malaria treatment	Onwujekwe O, Uzochukwu B, Ojukwu J, et al. 2007. Feasibility of a community health workers strategy for providing near and appropriate treatment of malaria in southeast Nigeria: An analysis of activities, costs and outcomes. *Acta Tropica* 101(2):95-105.
Kenya	Selection, training and job aids for community health workers	Rowe SY, Kelly JM, Olewe MA, et al. 2007. Effect of multiple interventions on community health workers' adherence to clinical guidelines in Siaya district, Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 101(2):188-202.
Burkina Faso	Home management of malaria using community health workers /key opinion leaders	Tiono AB, Kabore Y, Traore A, et al. 2008. Implementation of home-based management of malaria in children reduces the workload for peripheral health facilities in a rural district of Burkina Faso. *Malaria Journal* 7:201.
Intervention did not seek to improve the ability of health workers: Assesses efficacy of clinical algorithm		
India	Clinical algorithm for malaria diagnosis	Chandramohan D, Carneiro I, Kavishwar A, et al. 2001. A clinical algorithm for the diagnosis of malaria: results of an evaluation in an area of low endemicity. *Tropical Medicine and International Health* 6(7):505-510.
Kenya	Clinical algorithm for IMCI	Perkins BA, Zucker JR, Otieno J, et al. 1997. Evaluation of an algorithm for integrated management of childhood illness in an area of Kenya with high malaria transmission. *Bulletin of the World Health Organization* 75(S1):33-42.

Gambia	Clinical algorithm for IMCI	Weber MW, Mulholland EK, Jaffar S, et al. 1997. Evaluation of an algorithm for the integrated management of childhood illness in an area with seasonal malaria in the Gambia. *Bulletin of the World Health Organization* 75(S1):25-32.
Intervention did not seek to improve the ability of health workers: Assesses efficacy of diagnostic tests		
Philippines	Compares symptom-based diagnosis, RDTs and microscopy	Bell D, Go R, Miguel C, Walker J, et al. 2001. Diagnosis of malaria in a remote area of the Philippines: comparison of techniques and their acceptance by health workers and the community. *Bulletin of the World Health Organization* 79(10):933-941.
Intervention did not seek to improve the ability of health workers: Assesses patient response to drug formulation		
Ghana	Pre-packaged chloroquine tablets and syrup	Ansah EK, Gyapong JO, Agyepong et al. 2001. Improving adherence to malaria treatment for children: the use of pre-packaged chloroquine tablets vs chloroquine syrup. *Tropical Medicine and International Health* 6(7):496-504.
Myanmar	Introduces blister packaging	Shwe T, Lwin M, Aung S. 1998. Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community based treatment of non-severe falciparum malaria in Myanmar. *Bulletin of the World Health Organization* 76(S1):35-41
Intervention did not seek to improve the ability of health workers: Assesses patient response to national malaria programme		
Vietnam	Malaria programme on prevention, early diagnosis and treatment	Giao PT, Vries PJ, Binh TQ, et al. 2005. Early diagnosis and treatment of uncomplicated malaria and patterns of health seeking in Vietnam. *Tropical Medicine and International Health* 10(9):919-925.
Descriptive study without intervention		
Zambia	Descriptive study reporting on treatment in health centres with microscopy available	Barat L, Chipipa J, Kolczak M, et al. 1999. Does the availability of blood slide microscopy for malaria at health centers improve the management of persons with fever in Zambia? *American Journal of Tropical Medicine and Hygiene* 60(6):1024-1030.
Cambodia	Descriptive study of rational drug use	Chareonkul C, Khun VL, Boohshuyar C. Rational drug use in Cambodia: study of three pilot health centers in Kampong Thom Province. *Southeast Asian Journal of Tropical Medicine and Public Health* 33(2):418-424.
Intervention, but without comparison group		
Madagascar	Training course open to international participation	Domarle O, Randrianarivelojosia M, Duchemin JB, et al.. Atelier paludisme: an international malaria training course held in Madagascar. *Malaria Journal* 7:80.
International	Online training course in microscopy	Icke G, Davis R, McConnell W. 2005. Teaching health workers malaria diagnosis. *PLoS Medicine*. 2(2):108-110.
Uganda	Provider Training (IMCI)	Karamagi CAS, Lubanga RGN, Kiguli S, et al.. 2004. Health providers' counselling of caregivers in the integrated management of childhood illnesses (IMCI) programme in Uganda. African Health Sciences 4(1):31-39.
Burkina Faso	Training of community health workers	Sirima SB, Konate A, Tiono AB, et al.. 2003. Early treatment of childhood fevers with pre-packaged antimalarial drugs in the home reduces severe malaria morbidity in Burkina Faso. *Tropical Medicine and International Health* 8(2):133-139.
Do not report on malaria-related outcomes		
Bangladesh	Provider Training (IMCI)	Arifeen Se, Hoque DE, Akter T, et al.. 2009. Effect of the Integrated Management of Childhood Illness strategy on childhood mortality and nutrition in a rural area of Bangladesh: a cluster randomised trial. *Lancet* 374(9687):393-403.

India	Quality improvement intervention (feedback to providers on case management)	Chakraborty A, D'Souza SA, Northrup RS. 2000. Improving private practitioner care of sick children: testing new approaches in rural Bihar. *Health Policy and Planning* 15(4):400-407.
Peru	Provider Training (IMCI)	Huicho L, Davila M, Gonzales F, et al. 2005. Implementation of the Integrated Management of Childhood Illness strategy in Peru and its association with health indicators: an ecological analysis. *Health Policy and Planning* 20(S1):i32-i41.
Pakistan	Provider Training (IMCI)	Luby S, Zaidi N, Rehman S, et al. 2002. Improving private practitioner sick-child case management in two urban communities in Pakistan. *Tropical Medicine and International Health* 7(3):210-219.

Appendix B: Detail of the different types of interventions

Intervention	Detail of Intervention	Malaria Specific	Facility or Outlet	Country, Year	Study
Provider Training (malaria)	Provider Training: 2-day workshop on malaria. Covered symptoms, treatment, prevention, drug resistance, referral, storage and expiry of drugs, and communication skills Printed Educational Materials: Training booklets. Posters. Supervision: Local monitoring by public health officers Consumer Education: Widespread public information campaigns National policy or initiative: MoH training programme during change from SP to ACT. Though as ACT were not OTC then were promoting AQ in drug retailers.	Yes	60 Private sector drug retailers	Kenya, 2005	[1]
Provider Training (IMCI)	Provider Training: 11-day training on IMCI, tailored to country context. Covered assessing signs, symptoms, classifying the illness based on treatment needs and providing appropriate treatment and education of the child's caregiver. Printed Educational Materials: Training materials in local language	No, childhood illnesses	20 Primary health facilities	Tanzania, 2000	[2, 3]
Provider Training (laboratory tests)	Provider Training: Workshops and workplace training covering 7 common tests including microscopy National Policy or Initiative: Assess feasibility of nationwide system for quality assurance of laboratory testing	No, training on several laboratory tests	205 Public sector peripheral laboratories	Ghana, 2000	[4]
Educational Process (self-assessment)	Provider Educational Process: 2-3 day workshop to initiate participatory approach. Followed by self-assessment to reflect on service quality and planning. Also, i) a client exit interview tool to encourage staff to talk with and listen to their clients about quality of services offered; ii) a client flow analysis tool to measure how long clients wait for services and how much contact time they have with service providers; and iii) an action planning tool to help identify root causes of problems and to develop a realistic, time bound plan. Printed Educational Materials: Self-administered guides with questions on client rights and health care needs.	No quality improvement approach	8 Primary care clinics in each country	Guinea and Kenya, 2001	[5]

Intervention	Detail of Intervention	Malaria Specific	Facility or Outlet	Country, Year	Study
Provider Training & Pre-packaged AMs	Pre-packaged antimalarials Age-specific packs of CQ and SP Provider Training 2-day training for peer educators, who then conducted 1-day training for drug retailers. Printed Educational Materials: Training manual. Materials, such as flip charts, were developed by the peer educators to use in their training workshops Consumer Education: Retailers were provided with caregiver manuals, and logos and stock to show completed malaria training. Also mass media (including radio, billboards) to encourage prompt treatment of malaria.	Yes	200+ Private drug retailers	Nigeria, 2003	[6]
A) Provider Training (RDT) & Job Aid B) Job Aid	Provider Training: 3-hour training course in preparing RDTs, including practical and an assessment of skills in conducting the test and interpreting the results. Printed Educational Materials: Job aid developed and tested with focus groups	Yes	79 Community health workers	Zambia	[7]
Educational Process (self-assessment & peer feedback)	Provider Educational Process: Self-monitoring tool and peer feedback mechanism to improve the quality of care for fever and to improve aspects of structural quality, such as cleanliness and drug availability. Self-assessment contained questions to the provider on care of fever and was used weekly for 3 months. Providers would ask colleague to observe consultation and assess compliance to fever care standards. Head of the facility completed a monthly questionnaire on the facility: services offered; supervision and oversight; drug commodities and vaccine availability; quality of physical space and equipment; and cleanliness and hygiene.	No, all febrile illness	Public health facilities	Mali, 2001	[8]
Provider Training (IMCI)	Provider Training: 5-day training on IMNCI, tailored to country context. Covered assessing signs, symptoms, classifying the illness based on treatment needs and providing appropriate treatment and education of the child's caregiver. Printed Educational Materials: Training materials in local language	No, neonatal and childhood illnesses	Public health facilities (85 health workers)	India	[9]

Intervention	Detail of Intervention	Malaria Specific	Facility or Outlet	Country, Year	Study
Provider Training (malaria)	Provider Training: 3-day training, that encouraged active participation, provides practical training. Covered brand name drugs frequently stocked. Trained to use dosage charts for CQ and rubber-stamps that depict correct CQ regimen in children of different ages. Also trained on symptoms that require referral to a trained HW. Printed Educational Materials: Training materials, including dosage charts Supervision: 1-2 hour individual sessions to observe retailers' skills in his/her normal workplace. Refresher training: 2-day refresher workshop after 6 months. Consumer Education: Information on regimen using rubber-stamps.	Yes	23 Private sector drug retailers	Kenya, 1995-1997	[10]
Provider Training (malaria)	Provider Training: 4-day malaria training using participatory methods, including role-play, practicals, small group discussions and exercises. Covered causes; symptoms; treatment; drug resistance; stock management; referral; and communication skills. In 1999 trained on CQ, from 2000 trained on SP as it became first-line OTC AM. Printed Educational Materials: Training materials. Accreditation certificates. Supervision: Two annual supervisory visits Refresher Training: 1-day workshops each year Consumer Education: Raised awareness on trained retailers and importance of prompt and effective treatment, changes in first-line AM and when to consult health professional.	Yes	Private sector drug retailers	Kenya 1999-2000	[11, 12]

Intervention	Detail of Intervention	Malaria Specific	Facility or Outlet	Country, Year	Study
A) Provider Training (microscopy + clinical diagnosis) B) Provider Training (clinical diagnosis)	Provider Training: (both arms) 5-day training on clinical diagnosis and malaria treatment malaria. Used presentations and practicals. Covered signs and symptoms, history taking, physical examination, referral, appropriate treatment and counselling patients on use of drugs. Malaria Diagnostic Testing: (one arm) 5-day training on malaria microscopy (in intervention arm). Covered how to prepare thick blood smears, identify and count malaria parasites, maintain microscope and store blood slides. Printed Educational Materials: Clinical algorithm (both arms) Malaria microscopy training manual (one arm). Supervision: Weekly supervision	Yes	16 public health centres & 13 dispensaries	Tanzania 2003-2004	[13]
Provider Training (childhood illness)	Provider Training: 1-hour individual training to improve retailers' adherence to national guidelines for malaria and common childhood illnesses (diarrhoea, ARI). Covered rational prescribing, dispensing, correct labelling, correct information or instructions on how to use or administer AM, antibiotics, anti-diarrhoea. Printed Educational Materials: Included wall charts on approved brands, and dosage charts of SP and antipyretics. Posters on how to dispense drugs given to both arms.	Yes	40 private sector drug retailers	Tanzania, 2004	[14]
Provider Training (rational drug use)	Provider Training: 1-day workshop: presentations on rational use of drugs, & national treatment policy. Also opportunity to discuss findings from baseline surveys to reinforce importance of good prescribing. Printed Educational Materials: Copies of WHO guidelines on Good Prescribing and other printed materials on treatment of ARI, malaria and diarrhoeal diseases were distributed.	No, several illnesses	private providers	Uganda, Not specified	[15]
Provider Training (malaria)	Provider Training: In-service training for medical assistants. 2-hour lecture on malaria. Covered clinical features, diagnosis and treatment, severe and un complicated malaria, chemoprophylaxis and AM side-effects of drugs. Followed by workplace training.	Yes	Medical assistants from 40 public health centres	Ghana, Not specified	[16]

Intervention	Detail of Intervention	Malaria Specific	Facility or Outlet	Country, Year	Study
Provider Training (microscopy) + Refresher Training (microscopy)	Provider Training: 12-day course on malaria microscopy. Involved laboratory practical, lectures, group discussions, demonstrations, and take home assignments. Printed Educational Materials: Training materials including microscopy slides Refresher Training: 4-day course on malaria microscopy offered to those that had previously completed the 12-day course.	Yes	Kenyan & international microscopists	Kenya	[17]
Provider Training (childhood illnesses)	Provider Training: 8 weekly 2-hour sessions on malaria, diarrhoea, guinea worm, gonorrhoea, cough, malnutrition, medication counselling and reading prescriptions. Used a participatory approach with cultural appropriate methods such as storytelling, role play and use of proverbs. Printed Educational Materials: Written and pictorial hand out materials based on lesson plans.	No, several illnesses	28 private sector drug retailers	Nigeria	[18]
Provider Training (IMCI)	Provider Training: 11-day training on IMCI, tailored to country context. Covered assessing signs, symptoms, classifying the illness based on treatment needs and providing appropriate treatment and education of the child's caregiver. Printed educational materials: Training materials in local language	No, childhood illnesses	public and NGO facilities	Uganda, 2000, 2001, 2002	[19] [3]
Economic Incentive A) Price subsidy, BCC, training, & suggested retail price B) Price subsidy, BCC & training C) No intervention	Economic incentives to providers: Pilot ACT subsidy: AL is sold to private wholesalers at subsidized prices in intervention areas using the supply chain. Then uses existing distribution channels to deliver AL to private drug retailers. Provider Training: Shopkeeper training Printed Educational Materials / Pre-packaged drugs: Simplified dosing instructions in local language. Drugs and behaviour change materials with a suggested retail price (in one of two intervention areas) Consumer Education: Behaviour change campaign (BCC)	Yes	private sector drug retailers	Tanzania, 2007-08	[20, 21]

Intervention	Detail of Intervention	Malaria Specific	Facility or Outlet	Country, Year	Study
Economic Incentive (Franchise scheme)	Economic incentives to providers: ACTs made available through private shops in targeted rural areas. Shops operate via franchise and provide a range of services. Participating shops were upgraded to private clinics by recruiting a qualified nurse. AL distributed by government central medical stores and administered free of charge to patients with malaria after confirmation with RDT. Patients pay for consultation and RDT.	Yes	9 Community & family wellness shops that joined franchise	Kenya, 2007	[21]
Provider Training (IMCI)	Provider Training: 9-day training using pre-tested IMCI course. Covered assessment and classification, identification of treatment, treat the child, counsel the mother. Involved written exercises, role plays, group discussions and drills, & practice sessions in the clinic. Printed Educational Materials: 3 case management wall charts, booklets of the wall charts, recording forms for the assessment of the sick child, draft video and photo booklet	No, childhood illnesses	3 public health facilities without laboratories (6 nurses)	Ethiopia	[22]
A) RDT provision vs No RDTs B) Pre vs post training, guidelines, supervision	Provider Training: (both arms) 3-day training course on malarial guidelines, use of AL and diagnostic tests (microscopy and RDTs) for at least one provider per facility. Provision of RDTs: (intervention arm) Provided RDTs and supplies for safe use and disposal. Printed Educational Materials: (both arms) Copy of the revised national malaria treatment guidelines and supervision. Supervision: Half-day on-site interactive discussion on RDT use, revised national malaria treatment guidelines for outpatients >=5yrs, dosing and administration of AL, management of severe malaria. National Policy or Initiative: MoH supplied AL. Training was part of the national implementation of new antimalarial policy.	Yes	60 government health facilities (hospitals, health centres, dispensaries)	Kenya, 2006	[23]

Intervention	Detail of Intervention	Malaria Specific	Facility or Outlet	Country, Year	Study
Provider Training (microscopy)	Provider Training: 6-day training on malaria for medical officers, clinical officers, nurses, midwives, laboratory staff and records clerks. Involved didactic and practical sessions. Covered malaria epidemiology, national malaria policy, medical ethics, clinical management of malaria, management of patients with fever and a negative blood slide, and medical record keeping. Malaria Diagnostic Testing: Training on preparation of blood slides and microscopy skills. Printed Educational Materials: Training materials Supervision: Supervisory visits were held after 6 and 12 weeks	Yes	8 public facilities with microscopy services (also malaria surveillance sites)	Uganda 2006	[24]
Provider Educational Process (peer educators)	Provider Educational Process: Train and equip drug wholesalers to be unpaid outreach educators of new malaria guidelines (SP now OTC). Following 3-hour orientation wholesalers offered, 1-day training for wholesaler attendants and retailers. Supervision after 3 months. Provider Training: 1-day training with wholesalers, with role play on using posters as communicate tool. Wholesalers distributed the job aids at the point of sale to vendors from wholesale and retail outlet. Printed Educational Materials: Poster for a retailer on AMs: listing malaria symptoms, dosage chart of approved brands of SP and antipyretics, and treatment advice Consumer Education: Poster at retailer to generate demand for 5 approved brands of SP and to communicate SP was now available OTC.	Yes	Private sector wholesalers and drug retail outlets	Kenya, 2000	[25]
Provider Training (childhood illness)	Provider Training: 3-day negotiation participatory sessions intended to improve private practitioners' quality of management of childhood illness. Baseline survey results were used to stimulate participants to consider their own practice compared to desired practice. Printed Educational Materials: Illustrative materials such as posters were used to explain correct malaria treatment doses. Supervision: Support visit after 1-2 months.	No, childhood illnesses	Private clinics and drug shops	Uganda, 2002-2003	[26]

Intervention	Detail of Intervention	Malaria Specific	Facility or Outlet	Country, Year	Study
Provider Training (IMCI)	Provider Training: 4-day IMCI training (not recommended 11 days). Training on case malaria management, diarrhoeal disease, pneumonia and measles. Covered signs and symptoms, classifying the illness, appropriate treatment, counselling to caregiver about how to administer medicines and appropriate home care, and when caregiver should return to facility Printed Educational Materials: Training materials Supervision: Supervision visit after 4 weeks	No, childhood illnesses	4 urban public health centres (32 health workers)	Nigeria, Not specified	[27]
Provision of RDTs (including training)	Provider Training: 2-day training and practical on RDTs for dispensary staff (in intervention arm). Covered diagnosis and treatment algorithms, and RDT (including how to perform and interpret the test, and storage and disposal). Providers instructed to prescribe per national guidelines (negative result = no AM and investigate other causes of febrile illnesses). Provision of RDTs: RDT training and sufficient supplies of RDTs (Paracheck) were distributed to each dispensary. Printed Educational Materials: Training guides	Yes	6 rural public dispensaries (without microscopy services)	Tanzania, 2005	[28]
Pre-packaged AMs (compared to routine prescription)	Pre-packaging of drugs: Pre-packaged CQ and paracetamol available in seven weight-specific regimens. Packs of CQ tablets were divided into three compartments, each containing a daily dose. Syrups pre-packaged in plastic bottles purchased by the district health management team. Patients charged for medicines. Intervention facilities charged for cost of pre-packaging, while control charged for prescribing envelopes, CQ syrup included small fee to cover the cost of the bottles.	Yes	6 public health facilities	Ghana, Not specified	[29]

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Appendix B

Research Paper VI: 'As a clinician, you are not managing lab results, you are managing the patient': How the enactment of malaria at health facilities in Cameroon compares with new WHO guidelines for the use of malaria tests

This research paper is a qualitiative study on the preferences of providers at public and mission health facilities in Cameroon. It complements the formative research using quantitative methods that is included in the main body of the thesis (Papers II, III and IV). This paper explores the role of malaria testing in the therpeutic process and reasons why providers prescribe an antimalarial when the malaria test was negative. The findings from this paper were usedto inform the design of enhanced training intervention in Cameroon.

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Article Title: 'As a clinician, you are not managing lab results, you are managing the patient': how the enactment of malaria at health facilities in Cameroon compares with new WHO guidelines for the use of malaria tests

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Abstract

In response to widespread overuse of antimalarial drugs, the World Health Organisation changed guidelines in 2010 to restrict the use of antimalarials to parasitologically confirmed malaria cases. Malaria rapid diagnostic tests (RDTs) have been presented as a means to realize the new guidelines, and National Malaria Control Programmes, including that of Cameroon, are developing plans to introduce the tests to replace microscopy or clinical diagnosis at public health facilities across the country.

We aimed to understand how malaria tests and antimalarial drugs are currently used as part of social interactions between health workers and patients at public and mission health facilities in Yaoundé and Bamenda and surrounding districts in the Northwest region of Cameroon. In May to June 2010, we held 17 focus group discussions with 146 health workers involved in clinical care from 49 health facilities.

Clinicians enacted malaria as a 'juggling' exercise, involving attention to pathophysiology of the patient as well as their desires and medical reputations, utilising tests and medicines for their therapeutic effects as symbols in the process of care. Parasites were rarely mentioned in describing diagnostic decisions.

These enactments of malaria contrast with evidence-based guidelines emanating from WHO, which assume the parasite is the central driver of practice. If RDTs are to be taken up in practice, public health practitioners need to pay careful attention to the values and priorities of health workers and patients if they are to work with them to improve diagnosis and treatment of febrile illnesses.

Background

In response to the recognition of widespread overuse of antimalarial drugs, and the consequent potential for unnecessary expenditure on subsidised antimalarial drugs, the WHO revised its guidelines in 2010 to restrict the use of ACT to parasitologically confirmed malaria cases, where diagnostics are available (World Health Organisation, 2010). This change intends new technologies to be adapted into the everyday practice of malaria.

Although microscopy is considered to be the gold standard for malaria diagnosis (World Health Organisation, 2010), it has been found to be impractical in many remote and resource-poor settings due to its requirements for trained personnel, equipment, regular supply of reagents and continued quality assurance supervision (Bell & Peeling, 2006; Moody, 2002; Zikusooka et al., 2008). Rapid Diagnostic Tests (RDTs) are being promoted as a solution to these diagnostic challenges in settings with no or poor quality microscopy. Malaria RDTs have been found to be accurate under controlled conditions, easy to use and interpret and can be performed with basic training and equipment (Nankabirwa et al., 2009; Zikusooka et al., 2008). Several studies have also suggested RDTs can be cost-effective when compared with no testing or microscopy although this depends on the prevalence of malaria, costs of testing and treatment and critically whether the treatment prescribed is consistent with the outcome of the malaria test (Lubell et al., 2008; Shillcutt et al., 2008; Zikusooka et al., 2008; Zurovac et al., 2008).

This kind of evidence has encouraged the global procurement of malaria RDTs which rose from approximately 2.9 million tests in 2000 to an estimated 80 – 90 million in 2008 (Baik & Bell, 2007).

Unfortunately many of the perceived benefits to malaria management are yet to be realized. In many settings where RDTs have been introduced, the tests have been underused and the overuse of antimalarial drugs has remained high. Even when tests are carried out, findings are accumulating from studies in different countries that show between 35 and 85% of RDT negative patients have been prescribed antimalarials (Ansah et al., 2010; Bisoffi et al., 2009; Chinkhumba et al., 2010; Elmardi et al., 2009; Hamer et al., 2007; Kyabayinze et al., 2010; Reyburn et al., 2007; Skarbinski et al., 2009). By contrast, other studies have found a reduction in overdiagnosis, down to between 4% and 16% RDT negative patients receiving antimalarials after the introduction of RDTs with various supporting interventions (Bastiaens et al., 2011; D'Acremont et al., 2009; Hopkins, 2008; Masanja et al., 2010; Mawili-Mboumba et al., 2009; Msellem et al., 2009; Thiam et al., 2011; Williams et al., 2008). In spite of this mixed evidence over the effect of introducing RDTs, and in the absence of good information about the best way to support their introduction for effective adoption, scale-up of the tests is being promoted (World Health Organisation, 2010), and many countries including Cameroon have included the tests in their Global Fund grant applications (Ministry of Public Health, 2009).

An understanding of how testing is conceptualised is needed in order to maximise investment in the scale-up of RDTs. In spite of the high quality of many RDTs (World Health Organisation et al., 2008), studies have suggested that providers are unsure about the accuracy of tests, especially negative results. This persists even when they perform the test themselves and particularly when the results clash with observed signs and symptoms (Kyabayinze et al., 2010; Moonasar et al., 2007; Rowe et al., 2009; Uzochukwu et al., 2010). Results from a recent survey of health facilities in Cameroon in 2009 indicate malaria is significantly overdiagnosed and mistreated (Mangham et al., 2011). The Ministry of Public Health in Cameroon promotes the rational use of ACTs using microscopy before providing treatment in all cases of fever in patients over five years (Ministry of Public Health, 2008).The survey, a baseline to

the current qualitative study and precursor to a randomised controlled trial to introduce RDTs, found that 81% of febrile patients on exit from public and mission health facilities were prescribed antimalarials, though only 35% of febrile patients on exit had malaria parasites according to the results of RDTs conducted by the study team.

Social relationships have been underscored as important in diagnostic decision making and are shown to have an important bearing on whether negative test results are adhered to. Social relationships are often based on a perceived or real demand from patients for antimalarials (Chandler et al., 2008b; Onwujekwe et al., 2009) as well as habitual practice built on observation and expectations from colleagues within communities of practice (Chandler et al., 2008a; Chandler et al., 2010). Undertaking qualitative studies to understand local conceptualisations of malaria treatment and diagnosis is essential in order to design supporting interventions for the introduction of new technologies such as RDTs in different settings. In this study qualitative methods were used to understand how new diagnostic guidelines to restrict antimalarials to patients with malaria parasites on blood testing could be implemented, alongside the introduction of RDTs, in an upcoming cluster randomised controlled trial (clinicaltrials.gov NCT01350752).

Theoretical orientation

In this work, we adopt a meaning-based, interpretive approach to understanding malaria in practice, well established in the field of medical anthropology (Nichter, 2008). We see 'malaria' as a term with multiple meanings, held by and communicated between health workers and their patients as well as other communities of stakeholders across educational, economic and geographic boundaries (Beisel,

2010). We conceive that constructions such as 'malaria' become apparent as such diseases are 'enacted' or practiced, following Mol (2002) who presented an ethnography or 'praxiography' of arthrosclerosis as a disease, showing how medical technologies, arteries, doctors and patients enact different versions of the disease through coordination, interference and contradiction in medical practices.

We have problematised the enactment of malaria by health workers through analysis of the roles of different processes and paraphernalia. To do this, we draw on long-standing work on symbolism in medical practice (Kleinman, 1973) and the role of tangibles such as medicines that can facilitate communication about experiences that may be difficult to express (Van der Geest & Whyte, 1989). In the case of artefacts involved in diagnostic procedures, we are sentient to the arguments of the 'technological imperative' of medicine as practiced in Northern societies (Koenig, 1988), with diagnostic technologies representing reductionist notions of health as localised and identifiable within the body, privileged over clinical information gathered from listening, looking and feeling patients, as 'paraclinical' information (Feinstein, 1975).

We view the introduction of new guidelines and technologies for diagnosing 'malaria' that have emerged from outside of Cameroon through the analytical lens of evidence based medicine (EBM) as a social movement, following Pope (2003). Emerging within the medical profession in Northern countries, EBM has been observed to have shifted notions of 'evidence' from clinical reason, based on experience of what worked, and rooted in pathophysiology together with social and cultural knowledge of the individual patient, to probabilistic rationality based on the results of clinical trials (Armstrong, 2002; Mykhalovskiy & Weir, 2004). In this paper, we analyse how malaria and its treatment are enacted by health workers and consider how this relates to emergent evidence based guidelines.

Methods

We carried out focus group discussions (FGDs) with health care providers and with community members in two areas of Cameroon. This paper presents analysis drawn from the provider side. Findings from the community FGDs will be presented elsewhere in order to allow sufficient space to present each perspective. The two areas were chosen by the broader study team to represent Anglophone and Francophone areas in which an upcoming trial of different supporting interventions for the introduction of RDTs would take place. This qualitative research aimed to contribute to the design of supporting interventions by identifying factors important to consider across different areas, cadres and administrative types of providers.

Study area

The study areas were Yaoundé, the bustling capital city of Cameroon, situated in the Central region in the Francophone area of the country, and Bamenda and surrounding area in the Northwest region in the Anglophone area of the country. Yaoundé has 8 health districts within the urban capital, five of which were included in our study. In the Bamenda study area, we included the urban district plus seven neighbouring rural districts: Tubah, Batibo, Ndop, Santa, Bafut, Mbengwi and Bali. Both areas have a mix of formal health facilities and medicine retailers. Public and mission hospitals and health centres form the bulk of the formal health system, although there are many more private pharmacies and others selling medicines privately. Malaria is endemic in both study areas.

Participant selection

Potential recipients for future introduction of malaria RDTs at health facilities were invited to participate in the FGDs. All health workers who had a role of prescribing or dispensing and administering medicines at public or mission health facilities in the study areas were therefore eligible. We separated the participants into different cadres of medical doctors or nurses/midwives/nurse assistants in order to foster more openness amongst participants. We identified potential participants from an earlier census survey of health facilities in the two study areas and from lists provided by the person in charge of the health facilities. We aimed for 8-12 participants per FGD, and if there were too few eligible to participate from one health facility, we grouped together participants from neighbouring health facilities. Health workers were invited to attend the FGD in a meeting area that was convenient for participants and provided a private space to discuss. No incentives were provided, other than transport refund for those health workers travelling to attend the discussion.

Focus group discussions

We chose to carry out FGDs rather than one-to-one interviews in order to stimulate and observe discussion amongst participants about the research topics. Health workers were given information sheets and consent forms which were explained and discussed in the group. Those choosing to participate were asked to sign consent forms prior to the start of the FGD and were given identification numbers for anonymity. The FGDs were facilitated by one member of the study team, accompanied by a note taker and a co-ordinator. The facilitator followed a topic guide to stimulate discussion with open-ended questions on the role of antimalarial drugs and tests in participants' practice, perceived reliability and logistics of existing tests, perceptions of community preferences, and their relationships with practice. Discussions were held in French in Yaoundé and Pidgin English in Bamenda, although

facilitators were flexible to the preferences of participants to use different languages. The note taker recorded the discussion with a digital recording device and made detailed notes to record participants' contributions, non-verbal communication and the atmosphere of the FGD. The coordinator collected demographic and work history information and provided refreshments after the discussion. After each FGD, the study team reflected on the discussion held and any challenges faced in facilitation, or new ideas arising, and circulated a summary for further discussion with investigators.

The study team consisted of five facilitators, all of whom were researchers at the University of Yaoundé in biomedical departments, although none were health care providers, and eight note takers/coordinators. The team completed an intensive 7-day training carried out by CC, an experienced social researcher, to orient them to the study's objectives and methods and to practice skills in carrying out FGDs, following exercises for communication skills development (Haaland et al., 2006). Fieldwork took place after a period of pretesting and revision of tools, in May and June 2010.

Data handling and analysis

Audio recordings and notes were transcribed using a word processor. The transcription was then checked and edited by another member of the study team before it was translated into English. Translations were then cross-checked and finalised by the study coordinator.

FGD summaries, translations and enrolment form information were imported into NVivo 8 (QSR International). They were read carefully for the overall flow of the discussion and then coded line-by-line, labelling ideas described or implied by participants. These ideas were then grouped together into themes in a continuous revision process as more transcripts were reviewed. A coding template was set up by CC and two social science research assistants completed the coding, with agreements on coding reached through close communication and frequent reviews and revisions to the template. Higher level

concepts were interpreted from the themes together with review of literature and theory relevant to the themes emerging. Findings in the paper represent a narrative of the central conceptualisations developed through this analysis process.

Ethics

The study was approved by the National Ethics Committee, Cameroon (reference: 030/CNE/DNM/09) and ethics review board of the London School of Hygiene & Tropical Medicine, UK (reference: 5885).

Study participants

We held 17 focus group discussions with health workers from public and mission facilities across the two study areas in Bamenda and Yaoundé. A total of 146 health workers participated in focus groups, with a median FGD size of 9 participants. Eight health worker FGDs were held in the Bamenda study area and 9 in Yaoundé and each site included FGDs with medical doctors and with nurses of different cadres, the majority (90%) of whom reported their responsibilities currently included prescribing treatment (Table 1). In Yaoundé, nurses who prescribed were of a higher cadre, including staff nurses and registered nurses. In Bamenda, nurses also included nurse assistants. Otherwise, characteristics of health workers were similar between sites (Table 2). Most of the health workers were female, although the medical doctors were predominantly male. The median age was 39 and around a third of the participants were originally from the region in which they were now working. Most had at least a secondary school education, and 34 held medical degrees. Most health workers had undergone at least 3 years of professional training, although Yaoundé participants had undergone more years of training than staff in Bamenda. Overall, almost half had graduated in the past 10 years. Many (56% overall) had never

received malaria related in-service training, while a small minority had attended more than three malaria trainings. None had used a rapid diagnostic test for malaria, whilst almost all facilities did have microscopy available.

Results

We identified key themes that were important across the different sub-groups in the study. We found antimalarial prescriptions, antimalairal drugs and malaria tests to have multiple functions in the practice of health care, including but not limited to pathophysiological functions. Malaria drugs and tests also performed psychological and social functions. Drugs, prescriptions and testing procedures were imbued with different meanings, based on an understanding of what is required by patients in general, and each patient in particular. Underlying the varied use of malaria drugs and tests was flexibility in the category of 'malaria' that allowed various ailments to be incorporated within its socially acceptable label. This flexibility is assisted by the ambiguity of malaria in local clinical guidelines, with presumptive malaria treatment recommended as the default course of action.

Enacting malaria: pathophysiology

Foremost amongst reasons given by health workers in all groups for antimalarial prescription was to treat particular signs and symptoms, particularly fever, headache, vomiting and body or joint pains. Such symptoms were 'clearly' malaria, a diagnosis that overshadowed all potential others in the narratives of participants. Health workers talked about how their clinical experience shaped their recognition of malaria symptoms, particularly observing positive responses to antimalarial drugs:

> 'From my day to day experience, the patients to whom I had prescribed, they got well. So, that one can also influence me to go on with the sign and symptoms that they are giving, so that I know that the other one had it and I gave this drug and the patient is well, so I can continue with it to the others.' (P5, FGD104 Bamenda, mission facility midwives/nurses)

Health workers described tests as important and desirable, but their results were overshadowed by the role of clinical judgement when it came to prescribing,

> 'There are clinical and biological reasons [to prescribe antimalarials]. Biologically, the thick blood smear, or a previous history. Priority is always given to the clinical despite the results of the thick blood smear. But at least, the malaria test is an important stage.' (P4, FGD307 Yaoundé, mission facility medical doctors)

The importance of treating cases as malaria presumptively was highlighted by many respondents who discussed their personal experiences of the risks of malaria – both in its frequency and its dangers,

> 'I would also like to say, we are in an endemic zone. That is, in particular, in Cameroon, the species of malaria is the *Plasmodium falciparum* ... It is the most devastating species which has after effects. There are some children who remain paralysed ... I saw children at the Central Hospital who were completely in a vegetative state because of malaria ... And for us, the first thought is that it is malaria. When we fall ill we think it is malaria' (P10, FGD300, Yaoundé public facility nurses).

In contrast with the strong feeling that malaria is well known, common and serious and therefore must be treated presumptively, feelings about testing were ambivalent. When asked about practice with negative malaria test results, respondents in all 17 FGDs stated that results do not change their treatment with antimalarials. In most cases, what health workers saw and heard from patients ('signs and symptoms') dictated treatment regardless of test results,

> 'When we do the malaria test and it comes out negative, it does not prevent the patient from having his malaria ... We continue with the antimalarial treatment.' (P11, FGD305 Yaoundé, mission facility midwives/nurses)

Malaria as a clinical entity was thus defined beyond the boundaries of laboratory diagnosis. Clinical judgement of the health worker was most important, especially as the quality of laboratory staff and resources was sometimes questioned. Notable was the absence of statements of the reason for prescribing antimalarials being related to killing parasites, mentioned in only one focus group.

Enacting malaria: psychology

Health workers in both regions and across cadres repeatedly emphasised the importance of 'psychological treatment' for patients as central to their healing and satisfaction,

> 'In the definition of medicine, we say the doctor treats the body and the soul, isn't it? It implies that when a patient comes to you, if he is uncomfortable in his head, even if you give him the best drug, he would not be healed, isn't it? So, a patient who comes, the psychological treatment is the first thing.' (P3, FGD306 Yaoundé, public facility medical doctors)

Health workers related that it was the welcome they gave to patients (at 15 FGDs) and the good interpersonal skills of the staff (at 13 FGDs) that satisfied patients. In only four FGDs did health workers discuss the availability of testing services as important to patients.

In this context, where psychological treatment of patients was apparently so central to practice, it is perhaps unsurprising that medicines were sometimes given to patients as a 'placebo,' including antimalarials, other medicines and the mode of delivery. For example, drips were often symbols of care for patients,

> ‘We can just put an IV line and some B-complex inside just for placebo to flatter them. Because when they see that thing they think that it is malaria, but we are giving our antibiotic!’ (P8, FGD100 Bamenda, public facility nurses).

However, health workers also described diagnostic tests as psychological, or ‘placebo’ treatment. Health workers from different cadres and in both areas said they felt that most patients liked to have tests performed, although there are some who did not ‘know the lab.’ Respondents made it clear that a key reason tests were done was for the psychological rather than diagnostic benefits,

> ‘Some patients when they come, they already have in mind that they must do a laboratory test. So even when you observe that they do not necessarily need the test, we simply request the test because they want it to be done. We also request the test because they also require some psychological treatment. If you observe the symptoms they present, we simply prescribe them drugs, and to boost their psychological treatment we prescribe the test.’ (P8, FGD301 Yaoundé, mission facility nurses)

> ‘According to me, most of the times I will send the patient for a malaria test just for the psychology of the patient, just to please the patient... but if I have to decide, the lab test will not count. Clinically I take my decision to treat my patients.’ (P4, FGD107 Bamenda, mission facility medical doctors)

Enacting malaria: social context

In addition to responding to clinical and psychological needs of patients, health workers across different sub-groups recognised the importance of considering other aspects of the backgrounds and needs of

their patients, including their educational background, their financial capabilities and the beliefs of the patient about their illness.

Considering education and economics

Health workers identified differences amongst their patients in expectations for malaria treatment and laboratory investigations. Broadly, those considered better educated and more able to pay would ask more questions and expect laboratory tests in order to know what their disease was. For others, who were described as 'not knowing' the lab, or who could not afford it, health workers reported that they would usually not test but move straight to treatment. For context, our baseline survey suggests patients pay on average 1 USD for a consultation, 2-3 USD for a malaria test and around 6 USD for all medicines received.

> 'When a patient comes in and then you see that the patient hasn't money you just go straight to giving the treatment rather than sending the patient to the lab, while when coming back from the lab he will not be able to buy drugs.' (P6 FGD103 Bamenda, public facility nurses)

This may be partly based on fears that patients may be dissatisfied upon receiving negative results,

> 'Yes, we have already had a lot of problems with patients as regards the results. Because some patients, when you tell them it is negative, he puts in his mind that he has lost his money whereas when it is positive, he is happy.' (P3 FGD302 Yaoundé, public facility nurses)

Some health workers in Bamenda also expressed fears that they may be left to pay the expenses for very poor patients, leading to decisions for a less expensive consultation.

Considering the patient's concerns

Aside from the patient's educational and financial status, health workers described that for a patient to feel properly 'treated,' their concerns needed to be recognised and responded to. In some cases, this meant treating *their* malaria, even if it wasn't strictly what the health worker would define as malaria,

> ‘So they come in saying “I have malaria,” so they consider all fevers to be malaria. So if you do not prescribe what treats their malaria, you have not prescribed what treats their illness. So, they feel well. They feel satisfied because you have responded to their concerns.’ (P6, FGD301, Yaoundé Mission facility nurses)

Proper management of patients also meant giving confidence to the patient in the ability of the health worker. This involved specific processes of care and the use of particular artefacts such as drips and tests, and the declaration of ‘malaria’ if this was suspected to be the patient’s expectation. Health workers in all groups noted malaria as a more acceptable diagnosis than others. The acceptability of malaria was demonstrated by the ownership participants attributed to the disease, as ‘my malaria’,

> ‘Patients prefer malaria because, when they have malaria, they already conclude that it is “their malaria.” They even come to the hospital and say: “no, I know that it is malaria that has been troubling me. It is my illness.” And when you confirm to them that it is malaria, he is happy.’ (P9 FGD100 Bamenda, public facility nurses)

Health workers identified that patients were generally relieved to receive malaria treatment or diagnoses because it is a disease that is common and well known, possible to cure, with simple treatment, and a less distressing diagnosis overall than others such as diabetes, hypertension, TB or HIV, which health workers found far harder to deliver to patients.

> ‘I usually say that it [malaria] is an elegant sickness. “What do you have?” “I have malaria!” So when they get to the hospital and it is truly confirmed that they have malaria, they are happy. They say to themselves “No, it’s ok.” It means he knows that malaria is easy. It is a sickness which can be easily treated. (P3 FGD301 Yaoundé, mission facility nurses)

Juggling patient concerns and clinical reputation

The many reasons for malaria acceptability meant that health workers found it hard to give non-malaria diagnoses and treatments, with an array of difficult patient responses to navigate. In the case of negative results, some health workers reported the need to emphasise their knowledge of malaria over that of the patient in order to persuade them of another diagnosis. However, this was not always easy, particularly with 'those who have been to school and believe that they know all in all the domains' who would not accept a negative malaria diagnosis. For fear of their competence being undermined, participants, particularly the medical doctors, said they often made the malaria diagnosis anyway,

> 'Yes as a clinician ... you are not managing lab results you are managing the patient ... when the lab results come back you are not going to tell the patient that you don't have malaria. You are going to explain to the patient that "this test is negative but it doesn't mean that you don't have malaria," so you still go ahead and treat. So it depends on how you disclose the information to the patient because if you just sit back and tell the patient that you don't have malaria then the patient will even have the impression that you don't know what you are doing.' (P3 FGD107 Bamenda, mission facility medical doctors)

> 'What could we also say to the patients who comes with a negative malaria test whereas we are suspecting malaria? We could only tell him that it is a drop of blood that was taken for analysis. If we had taken a good quantity of blood we could find malaria, we could find the parasites. So, it is just a drop of blood, he needs not worry, yes he has malaria.' (P6 FGD306, Yaoundé public facility medical doctors)

This left health workers to juggle patient expectations alongside the need to maintain professional and institutional authority, sometimes through bending realities in explanations to patients and contributing

to malaria overdiagnosis,

> 'If the test is negative whereas we suspect malaria in a patient, I try to, it would first of all depend on the attitude that I had with the patient at the start, the degree of confidence that I did have with him. I would not try to explain him the things of the hospital, like to tell him the laboratory things. I just try to tell him "it could happen that the thick blood smear, your blood that was taken, the parasitaemia was not high, but you are supposed to have malaria." I tell him like that and I put him on treatment. So, I try to reassure him that it is just as a result of the blood that was collected, in order not to incriminate the hospital.' (P2 FGD306, Yaoundé public facility medical doctors)

Enacting malaria: 'evidence'

In around half of the FGDs, across the participant sub-groups, discussions of malaria diagnosis included citation of guidelines, mostly noting that presumptive treatment was the malaria policy,

> 'To respect the standard policy for the management of malaria, once there is a fever, you have to put an antimalarial treatment.' (P3, FGD306 Yaounde, public facility medical doctors).

Indeed, the 2008 guidelines promote presumptive treatment of fevers with antimalarial drugs (Ministry of Public Health, 2008) by stating:

> **'Fever** is the most frequent symptom and the most reliable criterion in the diagnosis, treatment and follow-up of malaria.' (emphasis in original)
>
> Then,

> ‘Malaria diagnosis is based on the identification of plasmodium with the microscope either on a blood film and/or a thick blood smear. However, a negative result does not rule out the presence of malaria.’
>
> And, as a ‘hint’ on the last page,
>
> ‘Malaria is a costly disease to the household and to society. The importance of an appropriate treatment cannot therefore be overemphasized.’

The word ‘evidence’ does not appear in the guidelines at all, and their style conveys authoritative information, based on objective knowledge. It also carries an implicit assumption that clinicians can identify malaria in spite of laboratory results that may be negative. Respondents, particularly medical doctors, did show awareness of an apparent paradox in this practice, but this awareness was not sufficient for most to challenge its premise,

> ‘[sending patients for tests] allows them to be reassured but it is a little bit paradoxical because there are patients who come, who would do the malaria test which would turn out negative, but you would nonetheless put him on antimalarial treatment.’ (P1, FGD307, Yaoundé, mission facility medical doctors)

Uniquely, one medical doctor did use the term ‘evidence based medicine’ to account for his decisions to restrict antimalarial drugs to those with parasites,

> ‘As I said earlier, I believe in evidence-based medicine. If I have a patient who has not taken antimalarial drug before coming to me and the malaria parasite is negative. I know that you people will disagree with me but I am not tempted in treating that patient for malaria. I know that you disagree with me. But I will look for other causes. Because we have the tendency of treating everybody in Africa for malaria, when we have many other pathologies who can present the

> commonest symptoms which is fever. So I believe in evidence based medicine. I don't treat [by] giving malaria drugs [P1 and P5 and start smiling] just like that.' (P2 FGD307 Yaoundé, mission medical doctors)

However, in the main, malaria diagnosis and treatment at health facilities could be described as based on 'evidence' that could be captured from observation and listening to the patient. This is in line with existing guidelines. However, in line with the international move towards evidence-based medicine, the country's 2009 Global Fund application declared promotion of the 'rational use' of ACTs by using RDTs or microscopy before providing treatment in all cases of fever in patients over five years (Ministry of Public Health, 2009).

Discussion

Antimalarials are overprescribed in Cameroon. This practice appears to be embedded in the social enactment of malaria, a wider concept than *Plasmodium* parasites. The richness of medical decision making is not usually targeted by evidence-based guidelines, but is crucial for understanding the context within which guidelines are enacted. This paper highlights three areas that are downplayed in such guidelines: individual experiences of clinicians, perceived psychological responses of patients and the social context of the patient and clinician; each reflecting what is valued as 'evidence' in local schools of medical thought.

The clinical rather than 'paraclinical' mode of diagnosis described here is in line with observations from elsewhere that clinicians often practice with a more 'interpretive' than 'probabilistic' model, whereby interpretation seeks to make sense of 'the whole story' of a patient's condition, and is 'therefore irreducible to probabilities, no matter how rigorously derived' (Tanenbaum, 1994)(p31). In this interpretive line of practice, based on a realist rather than empiricist school of medical thought, diagnosis is not limited to the black-and-white ideal of restricting treatment as dictated by a laboratory. The use of 'psychological' treatment – in the form of medicines but also procedures such as tests or drips – also demonstrates a more interpretive, as well as paternalistic approach, providing what is perceived as needed for that patient. Malaria test results may have been largely ignored in the face of clinical symptoms, but they served an important function in providing care to patients. This extends the idea of the 'placebo' beyond the idea of the accompanying therapeutic effect of giving a drug to a patient from a specific prescriber in a specific context (Claridge, 1970), to the therapeutic effect of entering a diagnostic process. The belief of health workers in this study that processes of care play a role in therapy mirrors findings of trials that various processes, including the use of instruments and labels

for diagnoses, affect health outcomes (Moerman, 2000), reflecting the power of their symbolic value. It is interesting to ask why the health workers in this study use these concepts of 'placebo' and 'psychological' treatment. This can be interpreted within the paternalistic paradigm of medicine, whereby the clinician is making decisions they believe are best for patients, including concealing certain truths, on their behalf (Lynoe et al., 1993). This presents a particular challenge for the expectation for clinicians to follow evidence solely based on laboratory data. Together with clinicians' consideration of the whole person, including their capacity for appreciating and/or paying for tests, this points to a broader interpretation of the role of clinician that is often neglected in simplified clinical algorithms and epidemiology based targets for 'rational drug use.' These findings, of broader context and expectations affecting diagnostic practice for malaria, are in line with the theory that clinicians operate with 'mindlines' rather than guidelines, as previously described in Tanzania (Chandler et al., 2008a) and Ghana (Chandler et al., 2010).

The 'juggling' that clinicians conveyed, between patients' desires, clinical guidelines and protecting medical reputations, was most commonly described by medical doctors, who perhaps feel in a stronger position to blame tests or 'quantity of blood' than lower cadre colleagues. This diversion of blame away from individuals and institutions may reflect difficulties with dealing with not knowing, and the primacy of the 'art' of medicine. The challenge of integrating new technologies and probabilistic-oriented guidelines into medicine is long standing and well described in Europe and the USA, where such 'evidence' has been doubted, reinterpreted, used as a starting point, added as one part of a tool-kit, or cast out in favour of other better established knowledges (Gordon, 1988; Kassirer, 1992; Tanenbaum, 1994). The introduction of parasite-based guidelines and equipment represents the same challenge, instigated by the evidence-based movement in the North, but expected to be played out far more rapidly in the South. Lessons from the adoption of evidence-based approaches elsewhere suggests

expectations for rapid scale-up of RDTs may need to be reined-in. In addition, those aiming for targets for all patients to be tested for malaria and treated in line with results may need to accept that while the strategy of appealing to 'the evidence' as the bottom line is attractive as a rationalisation project, this may be fought for at the expense of other aspects of the complex social process of health care (Goldenberg, 2006).

We recommend that the interpretive style of medicine should be valued and maintained rather than attempting to overwrite this with a probabilistic approach. Clinicians should be supported in continuing to respond to the complex social context of their work including crucially to the patient as a whole. Change towards improved clinical care and better use of resources may be achieved within this approach through different means that go beyond training in case management. Firstly, raising consciousness amongst clinicians of the reasons for and consequences of certain practices, such as providing 'placebo' tests or drugs, and stimulating problem-solving to achieve desired results without compromising clinical outcomes could enable change (Freire, 1975). Secondly, encouraging clinicians to experiment with their new tools in practice, including assessing the responses of patients, may also help to shift behaviour (Armstrong & Ogden, 2006). Thirdly, equipping clinicians with skills to communicate with patients in order to elicit their specific needs, for example to understand the meaning of a negative malaria test result, and to respond to these without reliance on the use of commodities could provide a channel through which to implement change. Findings from elsewhere in Cameroon suggest that there is still significant room for improvement in patient-centred care from biomedical providers (Labhardt et al., 2010). Such clinician-oriented interventions have been successful elsewhere when carried out at a local level through participatory workshops (Fonn et al., 2001). We have designed a supporting intervention for providers based on these principles, which will be compared with standard introduction of RDTs in a cluster randomised controlled trial in 2011-12 (clinicaltrials.gov NCT01350752) (Wiseman et

al., 2012). Our results also suggest that the role of probabilistic guidelines in routine case management needs to be debated amongst the wider community of clinicians in the professions of medicine and nursing.

In this paper, we have attempted to outline the 'reality' of malaria from the perspective of health workers. We know that the enactment of malaria is also different from the perspective of patients, researchers of varying disciplines and those involved in public health enterprises (Beisel, 2010). We therefore only present our partial interpretation, and these other perspectives will also be important to explore when considering the uptake of RDTs. Our interpretation is also only partial because of the perspectives of those asking questions in FGDs and the set-up of the project as part of a biomedical research organisation. Participants may have aligned their responses with expected biomedical norms, although this could strengthen our conclusion that malaria is constructed as paramount amongst diseases. The study could have been strengthened further with the use of observational methods such as ethnography, particularly given our focus on the praxis of malaria. The use of FGDs rather than interviews reduces our ability to analyse findings across different health worker characteristics, such as length of professional experience. However, our intention was to understand factors in common between different groups, and although the study was only in two areas of Cameroon, we suggest the common ground between the sub-groups and with findings elsewhere does provide some transferable concepts, such as the important place of the social roles of health workers, tests and medicines in health care.

Conclusion

Few would dispute that rapid diagnostic tests have a potentially useful role to play in limiting malaria over-diagnosis and over-treatment. This study illustrates the divide between parasite-based guidelines initiated in Geneva and patient-based practice in Cameroon for the diagnosis and treatment of malaria. Careful attention must be paid to the values and priorities of health workers and patients if they are to be partners in improving diagnosis and treatment of febrile illnesses.

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Tables

TABLE 1. SUB-GROUP CHARACTERISTICS OF HEALTH WORKER FGDS

	Number of FGDs	
	Bamenda	**Yaoundé**
Health facility type		
Public	5	5
Mission	3	4
Cadre		
Medical Doctors only	2	3
Staff nurses/registered nurses only	0	6
Nurses and nursing assistants mixed	6	0
Total	**8**	**9**

.

TABLE 2. DEMOGRAPHIC AND WORK HISTORY CHARACTERISTICS OF HW FGD PARTICIPANTS

	Number of participants (%)	
	Bamenda	**Yaoundé**
Gender		
Female	56 (82%)	55 (71%)
Male	12 (18%)	23 (29%)
Age		
30 and younger	15 (22%)	13 (17%)
31-45	39 (57%)	40 (51%)
46 and older	14 (21%)	25 (32%)
Originally from region		
Yes	24 (35%)	24 (31%)
No	44 (65%)	54 (69%)
Highest education level		
Primary School	7 (10%)	1 (1%)
Secondary School	18 (27%)	35 (45%)
High School	28 (41%)	22 (28%)
Bachelor's Degree/diploma	15 (22%)	20 (26%)
Number of years health profession training		
1 year	26 (38%)	1 (1%)
2 years	7 (10%)	23 (30%)
3 years	16 (24%)	32 (41%)
4 + years	19 (28%)	22 (28%)
Health profession graduation year		
1990 and before	14 (21%)	20 (25%)
1991-2000	18 (26%)	27 (35%)
2001-2010	36 (53%)	31 (40%)
Number of malaria trainings attended		
None	42 (62%)	40 (51%)
1	13 (19%)	24 (31%)
2	7 (10%)	7 (9%)
3+	6 (9%)	7 (9%)
Total	**68**	**78**

Appendix C

Research Paper VII: What does it take to improve diagnosis and treatment for uncomplicated malaria? A three-arm cluster randomised trial in two areas of Cameroon

This research paper contains information about the implementation and effectiveness of the introducing RDTs with basic and enhanced training at public and mission facilities in Cameroon. It complements Research Paper V, which reports the cost-effectiveness analysis.

The interventions developed to improve providers' practice in diagnosing and treating malaria were evaluated using a cluster-randomized trial. Public and mission health facilities in the study sites were randomly allocated to one of three arms: basic, enhanced and control. Facilities in the basic and enhanced arms were supplied RDTs each month and up to three providers per facility were trained on the basic knowledge and practical skills needed to effectively diagnose and treat malaria. Providers in the enhanced arm also received two-days of supplementary training using participatory methods that explicitly sought to change providers' practice.

The proportion of patients who were tested for malaria and the proportion of patients with a positive test result who were prescribed or received an ACT were similar across the study arms. However, the proportion of patients with a negative test result who were prescribed or received an antimalarial was significantly reduced in the enhanced arm, and non-significantly reduced in the basic arm.

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Contribution: VW & WM conceptualised the study and secured funding for the trial. WM, LMJ, OA & VW designed the interventions. VW, WM, BC, LMJ & CC designed the trial. WM, LMJ, BC, OA & VW supervised the evaluation activities. BC undertook the analysis. VW coordinated the preparation of the manuscript. VW, WM, LMJ, BC, & CC drafted the manuscript. AN, DFA, VN, OT and PO, contributed to the study design in conformity with NMCP requirements

and served as facilitators during training and supervisors during evaluation. All authors read and approved the final manuscript.

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Basic or enhanced clinician training to improve adherence to malaria treatment guidelines: a cluster-randomised trial in two areas of Cameroon

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Summary

Background The scale-up of malaria rapid diagnostic tests (RDTs) is intended to improve case management of fever and targeting of artemisinin-based combination therapy. Habitual presumptive treatment has hampered these intentions, suggesting a need for strategies to support behaviour change. We aimed to assess the introduction of RDTs when packaged with basic or enhanced clinician training interventions in Cameroon.

Methods We did a three-arm, stratified, cluster-randomised trial at 46 public and mission health facilities at two study sites in Cameroon to compare three approaches to malaria diagnosis. Facilities were randomly assigned by a computer program in a 9:19:19 ratio to current practice with microscopy (widely available, used as a control group); RDTs with a basic (1 day) clinician training intervention; or RDTs with an enhanced (3 days) clinician training intervention. Patients (or their carers) and fieldworkers who administered surveys to obtain outcome data were masked to study group assignment. The primary outcome was the proportion of patients treated in accordance with WHO malaria treatment guidelines, which is a composite indicator of whether patients were tested for malaria and given appropriate treatment consistent with the test result. All analyses were by intention to treat. This study is registered at ClinicalTrials.gov, number NCT01350752.

Findings The study took place between June 7 and Dec 14, 2011. The analysis included 681 patients from nine facilities in the control group, 1632 patients from 18 facilities in the basic-training group, and 1669 from 19 facilities in the enhanced-training group. The proportion of patients treated in accordance with malaria guidelines did not improve with either intervention; the adjusted risk ratio (RR) for basic training compared with control was 1·04 (95% CI 0·53–2·07; p=0·90), and for enhanced training compared with control was 1·17 (0·61–2·25; p=0·62). Inappropriate use of antimalarial drugs after a negative test was reduced from 84% (201/239) in the control group to 52% (413/796) in the basic-training group (unadjusted RR 0·63, 0·28–1·43; p=0·25) and to 31% (232/759) in the enhanced-training group (0·29, 0·11–0·77; p=0·02).

Interpretation Enhanced clinician training, designed to translate knowledge into prescribing practice and improve quality of care, has the potential to halve overtreatment in public and mission health facilities in Cameroon. Basic training is unlikely to be sufficient to support the behaviour change required for the introduction of RDTs.

Funding ACT Consortium (Bill & Melinda Gates Foundation).

Introduction

Presumptive treatment of fever as malaria is entrenched in medical practice in malaria-endemic countries. In many African countries, fewer than 20% of suspected malaria cases were confirmed through parasitological testing in 2009.[1] Increased awareness of the overdiagnosis of malaria and concerns about inappropriate treatment of fevers, drug wastage, and the potential for drug resistance have led WHO to recommend universal parasitological confirmation before the use of artemisinin-based combination therapy.[2] Malaria rapid diagnostic tests (RDTs) offer the potential for improved targeting of artemisinin-based combination therapy in settings where microscopy is absent or of uncertain quality.[3–5]

Studies of malaria diagnosis in public health facilities have shown that clinicians rely on clinical judgment over the results of diagnostic tests.[6–9] Challenges faced by clinicians in the diagnostic process include insufficient training in the use of tests,[10] a distrust of negative test results,[11–13] little confidence or resources to treat alternative causes of fever,[10,12] and the perception of patient demand for antimalarial drugs.[14,15] These challenges seem to persist even when highly sensitive and specific RDTs are used[12] and when the evidence suggests that adhering to RDT results does not have a negative effect on health outcomes.[16] Interventions are urgently needed to address such problems in routine health-care settings.

Few studies have assessed interventions intended to change clinician practice when introducing RDTs, and

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For more on the **REACT study** see www.actconsortium.org/REACTCameroon

those that have investigated such interventions have produced mixed results, have often used weak study designs, and have provided little information about the interventions used.[17] Policy makers therefore remain uncertain about the types of intervention needed and about which interventions can be implemented within a realistic budget. This study, Research on the Economics of Artemisinin-based Combination Therapy (REACT), was done in two phases and was undertaken to identify interventions that could be adopted by the National Malaria Control Programme to support the distribution of RDTs in Cameroon. In the first phase,[18] formative research showed that microscopy was available at 90% of public health facilities and all mission and private health facilities, and that 35% of patients at public and 44% at mission facilities were tested. Of patients tested during their consultation, 78% of those who had a positive test result were prescribed or received an antimalarial drug (52% artemisinin-based combination therapy), but so were 82% of those who had a negative test result (56% artemisinin-based combination therapy).[18] We therefore recognised a need for changes in clinician knowledge, skills, and mindset to make test-driven diagnoses the norm in this setting.[9,18] The second phase, the results of which are reported here, was a stratified cluster-randomised trial done in a real-world setting to compare the introduction of RDTs in two intervention packages (involving different content and modes of clinician training) to routine care where microscopy is widely available. The overall aim of the study was assess how to improve the targeted use of antimalarial treatment and to optimise the implementation of malaria treatment guidelines.[2]

Methods

Study setting and population

We did a stratified, cluster-randomised trial at 46 public and mission health facilities (clusters) in two study sites (strata) in Cameroon (Yaoundé in the Centre region and Bamenda in the Northwest region). Facilities were eligible for inclusion if they were not included in the Government's pilot rollout of RDTs,[19] did not offer specialist services, received more than four febrile patients per day on average, and were more than 2 km (1 km in Yaoundé) away from another facility. All patients (or their carers) who attended the health facilities between Oct 3 and Dec 14, 2011, were approached on exit for consent to participate in the study and screened for their eligibility. Patients were eligible for inclusion in the exit survey if they reported seeking treatment for fever or suspected malaria, but were excluded if they were pregnant, younger than 6 months, or had signs of severe malaria. Individuals were also excluded if the patient was not present (when a carer was the respondent). Medical doctors, nurses, laboratory technicians, and pharmacy attendants were eligible for the clinician training, and all clinicians responsible for the diagnosis and treatment of malaria were eligible for participation in the assessment of provider knowledge. The nature and purpose of the trial was explained to the participants, all of whom provided written informed consent (consent for child participants was obtained from parents or carers).

Ethics approval was obtained from the London School of Hygiene & Tropical Medicine (number 5885) and the Cameroon National Ethics Committee (number 030/CNE/DNM/09). Administrative clearance was obtained from the Cameroon Ministry of Public Health (number D30-343/AAR/MINSANTE/SG/DROS/CRC/JA). An independent data safety monitoring board monitored the trial and approved the analysis plan.

Randomisation and masking

Within each study site, facilities were randomly selected from those that met the eligibility criteria and had agreed to participate in the study, and were randomly allocated in a 9:19:19 ratio to the control, basic-training intervention, or enhanced-training intervention groups by a process of constrained or restricted randomisation (to improve the balance across the study groups).[20] The study statistician (BC), who had no involvement in the delivery or assessment of the interventions, did the random assignment using a program written in R statistical software version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria). Patients (or their carers) and fieldworkers who administered the surveys were masked to study group assignment.

Procedures

Clinicians in the control facilities did not receive RDTs or training as part of the study. Facilities in both intervention groups were supplied with 100 RDTs (SD Bioline Malaria Ag Pf/Pan, Standard Diagnostics, Yongin, South Korea) each month without charge. Facilities could charge patients for the use of RDTs, but, in line with national policy, facilities were asked not to charge for their use in children younger than 5 years, and 100 CFA francs (US$0·20) was the recommended price per test for other patients. The availability of artemisinin-based combination therapy was not controlled.

The training interventions were designed to be suitable for implementation on a large scale. Clinicians working at facilities assigned to the basic-training intervention group were invited to a 1-day training course with three separate modules. These modules covered malaria diagnosis, RDTs, and malaria treatment. Together these modules explained to participants that all febrile patients should be tested for malaria using microscopy or an RDT, described the procedures for using an RDT, and explained that confirmed cases of uncomplicated malaria should be treated with artemisinin-based combination therapy, whereas patients with a negative malaria test should not be given antimalarial drugs. The training also included advice about other causes of febrile illness. The training was

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provided by representatives of the National Malaria Control Programme and members of the research team who had been trained to deliver the material. Information was disseminated through lectures, and a practical session was run to show participants how to use an RDT.

Clinicians working at facilities in the enhanced-training intervention group received 3 days of training. The first day was identical to that attended by those in the basic-training group, and the remainder of the course covered three additional modules targeting improvements in quality of care. These modules covered adapting to change, professionalism, and effective communication. The module on adapting to change sought to provide clinicians with the opportunity to reflect and discuss the WHO malaria treatment guidelines[2] and to learn from others. It included testimonials about the use of RDTs, and participants reflected on and discussed recommendations in the malaria guidelines.[2] As well as discussions in small groups, the module included a card game for four to six players designed to reinforce the treatment algorithm.

In the professionalism module, clinicians were asked to identify and agree on the values and behaviours that are important when providing care. The module included an exercise in which participants considered real-life scenarios that often interrupt the process of care and were encouraged to develop strategies for managing these situations. The final module focused on improving the clinicians' skills in communicating with patients. It began by reflecting on what patients think about malaria and its treatment. The module also looked at different ways of managing patients' expectations and allowed participants to develop skills and techniques for explaining to patients why they should be tested for malaria and for dealing with the situation in which the test is negative and an antimalarial should not be prescribed. Participants developed and acted out dramas to help them to understand the consequences for patients of not being prescribed an antimalarial drug and the alternative courses of action that could be pursued. These additional modules were designed to reinforce material contained in the malaria treatment guidelines and to address challenges brought by RDTs for the interactions between health workers and patients.[9,18]

In both intervention groups, participants received copies of training materials and job aids (including posters and table-top flip charts) and were strongly encouraged to train other clinicians at their facilities. We used this form of in-facility cascade training because it seemed to be the most feasible approach for this resource-constrained setting. The training materials used are available from the ACT Consortium website.

Data were collected on the process of implementing the interventions: the research team kept records of RDTs supplied to each facility; clinician satisfaction and understanding of training materials was assessed by use of a structured questionnaire at the start and end of the training workshops; and the training facilitators completed an assessment form recording details of the running of the workshops.

Outcomes

The primary outcome was the proportion of patients attending study facilities that reported a fever or suspected malaria and received treatment in accordance with the WHO malaria treatment guidelines.[2] This outcome is a composite measure that requires febrile patients to be tested for malaria (with either microscopy or an RDT), patients with a positive malaria test result to be given artemisinin-based combination therapy, and patients with a negative malaria test result not to receive an antimalarial drug.

The primary outcome was assessed through an interviewer-administered patient exit survey to all eligible and consenting patients (or carers) exiting the study facilities. The survey started 3 months after the interventions were implemented and ran for 3 months. The exit survey asked about the patient's previous treatment seeking, whether the patient was tested, what treatment was prescribed and received, and whether the patient was satisfied with the visit (with options ranging from completely satisfied to not at all satisfied).

Clinicians were asked to complete a register of all malaria tests done by microscopy or RDTs to supplement the exit survey, since patients might not always know whether they were tested for malaria or the result of the malaria test. The register data included facility code, date, patient name, age, sex, type of test done (microscopy or RDT), test result, and the name of the health worker who did the test. A fieldworker collected the register at the end of every week and combined this information with the exit survey results. A subsample of patients (roughly 5%) was independently tested by the research team to determine the degree of consistency between the test results reported by the patients, clinicians, and research team. A facility audit was done once the exit survey was complete to collect details about the health facility (such as type of facility, how long it had been in operation, and the average number of patients treated per day), available resources (such as number and type of staff, testing equipment, and drugs), and management procedures (such as stocking and procurement). Fieldworkers obtained these data by interviewing the head of the facility with a structured questionnaire.

On the basis of our formative research,[18] we assumed that the proportion of patients treated in accordance with malaria treatment guidelines (the primary outcome) would be 15% in the control group and that the coefficient of variation between clusters within each stratum would be 0·25. On the basis of these assumptions, we estimated that a sample size of nine facilities per group with 100 patients per facility would be needed (with allowance for facility withdrawals) to provide 80% power at the 5% significance level to detect a 15 percentage point increase in the primary outcome (ie, increasing the

For the **study training materials** see http://www.actconsortium.org/REACTCameroonmanuals

proportion to at least 30%) in either of the intervention groups.[19] To test whether the basic training was as effective as the enhanced training, we estimated that a sample size of 19 clusters per group would have 80% power to show that the basic intervention is non-inferior (with a margin of 10%) to the enhanced intervention at the 5% significance level (two-sided). Thus, the number needed for the non-inferiority comparison was greater, and the final sample size was set at nine for the control group and 19 for each intervention groups.[20]

All clinicians responsible for diagnosis and treatment of suspected cases of malaria were asked to take part in a clinician survey. This survey was done after completion of the patient exit survey and measured changes in secondary outcomes between study groups including changes in clinicians' knowledge and preferences for treating patients presenting with symptoms of uncomplicated malaria. The assessment of clinicians' knowledge included a mean score for how to use an RDT, which was derived from the correct identification of 11 steps required to do the test. The logic model in figure 1 shows the expected effect of the provider interventions on primary and secondary outcomes.

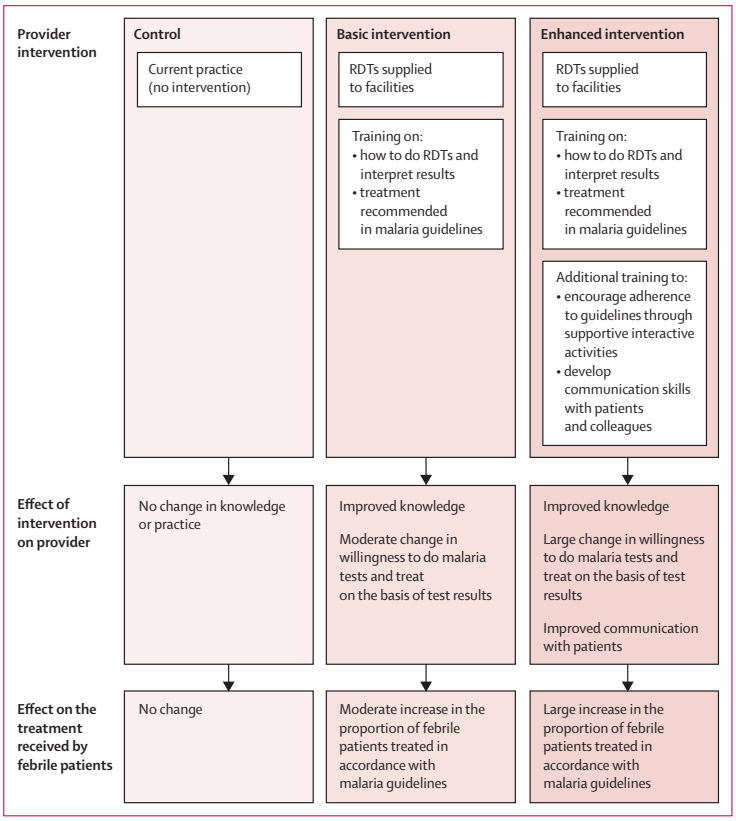

Figure 1: **Logic model for the effect of provider interventions on treatment received by patients**
RDTs=rapid diagnostic tests. Reproduced from reference 20.

Further information about the design of the trial and the interventions is reported in the study protocol.[20]

Statistical analysis

All data were double-entered in Microsoft Access 2007 (Microsoft, Redmond, WA, USA), verified with the data compare utility in Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA), and analysed with Stata version 12.0 (Stata Corporation, College Station, TX, USA). All analyses were by intention to treat. We used methods suitable for stratified, cluster-randomised trials with fewer than 20 clusters per group[21] to assess the effect of each intervention compared with control. Within each stratum, we calculated the risk ratio (RR) from the mean risks across facilities in each intervention group. We calculated an overall estimate of the RR as the geometric weighted average of the stratum-specific RRs, with the weights inversely proportional to the stratum-specific variances. We calculated 95% CIs taking into account the observed between-cluster variation[21] and did formal hypothesis testing by use of a stratified t test on the logarithm of the RR.

We adjusted for covariates by fitting a logistic regression model to data for individual patients, including terms for stratum and the covariates of interest, but excluding the intervention effect. We estimated ratio-residuals for each facility by comparing expected and observed values, and we applied the same methods for estimating the RRs and 95% CIs and for hypothesis testing as we used in the main analysis, but with the residuals replacing facility-specific risks. We assessed non-inferiority between the two intervention groups using the same methods used for the main analysis to calculate an overall estimate of the risk difference and a corresponding one-sided 95% CI.

The trial is registered with ClinicalTrials.gov, number NCT01350752.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The study took place between June 7 and Dec 14, 2011. 122 facilities were assessed for eligibility (50 in Yaoundé and 72 in Bamenda); after exclusions, 46 facilities were included in the analyses (24 in Yaoundé and 22 in Bamenda), with nine randomly allocated to the control group, 18 to the basic-training intervention, and 19 to the enhanced-training intervention (figure 2).

The basic and enhanced training workshops were successfully delivered across both study sites, with all 37 intervention facilities represented and the

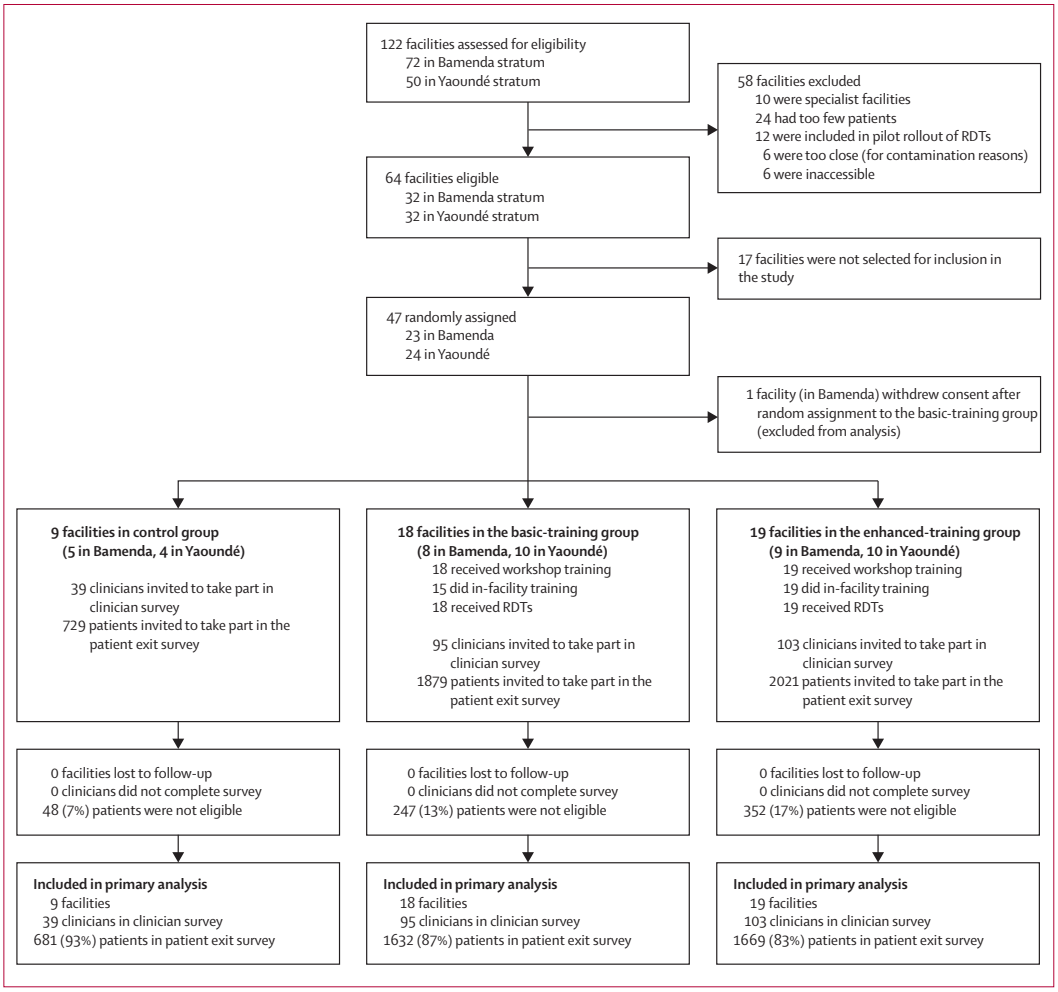

Figure 2: **Study profile**
Flow of facilities (clusters), clinicians, and patients through the study.

training materials delivered as planned. Participant satisfaction was high in both intervention groups, with more than three-quarters of participants (77% [37/48] in the basic-training group and 83% [40/48] in the enhanced-training group) strongly agreeing that they were satisfied with the training (as defined by knowledge gained and the relevance and acceptability of the material). Seven of eight facilitators responsible for delivering the training also strongly agreed that the learning objectives for each module had been achieved successfully. Three facilities in Yaoundé assigned to the basic-training intervention did not do any in-facility cascade training for clinicians who did not attend the workshops (figure 2).

Each month 100 RDTs were supplied to all facilities in the intervention groups, from the end of the training until all assessments were complete (6 months). Despite requests not to charge more than 100 CFA francs (US$0·20) per test, most facilities charged substantially more, with a mean charge of 611 CFA francs ($1·28) per test in facilities in the basic-training group and 997 CFA francs ($2·09) in the enhanced-training group. Facilities were supplied with artemisinin-based combination therapy by the Government or mission authorities, and availability was reasonably good; four public facilities reported stock-outs in the 4 weeks before the facility audit, and eight reported problems obtaining stock in the previous year.

Characteristics of the facilities and patients were generally similar across the groups (tables 1, 2), but with some exceptions: there were disproportionately more public than mission facilities in the control group;

	Control (n=9)	Basic training (n=18)	Enhanced training (n=19)
Stratum			
Bamenda	5 (56%)	8 (44%)	9 (47%)
Yaoundé	4 (44%)	10 (56%)	10 (53%)
Type of facility			
Public district hospital	1 (11%)	6 (33%)	4 (21%)
Public health centre	7 (78%)	5 (28%)	6 (32%)
Mission hospital	0 (0%)	0 (0%)	1 (5%)
Mission health centre	1 (11%)	7 (39%)	8 (42%)
Time established*			
≤5 years (at time of facility audit)	1 (11%)	2 (11%)	2 (11%)
>5 years (at time of facility audit)	8 (89%)	15 (83%)	15 (79%)
Unknown	0	1 (6%)	2 (11%)
Median number of patients per day (IQR)	8 (5–10)	20 (15–30)	30 (10–75)
Median number of clinicians (range)			
Who regularly work at the facility	17 (4–32)	16 (4–35)	11 (4–61)
Who are involved in the treatment of patients with malaria†	8 (2–14)	8 (4–18)	9 (4–20)
Types of clinician†			
Doctor	4 (44%)	9 (50%)	9 (47%)
Nurse or midwife	8 (89%)	16 (89%)	14 (74%)
Nurse assistant or midwife assistant	5 (56%)	11 (61%)	12 (63%)
Laboratory technician or assistant	8 (89%)	16 (89%)	19 (100%)
Pharmacist	2 (22%)	1 (6%)	3 (16%)
Pharmacy technician or assistant	7 (78%)	15 (83%)	14 (74%)
Services available			
Weighing scale	8 (89%)	18 (100%)	18 (95%)
Functioning thermometer	8 (89%)	17 (94%)	15 (79%)
Functioning microscope‡	9 (100%)	18 (100%)	18 (95%)
Malaria microscopy testing‡	9 (100%)	18 (100%)	19 (100%)
RDT, ACT, and antibiotic availability			
ACTs currently in stock	8 (89%)	18 (100%)	19 (100%)
Stock-outs of ACTs in past 4 weeks	1 (11%)	2 (11%)	1 (5%)
ACT supply problems in past year	2 (22%)	3 (17%)	3 (17%)
RDTs currently in stock§	1 (11%)¶	8 (47%)‖	13 (72%)‖
Stock-outs of RDTs in past 4 weeks§	1 (11%)¶	10 (59%)‖	10 (56%)‖
Antibiotics currently in stock	8 (89%)	16 (89%)	18 (95%)

Data are number of facilities (%), unless otherwise indicated. RDT=rapid diagnostic test. ACT=artemisinin-based combination therapy. *All facilities had been established for a minimum of 3 years. †Clinicians who diagnose, prescribe, or dispense malaria treatment at the facility. ‡One facility in the enhanced-training group noted that it provided microscopy testing, but it did not have a functioning microscope ; all facilities that offered malaria microscopy testing had at least one laboratory technician or assistant who regularly worked at the facility, apart from four facilities in the enhanced-training group for which this information is unavailable. §The facility audit was done after the exit survey was complete. ¶One facility in the control group received RDTs as a donation and not as part of the intervention; they did not receive any training associated with the use of RDTs. ‖Information was unavailable for one facility in the basic-training group and one facility in the enhanced-training group (these facilities were excluded from the percentage calculations).

Table 1: **Characteristics of facilities (clusters), by study group**

intervention facilities treated a larger number of patients per day; and patients seeking treatment at control facilities were of a higher socioeconomic status than those at intervention facilities. Concordance between RDT reporting in registers and exit-poll information was high (sensitivity 96%, specificity 94%, observed agreement 95%, κ=0·89).

Neither training intervention had a significant effect on the proportion of febrile patients treated in accordance with malaria treatment guidelines (table 3). The proportion of patients tested for malaria was high across all groups. Compared with the control group, the proportion of patients with a negative test result who were prescribed or received an antimalarial drug was significantly reduced in the enhanced-training group and non-significantly reduced in the basic-training group (table 3). The proportion of patients with a positive test result who were prescribed or received

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artemisinin-based combination therapy was similar across the study groups at 72–75% (table 3); most of the remaining patients with a positive test result received either another antimalarial treatment or an antibiotic (figure 3). The proportion of febrile patients who were prescribed or received an antimalarial receiving artemisinin-based combination therapy was similar across the study groups: 508 (85%) of 598 in the control group, 790 (79%) of 997 in the basic-training group, and 694 (79%) of 873 in the enhanced-training group; the unadjusted RR was 0·91 (95% CI 0·74–1·13; p=0.38) for basic training compared with control and 0·81 (0·51–1·28; p=0.35) for enhanced training compared with control.

The study was powered to assess non-inferiority between the two intervention groups, and the crude risk difference between the two groups was 0·15 (90% CI –0·29 to 0·60); since the difference and the upper bound of the CI is more than 10%, non-inferiority is not shown in the analysis.

	Control (n=681)	Basic training (n=1632)	Enhanced training (n=1669)
Median number of patients per facility (range)	80 (28–101)	100 (49–102)	98 (17–114)
Sex			
Male	312 (46%)	735 (45%)	733 (44%)
Female	369 (54%)	897 (55%)	934 (56%)
Missing data	0	0	2 (<1%)
Age			
<5 years	236 (35%)	600 (37%)	610 (37%)
5–19 years	194 (28%)	370 (23%)	368 (22%)
20–40 years	131 (19%)	431 (26%)	438 (26%)
≥40 years	120 (18%)	231 (14%)	253 (15%)
Main activity of patient			
Paid work or self-employed	141 (21%)	294 (18%)	352 (21%)
Domestic work	55 (8%)	159 (10%)	146 (9%)
Looking for work	7 (1%)	27 (2%)	37 (2%)
At school, college, or university	293 (43%)	687 (42%)	606 (36%)
At leisure	22 (3%)	35 (2%)	51 (3%)
Child and does not go to school	158 (%)	401 (25%)	438 (26%)
Other or missing data	5 (1%)	29 (2%)	39 (2%)
Education of respondent			
None	49 (7%)	140 (9%)	141 (8%)
Primary	206 (30%)	426 (26%)	409 (25%)
Secondary	314 (46%)	705 (43%)	731 (44%)
Tertiary	104 (15%)	338 (21%)	371 (22%)
Missing data	8 (1%)	23 (1%)	17 (1%)
Wealth index*			
Poorest	160 (23%)	553 (34%)	548 (33%)
Less poor	232 (34%)	537 (33%)	492 (29%)
Least poor	263 (39%)	460 (28%)	537 (32%)
Missing data	26 (4%)	82 (5%)	92 (6%)
(Continued from previous page)			
Median days of illness (range)	3 (0–14)	3 (0–30)	3 (0–60)
Seeking treatment for first time			
No†	181 (27%)	656 (40%)	582 (35%)
Yes	492 (72%)	962 (59%)	1071 (64%)
Missing data	8 (1%)	14 (1%)	16 (1%)
Previous treatment seeking‡			
Public facility	81 (45%)	133 (20%)	122 (21%)
Mission facility	16 (9%)	82 (13%)	39 (7%)
Private facility	55 (30%)	263 (40%)	244 (42%)
Other§	24 (13%)	164 (25%)	156 (27%)
Missing data	5 (3%)	14 (2%)	21 (4%)

(Table 2 continues on next page)

	Control (n=681)	Basic training (n=1632)	Enhanced training (n=1669)
(Continued from previous page)			
Previous treatment received¶			
Had RDT or microscopy‡			
Yes	67 (37%)	92 (14%)	127 (22%)
No	99 (55%)	536 (82%)	431 (74%)
Missing data	15 (89%)	28 (4%)	24 (4%)
Received ACT‡			
Yes	46 (25%)	152 (23%)	148 (25%)
No	116 (64%)	474 (72%)	387 (66%)
Missing data	19 (10%)	30 (5%)	47 (8%)
Received appropriate treatment||			
Yes	23 (34%)	47 (51%)	75 (59%)
No	18 (27%)	29 (32%)	19 b(15%)
Missing data	26 (39%)	16 (17%)	33 (26%)

Data are n (%), unless otherwise indicated. RDT=rapid diagnostic test. ACT=artemisinin-based combination therapy. *Generated through principal component analysis and based on ownership of household possessions (eg, electricity, radio, mobile telephone, generator, bicycle, and car), access to utilities (toilet type and source of drinking water), and housing characteristics (floor type, fuel, people per sleeping room), in line with the Demographic and Health Survey wealth index[22] and the technique described by Vyas and colleagues;[23] tertiles were used for tabular analysis of the wealth index. †For patients who had previously sought treatment for this illness episode across all groups, 562 (40%) of 1419 had sought treatment once before, 503 (35%) twice before, and 211 (15%) three or more times before (data were missing for 143 [10%]). ‡Patients not seeking treatment for the first time used as totals for percentage calculations. §Other places patients sought treatment include non-specified hospitals, at home, from friends, and from traditional healers. ¶Treatment received at the last place the patient previously sought treatment for this illness, as reported by the patient. ||Appropriate treatment is defined as receiving an ACT if RDT or microscopy was positive for malaria, and not receiving an antimalarial drug if RDT or microscopy was negative for malaria; patients who had RDT or microscopy used as totals for percentage calculations.

Table 2: **Characteristics of patients who participated in the exit survey, by study group**

A higher proportion of patients tested by microscopy had positive test results than those tested by RDT. For microscopy, 53% of cases in the control group, 40% in the basic-training group, and 45% in the enhanced-training group had positive test results. For RDT, 53% of cases in the control group, 23% in the basic-training group, and 31% in the enhanced-training group had positive test results.

With the possible exception of how to use an RDT, there were no significant differences between study groups in clinicians' responses to knowledge questions and treatment preferences (table 4). This finding was consistent with the treatment of such patients during the study. With respect to patient satisfaction, 616 (90%) of 681 febrile patients in the control group, 1393 (85%) of 1632 in the basic-training group, and 1478 (89%) of 1669 in the enhanced-training group were satisfied with the care received. Thus, no significant differences from control were seen in either the basic-training group (unadjusted RR 1·01, 95% CI 0·95–1·07; p=0·70) or the enhanced-training group (0·99, 0·93–1·04; p=0·59).

Discussion

Although the two training interventions did not lead to a significant increase in the proportion of patients treated in accordance with malaria treatment guidelines (the primary outcome), we did note a substantial and significant reduction in the unnecessary use of antimalarial drugs in patients with a negative test result in the enhanced-training group compared with control. Use of this intervention could potentially halve overtreatment in public and mission health facilities in Cameroon. However, further studies are necessary to substantiate this finding.

We also noted improvements in two other key indicators compared with our findings from the formative research in 2009.[18] First, nearly 80% of febrile patients were tested for malaria across all study groups, representing a substantial improvement from the 35–44% noted in 2009. Second, about 75% of patients who tested positive for malaria across all study groups were prescribed or received artemisinin-based combination therapy, compared with 59% during the formative research period. Both of these practices had been targeted by an extensive malaria communication campaign.

Changing established clinical behaviours can be difficult.[24,25] We undertook this study in response to calls for more evidence and for theory-driven approaches to intervention design.[26,27] We compared a conventional, knowledge-based and skills-oriented, didactic training approach (the basic-training intervention) with a mindset-oriented, interactive training approach (the enhanced-training intervention). The interventions were designed in conjunction with the National Malaria Control Programme and the enhanced-training intervention was carefully designed and piloted to tackle issues raised by clinicians in their communities of

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	Number of clusters	Number of patients (n/N [%])	Stratum-specific RR (95% CI)	Unadjusted RR (95% CI)*	Adjusted RR (95% CI)†	p value	k
Treatment in accordance with malaria treatment guidelines (composite outcome)							
Control	9	246/659 (37%)	..	1·00	..	..	..
Bamenda	5	86/388 (22%)	1·00	..	..	..	..
Yaoundé	4	160/271 (59%)	1·00	..	..	..	..
Basic training	18	670/1576 (42%)	..	1·18 (0·56–2·49)	1·04 (0·53–2·07)	0·90	0·15
Bamenda	8	265/678 (39%)	2·01 (1·27–3·16)	..	..	..	..
Yaoundé	10	405/898 (45%)	0·66 (0·41–1·06)	..	..	..	..
Enhanced training	19	890/1613 (55%)	..	1·76 (0·83–3·70)	1·17 (0·61–2·25)	0·62	0·16
Bamenda	9	427/754 (57%)	3·61 (2·33–5·59)	..	..	..	..
Yaoundé	10	463/859 (54%)	0·78 (0·49–1·24)	..	..	..	..
Febrile patients tested for malaria							
Control	9	539/681 (79%)	..	1·00	..	..	..
Bamenda	5	313/400 (78%)	1·00	..	..	..	..
Yaoundé	4	226/281 (80%)	1·00	..	..	..	..
Basic training	18	1250/1632 (77%)	..	0·97 (0·76–1·23)	0·95 (0·76–1·18)	0·62	0·05
Bamenda	8	494/699 (71%)	0·92 (0·79–1·07)	..	..	..	..
Yaoundé	10	756/933 (81%)	1·02 (0·88–1·19)	..	..	..	..
Enhanced training	19	1309/1665 (79%)	..	1·01 (0·74–1·37)	0·96 (0·72–1·28)	0·78	0·06
Bamenda	9	617/776 (80%)	1·08 (0·90–1·30)	..	..	..	..
Yaoundé	10	692/889 (78%)	0·94 (0·77–1·13)	..	..	..	..
Patients with positive test results received ACT							
Control	8	208/278 (75%)	..	1·00	..	..	..
Bamenda	4	56/75 (75%)	1·00	..	..	..	..
Yaoundé	4	152/203 (75%)	1·00	..	..	..	..
Basic training	17	287/398 (72%)	..	1·01 (0·67–1·52)	1·09 (0·76–1·56)	0·61	0·06
Bamenda	7	33/47 (70%)	1·14 (0·86–1·51)	..	..	..	..
Yaoundé	10	254/351 (72%)	0·91 (0·70–1·17)	..	..	..	..
Enhanced training	19	363/498 (73%)	..	0·87 (0·52–1·44)	0·89 (0·55–1·44)	0·62	0·11
Bamenda	9	117/147 (80%)	0·85 (0·71–1·01)	..	..	..	..
Yaoundé	10	246/351 (70%)	0·88 (0·74–1·05)	..	..	..	..
Patients with negative test results received an antimalarial drug‡							
Control	8	201/239 (84%)	..	1·00	..	..	..
Bamenda	5	196/226 (87%)	1·00	..	..	..	..
Yaoundé	3	5/13 (38%)	1·00	..	..	..	..
Basic training	18	413/796 (52%)	..	0·63 (0·28–1·43)	..	0·25	0·15
Bamenda	8	194/426 (46%)	0·43 (0·26–0·70)		..	..	..
Yaoundé	10	219/370 (59%)	1·04 (0·59–1·86)	..	..	..	..
Enhanced training	19	232/759 (31%)	..	0·29 (0·11–0·77)	..	0·02	0·20
Bamenda	9	138/448 (31%)	0·14 (0·08–0·26)		..	..	..
Yaoundé	10	94/311 (30%)	0·74 (0·37–1·48)	..	..	..	..

RR=risk ratio. ACT=artemisinin-based combination therapy. *Crude analysis adjusted for stratum only, based on geometric means of cluster summaries; overall *F*-test of the null hypothesis that there are no differences between any of the treatment arms provides p value of 0·08. †Adjusted for the following facility and patient characteristics: stratum; facility type; stock-outs of ACTs in past 4 weeks; average number of patients per day; patients' sex, age, job or main activity, and socioeconomic status; whether patient had previously sought treatment for this illness; and whether they asked for a blood test at the facility. ‡The sample size in some clusters within the strata was too small to do an adjusted analysis for this outcome.

***Table 3*: Unadjusted and adjusted effects of the training interventions on treatment in accordance with malaria guidelines, compared with control**

practice and to use best-practice methods for adult learning.

In making choices about our interventions and methods for assessment, we sought to investigate the effectiveness of the interventions in a real-world setting, rather than their efficacy in a highly controlled environment. For example, RDTs were supplied on a monthly basis and the quantity set in consultation with the National Malaria Control Programme to represent a realistic disbursement schedule. Despite this forward planning, stock-outs of RDTs in the past 4 weeks were still reported across all study groups during the

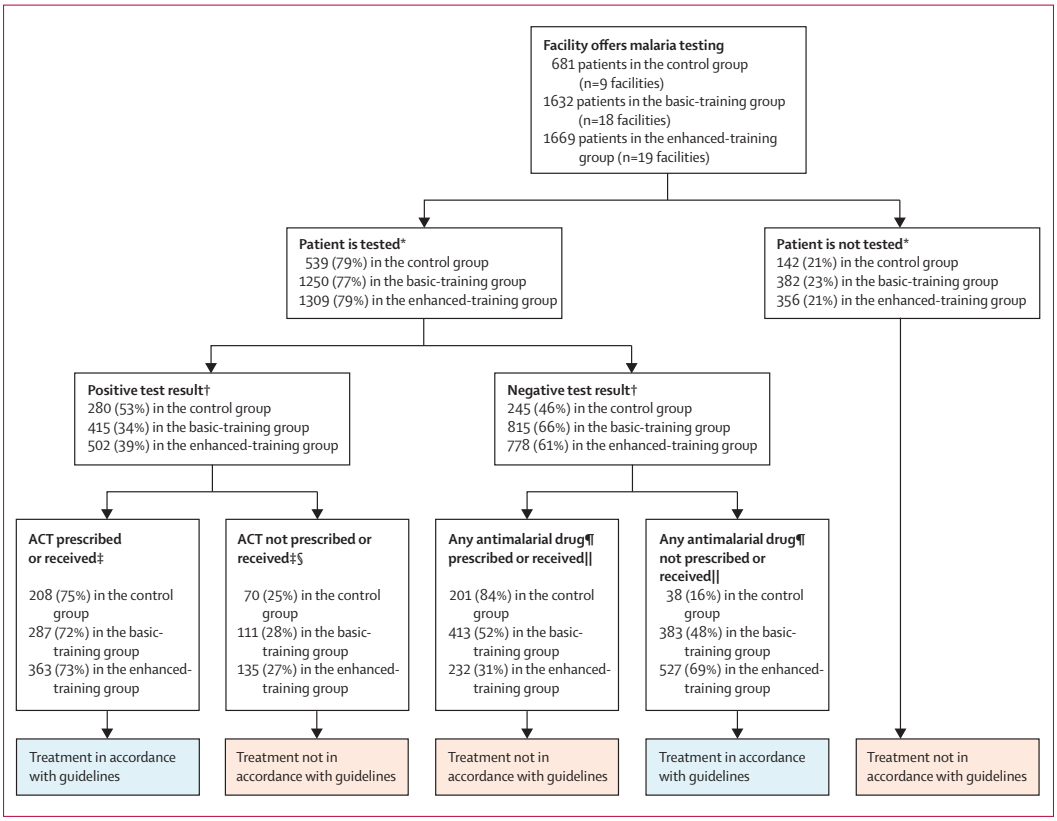

Figure 3: **Flow chart for the definition of the primary outcome**

Missing data were excluded from percentage calculations. ACT=artemisinin-based combination therapy. *Testing could not be established from malaria registers for eight (1%) patients in the control group, 69 (4%) in the basic-training group, and 83 (5%) in the enhanced-training group (in these cases testing was established as reported by the patient); whether or not a patient was tested was not known for four of 1669 (<1%) patients in the enhanced-training group (treated as missing data). †Among patients who were tested, test result could not be established from malaria registers for 18 (3%) in the control group, 89 (7%) in the basic-training group, and 79 (6%) in the enhanced-training group; of these, 14 (3%) in the control group, 20 (2%) in the basic-training group, and 29 (2%) in the enhanced-training group did not have a test result reported by the patient or had an invalid result (treated as missing data). ‡Among patients with a positive test result, whether a treatment was prescribed or received was not known for two (1%) in the control group, 17 (4%) in the basic-training group, and four (1%) in the enhanced-training group (treated as missing data). §Among patients with a positive test result who were not prescribed or receiving ACT, 58 (83%) in the control group, 69 (62%) in the basic-training group, and 89 (66%) in the enhanced-training group were prescribed or received an antimalarial drug; of those not prescribed or receiving any antimalarial drug (including ACT), six (50%) in the control group, 19 (45%) in the basic-training group, and 17 (37%) in the enhanced-training group were prescribed or received either paracetamol or an antibiotic, with the remainder being prescribed or receiving either vitamins, iron, or nothing. ¶Any antimalarial drug includes ACT. ||Among patients with a negative test result, whether a treatment was prescribed or received was not known for six (2%) in the control group, 19 (2%) in the basic-training group, and 19 (2%) in the enhanced-training group (treated as missing data).

assessment. Moreover, cascade training was used to limit the direct costs of the interventions, making them more affordable for large-scale implementation.

The independent verification of malaria test results lends support to the internal validity of outcomes that relied on patients' recall and clinicians' ability to do the diagnostic tests and accurately interpret their results. However, two methodological constraints limit the external application of the findings from this study. First, many of the clinicians surveyed did not attend the training workshops and therefore the knowledge and practice of those treating patients in whom the outcomes were measured was most likely informed by in-facility training, or no training. This issue limits our ability to estimate the effect of attending workshops compared with participating in in-facility training. Second, the assessment was done 3 months after the workshops took place, and we do not know the long-term effects of intervention on clinicians' practice.

The Government of Cameroon, along with those of other malaria-endemic countries, is preparing for the national scale-up of RDTs. Our results suggest that supporting interventions should be employed alongside RDT rollout if presumptive practices are to be changed (panel). This study, the first of its kind in Cameroon, provides timely evidence about the effects of different types of intervention,

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	Control (n=39)	Basic training (n=95)	Enhanced training (n=103)	Crude RR* (95% CI)	Adjusted RR† (95% CI)	p value
Clinician knowledge						
Fever is a symptom of uncomplicated malaria	38/39 (97%)	89/95 (94%)	99/103 (96%)	..	..	..
Basic training *vs* control	..	..	..	0·93 (0·81–1·08)	0·97 (0·83–1·12)	0·63
Enhanced training *vs* control	..	..	..	0·95 (0·86–1·05)	0·97 (0·87–1·07)	0·53
Febrile patients should be tested for malaria	37/38 (97%)	90/91 (99%)	100/101 (99%)	..	..	..
Basic training *vs* control	..	..	..	1·01 (0·97–1·06)	1·00 (0·95–1·05)	0·91
Enhanced training *vs* control	..	..	..	1·01 (0·97–1·06)	1·00 (0·96–1·04)	0·97
How to use an RDT‡§	4·3 (4·1)	6·2 (3·7)	6·7 (3·5)	..	..	..
Basic training *vs* control	..	..	..	1·95 (0·42–4·32)	..	0·10
Enhanced training *vs* control	..	..	..	2·55 (0·23–4·86)	..	0·03
How to interpret an RDT result‡	11/13 (85%)	56/73 (77%)	53/77 (69%)	..	..	..
Basic training *vs* control	..	..	..	0·86 (0·59–1·26)	..	0·84
Enhanced training *vs* control	..	..	..	0·76 (0·46–1·24)	..	0·83
Patients with a positive test results should receive an ACT	35/38 (92%)	79/87 (91%)	76/91 (83%)	..	..	..
Basic training *vs* control	..	..	..	0·96 (0·85–1·08)	1·01 (0·87–1·17)	0·91
Enhanced training *vs* control	..	..	..	0·89 (0·74–1·07)	1·08 (0·93–1·25)	0·31
Patients with a negative test results should not receive an antimalarial drug	19/35 (54%)	57/83 (69%)	66/95 (69%)	..	..	..
Basic training *vs* control	..	..	..	1·15 (0·86–1·54)	1·06 (0·73–1·54)	0·73
Enhanced training *vs* control	..	..	..	1·26 (0·88–1·79)	1·28 (0·80–2·06)	0·29
First-line treatment as recommended by the Government	21/35 (60%)	60/77 (78%)	67/90 (74%)	..	..	..
Basic training *vs* control	..	..	..	1·25 (0·75–2·11)	0·97 (0·59–1·60)	0·91
Enhanced training *vs* control	..	..	..	1·12 (0·74–1·69)	1·11 (0·73–1·67)	0·61
Clinician treatment preferences						
Believes that using a patient's symptoms to diagnose malaria is reliable	25/39 (64%)	29/94 (31%)	21/102 (21%)	..	..	..
Basic training *vs* control	..	..	..	0·50 (0·30–0·83)	0·72 (0·39–1·33)	0·28
Enhanced training *vs* control	..	..	..	0·33 (0·21–0·53)	0·94 (0·49–2·50)	0·10
Takes history, signs and symptoms, examination, or temperature	33/39 (85%)	70/95 (74%)	71/103 (69%)	..	..	..
Basic training *vs* control	..	..	..	0·83 (0·58–1·19)	0·97 (0·68–1·38)	0·85
Enhanced training *vs* control	..	..	..	0·78 (0·59–1·02)	0·96 (0·74–1·25)	0·76
Uses RDT or microscopy to diagnose malaria	34/39 (87%)	88/95 (93%)	90/102 (88%)	..	..	..
Basic training *vs* control	..	..	..	1·04 (0·91–1·18)	0·99 (0·86–1·13)	0·83
Enhanced training *vs* control	..	..	..	0·95 (0·76–1·19)	0·95 (0·77–1·18)	0·63
Believes that test results are reliable	16/37 (43%)	49/89 (55%)	69/100 (69%)	..	..	..
Basic training *vs* control	..	..	..	1·39 (0·73–2·68)	1·06 (0·57–1·95)	0·85
Enhanced training *vs* control	..	..	..	1·93 (1·22–3·03)	1·22 (0·76–1·95)	0·39
Believes that ACT is the best treatment for malaria in adults	34/37 (92%)	69/88 (78%)	72/95 (76%)	..	..	..
Basic training *vs* control	..	..	..	0·88 (0·71–1·09)	1·01 (0·80–1·28)	0·92
Enhanced training *vs* control	..	..	..	0·73 (0·44–1·21)	0·94 (0·58–1·54)	0·81
Believes that ACT is the best treatment for malaria in children	37/38 (97%)	73/88 (83%)	80/96 (83%)	..	..	..
Basic training *vs* control	..	..	..	0·87 (0·74–1·02)	1·00 (0·87–1·15)	0·98
Enhanced training *vs* control	..	..	..	0·79 (0·58–1·09)	0·96 (0·71–1·30)	0·77
Thinks that it is good to give antimalarial drugs to patients with negative test results	34/39 (87%)	50/91 (55%)	39/101 (39%)	..	..	..
Basic training *vs* control	..	..	..	0·52 (0·34–0·81)	0·89 (0·58–1·37)	0·60
Enhanced training *vs* control	..	..	..	0·33 (0·19–0·56)	0·91 (0·55–1·52)	0·71

Data are n/N (%), unless otherwise indicated. Missing data were excluded from percentage calculations. Clinician knowledge was measured through specific knowledge-based questions in the clinician survey; clinician treatment preferences were based on questions in the clinician survey about what the clinician thinks and would do in specific circumstance. RDT=rapid diagnostic test. ACT=artemisinin-based combination therapy. *Crude analysis adjusted for stratum only; data are risk difference for continuous outcomes. †Adjusted for the following facility and clinician characteristics: stratum, facility type, and clinician sex, education, and type (for some outcomes only stratum and facility type were included because of multicollinearity and perfect prediction of the clinician characteristics). ‡Adjusted analysis could not be done for these outcomes because the the sample sizes were too small to provide robust estimates. §Data are mean (SD); based on a score (out of 11) derived from correct identification of several steps taken in the use of an RDT; only measured in 23 clinicians in the control group, 85 in the basic-training group, and 93 in the enhanced-training group.

Table 4: **Effect of the intervention on clinician knowledge and treatment preferences**

***Panel:* Research in context**

Systematic review

We sought to identify studies that have assessed interventions intended to improve the ability of health workers to diagnose and treat patients with uncomplicated malaria. We systematically searched Medline, Embase, the CABI Global Health database, the International Bibliography of Social Sciences, CAB Abstracts, and the International Network for the Rational Use of Drugs for reports published in English between Jan 1, 1990, and Nov 26, 2009, using a list of truncated synonyms for the search terms "malaria" AND "treatment" AND "intervention" AND "provider". Studies were regarded as eligible irrespective of the type of health provider so long as the effect of the intervention included a malaria-related outcome. Eligibility was restricted to studies that took a comparative approach, using either a before-and-after study design or comparing an intervention with a comparison group. 28 studies (assessing 33 different interventions) met the eligibility criteria. 20 of the interventions focused on provider training and used learning techniques to improve diagnosis and treatment of malaria. Only six provider-training interventions included malaria diagnostic tests. Although the results showed that these interventions led to improvements in the appropriate treatment of malaria, the proportion of patients receiving an antimalarial drug after a negative test result remained fairly high. Recent reviews of interventions designed to improve clinician management of malaria have had similar findings,[16,28] showing that the links between staff training and clinical performance remain mixed and in short supply. A recent systematic review[16] that assessed the introduction of rapid diagnostic tests (RDTs) into diagnostic algorithms for patients with fever showed that health-worker adherence to test results was highly variable—between 0% and 80% of patients with a negative test result received an antimalarial drug. Notably, all the reports included in these reviews[16,28] included little detail of the interventions used, limiting the extent to which these studies can usefully guide policy makers and programme managers in the selection of methods to support a shift in practice towards appropriate use of antimalarial drugs alongside RDTs.

Interpretation

Governments of many malaria-endemic countries are preparing to scale up the use of RDTs nationally. WHO malaria treatment guidelines[2] acknowledge the need for provider training alongside the deployment of RDTs and artemisinin-based combination therapy to address key problems such as the habitual presumptive treatment of malaria. Our study provides timely evidence about the effects of different types of supporting interventions. Our results show that enhanced training, designed to translate knowledge into prescribing practice and improve quality of care, has the potential to substantially improve adherence to negative RDT results, which in Cameroon could halve overtreatment in public and mission health facilities. Basic training is unlikely to be sufficient to support the behaviour change required for the introduction of RDTs.

with potentially substantial effects on the overuse of antimalarial drugs. Specifically, we have shown that an enhanced training programme, designed to translate knowledge into prescribing practice and improve quality of care, has the potential to significantly reduce the unnecessary use of antimalarial drugs in patients who have tested negative for malaria. Basic training that focuses only on how to use RDTs and the content of malaria treatment guidelines is unlikely to bring about the behaviour change needed to support the national rollout of RDTs.

Contributors

WFM and VW conceived the study. VW, WFM, LM-J, CIRC, and BC designed the study. BC led the data analysis. OAA, JNA, and LM-J designed the interventions and managed their implementation. VN, OT, and PO-Z reviewed training materials and supported implementation of the interventions in Yaoundé. DF-A and AN reviewed training materials and supported implementation in Bamenda. VW and WFM prepared the first draft of the report with input from all authors, and all authors contributed to subsequent drafts. All authors approved the final draft of the report.

Declaration of interests

We declare that we have no competing interests.

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Appendix D

Intra-class correlation coefficients and variance partition coefficients from Research Papers I-V

All of the data analysed in this thesis had a hierarchical data structure. Thus, it could not be assumed that the observations in a sample were independent from each other. The statistical methods used acknowledge that observations within a cluster tend to be more similar to each other, than to individuals in the rest of the sample. In Research Papers I-IV this clustering arose because the survey design used multi-stage cluster sampling (communities were selected, then facilities were selected, and then patients and providers were surveyed at the selected facility). In Research Paper V the clustering arose because the evaluation used a cluster-randomized design, in which facilities were allocated to one of three arms and the primary outcome was measured using data from patients seeking treatment at the facilities participating in the trial.

The amount of clustering can be measured using the intra-class correlation coefficient (ICC), and this determines the proportion of the total variance that was attributable to the each level of the data hierarchy. Thus, the ICC can be calculated as:

ICC at level 2 = (variance at level 2 / total variance)

ICC at level 3 = (variance at level 3 / total variance)

The variance partition coefficient (VPC) is similar to the ICC, though it is used when the dependent variable is discrete. The key distinction is that when the analysis uses logistic regression, the variance at level 1 is the variance of the standard logistic regression ($\pi^2/3 = 3.29$).

The following tables summarize the data used in Research Papers I-V and lists the ICC or VPC for each level of the hierarchy included in the analysis (before the inclusion of any covariates). For example, in Research Paper I the VPC shows that 27.9% of the total variance was attributable to variation at the facility level.

Research Paper I

Country	Nigeria
Data source	Formative phase: Patient exit data
Study population	Patients were eligible if they: • Reported having a fever in the past 24 hours AND were not pregnant AND not less than 6 months AND had no signs of severe malaria OR • had received an ACT
Data structure	Level 1: 1642 eligible patients Level 2: 100 facilities (public facilities, medicine retailers) Level 3: 16 communities
Primary outcome	% of patients who received an ACT
ICC / VPC at level 2	0.279
ICC / VPC at level 3	0.095

Research Paper II

Country	Cameroon
Data source	Formative phase: Patient exit data
Study population	Patients were eligible if they: • reported having a fever in the past 24 hours AND were not pregnant AND not less than 6 months AND had no signs of severe malaria OR • had been prescribed or received an ACT
Data structure	Level 1: 938 eligible patients Level 2: 174 facilities (public facilities, mission/private clinics, medicine retailers) Level 3: 20 communities
Primary outcome	% of patients who were prescribed or received an ACT
ICC / VPC at level 2	0.367
ICC / VPC at level 3	<0.001

Research Paper III

Country	Pooled analysis for Cameroon and Nigeria
Data source	Formative phase: Provider data
Study population	Providers were eligible if: • their responsibilities included prescribed or dispensing of medicines • they worked at a facility where the patient exit survey had been conducted • they were available on the day of the survey
Data structure	Pooled data for Cameroon and Nigeria Level 1: 518 providers Level 2: 245 facilities (public, mission, pharmacies and drug stores) Level 3: 36 geographic areas
Primary outcome	% of providers who stated a preference for ACT when asked which antimalarial do you think is the best drug for treating patients with uncomplicated malaria
ICC / VPC at level 2	0.377
ICC / VPC at level 3	0.209

Research Paper IV

Country	Separate analyses for Cameroon and Nigeria
Data source	Formative phase: Patient exit data
Study population	Patients were eligible if they: • reported having a fever in the past 24 hours • were not pregnant • not less than 6 months • had no signs of severe malaria • had been prescribed or received an antimalarial
Data structure	Cameroon: Level 1: 304 eligible patients Level 2: 91 facilities (public facilities, mission facilities, pharmacies & drug stores) Nigeria: Level 1: 473 eligible patients Level 2: 73 facilities (public facilities, pharmacies & drug stores)
Primary outcome	% of patients who received an ACT (of those who were prescribed or received an antimalarial)
ICC / VPC at level 2	For Cameroon (complete cases): 0.380 For Nigeria (complete cases): 0.476

Research Paper V

Country	Cameroon
Data source	Evaluation: Patient exit data
Data structure	Level 1: 3982 eligible patients Level 2: 46 public and mission facilities
Study population	Patients were eligible if they: • reported having a fever in the past 24 hours • were not pregnant • not less than 6 months • had no signs of severe malaria • were present at the facility
Primary outcome	% of patients who were correctly treated according to the malaria treatment guidelines* * which is a composite measure that requires: i) the patient to be tested for malaria, ii) to be prescribed or receive an ACT if the malaria test was positive, and iii) not to be prescribed or receive an antimalarial if the malaria test was negative
ICC / VPC at level 2	For effects: 0.302 For societal costs in base case: 0.293 For provider costs in base case: 0.545