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Towards a functioning retail health market

*Evaluating the integrated Community Case
Management Intervention for Pediatric Febrile
Illness in Drug Shops in Rural South Western
Uganda*

FREDDY ERIC KITUTU



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Abstract

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Objectives: This thesis examined the health systems effects of implementing the integrated Community Case Management (iCCM) intervention for paediatric febrile illnesses in a retail health market in South Western Uganda. More specifically, it evaluated drug seller interpretation of malaria Rapid Diagnostics Test (RDT) results (*study I*), adherence to iCCM guidelines (*study II*) and the intervention effect on households' perceived quality of drug seller fever care and care-seeking choice. *Study IV* qualitatively analysed the iCCM intervention implementation and causal mechanisms for observed effects. Improved understanding of such retail health markets will inform policy decisions and interventions for Universal Health Coverage.

Methods: The study used mixed-methods design with an intervention and comparison arm, and pre-test assessment in both study arms. Data collection methods included care-seeker drug shop exit interviews and household surveys using structured questionnaires, focus group discussions, in-depth interviews, review of secondary data and a laboratory analysis of finger-prick capillary blood samples.

Results: Among those tested for malaria parasites, there was 93% (95% CI 88.3, 96.2) agreement between drug sellers and laboratory scientist re-reading and with a kappa value of 0.84 (95% CI 0.75, 0.92) (*Study I*). The drug seller compliance with the reported malaria RDT results was 92.5% (95% CI 87.9, 95.7) (*Study I*). The iCCM intervention improved appropriate treatment for uncomplicated malaria by 34.5% (95% CI 8.6, 60.4), for pneumonia symptoms by 54.7% (95% CI 28.4, 81.0) and reduced appropriate treatment for non-bloody diarrhoea -11.2% (95% CI -65.5, 43.1), after adjusting for extraneous variables (*Study II*). Implementing the iCCM intervention in drug shops decreased the odds of households perceiving drug seller fever care as good but increased the household odds of choosing to seek care from private health facilities versus within the community (*Study III*). Drug sellers operated in a retail market system influenced by knowledge and actions of care-seekers, CHWs, government health workers and regulators, and also how formal and informal rules and norms were applied (*Study IV*). Implementation of the iCCM intervention at drug shops was modified and shaped by the emerging actor perceptions and behaviours (*Study IV*).

Conclusions: This thesis demonstrates the *implementation, causal mechanisms* and *contextual factors* of the iCCM intervention in a rural retail health market. Fidelity and quality of iCCM intervention by drug sellers was acceptably high, probably as a result of co-interventions. Interventions in retail health markets should comprise of components that target the multiple actors or influences that shape that market. Multi-component health system interventions are complex to implement and also create complexity in their evaluation. When technologies are involved, their analysis should go beyond their substance as products and view them as items that encapsulate interests of different actors, some of which maybe converging with or competing against societal goals.

Keywords: Integrated community case management; Malaria, Pneumonia symptoms, Drug shops, Retail health markets, Uganda, Under-five, Evaluation, Mixed-methods, Febrile illness, Universal Health Coverage

Freddy Eric Kitutu, Department of Women's and Children's Health, International Maternal and Child Health (IMCH), Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

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To my dad and mum, Bernard and Catherine Wakwaale, my spouse Juliet and children, Paula, Felipe, Ziva and all the children who were 5 years or younger between 2013 and 2018

“A mind that is stretched by new experience will never go back to its old dimensions.” - Oliver Wendell Holmes, Jr

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I **Kitutu FE**, Wamani H, Selling KE, Katabazi FA, Kuteesa RB, Peterson S, Kalyango JN, Mårtensson A. (2018) Can malaria rapid diagnostic tests by drug sellers under field conditions classify children five years old or less with or without *Plasmodium falciparum* malaria? Comparison with nested PCR analysis. *Submitted*.
- II **Kitutu FE**, Kalyango JN, Mayora C, Selling KE, Peterson S, Wamani H. (2017) Integrated community case management by drug sellers influences appropriate treatment of paediatric febrile illness in South Western Uganda: a quasi-experimental study. *Malaria Journal*, 16:425
- III **Kitutu FE**, Mårtensson A, Wamani H, Selling KE, Peterson S, Kalyango JN. (2018) Perceived quality of paediatric fever care from private drug shops and care-seeking choice in South West Uganda: data from household surveys. *Submitted*.
- IV **Kitutu FE**, Mayora C, Johansson EW, Peterson S, Wamani H, Bigdeli M, Shroff ZC. (2017) Health system effects of implementing integrated community case management (iCCM) intervention in private retail drug shops in South Western Uganda: a qualitative study. *BMJ Global Health*, 2

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List of Related Papers

The papers listed below were published within the same project as the thesis. They do not make direct contribution. However, they are related and relevant to the thesis.

- V Johansson EW, **Kitutu FE**, Mayora C, Awor P, Peterson SS, Wamani H, Hildenwall H. (2016): It could be viral but you don't know, you have not diagnosed it: health worker challenges in managing non-malaria paediatric fevers in the low transmission area of Mbarara District, Uganda. *Malar J*, 15:197
- VI Mayora C, **Kitutu FE**, Kandala NB, Ekirapa-Kiracho E, Peterson SS, Wamani H. (2018) Private retail drug shops: what they are, how they operate, and implications for health care delivery in rural Uganda. *BMC Health Serv Res*, 18:532.

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Abbreviations

A2L	Access to Life
ACTs	Artemisinin-based Combination Therapy
AMFm	Affordable Medicine Facility-Malaria
ARI	Acute Respiratory Infection
CHAI	Clinton Health Access Initiative
CHWs	Community Health Workers
CI	Confidence Interval
DiD analysis	Difference-in-differences analysis
DNA	Deoxyribonucleic acid
DT	Dispersible Tablets
FGDs	Focus Group Discussions
FTA	Fast Transient Analysis
GFATM	Global Fund for AIDS, Tuberculosis and Malaria
HBMF	Home Based Management of Fevers
HDREC	Higher Degree Research and Ethics Committee
Hib	<i>Haemophilus influenza</i> type B
HMIS	Health Management Information System
HRP2	Histidine Rich Protein 2
iCCM	Integrated Community Case Management intervention for pediatric febrile illness
IDIs	In-depth Interviews
IEC	Information, education and communication
IMCI	Integrated Management of Childhood Illness
ITNs	Insecticide Treated Nets
LLINs	Long Lasting Insecticidal Nets
LMICs	Low and middle income countries
MakSPH	Makerere University School of Public Health
MDG	Millennium Development Goals
MoH	Uganda Ministry of Health
MRC	Medical Research Council
RDTs	Rapid Diagnostic Tests
NDA	National Drug Authority
NMCP	National Malaria Control Program
NPV	Negative Predictive Value
OR	Odds Ratio
ORS	Oral Rehydration Salts
PCV	Pneumococcal conjugate vaccine

PCR	Polymerase Chain Reaction
<i>P. falciparum</i>	<i>Plasmodium falciparum</i>
PPV	Positive Predictive Value
PSU	Pharmaceutical Society of Uganda or Primary Sampling Unit
QAACT	Quality Assured Artemisinin-based Combination Therapy
SDGs	Sustainable Development Goals
SIHI	Social Innovation in Health Initiative
SSA	Sub Saharan Africa
TBE	Theory Based Evaluation
TDR	Special Programme for Research and Training in Tropical Diseases
U5	Under-five
UHC	Universal Health Coverage
UNCST	Uganda National Council of Science and Technology
UNICEF	United Nations Children's Fund
USD	United States Dollars
VHT(s)	Village Health Team(s)
WHO	World Health Organization

Operational definitions

Access to health technologies: People's ability to obtain and use good quality health technologies when they are needed. In this thesis, I interpret ACCESS as a continuous phenomenon premised on different actors and actions over time, not as a discrete event (Frost & Reich, 2009).

Antimicrobial medicine: A medicine that selectively destroys or inhibits the growth of susceptible microorganisms. Sometimes, it is referred to as an 'antimicrobial agent'.

Appropriate treatment: Receiving the recommended drug, in the recommended dose, and for the recommended frequency and duration. Other words used include appropriate medicine use (Nsungwa-Sabiiti et al., 2005).

Case: An occurrence or instance of infection or disease. The word is vague that it requires the type of case to always be specified (WHO, 2016).

Child medicines: Medicines of appropriate strengths with dosage form attributes that permit dosing, dispensing and administering the right dose for age or weight of the child. Other words used include 'child-friendly medicines', 'child-appropriate dosage forms', 'child-size medicines' (WHO, 2012).

Correct dose: Right number and strength of tablets, treatment frequency and duration according to the national standard guidelines (WHO, 1993).

Complex interventions: Those which contain several interacting components, their interaction with the context, inclusive. Additional dimensions include the number and difficulty of behaviors required by interveners, the number of groups or organizational levels of beneficiaries, the number and variability of outcomes and the degree of flexibility or tailoring of the intervention permitted (Craig et al, 2008, Moore et al, 2013).

Drug shops: Drug shops are lower-tier retail outlets, usually with no pharmacist on staff that are granted licenses to sell a limited list of medicines (over-the counter drugs, chemical products and household remedies) by the National Drug Authority (NDA) following successful vetting of personnel, physical premises and payment of prescribed fees (Pamela et al, 2017, NDA, 2015).

Fever: History (current or recent) of hot body with or without other symptoms, with or without confirmation of high temperature (WHO, 2000).

Fidelity: Refers to the consistency of what is implemented with the intervention as planned.

Health market: The environment in which all actors relevant to a particular health problem interact in a manner that these interactions determine the basis on which health related products and services are provided to the population. Public sector employees are considered part of this market since they are an option from whom users can seek health related products and services.

Integrated Community Case Management (iCCM) intervention of paediatric febrile illness intervention: A community level intervention to provide integrated case assessment and management of childhood fever, recommended by WHO & UNICEF for rural areas in low and middle income countries (LMICs), where government provision of health services is severely under-resourced and sometimes non-existent (WHO/UNICEF, 2012).

Intervention: In this thesis, it refers to combinations of technologies (e.g. medicines and rapid diagnostics), inputs into service delivery, organizational changes and modifications in processes related to decision making, planning and service delivery (Rifat et al, 2010).

Recommended medicine: Medicines recommended for illness based on the national (Ministry of Health, 2016) and community health worker's treatment guidelines. It is also referred to as the correct medicine (Ministry of Health, 2010).

Collaborating Partners and Funding

All studies in this thesis were carried out in a collaboration among: Uppsala University and Karolinska Institutet in Sweden; Makerere University in Uganda; the World Health Organization Alliance for Health Policy and Systems Research (WHO AHPSR) in Switzerland. The collaboration was initially funded by a grant through the Access to Medicines Research Programme of the WHO AHPSR. Additional funds were provided by the Einhorn Family Foundation and Pehr Lagermans Family of Sweden. Makerere University School of Public Health took a leading role in implementing the field work in South West Uganda. Together with Uppsala University, they had the overarching responsibility for the research activities and support of study implementation and conduct. Makerere University, Uppsala University and WHO AHPSR provided scientific expertise and technical support. The research activities continued beyond the Access to Medicines Research Programme through funding from the Swedish Research Council. Findings were disseminated in Uganda, Sweden and at relevant international scientific meetings.

Preface

These two past experiences highlighted to me how important private health providers are in ensuring adequate access to proven health technologies and even saving lives.

It was about 11:00 am, on July 2nd 2013, when my phone, safely tucked away in my pocket, vibrated. Juliet my wife was on the other end; she could hardly speak through her weeping. All she said was, “George is dead”. “What!” I was in surprise and disbelief as she repeated the message. Baby George was one week away from celebrating his first birthday when he passed on, as a result of bronchopneumonia as the autopsy confirmed later. He was the first child of our family friends, Nelson and Maria¹. To this day, we do not understand what happened. But we do know what a tragedy it is and we still share that tragic loss with George’s parents. That children do not live to celebrate their fifth birthday because of preventable and treatable acute febrile illnesses is a scar on the world’s collective conscience. Unfortunately, this loss is too many times a reality for families and communities in sub Saharan Africa.

That phone call came while I was facilitating an inception meeting with members of the district health team and other stakeholders in Mbarara (the intervention district for my doctoral thesis), to start an intervention project that aimed to improve access to child appropriate medicines and diagnostics. It was a sad but timely reminder of the urgency of efforts to improve the functioning of the health system to meet the challenges it faces. Although, George was gone, our project if successful would shape national and global health policies to improve access to life-saving medicines and diagnostics and hopefully save lives of countless under-five febrile children in low and middle income countries.

At the age of 16 while on vacation after the Ordinary level national exams, also referred to as the Uganda Certificate of Education exams, I experienced symptoms from my epigastric region that I could only describe as piercing nails. With no knowledge of medicine or any inclination that I would go on to study pharmacy at University, late alone study interventions aimed at improving quality of healthcare provided by drug shops in rural areas, I presented my case to my mother. Mummy, in her wisdom concluded that I had ulcers and she knew exactly which health provider would manage

¹ Names changed with mutual consent

my ailment. Mr. Bitai listened to my story and without missing a heartbeat, prescribed some capsules for me to swallow, starting immediately, and continuing for the next ten days. I cannot put into words the relief I got after swallowing my first dose. It was magical. Mr. Bitai is a veterinary assistant who operates a drug shop for human medicines in a trading centre about three kilometers from my parents' home in Bunangabo, Manafwa district. To this day, my mum seeks healthcare for all sorts of uncomplicated ailments ranging from pain in the ears to wounds on the legs from Mr. Bitai.

These two personal realities in different contexts in the same country leading to opposite outcomes illustrate in many ways the failures or wrongs in our current health system arrangements, some of which are by design and others, simply coping mechanisms. The least we can do is seek to understand the roles and possibilities of private sector even in rural areas to better inform policies on their possible contribution to achieving universal health coverage. In May 2013, I joined a research team that has implementing and evaluating a drug shop intervention study. This thesis is based on the inquiry that I went on to conduct as doctoral student, more than a year later.

Introduction

Private sector, Markets and Universal Health Coverage

Private sector and Universal Health Coverage

Uganda, like other low and middle income countries (LMICs) has an extensive and heterogeneous private health sector [4, 5]. It ranges from itinerant medicine sellers and individual health practitioners to medical centers and high-end hospitals and corporate health insurers. Usually drug shops and small private clinics exist in rural areas, medical centres, pharmacies and hospitals in urban centers. Some are formal and others informal. Evidently, private sector must be complementary and integrated with the local health system.

Extreme positions about the role of private sector in health systems at national and global level are frequently informed by comprehensive assumptions about the nature of the private sector and seldom take in account the strong degree of interlinkage, dependence and dynamic interactions between the public and private sectors in the health system [6-8], a phenomenon described by Nishtar and other researchers as mixed health systems [9-12] [7, 13-15]. Debate on performance of health systems that draws on comparisons between public and private sectors doesn't reflect the reality of health systems and neglects their heavily overlapping organizational, social, economic and shared history and propagates the false message that policy choices in regard to the public-private mix are binary [16, 17].

As countries push for Universal Health Coverage (UHC), the central plank of the Sustainable Development Goals (SDGs), there is a need to mobilize all available resources and possibilities offered in a mixed health system. The current paradigm of UHC aims to maximize health outcomes by distributing good-quality health services that are financially and geographically accessible, equitably. In addition, the healthcare services should be delivered efficiently at low levels of out-of-pocket burden according to ability to pay [18, 19]. Many LMICs will undermine their progress towards UHC if they do not harness the private sector.

Health markets and Universal Health Coverage

Private health providers also exist in a system where dynamic interactions and dependence among actors including public health sectors occurs, creating a health market. A health market is the environment in which all actors relevant to a particular health problem interact in a manner that these interactions determine the basis on which health products and services are provided to the population. Public sector employees are considered part of this market since they are an option from whom users can seek health products and services [5, 8, 15, 20, 21]. This description is important when analyzing or intervening to improve performance, as it starts to cure the deficiency in evidence resulting from assuming a false dichotomy between private and public health sectors. The correct analytical or interventional unit should be the health market system, not the private providers or broader healthcare system.

Many implementers and commentators have questioned the role of private sector in delivering healthcare. They highlight ills such as the profit made from the sick, catastrophic expenditures they may cause, or the latitude they enjoy to exploit the poor in systems where government regulation is weak or non-existent. Scholars argue against these simplistic views as they may hinder rather than facilitate our understanding about what the private sector is and how it can add value towards achieving universal health coverage [6, 15, 17, 21-23]. These scholars recognize the well-known reasons that compromise the contribution of health markets to societal objectives of offering equal access to equal care for those in equal need.

Prominent is the information asymmetry between the supply side and demand side [5, 7, 13, 24]. Coupled with weak governments and inadequate investments in health sector, health markets manifest these symptoms of inadequate regulation; namely, insufficient access for the poor, increased risk of inappropriate treatment that maximizes provider profit, and over reliance on public sector trained staff [25]. In health outcome terms, there is increased morbidity and mortality from largely preventable and treatable diseases. However, the same scholars argue that it is important to understand both what factors influence functioning of the health system and how they interact [6, 7, 13-15, 17, 21-23]. Understanding these interactions from a health systems lens helps the development of policy and interventions that focus on different parts of the mixed health systems, with the aim of improving overall health sector performance and population health.

The retail health market in the rural Ugandan context

Uganda is low income country with a population of 37.85 million based on the 2014 census and gross national income per capita of USD 680 [26]. Pov-

erty levels remain high with half of the population subsisting on less than USD 1.25 per day. With government contribution to health of USD 13.7 per capita [27], out-of-pocket expenditure on health that stands at 41% [28]. Acute febrile illnesses of malaria, pneumonia and diarrhoeal diseases are the major child killers accounting for 6.7%, 16.2% and 7.8% of under-five mortality, respectively [29]. Most Ugandans (97-99%) are at risk of *Plasmodium falciparum* infection [30, 31]. Similar to other low income countries, children die from these preventable and treatable illnesses because they do not receive timely or appropriate diagnostics and medicines [32, 33]. Private providers including informal ones administer more than half of all health care in Africa [33-35].

In rural areas in Uganda where 82% of the population resides [26], up to 50% of care-seeking for under-five febrile illness is from private drug shops and clinics [33, 34, 36-38]. Drug shops are lower-tier retail outlets, usually with no pharmacist on staff, that are granted licenses to sell a limited list of medicines (over-the counter drugs, chemical products and household remedies) by the National Drug Authority (NDA) following successful vetting of personnel, physical premises and payment of prescribed fees [39, 40]. However, these drug outlets occasionally provide treatments that are inconsistent with evidence-based clinical guidelines and are potentially harmful [34, 36]. They are part of the existing retail market and thus their performance is patterned by the size and behavior of the public health sector [15].

Pilot studies in high malaria transmission settings in Uganda demonstrated that with targeted interventions, drug seller treatment practices can be brought closer to recommendations by the national treatment guidelines [41-46]. Additionally, the Affordable Medicines Facility-malaria (AMFm) launched by the Global Fund to fight AIDS, Tuberculosis and Malaria in 2010 in Uganda as one of the pilot countries, was deemed successful in achieving the goals set. Availability and market share of quality-assured Artemisinin-based Combination Therapy (QAAC) increased by 26 to 52 and 16 to 40 percentage points, respectively, in five of the seven AMFm pilot countries. QAAC retail prices and absolute retail mark-ups decreased by US\$ 1.28 to 4.34 and US\$ 0.31 to 1.03, respectively, in six of the seven pilot countries [47-51].

However, as acknowledged by Kara Hanson and Barbara McPake and colleagues in the 2016 Lancet series on *UHC: markets, profits and the public good* [6, 15, 17, 21, 23], and Bennet et al [22] before them, evidence on which to make wise policy decisions concerning private health sector is still weak or absent. Hence, an urgent need to describe, analyze and evaluate the private sector while taking in account the different health system contexts with a view to delineating how it can add value. It requires engaging with

health markets that may actually be outside the formal healthcare system but provide important supporting functions to it.

This thesis evaluates the retail health market in relation to management of acute febrile illness in a relatively low malaria transmission setting in rural South Western Uganda. This health market includes drug shops on the supply side and care-seekers on the demand side. It acknowledges that their interactions and relationships are dynamic and are shaped by the community health workers, Ministry of Health (MoH), district and sub-district health officials, government and global health policies, and existing formal and informal norms, rules and regulations. The analysis in this thesis takes a creative process that initially breaks delineates the retail health market existing in South Western Uganda and breaks down the integrated Community Case Management (iCCM) intervention for pediatric febrile illness into smaller units, and later rebuilds them into a more complete system to aid our understanding.

The thesis examines the characteristics and behavior of the drug shops sellers (paper VI), drug seller interpretation of and compliance with malaria Rapid Diagnostic Test (RDT) results paper I, effect of the iCCM intervention on drug seller treatment of uncomplicated malaria, pneumonia symptoms and diarrheal diseases (paper II), and on care-seeker perceived quality of drug seller fever care (paper III). Lastly, paper IV and V examine qualitatively how the intervention components were *implemented*, *contextual factors* as mediators or moderators, and *causal mechanisms* that led to the observed effects.

Under-five mortality

Globally, the risk of a child dying before the age of five has reduced by 56% from 93 in 1990 to 41 deaths per 1000 live births in 2016 [52]. However, under-five (U5) mortality risk is still highest in Sub Saharan Africa (SSA) at 76.5 per 1000 live births, about 8 times higher than that in Europe (9.6 per 1000 live births) [52, 53]. The Sustainable Development Goals (SDGs) framework has proposed for at least 79 countries to reduce U5 mortality rate to as low as 25 deaths per 1000 live births. Six out of the seven countries with U5 deaths per 1000 live births higher than 100 are in SSA. At the current reduction rate, 47 countries (34 in SSA) will fall short of the SDG U5 mortality target by 2030 [53]. This calls for acceleration of implementation of low cost child survival interventions to save more lives.

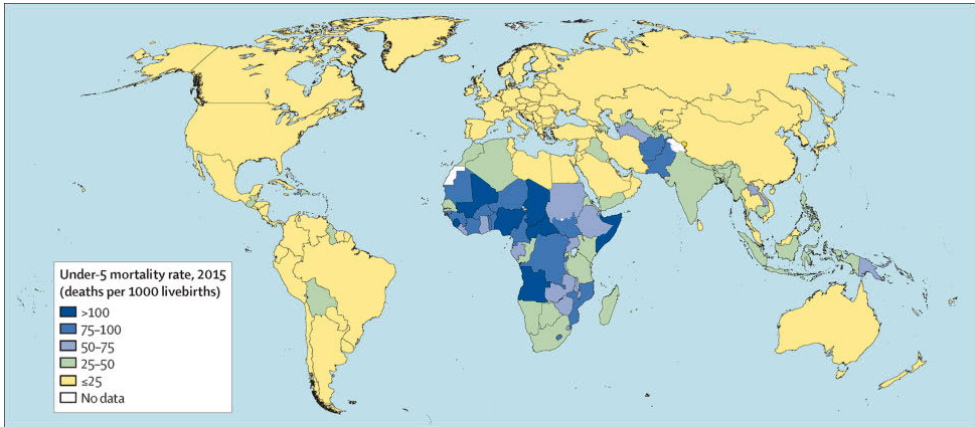


Figure 1. Under-5 mortality rate in 2015 by country

Source: You et al, 2016 [54]

Forty six percent of the U5 deaths occur in the first 28 days of life [55]. Children from the poorest households and rural areas are, on average, nearly twice as likely to die before the age of five as their counterparts in the richest households and urban areas, respectively. Children born to uneducated mothers are nearly three times as likely to die before the age of five as children born to mothers with secondary or higher education [56]. Thus, interventions to target such most affected populations are a priority.

Causes of child mortality

Infectious diseases remain the leading child killers of U5 children in SSA. In 2016, the leading killers were pneumonia 15.6%, diarrhoea 8.4%, sepsis 7%, malaria 5.1%, tetanus and meningitis 2.4%, measles 1.3%, AIDS 1.2%, other causes at neonatal age 38.6% and other causes post-neonatal age 20.4% [29]. Undernutrition is reported to underlie nearly half of these deaths [55]. The leading causes of U5 in-patient mortality in Uganda in 2016 are shown in figure 2. Whereas the proportion of U5 mortality attributed to malaria has declined, it remains the most geographically concentrated cause of child mortality – 96% of all malaria deaths occur in SSA [53]. Malaria and the other causes of U5 mortality are either preventable or treatable with available low cost interventions.

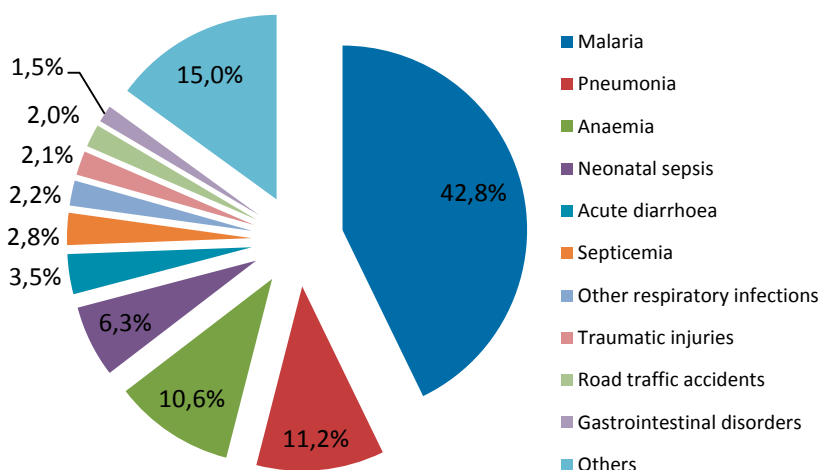


Figure 2. Leading causes of under-five in-patient mortality in Uganda.
Source: Uganda Ministry of Health, 2016 [57]

Coverage of child survival strategies

Child survival interventions are categorized into two:

- i) Interventions that target causes of child mortality among children one to fifty nine months,
- ii) Interventions that target to reduce neonatal deaths (first 28 days of life).

Coverage of child survival interventions against the child killers of malaria, pneumonia, diarrheal diseases and undernutrition, which are responsible for more than half deaths of children between 1 to 59 months, is elaborated in this thesis.

In SSA, the proportion of the population at risk of malaria that had access to an ITN is 60% and nearly all of them (53%) slept under an ITN in 2015 [58]. From national surveys in SSA, access to a trained provider for febrile children is low at 54% and 36% of febrile children are not brought for care at all. Malaria diagnostic testing remains low at 51% in public sector, 40% in private sector and only 9% in the informal sector. The median proportion of U5 children with evidence of recent or current *Plasmodium falciparum* (*P falciparum*) infection and a history of fever, who received any antimalarial medicine, is 30% in SSA in 2013 – 2015 and the median proportion receiving an ACT is 14% [58].

In 2014, coverage of third doses of the pneumonia related vaccines of *Haemophilus influenza* type B (Hib) vaccine and pneumococcal conjugate vaccine (PCV) in SSA was at 77% and 53%, respectively. Three of five children with acute respiratory infection (ARI) symptoms are taken to health providers for appropriate care. More than 90% of the global population use improved drinking water sources and two thirds use improved sanitation facilities. In 2015, 663 million people still lacked improved drinking water sources, and 2.4 billion lacked improved sanitation sources with nearly 1 billion practicing open defecation. Recent adoption of the rotavirus vaccine – a virus that causes severe diarrhea in children – onto immunization schedules of more than 79 countries offers additional reduction in diarrhea related morbidity and mortality. Just two in five children who suffer from diarrhea receive Oral Rehydration Salts (ORS) while coverage of zinc supplementation is very low with median of 1% out of 49 countries surveyed. Lastly, in 2013, two thirds of the targeted children were reached with two doses of the Vitamin A supplementation [53]. Vitamin A supplementation can reduce child mortality by nearly a quarter.

Health systems, goals and functions

The 2000 World Health Report defined a health system as '*all the organizations, people, and actions whose primary purpose is to promote, restore or maintain health*'. Scholars have opined that such a definition narrowly focuses on the health sector – *those actors, institutions and resources whose primary intent is to improve or preserve individual or population health* - whilst excluding the form and dynamics in the linkages between components within and beyond the health sector.

In the view of this thesis, a health system includes a broader range of activities, together with the complex interactions and relationships among them that improve population health, in a world where sectoral and international boundaries have become increasingly permeable.

Taking the WHO definition of health - '*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*' - as a starting point, a health system includes all factors that may directly or indirectly impact upon population health.

Figure 3 shows a simplified view of such a health system (adapted from Smith and Hanson, 2011 [59]). Broadly, the lower half shows inter-linkages among in-country domestic factors that influence health;

- i) Risk factors - genetic predisposition to disease, environmental influences, infectious disease,
- ii) The household economy - human capital and the individual investment in health,
- iii) The health sector - the impact of goods and services consumed primarily to improve health status, and
- iv) The national economy which represents the meta- influences of government structures and general economic well-being.

Captured in this illustration, is the acknowledgement that social determinants of health are perhaps equally or even more significant than the health sector in improving population health.

The upper half of figure 3 shows the influences outside the national context; first, risk factors of disease are influenced by rapid cross-border transmission of communicable diseases, increased environmental degradation, marketing of unhealthy products and behaviours; second, the national economy is affected by the provision and distribution of health related goods (pharmaceutical products), services (knowledge and technology) and people (patients and health professionals) and the global governance structures and regulations.

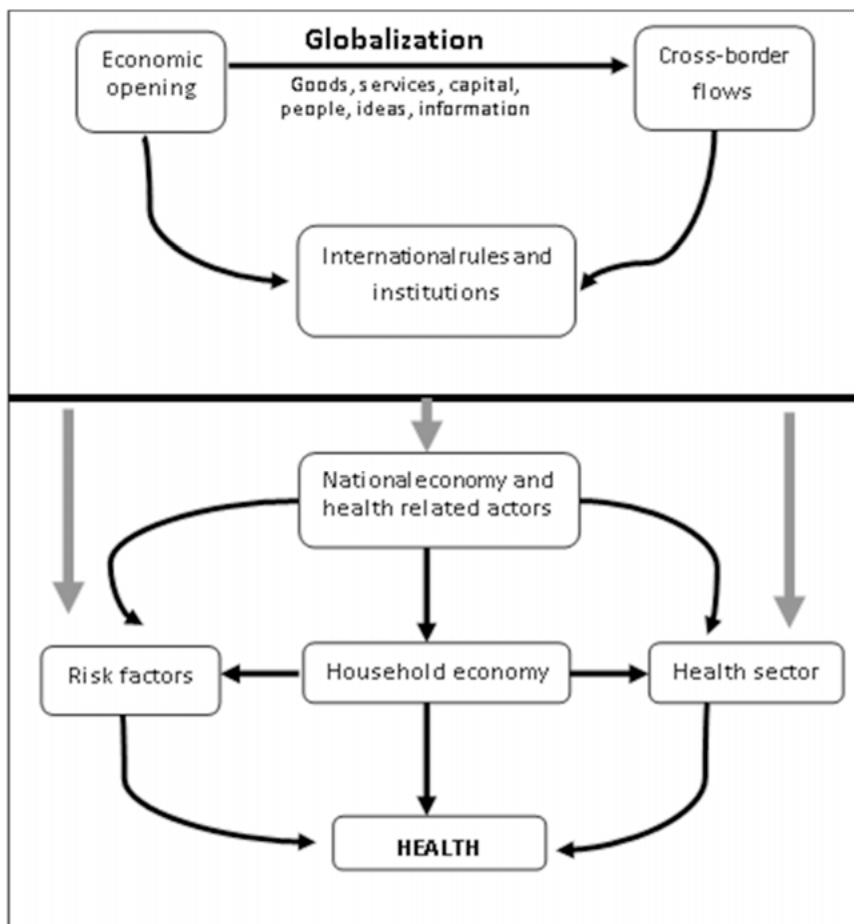


Figure 3. Simplified view of the health system

Source: Smith and Hanson, 2011 [59]

Despite the complexity illustrated above, the fundamental goals of health systems remain; improving the health of the population they serve, responding to people's expectations (responsiveness), and providing financial protection against the costs of ill health (fairness of financing) [60]. In order for a health system to provide services of acceptable quality, it should mobilise resources (through taxation, insurance and out-of-pocket expenditure), finance goods and services (human resources, medicines, equipment and infrastructure) and provide stewardship (through policy formulation and supervisory regulation) [60].

However, many low income country health systems are challenged. Structurally, they have heterogeneous establishments and providers, dominant unorganized private sector and inefficiencies in government delivery of health services [9, 11]. As a result, high out-of-pocket expenditures by users,

compromised quality of available healthcare, frequent ethical digressions by health providers and variation and inequity in physical availability and access are common place [12].

The current state of health systems in low income countries has been identified as a critical bottleneck in improvement of child health [61]. Medicines and diagnostics to treat or prevent the major causes of child mortality exist[62], but effective health systems to deliver them to children in need do not. With weak health systems and low funding for child health services in countries with highest child mortality [63], community based initiatives have been proposed as vehicles of high impact low cost interventions to areas with inadequate access to child health services [62]. Community based interventions can contribute to increasing adequate access to care and adherence [64-67].

Integrated Community Case Management (iCCM) intervention for pediatric febrile illness

It is a community level intervention to provide integrated case assessment and management of childhood fever, recommended by WHO & UNICEF for rural areas in LMICs, where government provision of health services is severely under-resourced and sometimes non-existent. It is based on the evidence that appropriately trained community health workers (CHWs) can be supervised and supported with an uninterrupted supply of medicines and equipment to identify, correctly treat and/or refer most children who have malaria, pneumonia symptoms, non-bloody diarrhoea and malnutrition [68, 69]. CHWs are community-based volunteers, also referred to as the village health teams (VHTs) selected by village elders and peers from within the community.

The iCCM intervention is composed of multiple components, three being the most fundamental ones; the health worker, health service and community components.

1) The health worker (CHW) component is aimed to improve integrated case management skills for tending to U5 febrile child, based on case detection using simple clinical signs and rapid diagnostics to guide choice of treatment. The CHWs are trained by a MoH certified trainer in a 6-day training comprising of lectures and hands-on sessions, following the MoH-iCCM curriculum. It addresses how to assess, test, classify and treat child illnesses of malaria, acute respiratory illness (ARI) and diarrheal diseases. Use of point-of-care diagnostic-testing, referral, filling in registers, and managing drug supplies are also explained. Monthly support supervision of CHWs is conducted shortly after the training by a diploma or degree-level clinician to reinforce the knowledge and skills.

2) The health service component focuses on distribution of medicines, diagnostics and other logistics necessary for service provision. The medicine products are artemether-lumefantrine dispersible tablets (DT), DT amoxicillin, DT zinc and oral rehydration salts (ORS) and artesunate suppositories. The preferred product forms are those that are single dose-packaged and color-coded for age. The diagnostics include malaria Rapid Diagnostic Tests (mRDT), specific for *P. falciparum* and respiratory counters. Other logistics include patient registers, referral slips, supply order forms and treatment algorithms.

3) The community component seeks to improve household and community care-seeking practices that affect U5 child health. The messages on fever care-seeking, diagnostic testing and treatment adherence are delivered through community meetings, workshops, radio talk shows and announcements and word-of-mouth by CHWs.

These iCCM intervention components were adapted for implementation in drug shops that are part of the retail health market. The alterations were necessary to achieve better contextual fit, given that the iCCM intervention proposed by WHO/UNICEF is intended to be implemented by community health workers working as volunteers with medicines, diagnostics and logistics provided by the public health sector. For simplicity, the adapted version of the iCCM intervention is referred to as the *AXEX (Access and Excess) intervention* in this thesis.

Progress of implementation of the iCCM intervention

In Uganda, the iCCM intervention was adopted by Ministry of Health as a national policy in 2010, to be implemented through the CHWs at village level [70]. After eight years, iCCM implementation is limited to just over half of the country (64 of the total 116 districts) and is supported mostly by health development partners. These include Malaria Consortium, UNICEF and Global Fund for AIDS, Tuberculosis and Malaria (GFATM) [71]. However, this iCCM intervention implementation has been afflicted by similar challenges as the broader public health system. These include inadequate supervision, motivation and retention of community health workers, unreliable medicine and equipment supply systems, weak monitoring and evaluation systems and low uptake of services provided by community health workers in certain areas [72, 73]. As a consequence, the poor children in remote areas in Uganda are denied the dividend of community case management of malaria, pneumonia and diarrhea that has been reported elsewhere [74-77]. Additionally, care-seeking from private sector has remained at about 50% for under-five children with fever [34, 36, 38].

Previous studies on implementation of the iCCM intervention

Our research team based at Makerere University College of Health Science, Kampala, Uganda in collaboration with Uppsala University and Karolinska institutet in Sweden and other global partners has conducted numerous studies on pediatric fever management over the years. Findings from these studies informed national and global policies on pediatric fever management. Studies by Nsungwa-Sabiiti, Karin Källander and colleagues evaluated the implementation of home based management of fevers (HBMF) [78-81] and how the strategy promoted prompt and appropriate malaria treatment in U5 children. Findings such as symptom overlap between malaria and acute respiratory infections from these studies informed the iCCM intervention for pediatric febrile illness [82-84]. Additional studies have evaluated different aspects on diffusion and implementation of the iCCM intervention including care-seeking from public and private health providers, use of the rapid diagnostic tests in the iCCM intervention and appropriate antimicrobial medicine use [77, 85-91]. More recently, following findings that over 50% of U5 febrile children in rural areas first seek care from private health outlets, intervention studies to assess the feasibility and effectiveness of introducing the iCCM intervention in private drug shops in a high malaria transmission setting in Uganda were conducted [34, 41, 92]. In 2015, this initiative to improve drug seller management of U5 febrile illness was recognized by the Special Programme for Research and Training in Tropical Diseases (TDR) and the World Health Organization (WHO) with the Social Innovation in Health Initiative (SIHI) award [93].

This thesis builds on this previous work and attempts to examine more broadly the health systems effects of implementing the iCCM intervention in drug shops as part of the retail health market in a relatively low malaria transmission setting in rural South Western Uganda.

The Uganda Country Profile

Uganda is one of the members of the East Africa Community. The country has a population of approximately 37.85 million based on the 2014 census [26] and has one of the highest population growth rates in the world at 3.03%. The majority of the population (59.3%) are younger, 19 years or less, 37.8% are between 20 to 64 years old and only 2.7% are 65 years or older. Females constitute 51% of the general population. Approximately 82% of the population resides in rural areas, in households with mean size of 4.7 persons [26]. The country has sustained one of the world's fastest economic growth rates of the last two decades, averaging over 6% per year. However, Uganda remains one of the least developed countries in the world with as

gross national income per capita of USD 680 in 2014 [26]. The life expectancy at birth has been increasing and currently is 63.3 years [26]. Poverty levels remain high with half of the population subsisting on less than USD 1.25 per day. Poverty related diseases of malaria, acute respiratory infection and diarrhoeal diseases account for substantial child morbidity and mortality in Uganda.

Malaria burden

Uganda is a high malaria transmission country with 95% population at risk of *P. falciparum* malaria all year round. Ugandans are the fifth largest population at risk of malaria in the world and the country accounts for 4% of the global burden. The country is ranked 3rd out of the 18 countries that account for 90% of *P. falciparum* infections in Sub-Saharan Africa [58]. However, recent investments have ripped dividends including a reduction of U5 child parasitemia from 42% in 2009 to 19% in 2014 and malaria specific mortality from 20,000 cases in 2005 to 6000 in 2015 and increase in household ownership of at least one bed net from 47% in 2009 to 90% in 2014/15 [94]. Bed net usage among children U5 increased from 33% in 2009 to 74% in 2014/15. However, malaria remains a major public health problem accounting for up to 50% of outpatient visits, 20% of hospital admissions and 20% of inpatient deaths [94, 95].

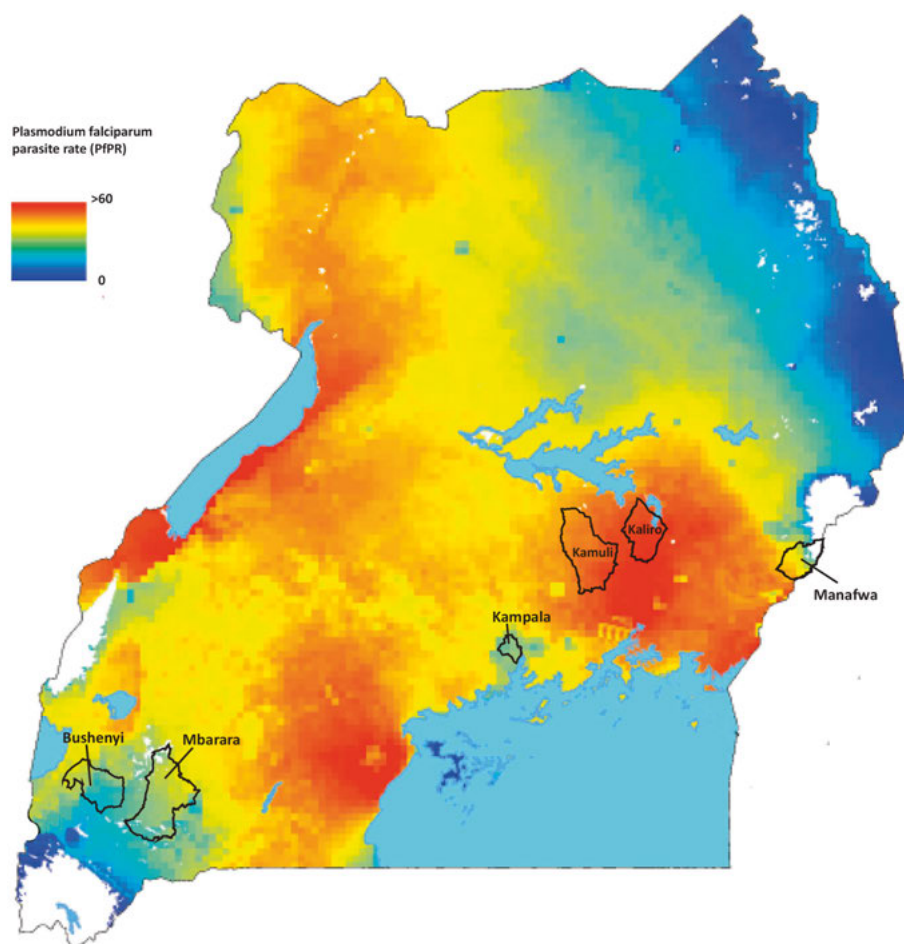


Figure 4. *Plasmodium falciparum* parasite rate (PfPR) in Uganda

Source: Wanzirah et al, 2015, [96]

Uganda's Health System

The health system in Uganda is composed of the public, private-not-for-profit and private-for-profit providers as well as traditional practitioners. The public sector and private sectors provide 51% and 49% of the health services, respectively [97]. Uganda has a total of 5,229 health facilities [98]. Fifty two per cent of all the hospitals and health facilities in the country are public, 41% are private-not-for-profit and 7% are private-for-profit. Uganda runs a decentralized health system with national and district levels. Considerable disparities exist in the quality and coverage of health services across the districts. The lowest rung of the district based health system consists of level 1 health services. The next levels are Health Centres level II-IV which

progressively provide a broader scope of health services and serve a larger number of people [30]. See table 1 for detailed Uganda Health Structure.

The Uganda Ministry of Health (MoH) has a public private partnership for health policy in place [99], and the private health providers such as private hospitals, medical centers and clinics undertake and accreditation process by MoH to be assigned a level of care.

Table 1. Uganda Health Structure

Govern- ance	Health unit, location	Health Worker	Roles and estimated service population
Parlia- ment TMC HPAC	Ministry of Health, Health Institu- tions, National	High level Admin- istrative Techno- crats	Stewardship & strategic planning, policy and standards, quality as- surance, supervision, resource mobilization, disease surveillance
National and Re- gional Level	Tertiary Hospitals, National	Specialists Medical officers	Advanced tertiary care Over 25,000,000 people
	Referral Hospitals, Region	Specialists Medical Officers	Specialist services 2,000,000 to 3,000,000 people
Local Government District Health Teams	General Hospitals, District	Medical Officers, Clinical Officers	Oversight of public, private and community health programs, management of personnel, hospi- tal, laboratory, X-ray 300,000 to 1,500,000 people
	HC IV level, County	Medical Officers Clinical Officers	Management and quality assur- ance, outpatients, wards, theatre, laboratory, blood transfusion 100,000 people
	Health Centre III, Sub-county	Clinical Officers, Nurses and mid- wives,	Maternity and laboratory services 20,000 people
Health Sub- Districts	Health Centre level II, Parish	Nurse and mid- wives Health Assistants	Outpatient services only, out- reach, support supervision to Village Health Teams (VHT) 5,000 people
	Health Centre I (VHT), Village	Community Health Workers	Health promotion and preventive care, 1,000 people, 5 VHTs/village

Conceptual framework

Multiple influential frameworks and theoretical debates exist in the domain of process and outcome evaluations of complex interventions. Complex interventions are those which contain several interacting components including how context mediates or moderates the intervention components. Additionally, complex interventions as defined by dimensions such as the number and difficulty of behaviors required by interveners, the number of groups or organizational levels of beneficiaries, the number and variability of outcomes and the degree of flexibility or tailoring of the intervention permitted [2, 3].

This thesis adapted the UK Medical Research Council (MRC) guidance [1] into a conceptual framework for key functions of process and outcomes evaluations and relationships among them. The framework was applied in assessing the fidelity and quality of implementation, clarify causal mechanisms and identify contextual factors associated with variation in outcomes of the intervention. Fidelity in this thesis refers to the consistency of what is implemented with the intervention as planned.

Implementation

As in the MRC guidance, this thesis applied the Oxford Implementation Index checklist [100] to describe and analyze the *AXEX intervention* and assess implementation fidelity and quality. Although that index is primarily for use by systematic reviewers to identify, extract and compare intervention implementation and characteristics across trials, it proposes four domains that are relevant to this thesis. These are *intervention design* (clear specification of the core components of the *AXEX intervention*), *delivery* (staff qualifications, the quality and use of materials -medicines, diagnostics, treatment algorithms and other logistical materials -, dosage administered), *uptake* and *context*. Its advantage is that in analyzing the outcomes, it permits consideration of resources, structures and processes needed to achieve successful implementation, rather than just what was delivered. The Oxford Implementation Index covers similar domains as earlier definitions of fidelity by Carroll et al [101] and Bellg et al [102].

Mechanism of effect

This thesis applies theory based evaluation (TBE) to examine and understand the causal pathways leading to change or effect i.e. mechanism of impact. Inspired by Weiss [103], data was collected about stages at which the causal chain may breakdown. The *AXEX intervention* hypothesized that if drug sellers are trained on diagnostic testing for malaria parasites and pneumonia symptoms and provided with the diagnostics, they would test and comply with the test results. *Mediation* was incorporated into this theory of change to acknowledge the role of care-seekers in bringing the children to the drug seller and accepting the drug seller interpretation of the test results. However, the role of care-seeker in the hypothesized change is also subject to contextual factors such as household care-seeking practices or perceptions of drug sellers, a phenomenon referred to as *moderation* in theory of change. This thesis navigated the need to breakdown the *AXEX intervention* into constituent parts versus the notion that complex interventions are greater than the sum of their parts with multiple components acting in synergy to produce change. This was possible because the MRC framework for evaluating complex intervention takes in account their distinguishing characteristics of unpredictability, emergence and non-linearity of outcomes [104].

Context

In this thesis, context is interpreted as pre-existing conditions that could have facilitated or impeded implementation fidelity i.e. a moderator of implementation, and beyond that, as a moderator of outcomes [105]. Actors in the *AXEX intervention* were seen as agents, whose pre-existing circumstances, attitudes, perceptions and beliefs shaped how they interacted with the constituent parts and the intervention as a whole. Also, these pre-existing conditions were dynamic in response to the gradual unfolding of the *AXEX intervention* implementation. Initial analysis of the context to identify the key stakeholders was carried using the theoretical framework for health markets proposed by Bloom et al [8].

Inspired by Pawson and Tilley [105], the *AXEX intervention* is construed as ‘a theory incarnate’, as it reflects assumptions about the cause of inadequate access to life-saving medicines and diagnostics that leads to child morbidity and mortality. It proposes a set of activities and assemblages that can interact with each other and context to produce change among populations of drug sellers and care-seekers. It also includes a set of structures and processes intended to facilitate change at organizational or retail market system level.

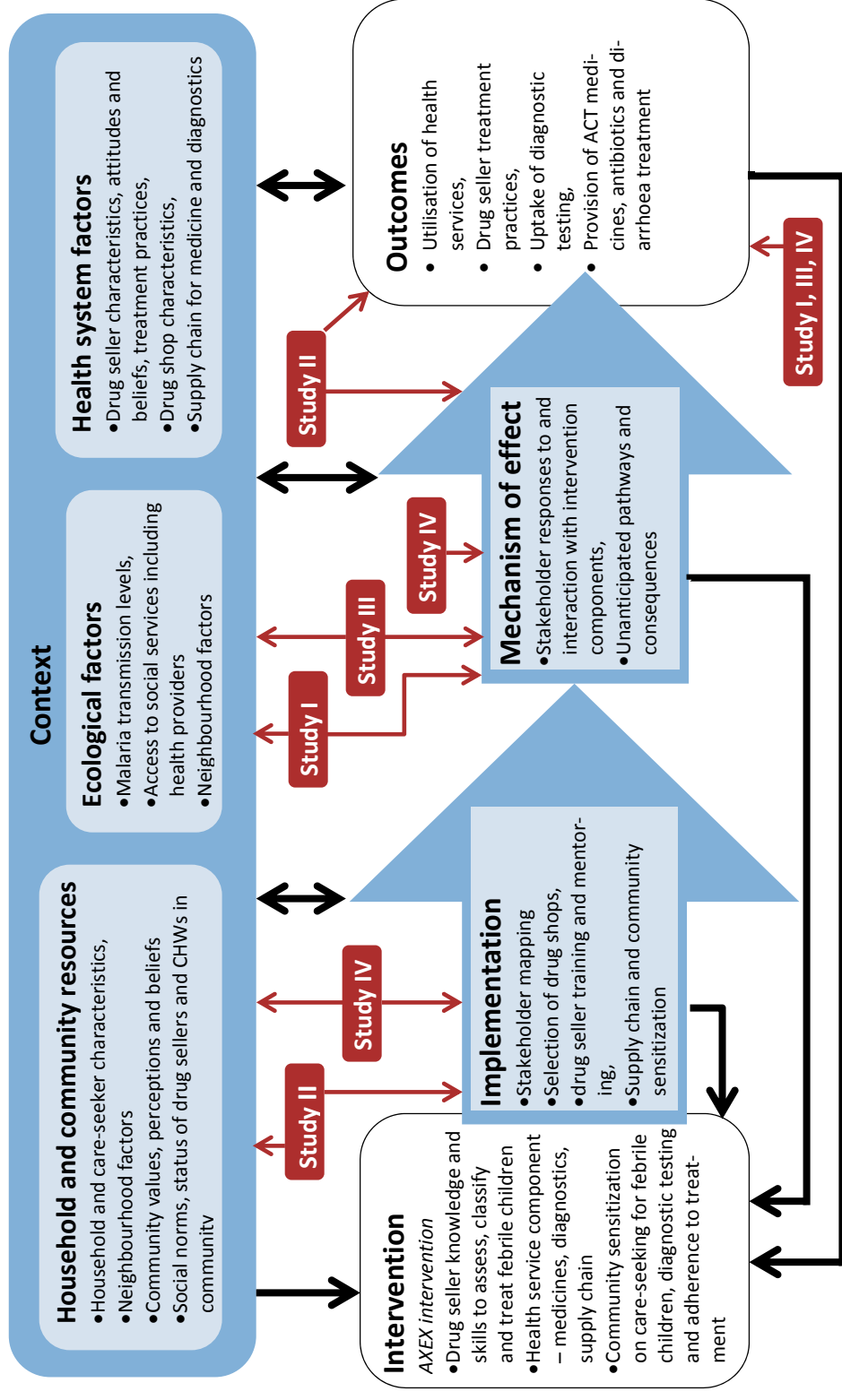


Figure 5. Conceptual framework for evaluation the iCCM intervention of pediatric febrile illness in drug shops in rural Uganda.

Source: Moore et al, 2013 [1] Craig et al, 2008 [2, 3], adapted by Freddy

Rationale for the Thesis

This thesis originated with the idea to adapt, implement and evaluate the integrated community case management (iCCM) of pediatric febrile illness intervention in a retail health market of a relatively low malaria transmission setting in South West Uganda. The iCCM intervention has been shown to be effective and feasible in a high malaria transmission setting [41, 92]. However, moving to a relatively low malaria transmission intensity setting - malaria parasite prevalence between 4.1% [94] and 9.3% [106], there is likely to be more non malaria febrile illnesses. Use of the iCCM algorithms to assess, classify and manage paediatric fevers may result in situations where fewer or no antimicrobial medicines are recommended for treatment of the febrile illness. Moreover, most fevers in Uganda have previously been attributed to malaria [107]. We do not know how the conflict of interest between drug sellers' motive to maximize sales of ACTs will affect their interpretation of malaria RDTs and eventual adherence to the observed diagnostic test results or iCCM treatment guidelines.

From a health systems lens, it is also not obvious how implementing the iCCM intervention in drug shops will affect perceived quality of care among care-seekers and thus their care-seeking choice. Additionally, it is important to understand the context, as well as the intervention's implementation and mechanism of effect, to better interpret the outcomes [108]. Borrowing from Robert Merton's social theory, and we argue that the iCCM intervention, like other purposive social actions, has unintended consequences [109, 110]. Some of these can be foreseen and prevented, and others cannot be predicted. Whereas the intended and anticipated consequences of the purposive action are always relatively desirable to the actor, unintended effects are not always undesirable.

Effective interventions have at times failed due to poor acceptability and implementation plans that have not been sensitive to the stakeholders' opinions [111, 112]. We thus, aim to understand how the iCCM intervention was implemented, its intended and unintended consequences and their interconnections, and we examine the dynamics and processes by which the effects were achieved.

Aim

The aim of the thesis is to examine health system effects of an integrated community case management intervention for U5 paediatric febrile illness in a retail health market in a relatively low malaria transmission setting in South Western Uganda.

The specific objectives for each study are:

Study 1 (Paper I)

To determine drug seller interpretation of and adherence to malaria RDT (*P. falciparum* specific histidine-rich protein 2 antigen-based test) results and performance of malaria RDTs under field conditions.

Study 2 (Paper I & Paper II)

To examine drug seller adherence to integrated community case management guidelines for U5 pediatric febrile illness.

Study 3 (Paper III)

To determine the effect of implementing the iCCM intervention in private drug shops on perceived quality of drug seller fever care and care-seeking choice among households in South Western Uganda.

Study 4 (Paper IV)

To describe and analyze the iCCM intervention to understand how it was implemented and examine the dynamics and processes by which the observed effects were produced.

Materials and Methods

Overview

Studies in this thesis were conducted in a mixed-methods approach. Table below summarizes the design and sample, setting, analysis and outcome for each study. All studies except small components of study I and II are based on primary data.

Table 2. Overview of the thesis methods.

Study	Design and sample	Setting	Analysis and outcome
iCCM by drug sellers influences appropriate treatment of paediatric febrile illness in South Western Uganda: a quasi-experimental study	<u>Care-seeker exit interviews pre- and post-intervention</u> Pre (n=428) and Post (n=553) <u>Secondary data (U5 febrile child registries) n=5975</u> <u>Direct observation n=49</u>	Mbarara Bushenyi	Difference-in-difference analysis of and trend analysis for proportions
Can malaria RDTs by drug sellers under field conditions classify U5 children with or without <i>P. falciparum</i> malaria? Comparison with nested PCR analysis.	<u>Cross sectional study</u> Laboratory based comparison of malaria diagnostic strategies (n=212) <u>Secondary data (n=199)</u>	Mbarara	Agreement between diagnostic strategies, sensitivity, specificity and predictive values
Perceived quality of paediatric fever care from private drug shops and care-seeking choice in South West Uganda: data from household surveys.	Pre- and post-intervention household surveys (n=5334)	Mbarara Bushenyi	Multi-level analysis for neighbor effects, predictors of perceived quality and care-seeking choice
Health system effects of implementing the iCCM intervention in private retail drug shops in South Western Uganda: a qualitative study.	<u>Qualitative process evaluation</u> Focus group discussions; care-seekers (n=18), community health workers (n=8) In-depth interviews (66)	Mbarara	Deductive manifest and content analysis, Perceptions and behaviours

Study area and population

Uganda has a population of 37.85 million and a total land area of 241,559 square kilometres. Since July 1st 2016, it has been demarcated along political and geographical boundaries into 115 districts and Kampala Capital City Authority. The central government interacts directly with local governments at the district level. Within the districts are counties, sub counties, parishes and villages.

Studies I and IV were conducted in Mbarara district while studies II and III occurred in both Mbarara and Bushenyi districts. Both Mbarara and Bushenyi districts are located in South Western Uganda.

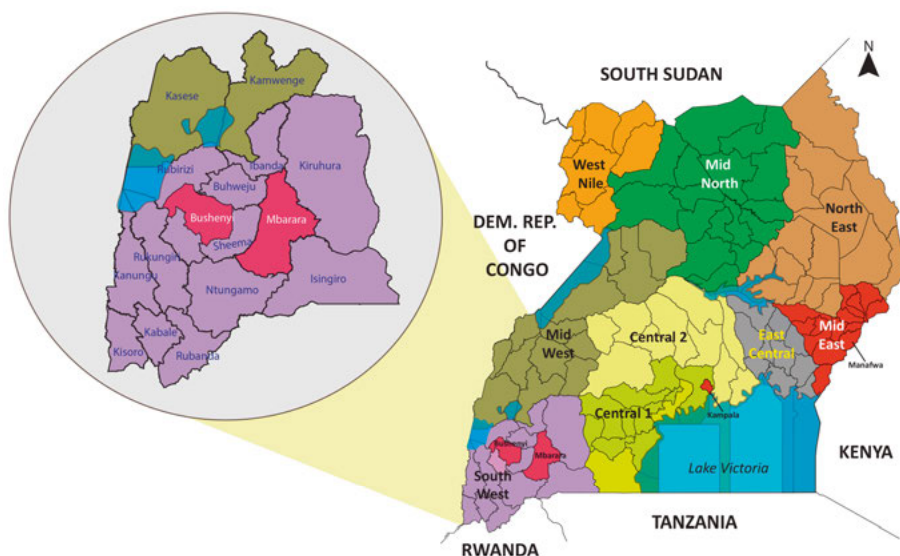


Figure 6. Map of Uganda showing Mbarara and Bushenyi districts in South Western Uganda

South West Uganda, a relatively low malaria transmission region with community malaria parasite prevalence of 4-5% [94] was selected for prospective evaluation of the implementation of iCCM in private sector drug shops. It is one of ten malaria indicator survey regions in Uganda, consisting of twelve administrative districts with relatively similar malaria burden. The region is located approximately 250 kilometers southwest of Kampala, the commercial and administrative capital of Uganda. It has typical tropical climate with rainfall peaks in April and October during the year [26]. The terrain is gentle undulating hills interspersed with plain savanna grasslands. The main source of livelihood is subsistence cultivation of food crops and livestock. Health service delivery in this area is structured along a pluralistic system with public health facilities and private pharmacies, clinics and drug

shops serving the population to a variable extent. The remote and geographically constrained areas are served by private health facilities and outlets with minimal health infrastructure[113] manned by people with health training from zero to two years [34, 114, 115].

Studies II and III compared an intervention arm and a comparison arm. The intervention arm was situated in Mbarara district while Bushenyi hosted the comparison arm. The approximate distance between the two districts is 45 km. Mbarara district has a population of 472,629 people served by 58 formal health facilities. The district drug inspector, district health educator, a cadre of CHWs and drug shops were the key participants within the district. Drug shops are small-scale medicine outlets that are granted licenses by the National Drug Authority (NDA) following successful vetting of personnel, physical premises and payment of prescribed fees to sell a limited list of medicines. Care-seekers (households with U5 children) in the catchment communities as the intended beneficiaries on the demand side completed the loop of stakeholders in studies presented in this thesis.

Bushenyi district was purposively selected as the comparison area. This rural area was deemed similar to Mbarara in geographical terrain, vegetation, rainfall patterns, ethnicity, and cultural practices and in having low malaria transmission rates. It has a population of 234,440 served by 36 formal health facilities [26, 116]. The district drug inspector, drug shops and households with U5 children were also enrolled to participate in the studies.

The AXEX intervention

The iCCM intervention is recommended by WHO/UNICEF and Uganda MoH to be implemented through the CHWs. In this thesis, the iCCM intervention detailed on page 22 was adapted for implementation in private sector drug shops in a rural South Western Uganda, a relatively low malaria transmission setting. The multiple components as adapted are outlined in Table 3. After adaptation, the intervention was referred to the *AXEX* (Access and Excess) *intervention* for simplicity. Preparation for field work and implementation of the *AXEX intervention* started in May 2013. The actual intervention implementation lasted from February 2014 to September 2015.

The *AXEX intervention* was implemented and evaluated using the conceptual framework (figure 2) adapted for this thesis. To examine the fidelity and quality of *implementation*, this thesis interpreted the *AXEX intervention* as a quality improvement tool to promote systematic drug seller practice in assessing and classifying pediatric febrile cases based on clinical signs and symptoms; in using rapid diagnostics to detect malaria parasites or pneumonia symptoms; and in prescribing child-appropriate antimalarials, antibiotics or diarrhea treatment based on the classification or referral. This interpretation is presented as an algorithm in Figure 7. Surrogate outcomes were iden-

tified from the iCCM indicator guide recommended by the monitoring and evaluation subgroup of the global iCCM task force [117] and assigned to each step.

Using a *factorial model*, we conceptualized the surrogate outcomes as intended effects on drug seller treatment practices into pre-defined discrete, static and quantifiable variables [118] and measured and compared in the intervention and comparison arm, before and after the *AXEX intervention*, respectively. We also adopted a health market theoretical framework [14] to describe and analyze qualitatively the *AXEX intervention*, its intended and unintended consequences and their interconnections, and to examine the dynamics and processes by which the effects were achieved. Identification of intended and unintended consequences was also inspired by Robert Merton's social theory of unanticipated consequences of purposive social action [109, 110]. Some of these can be foreseen and prevented, and others cannot be predicted. Whereas the intended and anticipated consequences of the purposive action are always relatively desirable to the actor, unintended effects are not always undesirable.

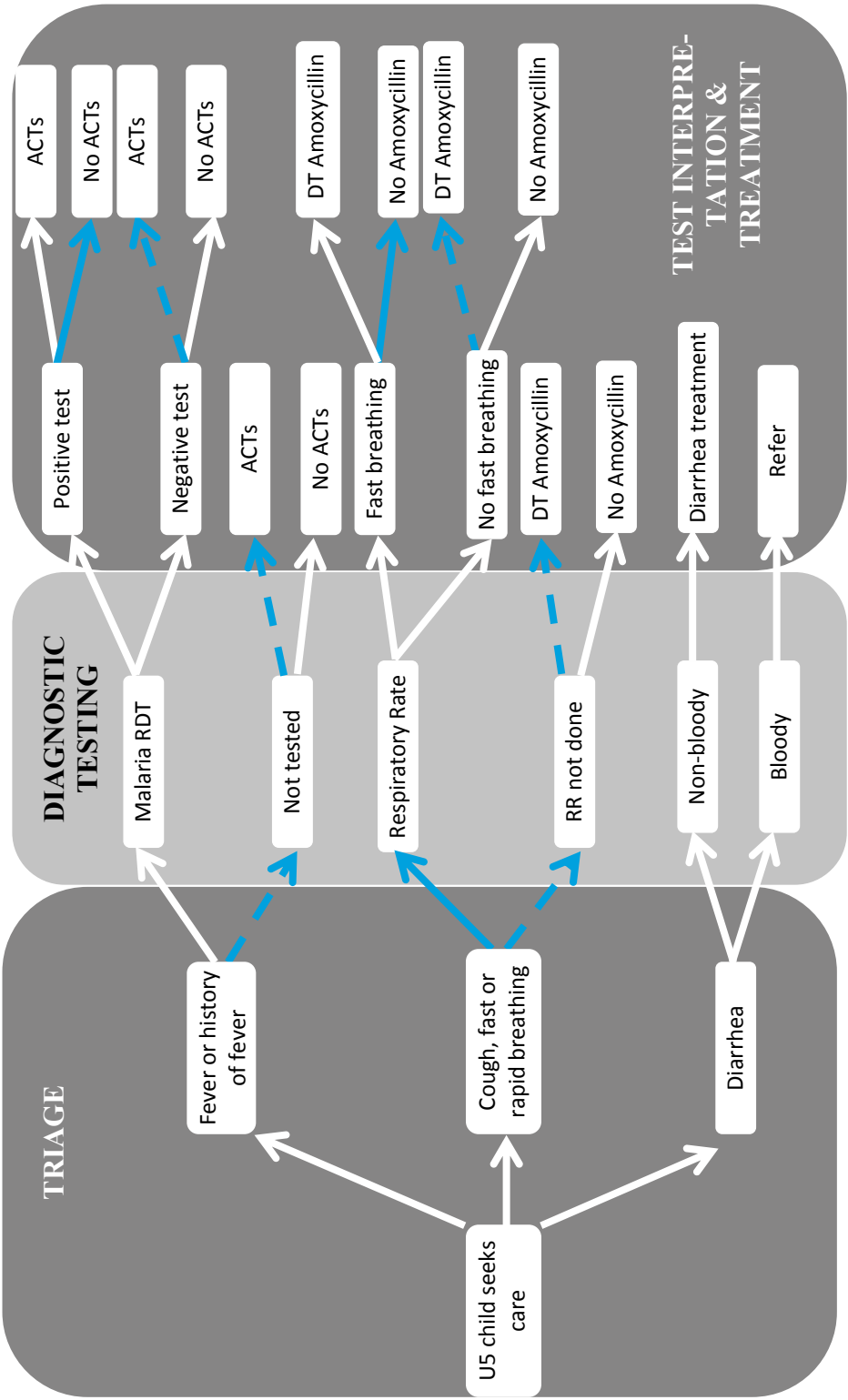


Figure 7. Algorithm for assessing, classifying, testing and treating U5 children in the AXEX intervention in South Western Uganda

Table 3. Description of the different components of the integrated community case management of pediatric febrile illness (iCCM) intervention implemented in study drug shops

Component	Actor	Mechanism	Description	Beneficiary
Health worker component Selection, training and work activities of drug sellers	<ul style="list-style-type: none"> Study team (study manager and field supervisor) District drug inspector District health educator 	<ul style="list-style-type: none"> Telephone invitation of the drug sellers Using national curriculum for the integrated community case management of paediatric febrile illnesses (iCCM) intervention [70, 119], drug sellers were trained in class lectures and hands-on practical sessions. 61 drug shops were supplied with iCCM treatment algorithms, patient registers, respiratory rate counters, malaria rapid diagnostic tests and child medicines. 	<ul style="list-style-type: none"> Drug sellers were trained on case detection and classification according to simple clinical signs and/or diagnostic testing of three febrile child illnesses of acute respiratory illness (ARI), malaria and diarrheal diseases. The training covered signs and symptoms, danger signs, transmission, prevention, diagnostic testing and populations at risk of pneumonia, malaria and diarrhea, respectively. Also, the drug sellers were trained on filling in patient registries, referral, managing drug supplies, counseling care-seekers, adverse reaction monitoring and patient follow-up for outcome. 	Drug sellers from 61 registered drug shops
Community component Information, education and communication (IEC)	<ul style="list-style-type: none"> Study manager, field supervisor District drug inspector District health educator 	<ul style="list-style-type: none"> Marking of intervention arm drug shops with A2L (Access to Life) poster Community sensitization campaign using the MoH child health and malaria messages delivered through monthly radio talk shows by study and district staff and radio announcements. CHWs attended sensitization workshops organized by study and district staff. 	<ul style="list-style-type: none"> Messages about febrile illnesses among children, importance of diagnostic testing, treatment adherence, and what to do if symptoms of the sick child persist and implementation of iCCM in drug shops were discussed in the workshop. CHWs delivered these messages to households with U5 children by word-of-mouth. 	Drug sellers Care-seekers CHWs
Health service component	Study manager and study field supervisor,	The project identified pharmaceutical wholesalers to supply the study medicines at subsidized prices and diagnostics at no cost to intervention arm drug shops.	The mRDT was a one-step, rapid, qualitative and differential test for detection of antigen - HRP-2 (histidine rich protein 2), specific for <i>Plasmodium falciparum</i> (CareStart™ from ACCESS BIO, INC.	Drug sellers

Supply mechanism for medicines and diagnostics	<ul style="list-style-type: none"> Pharmaceutical wholesalers 	<ul style="list-style-type: none"> The study purchased the pre-packaged medicines – ACTs, Amoxicillin, Zinc sulphate and ORS from manufacturers and provided them to pharmaceutical wholesalers in Mbarara. Drug sellers presented special study medicine order forms to pharmaceutical wholesalers for re-supply. Medicines were single-dose packed, color-coded for age and provided to drug shops at subsidized prices 	<p>Ethiopian Branch, Yeka, Addis Ababa, Ethiopia), in finger prick blood[120].</p> <ul style="list-style-type: none"> The respiratory rate counters from Moneray International Limited [121] The pre-packaged medicines included artemether-lumefantrine fixed-dose combination (from Ajanta Pharma Limited, Mumbai, India) dispersible tablets amoxicillin dispersible tablets (Amoxikid™, Kampala Pharmaceutical Industries (1996) Limited, Uganda) and for non-bloody diarrhea, combination of Zinc sulphate dispersible tablets and Oral Rehydration Salts (ORS) and artesunate suppositories for pre-referral treatment. 	
Health worker component Support supervision and use of drug shop patient registry	<ul style="list-style-type: none"> Field supervisor trained in either clinical medicine or pharmacy, District drug inspector, District health educator 	<ul style="list-style-type: none"> A field visit was conducted for every drug shop each month by field supervisor, other project staff and district health team. 	<ul style="list-style-type: none"> Intervention arm drug shops maintained a standard iCCM registry in triplicate copies where they recorded children seen, their symptoms (fever or history of fever, cough, fast or difficult breathing), diagnostic test done, the test results, treatment given and follow up action taken, respectively. Copies of filled drug registries register pages were retrieved from each study drug shop monthly. The study used all records of a total of 5975 children seen at the drug shops during the study period from February 2014 to September 2015. 	Drug sellers Pharmaceutical wholesalers

Main research methods

Mixed-methods research

Given the number and diversity of research questions that emerge in health systems research, it is recommended to consider from the outset how quantitative and qualitative approaches fit together into a mixed methods study [122]. Mixed methods confer onto the study opportunity for increased breadth and depth of understanding and corroboration. Additionally, it is possible to compensate for weaknesses inherent in one method, on strengths provided by the other and to offset inevitable method biases [123]. Triangulation to achieve convergence and corroboration of results can be done. Through complementarity of the different methods, researchers can seek elaboration, enhancement, illustration, clarification of observed results. The study can develop or evolve when researchers use results from one method to generate hypothesis to be tested in the next method thereby covering most aspects of the inquiry. And contradictions and inconsistencies within data sets can be addressed by reformulating questions [122, 124-126]. For these reasons, this thesis applied an iterative model in which data collected earlier was used to postulate causal processes and contextual factors which then became the basis for the proceeding data collection.

Quasi-experimental design

Study II and III were conducted in a quasi-experimental design. Quasi experiments lack the attribute of random assignment of study units to experimental conditions but aim to demonstrate causality between an intervention and outcome [127, 128]. This thesis used the variant of quasi-experiments with an intervention arm, untreated comparison arm, also known as the non-equivalent comparison group design, with pre-test assessment. This choice was justified as it was not logistically feasible or practical and acceptable to randomize. The iCCM intervention had been adopted as MoH policy and was being implemented in several districts through CHWs. Second, some of potential variables in the thesis were controlled at the district or national level; hence it would have necessitated randomizing higher units such as districts, regions or at national level.

Difference-in-differences analysis

Difference-in-differences (DiD) analysis of treatment effects has emerged as a reliable technique in non- or quasi-experimental evaluation method. It is widely used when panel data or repeated cross sections are available for assessments of intervention effects. DiD analysis facilitates causal inference analysis of an intervention when *time-invariant unobserved heterogeneity* might confound a

causal-effect analysis [129, 130]. DiD analysis requires four elements; first, availability of an intervention and comparison group; second, the existence of parallel paths in the pre-intervention trends; third, a clear time cut-off identifying when the intervention starts, so there is a pre- and post-intervention period; fourth, the assumption that without treatment, the intervention arm would show a trend similar to that observed in the comparison arm [131]. Extraneous variables that may confound the causal inference can be added to the DiD analytical model. This thesis applied the DiD analytical technical in study II.

Data collection methods

Data from two household surveys (study III) and two sets of drug shop care-seeker exit interviews (study II) conducted before and after the iCCM intervention in the intervention and comparison arms, respectively, were to answer the research questions for study I and study III. In addition, data from direct observation of drug seller-care-seeker encounters (study II) and review of secondary data (intervention arm drug shop U5 febrile child registries) (Study I and II) were abstracted and used. A laboratory component involving validation of malaria RDT result with Polymerase Chain Reaction (PCR) detection *P. falciparum* Deoxyribonucleic Acid (DNA) was also conducted (study I). Lastly, qualitative data collection using Focus Group Discussions (FGDs) with care-seekers and community health workers, In-depth Interviews (IDIs) with drug sellers, health workers in government health facilities, district health officials, ministry of health officials and other national level stakeholders was conducted for study IV.

Several methods have been recommended for evaluating the effect of health systems interventions. In this thesis, structured interviews, direct observations, unstructured interviews, FGDs, and review of secondary data were used. Secondary data mainly included the intervention arm drug shop U5 febrile child registries, field notes, project activity and progress reports.

Structured interviews

Structured questionnaires are common data collection instruments in health systems research. Such instruments have fixed questions, offering no flexibility to the enumerator to adjust any of its elements including content, wording or order of the questions. Usually collect self-reports, they are simple, cheap and convenient to gather information on key process variables. They are suitable in capturing mediating mechanisms or quantifying participant's interactions (e.g. reach and acceptability) with the intervention [122]. However, they are subject to social desirability biases when a participant responds in anticipation of what is perceived as interviewers expected response. Additionally, self-report questionnaires are not good when assessing

an intervention that involves applying skilled techniques. Implementers may not be well placed to rate their own competence [122].

A total of 48 interviewers (12 per intervention arm before and after) were used for data collection in the parent research project. Interviewers were University graduates with bachelors in arts, information technology, education, nursing, and statistics and were selected in consultation with the district health officials, who were part of the implementation of the project. Selection was based on literacy skills, ability to communicate in both the local language (Runyankole) and English and availability during the study period. The interviewers were trained in data collection for three days using general instructions, role plays, and practical exercises. Data collection tools that had been translated from English to Runyankole then back were used in this training. Each of the questions was discussed, translated into the local language for clarification and standard local terms were agreed on for the illness terms. The training session ended with pilot testing of the questionnaires, questions were revised where necessary. The PhD Student (Freddy Eric Kitutu) was part of the field activities and frequently conducted audit, supervision and gave feedback to the enumerators.

Focus Group discussions (FGDs)

Focus group discussions have wide application in health systems research, particularly to explore people's own experiences, expectations and knowledge, the way they think regarding a phenomenon, how their views are constructed and expressed in a certain context [132, 133]. They produce interactions which provide deep insights into consensus and conflict in the views and experiences of participants [122]. FGDs are also used to uncover factors related to complex behavior, for studies on decision making or when studying how people negotiate about their norms and belief systems [122, 134]. They elicit a wider range of perspectives more quickly than individual interviews [122]. In that regard, FGDs are very useful in examining diffusion, assimilation and adoption of interventions in health system research [122]. FGDs, however, may overlook minority opinions, and the researcher's preconceptions could drive the group's interaction [122, 135]. Also group size may compromise the depth in which a topical issue is explored [122]. In situations where hierarchy exists among participants, "lower status" participants are less likely to contribute or express disagreement, resulting in false consensus and over representation of views of "higher status" participants [122]. In study IV, data from FGDs were used to describe and analyze the iCCM intervention, to understand how it was implemented, the intended and unintended consequences, and to examine the dynamics and processes by which the effects were achieved. The participants in the FGDs were care-seekers at the drug shops and community health workers in the study area.

Unstructured interviews

Conversational interviews are often used in qualitative research. They may be in-depth or key informant interviews. They are suitable for discussing more sensitive issues or where there are concerns that group dynamics may repress individual voices rather than elicit a wide range of views [122, 132, 136]. They provide a greater opportunity to explore individual experiences and realities in depth [122]. Questions asked are open-ended and participants are encouraged to speak with their own words. These interviews require time and experience to construct good open-ended questions [136, 137]. For study IV, data were collected in unstructured interviews - in-depth interviews - with drug sellers, health workers in government health facilities, district health officials, ministry of health officials and other national level stakeholders. These interviews explored views and perceptions of the participants towards the ongoing or just completed iCCM intervention in drug shops and analyzed both the intended and unintended consequences and examined the dynamics and processes by which the effects could have been achieved.

Direct observation

Participant observation is a complementary tool to interviewing. It involves systematically watching and recording behavior and other characteristics. Observation may be passive or active depending on the degree of involvement [133, 138]. It offers a means to reduce potential discrepancy self-reports and what is actually done [122]. Hence, a change in behavior because one knows they are being watched, also referred to as the *Hawthorne effect* [139], is its pitfall. It is suitable when observation can be achieved unobtrusively or when evaluating the implementer's acquisition of specific skills. In the latter case, if implementers have not acquired the competence or skill, they will still not show that competence regardless of presence of an observer [122]. In addition to data obtained from care-seeker exit interviews in study I, direct observation of 49 drug seller–caretaker encounters at intervention drug shops by trained interviewers was done using a structure coding form. These interactions were selected by convenience sampling and data was collected using a pre-tested structured checklist. Interviewers assessed actual verbal and nonverbal behavior of the drug sellers against the standard iCCM sick child job aid (treatment algorithm). This data was analyzed to determine the quality of pediatric fever assessment and treatment of sick children [140].

Filter paper sampling for analysis of *Plasmodium* DNA

Analysis of biological fluids involves handling of potentially infectious material. Capillary blood sampled on malaria RDT cassettes (CareStart™ from ACCESS BIO, INC. Ethiopian Branch, Yeka, Addis Ababa, Ethiopia), in finger prick

blood[120] and fast transient analysis (FTA) Whatman™ 3MM filter paper is safe and convenient in field settings in rural areas. It reduces the need for high trained individuals and equipment such as centrifuge, deep freezer and needle prickers [141, 142]. Dried blood spots on RDT cassettes and FTA filter paper are stable in tropical climates, and they can be kept at normal working temperatures for long periods of time, hence facilitating blood sampling in the field [142, 143]. The blood spotted mRDT and filter paper samples do not require refrigeration or freezing and hence can be sent by ordinary mail from the field to the molecular laboratory. This technique of collection of biological fluids is advantageous as it requires small quantities of blood and can use finger-prick capillary blood samples instead of venous blood, hence it is of great value when taking blood samples from children.

Study designs

Study I

Study I was a cross sectional study where paired blood samples on malaria RDT strip and FTA cards were obtained by finger prick from children 5 years or less at two study drug shops in Mbarara district. The malaria RDT cassette was first read in the field and together with the blood spotted FTA card, they were analyzed for presence of *Plasmodium* DNA using PCR. This study compared drug seller interpretation with laboratory scientist re-reading of malaria RDTs and PCR detection of *Plasmodium* DNA on FTA cards. It also assessed drug seller compliance with the observed malaria RDT results. Table 4 defines the main variables in the analysis.

Table 4. Study I variables and their descriptions

Variable	Description and categories
Drug seller interpretation of malaria RDT strip	positive, negative
Laboratory scientist re-reading of malaria RDT strip	positive, negative, not conclusive
PCR analysis of <i>Plasmodium</i> DNA recovered from dry blood spotted FTA cards.	positive, negative
Medicines given to U5 child	artemether/lumefantrine tablets, dispersible amoxicillin tablets, zinc sulphate tablets, oral rehydration salts

To assess performance of the malaria RDTs under field conditions, the three diagnostic strategies listed in Table 5 were compared with PCR detection of *Plasmodium* DNA on FTA cards.

Table 5. Malaria diagnostic strategies used to classify the presence or absence of malaria parasites among the under-five children in the study.

No.	Sample/other information	Diagnostic strategy	Remarks
1	Finger prick blood on malaria RDT strip	Drug seller interpretation of Malaria RDT strip (drug seller)	Diagnostic test data obtained from drug shop patient registry
2	Retrieved malaria RDT strip at central lab	Laboratory scientist repeat reading of malaria RDT strip (laboratory scientist)	First comparator with drug seller interpretation of the malaria RDT strip
3	<i>P. falciparum</i> DNA extracted from the malaria RDT strip	PCR analysis of <i>P falciparum</i> DNA (RDT-PCR)	Used malaria RDT cassette transferred from the field to molecular laboratory
4	<i>P. falciparum</i> DNA extracted from FTA filter paper	PCR analysis of <i>P falciparum</i> DNA (FTA-PCR)	Second reference and gold standard for other three diagnostic strategies. Blood spotted FTA card.

Nested PCR for Detection of *Plasmodium falciparum*

Plasmodium DNA was extracted from blood spot collected on FTA card and malaria RDT strips using Chelex method [144] and QIAamp blood kit (QIAGEN, Inc., Chatsworth, CA), following manufacturer's instructions. The quantity and quality of the extracted DNA was assessed using Nano Spectrophotometry and QIAxcel advanced automated capillary electrophoresis following the manufacturer's guideline. Detection of *P. falciparum* was done using nested PCR that employed two sets of primers that targeted 18SrRNA gene to confirm the genus and species. Nested PCR was performed according to the protocol developed by Snounou *et al* in two sequential steps [145]. The first round PCR was performed in 50µL volume consisting of 1x of *Taq* 2X Master Mix (New England BioLabs, Massachusetts, USA) of 10pmol/µL each, of the forward and reverse genus specific outer primers (Table 1), PCR grade water and 5.0 µL of 50 ng/µL template DNA. The reaction was performed with an initial denaturation at 95° C for 5 minutes, followed by 35 cycles of 1 minute at 94° C, 2 minutes at 58° C, and 2 minutes at 72° C, and final extension at 72° C for 10 minutes in using a Thermal cycler (Bio-Rad, T100; Singapore). Two micro liters (µL) of the first round PCR amplicons were subjected to second PCR using the same amplification conditions and a *P. falciparum* specific internal primer. The

PCR products were analyzed using QIAexcel automated capillary electrophoresis. Detection of a 205 bp fragment indicated presence of *P. falciparum*. For each run, DNA from reference *P. falciparum* 3D7 strains and nuclease free water were used as positive and negative controls, respectively. Details of the primers used for nested PCR of 18S rRNA gene in malaria parasites are provided in Table 6.

Table 6. Primers for nested PCR of 18S rRNA gene in malaria parasites

Types of PCR	Primer name	Sequence (5'–3')	Species
Nested – first	rPLU6	TTAAAATTGTTGCAGTTAAAACG	<i>Plasmodium</i> sp.
	rPLU5	CCTGTTGTTGCCTTAAAC TTC	
Nested – second	rFAL1	TTAAACTGGTTTGGGAAAACCAAATATATT	<i>P. falciparum</i>
	rFAL2	ACACAATGAACTCAATCATGACTACCCGTC	

The malaria diagnostic strategies were analyzed for overall variation, then variations for either positive or negative readings and expressed as percentage of agreement and Cohen's kappa (κ) statistic. A 95 % confidence interval (95 % CI) was calculated for each κ value using the Stata "KAPPA" module [146]. The level of statistical significance was set to 0.05. Stata version 13.0 (Stata Corp., College Station, TX, USA) was used for analysis. We calculated the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) (with 95% confidence intervals (CI)) of the drug seller interpretation and laboratory scientist re-reading of malaria RDT strips compared to the PCR analysis of *P. falciparum* DNA extracted the FTA card as the reference method.

Study II

Study II was a quasi-experimental design with one intervention (Mbarara with iCCM in drug shops) and one comparison area (Bushenyi without iCCM in drug shops). Data was collected in drug shop care-seeker exit interviews using a structured self-report questionnaire before and after the intervention period to examine the drug seller adherence to the iCCM algorithm derived from the WHO/UNICEF recommended iCCM intervention for pediatric febrile illness. Secondary data was also extracted from drug shop patient registries to calculate proportions of U5 children diagnostically tested, prescribed ACTs, or antibiotics. The primary outcome variable was proportion of U5 children that received appropriate treatment (the right dose, frequency and duration for the right indication i.e. overall appropriate treatment) for each of uncomplicated malaria, pneumonia symptoms and non-bloody diarrhoea as assessed against the national treatment guidelines[70]

and WHO definition of rational medicine use [147] and were derived as follows:

Appropriate treatment for uncomplicated malaria – a child with fever or history of fever was tested by malaria RDT, if positive received the right regimen of ACT and an afebrile child was neither tested nor prescribed ACT. Children with malaria RDT positive results should have received artemether/lumefantrine 20/120mg DT as follows; 6 tablets in yellow pack for children aged 4 to 35 months (one tablet twice daily for three days), 12 tablets in blue pack for children aged 36 to 59 months (three tablets twice daily for three days).

Appropriate treatment for pneumonia symptoms – a child with cough and fast breathing (checked by respiratory timer to be 60 or more breaths per minute for a child 0 to 7 days, 50 or more breaths per minute for child 2 to 11 months and 40 or more breaths per minute for child 1 to 5 years) received right regimen of amoxicillin DT and child with cough and normal breathing was not prescribed amoxycillin DT. Children with cough and fast breathing should have received amoxicillin DT 125mg as follows; 20 tablets in pink pack for children aged 2 to 11 months (two tablets twice daily for five days), 30 tablets in green pack for children aged 12 to 59 months (three tablets twice daily for five days).

Appropriate treatment for non-bloody diarrhoea - child with non-bloody diarrhea (loose stool with no visible presence of blood) received zinc 200mg DT and ORS sachets as follows; 5 tablets for children aged 2 to 6 months (half tablet once a day for ten days), 10 tablets for children aged 7 to 59 months (one tablet once a day for ten days). Each of these children received 2 sachets of ORS and the drug seller demonstrated to care-seeker how to reconstitute. Each child was advised to drink at least half a 300ml cup after every loose stool.

Table 7 defines the main variables.

Table 7. Study II variables and their descriptions

Variable	Description and categories
Child's symptoms or signs	fever, cough, rapid or difficult breathing, diarrhoea, other symptoms
Child's sex	male, female
Care-seeker's sex	male, female
Whether care-seeker had ever attended school	yes, no
Care-seeker's highest level of school	primary, O-level, A-level and higher, none
Care-seeker's occupation	unemployed, housewife, self-employed, civil servant, other
Perceived severity of illness	very severe, moderately severe, not severe
Time illness was noticed	less than 24 hours, between 24-48 hours ago, more than 48 hours ago, do not know
Sought care elsewhere prior to drug shop visit	yes, no
How care-seeker decided to buy medicine	knew medicine or was advised by friend, advised by drug seller
Child's age	continuous variable, age in months
Care-seeker's age	continuous variable, age in years
Reason for seeking care at drug shop	short distance to drug shop, open all time, can borrow medicine, drug seller is my friend, regular supply of drugs, good customer service, recommended to me, has good or trained staff, other
Time to get to drug shop	<15 minutes, 15 to 30 minutes, 30 to 60 minutes, >60 minutes
If care-seeker paid for diagnostic tests	yes, no
Care-seeker able to meet treatment costs	yes, no
*If malaria RDT was done	yes, no
*If respiratory rate counting was done	yes, no
*Medicines given to U5 child	artemether/lumefantrine tablets, dispersible amoxicillin tablets, zinc sulphate tablets, oral rehydration salts, other medicines
If U5 child's body temperature was taken	yes, no
Study arm of care-seeker-child pair	intervention arm, comparison arm
Study participation time for care-seeker- child pair	pre-intervention, post-intervention

*data sources were both care-seeker exit interviews and patient registries

Difference-in-difference analysis was used to quantify the iCCM intervention net effect and confidence intervals under the assumption of normally distributed residuals, to facilitate presentation in percentage units. The outcome variables were derived prior to analysis. Care-seeker and U5 child pairs were clustered within drug shop identifiers. The adjustment for clustering used the intra cluster correlation estimated by large analysis of variance which applies a correction for imbalanced clusters[148]. Given the small number (10-12) of clusters per study arm, bootstrapping was done in 50 replications to improve inference with clustered standard errors [149]. Multivariable analysis was done to adjust for extraneous variables selected in the backward elimination stepwise regression process, after removing collinear variables from the full model. The level of statistical significance was set to 0.05. Stata version 13.0 (Stata Corp., College Station, TX, USA) was used for analysis.

Study III

Study III employs a quasi-experimental design to determine the effect of the iCCM intervention in drug shops and neighborhood effects on perceived quality of drug shop fever care and care-seeking choice among households in South West Uganda. Data was collected in cross-sectional household surveys conducted in two time periods: July to October 2013 and April to May 2015 in Mbarara (intervention arm) and Bushenyi (comparison arm) districts. The main binary outcome was perceived quality of childhood fever care at drug shops, derived by the Principal Components Analysis (PCA) technique to correlate multiple items (listed in Table 8) and determine the presence of coherent subsets of variables that collectively represented an underlying factor, perceived quality of fever care at drug shops. Also care-seeking choice from private health providers versus within the community was assessed. Table 9 defines the main variables in the analysis.

Table 8. Item list used to generate the index for perceived quality of paediatric fever care at drug shops among households in Mbarara and Bushenyi districts.

	Item	Agree	Neutral	Disagree
1	The private health facility closest to my household usually has the medicines my household needs	3	2	1
2	Medicines are more expensive at the private health facility than at government health facilities	1	2	3
3	My household can usually get credit from the private health facility if we need to	3	2	1
4	My household can usually afford to buy the medicine we need	3	2	1
5	In the past, my household had to borrow money or sell things to pay for medicines	1	2	3
6	The quality of health services delivered by the	3	2	1

	private health facility in my neighborhood is good			
7	I respect the drug sellers a health providers and follow their recommended treatment	3	2	1
8	The drug sellers usually treat me with respect and listen to my symptom descriptions	3	2	1
9	The drug sellers usually try to understand my illness by asking and examining me	3	2	1
10	The drug sellers endeavor to minimize the burden to me, maintain my privacy and confidentiality	3	2	1

Table 9. Study III variables and their descriptions

Variable	Description and categories
Study district/arm	Mbarara (intervention arm), Bushenyi (comparison arm)
Study period	July to Oct 2013 (pre-intervention), April to May 2015 (post-intervention)
Child's sex	Female, Male
Respondent's occupation	Housewife, subsistence, self-employed, civil servant, other
When U5 child illness occurred	In > 2weeks preceding survey, in 2 weeks preceding survey
U5 child presented with fever	Yes, no
Ever received Ministry of Health messages on care-seeking for childhood febrile illnesses	Yes, no
Slept under mosquito net on night preceding survey	Yes, no
Any medicines at home on day of survey	Yes, no
Time to government health facility	15mins or less, 15 to 60mins, >60mins, no accessible government facility
Time to drug shop	15mins or less, 15 to 60mins, >60mins, no accessible drug shop
Time to private clinic	15mins or less, 15 to 60mins, >60mins, no accessible private clinic
Time to community health worker	15mins or less, 15 to 60mins, >60mins, no accessible community health worker
Wealth quintile	Poorest, poorer, poor, less poor, least poor
Time to seek healthcare	Same day, next day, two days, >two days

Number of times U5 child had been sick in 12 months preceding survey	< 3times, 3 to 4times, 5 to 6times, > 6times
Number of people in household	<5people, 5 to 11people, >11people
Perceived quality of paediatric fever care	Good, bad
Care-seeking choice between private and government health providers	Yes, no
Care-seeking choice between private health providers and within the community	Yes, no

Multilevel mixed effects logistic regression models separately quantified the influence of neighbourhood effects, extraneous variables on the binary outcomes of perceived quality of childhood fever care at drug shops and care-seeking choice between private health providers versus within the community. All variables were evaluated in the model as categorical fixed effects nested within neighbourhoods, the primary sampling units (PSUs), and normal distribution of random effects was assumed. The single level and null multilevel logistic regression models were compared in a likelihood ratio test at p-value less than 0.05, to determine if between neighborhoods variance existed [150-152]. Simple variance components multilevel logistic regression models [150-152] with households (first level) nested within neighbourhoods (second level) were fitted to the data. In the first model, no covariates were entered (the empty model). In the second model, the full random intercept model with all possible covariates was fitted, as an initial step to building a prediction/prognostic model. Selection of covariates for multilevel logistic regression analysis was by backward elimination and stepwise regression, after removing collinear variables from the full model. The level of statistical significance was set to 0.05. Stata version 13.0 (Stata Corp., College Station, TX, USA) was used for all analyses.

Study IV

Study IV was conducted in the intervention arm in Mbarara district. It aimed to understand how the iCCM *intervention* was implemented, its intended and

unintended consequences and their interconnections, and it examined the dynamics and processes by which the effects were achieved.

A team composed of a social scientist, graduate in Bachelor of Arts and a pharmacist conducted face-to-face interviews using interview guides. Participants were purposively selected; drug sellers in study drug shops were consecutively invited to participate in the IDIs, care-seekers at baseline were identified by CHWs, and the inclusion criteria was having a child U5 as a dependent and previous care-seeking from private drug shops. CHWs within the catchment area of the drug shop were enrolled for FGDs.

FGDs were conducted in the study area at locations deemed convenient to participants including at sub-county halls, school classrooms and at health centers (HCs). IDIs with drug sellers were conducted at their drug shops and IDIs with government officials were held at their offices on appointment. Sample sizes for all categories of FGDs and IDIs were determined by topical saturation [136]. A total of 26 FGDs – 18 with care-seekers and 8 with CHWs – and 66 IDIs – 47 with drug sellers and 19 with government officials - were conducted at baseline, midpoint and end-line between September 2013 and September 2015. Each FGD included 4 to 11 care-seekers or community health workers. At the end of each interview, the lead interviewer or facilitator, note taker and lead author debriefed to improve the interview guide. Each interview was transcribed and translated into English by bilingual research assistants under supervision of the lead author. The lead author maintained a field journal and had record of project activity reports.

Interviews were based on an unstructured guide that explored common child illnesses treated at the drug shops, why community members sought care from them, what challenges care-seekers and drug sellers faced, at baseline. Drug sellers were asked about their interactions with care-seekers, community health workers, how they obtained operation permits, experiences of their encounters and interactions with district and NDA officials. The drug sellers, care-seekers, community health workers were asked hypothetically about their views and perceptions on implementing an intervention that trained drug sellers to use diagnostic tests to assess and classify children, prior to recommending medicines or otherwise. Mid and end-line interviews asked similar questions with a focus on first-hand accounts of experiences with the intervention or its components, perceptions formed, emergent opinions among the key stakeholders, challenges and opportunities posed by the *iCCM intervention*.

All interviews and conversations were audio-recorded and complemented by field notes. The lead author checked all the transcripts against the recordings to ensure accuracy, and reviewed and cleaned the transcripts. All transcripts were carefully read multiple times by the authors FEK (lead) and CK, and they were separately coded in OpenCode Software 4.03 (University of

Umeå, Sweden)[153] using the content and thematic analysis approach [154]. Data were extracted into meaning units. Together with pre-defined areas of interest identified from the theoretical framework for health market systems, the meaning units were used to draw up the initial coding scheme. Preliminary codes were refined by lead author and applied back to the transcripts. These were further refined into final categories that reflected on actual experiences and encounters of the different stakeholders with all or some of the components of the *AXEX intervention*.

Using a health markets and systems lens, transcripts from the interviews were analyzed to identify positions occupied by each of the key stakeholders, the direct and indirect relationships, interactions among them and other health system effects associated with the apparent success of the intervention.

Ethical Considerations

Studies in this thesis were nested in a larger research project entitled “ACCESS and EXCESS, EQUITY and INFORMATION: Point of Care Diagnostics and Pre-packaged Subsidized Drugs for Integrated Fever Management for Malaria, Pneumonia and Diarrhoea in Children at PRIVATE SECTOR Drug Shops in Uganda” This project was implemented by Makerere University School of Public Health, with Dr. Henry Wamani as principal investigator.

The ethical review and approval of this research project was granted by the Research and Ethics Committees at Makerere University School of Public Health (IRB00011353) and the World Health Organization (RPC553). The research project was cleared and registered by the Uganda National Council of Science and Technology (HS1385).

Written informed consent was obtained from all research participants who provided primary data in the drug shop care-seeker exit interviews, household surveys, focus group discussions, and in-depth interviews. Additionally, written informed consent was obtained to digitally record the interviews in qualitative interviews.

Permission to conduct the drug shop intervention was obtained from the district local government authorities and drug shop owners, respectively.

Confidentiality was maintained throughout data collection, management and analysis. Hard copies of data collection materials did not have identifiers and were locked in a secure cabinet or room with limited access by specified individuals. A de-identified version of the database was used for data analysis.

Results

Drug seller interpretation of and compliance with malaria RDT strips

Drug seller interpretation of malaria RDT strips

The overall agreement between the drug seller interpretation and laboratory scientist re-reading of the malaria RDT strip was 93% (n=186) with kappa value of 0.84 (95% CI 0.75, 0.92) (See Table 10).

The kappa value was 0.81 (95% CI 0.61, 1.00) among malaria positive cases and 0.41 (95% CI 0.11, 0.70) for negative cases, tested by the FTA-PCR diagnostic strategy (the gold standard).

Table 10. Comparison between drug seller interpretation and the laboratory scientist re-reading of the malaria RDT strips

Drug seller interpretation of the malaria RDT strip	Laboratory scientist re-reading malaria RDT strip				Methods agreement %, 95% CI	κ, 95% CI
		Positive	Negative	Total		
	Positive	50	8	58	93.0 88.3, 96.2	0.84 0.75, 0.92
	Negative	5	123	128		
	Total	55	131	186		

Of the five cases reported negative by drug seller but positive by laboratory scientist, three tested positive and two negative by FTA-PCR (the gold standard), respectively. Only one out of these five cases was prescribed ACTs by drug seller. All the eight cases reported positive by drug seller but negative by laboratory scientist, tested negative by FTA-PCR. Four of these eight cases were prescribed ACTs by the drug seller.

Drug seller compliance with observed malaria RDT results

The drug seller compliance with the reported malaria RDT results was 92.5% (95% CI 87.9 – 95.7) (See Table 11).

Table 11. Drug seller compliance with the observed malaria RDT results

Drug seller interpretation of the malaria RDT strip	Drug seller prescribed ACT medicines for the child				Compliance (%)
		Yes	No	Total	95% CI
	Positive	57	5	62	92.5 87.9, 95.7
	Negative	10	127	137	
	Total	67	132	199	

Compliance among malaria positive cases was 91.9% while that among negative cases was 92.7%, respectively. Up to 8.1% malaria positive cases did not receive ACTs while 7.3% negative cases received ACTs.

Performance of malaria RDT strips under field conditions

The sensitivity of the drug seller, laboratory scientist and RDT-PCR diagnostic strategies when compared to FTA-PCR strategy for *Pf* detection varied from 77% (95% CI 64.3 – 86.2) for RDT-PCR to 87% (95% CI 75.8 – 94.2) for the laboratory scientist strategy. The specificity of the three diagnostic strategies was > 90% when compared to the gold standard (FTA-PCR). The positive predictive values were 89% for both RDT-PCR and laboratory scientist and 79% for the drug seller strategy. Table 12 provides additional details of PPV, NPV methods agreement and kappa values.

Table 12. Comparison of performance of drug seller, laboratory scientist and RDT-PCR diagnostic strategies against PCR detection of *P. falciparum* DNA extracted from FTA card (FTA-PCR)

Diagnostic strategy	Sensitivity % 95% CI	Specificity % 95% CI	Predictive value		Methods agreement %	κ, 95% CI
			Positive test %	Negative test %		
			95% CI	95% CI		
Drug seller interpretation of malaria RDT strip (drug seller)	81.7	90.6	79.0	92.0	87.9	0.72
	69.6, 90.5	84.5, 94.9	66.8, 88.3	86.1, 95.9	82.6, 92.1	0.61, 0.82
Laboratory scientist re-reading of malaria RDT strip (laboratory scientist)	86.9	95.7	89.8	94.3	92.9	0.83
	75.8, 94.2	90.8, 98.4	79.2, 96.2	89.1, 97.5	88.5, 96.1	0.75, 0.92
PCR analysis of <i>P. falciparum</i> DNA extracted from malaria RDT nitrocellulose strip (RDT-PCR)	76.6	95.9	89.1	90.4	90.1	0.76
	64.3, 86.2	91.4, 98.5	77.8, 95.9	84.7, 94.6	85.3, 93.8	0.66, 0.85

Drug seller adherence to iCCM guidelines

Effect on provision of ACTs, Amoxicillin DT, diarrhoea treatment and uptake of diagnostic testing

The largest intervention effect was on provision of Amoxicillin DT to child cases with suspected pneumonia symptoms, 91.5% (95% CI, 82.5, 100.5) (Table) followed by provision of ACT to child cases with suspected uncomplicated malaria, 24.8% (95% CI, -3.3, 51.1) and lastly for provision of diarrhoea treatment to child cases with non-bloody diarrhoea, 17.1% (95% CI, -22.3, 53.7%)(See Table 13).

Table 13. Effects of the iCCM intervention on provision of ACTs, Amoxicillin DT and diarrhea treatment and uptake of diagnostic testing for febrile childhood conditions among U5 children at drug shops in South Western Uganda from 2013 to 2014; Difference-in-difference analysis of data from Care-seeker exit interviews

	Observed percentage		Effect estimate of the iCCM intervention		
	Intervention arm	Comparison arm	Change in percentage	95% CI	P-value
Child cases with fever, pneumonia symptoms and diarrhea					
Pre-intervention	n= 212	n= 216			
Post-intervention	n= 285	n= 268			
Provision of ACT, Amoxicillin DT and diarrhea treatment					
<u>Provision of ACTs for suspected uncomplicated malaria</u>					
Pre-intervention	46.2	32.0	24.8	-3.3,	0.090
Post-intervention	92.6	53.6		51.1	
<u>Provision of DT Amoxicillin for suspected pneumonia symptoms</u>					
Pre-intervention	4.8	3.1	91.5	82.5,	<0.001
Post-intervention	93.2	0		100.5	
<u>Provision of diarrhea treatment for non-bloody diarrhea</u>					
Pre-intervention	65.3	49.0	17.1	-22.3,	0.397
Post-intervention	58.0	24.6		53.7	
Uptake of diagnostic testing for uncomplicated malaria, pneumonia symptoms and fever					
<u>Malaria RDTs</u>					
Pre-intervention	18.5	23.6	52.6	27.3,	<0.001
Post-intervention	47.8	0.39		77.9	
<u>Respiratory timer</u>					
Pre-intervention	0	0	60.1	47.6,	<0.001
Post-intervention	60.1	0		72.6	
<u>Thermometer</u>					
Pre-intervention	8.5	32.4	41.2	19.4,	0.001
Post-intervention	28.3	10.9		63.0	
<u>No investigations done</u>					
Pre-intervention	53.6	43.5	-53.5	-93.9, -	0.013
Post-intervention	13.8	57.2		13.3	

Only the percentage increase in provision of Amoxicillin DT to child cases with suspected pneumonia symptoms was statistically significant at P-value <0.05.

The reported intervention effect on uptake of diagnostic testing from smallest to largest improvement was on use of thermometer, 41.2% (95% CI, 19.4, 63.0), followed by use of malaria RDTs, 52.6% (95% CI, 27.3, 77.9) and use of respiratory timers, 60.1% (95% CI, 47.6, 72.6) (Table 9). There was a reduction by half (-53.5%, 95% CI -93.9, -13.3) of child cases who were not subjected to any diagnostic test at all. These improvements or reduction were all statistically significant.

Effect on appropriate treatment for febrile U5 childhood conditions

The largest intervention effect on appropriate treatment was recorded for uncomplicated malaria, 80.2% (95% CI, 53.9, 106.5) followed by for pneumonia symptoms, 65.5% (95% CI, 51.2, 79.8) and lastly for non-bloody diarrhoea, 31.4% (95% CI 0.8, 62.0). Controlling for extraneous variables (See Table 11) reduced the effect sizes as follows; appropriate treatment for uncomplicated malaria 34.5% (95% CI 8.6, 60.4), for pneumonia symptoms to 54.7% (95% CI 28.4, 81.0) and for non-bloody diarrhoea was reduced to -11.2% (95% CI -65.5, 43.1). Except for non-bloody diarrhea, all percentage increases in appropriate treatment for the childhood conditions were statistically significant at p-value <0.05, even after controlling for extraneous variables (see Table 14). Also, a large negative change from 31.9% to 0.9% in appropriate treatment for uncomplicated malaria was observed in the comparison arm.

Table 15 shows proportions of U5 at each step of the iCCM algorithm as illustrated in figure 7. It summarizes the proportions presenting with fever, cough or diarrhoea, diagnostically-tested, prescribed with antimalarials, or antibiotics, given the correct regimen for each medicines and proportions appropriately treated for uncomplicated malaria, pneumonia symptoms and non-bloody diarrhoea, respectively. The findings are categorized by study arm (intervention and comparison arm) and study period (before and after intervention), respectively.

Table 14. Effects of the iCCM intervention on appropriate treatment for febrile childhood conditions among U5 children at drug shops in South Western Uganda from 2013 to 2014; Difference-in-difference analysis.

Observed percentage (Crude)			Effect estimate of the iCCM intervention (Crude)		Observed percentage (Adjusted)		Effect estimate of the iCCM intervention (Adjusted)	
Intervention arm	Comparison arm		Change in percentage, 95% CI	P-value	Intervention arm	Comparison arm	Change in percentage, 95% CI	P-value
Child cases with fever, pneumonia symptoms and diarrhea								
Pre-intervention	n= 212	n= 216						
Post-intervention	n= 285	n= 268						
Appropriate treatment for the childhood conditions								
Uncomplicated malaria*								
Pre-intervention	8.3	31.9	80.2 53.9, 106.5	<0.001	-65.3	-38.5	34.5 8.6, 60.4	<0.009
Post-intervention	57.4	0.9			-51.9	-59.6		
Pneumonia symptoms**								
Pre-intervention	0	0	65.5 51.2, 79.8	<0.001	-56.1	-56.9	54.7 28.4, 81.0	<0.001
Post-intervention	65.5	0			-0.4	-55.8		
Non-bloody diarrhea***								
Pre-intervention	51.3	45.7	31.4 0.8, 62.0	0.045	5.3	-10.1	-11.2 -65.5, 43.1	0.687
Post-intervention	65.6	28.6			-11.8	-16.0		

*Controlled for child presenting with fever or history of fever, testing child with malaria RDT, counting respiratory rate of child, care-seeker being friends with drug seller, if care-seeker paid for diagnostic tests, time to get from home to drug shop, R-square = 0.75

**Controlled for child presenting with fever or history of fever, child presenting with cough or difficulty in breathing, testing child with malaria RDT, if child did not undergo any diagnostic testing, how care-seeker decided to buy medicine, care-seeker being friends with drug seller, care-seeker sex, child's condition not being severe, R-square = 0.66

***Controlled for child presenting with signs of fever or history of fever, cough or difficulty in breathing, diarrhoea, counting respiratory rate of child, measuring temperature of child, if care-seeker was made to repeat treatment instructions, seeking care elsewhere before coming to drug shop, how care-seeker decided to buy medicine, care-seeker being able to take medicines on credit, good customer service at drug shop, R=0.29

Table 15. Proportions of child cases that presented with fever, pneumonia symptoms and non-bloody diarrhoea, were diagnostically tested and were given medicines from care-seeker drug shop exit interviews, respectively

Surrogate outcome	Intervention arm			Comparison arm		
	Before	After		Before	After	
	Proportion (%)	Proportion (%)		Proportion (%)	Proportion (%)	
Fever or suspected malaria						
Proportion presenting with fever or history of fever	128/212 (60.4)	172/281 (61.2)		111/216 (51.4)	112/259 (43.2)	
Proportions tested with malaria RDT	39/211 (18.5)	132/276 (47.8)		51/216 (23.6)	1/257 (0.4)	
Proportion given any antimalarials	93/211 (44.1)	68/276 (24.6)		75/216 (34.7)	69/257 (26.8)	
Proportion given ACT medicines	43/93 (46.2)	63/68 (92.7)		24/75 (32.0)	37/69 (53.6)	
Proportion with correct ACT dose, frequency and duration	9/43 (20.9)	54/63 (85.7)		2/24 (8.3)	27/37 (73.0)	
Proportion appropriately treated for uncomplicated malaria	11/133 (8.3)	108/188 (57.5)		38/119 (31.9)	1/112 (0.9)	
Cough or difficulty in breathing (pneumonia symptoms)						
Proportion presenting with cough or difficulty in breathing	139/212 (65.6)	200/285 (70.2)		154/216 (71.3)	149/268 (55.6)	
Proportion in whom respiratory rate was counted	0	166/276 (60.1)		0	0	
Proportion given any antibiotics	84/211 (39.8)	160/276 (58.0)		96/216 (44.4)	67/257 (26.1)	
Proportion given Amoxicillin DT	4/84 (4.8)	149/160 (93.1)		3/96 (3.1)	0	

Surrogate outcome	Intervention arm				Comparison arm			
	Before		After		Before		After	
	Proportion (%)	Proportion (%)	Proportion (%)	Proportion (%)	Proportion (%)	Proportion (%)	Proportion (%)	Proportion (%)
Proportion with correct Amoxicillin DT dose, frequency and duration	0		144/149 (96.6)		1/3 (33.3)		0	
Proportion appropriately treated for pneumonia symptoms	0		144/220 (65.5)		0		0	
Non-bloody diarrhoea								
Proportion presenting with non-bloody diarrhoea	70/212 (33.0)		60/281 (21.4)		44/216 (20.4)		42/259 (16.2)	
Proportion given any treatments for diarrhoea	72/212 (34.0)		69/281 (24.6)		49/216 (22.7)		57/259 (22.0)	
<i>Proportion given Zinc tablets and ORS</i>	47/72 (65.3)		40/69 (58.0)		24/49 (49.0)		14/57 (24.6)	
<i>Proportion appropriately treated for non-bloody diarrhoea</i>	40/78 (51.3)		40/69 (58.0)		21/49 (42.9)		12/57 (21.1)	

Effect of the *AXEX* intervention in drug shops on perceived quality of drug seller fever care and care-seeking choice among households

Between neighbourhoods variance on perceived quality of drug seller fever care and care-seeking choice among households was observed, hence the need for multilevel modelling.

Perceived quality of drug seller fever care

Table 16. Predictors of and the neighborhood effect on perceiving quality of paediatric fever care at drug shops as good among households in Mbarara and Bushenyi districts.

OR (95% CI)	P value	Neighbourhood effect		
		Neighbourhood level variance (SE)	Intra-neighbourhood correlation (%)	Median Odds Ratio
Empty model		0.275 (0.057)	7.7	1.65
Adjusted model				
Study period				
Pre-intervention				
Post-intervention	4.44 (3.64, 5.41)			
Study district				
Bushenyi (Comparison)				
Mbarara (Intervention)	3.32 (2.54, 4.35)			
Interaction term between study arm and period	0.22 (0.17, 0.28)			
Time to private clinic				
15 mins or less				
15 – 60mins	0.84 (0.71, 0.98)			
> 60mins	0.71 (0.57, 0.86)			
No accessible private clinic	0.84 (0.63, 1.11)			
Time to drug shop				
15 mins or less				
15 – 60mins	1.18 (1.00, 1.38)			
> 60mins	1.12 (0.88, 1.42)			
No accessible drug shop	0.64 (0.52, 0.79)			
Time to community health worker				
15 mins or less				
15 – 60mins	0.83 (0.69, 1.00)			
> 60mins	0.71 (0.49, 1.04)			
No accessible CHW	1.10 (0.93, 1.28)			
		0.180 (0.042)	5.2	1.50

After adjusting for covariates in the multilevel model for perceived quality of drug seller fever care, the median odds ratio (MOR) was 1.5. If a household moves to another neighbourhood with a higher probability of the perceiving quality of drug seller fever care as good, their risk of experiencing this outcome in the median case increases 1.5 times.

The iCCM intervention decreased the odds of perceiving drug seller fever care as good interaction term between the study arm and pre- or post-intervention period as seen from the interaction term between the study arm and pre- or post-intervention period. However, the residual heterogeneity between neighbourhoods (MOR = 1.5) was of greater relevance than the impact of the iCCM intervention (OR=0.22) for understanding variations in odds of households perceiving quality of drug seller fever care as good.

Perceiving quality of drug seller fever care as good by households was positively associated with participating in post-intervention surveys, location in the intervention arm and within 60 minutes of travel to the drug shop. Households that were 15 to 60 minutes travel or greater to private clinics, lacked routine access to a drug shop or were 15 to 60 minutes travel distance to a community health worker had decreased odds of perceiving drug shop fever care as good (See table 16).

Care-seeking choice from private health facility versus community

After adjusting for covariates in the multilevel model for household care-seeking choice from private health facilities versus community, the median odds ratio (MOR) was 1.65. It implies that in the median case the residual heterogeneity between the neighbourhoods increased by 1.65 times the odds of household care-seeking choice from private health facilities versus community randomly picking two households in different neighbourhoods.

The *AXEX* intervention increased the odds of the households seeking care from the private health facility versus community, (OR 3.39, CI 95% 2.24, 5.12). The residual heterogeneity of the iCCM intervention within households in a neighborhood (OR = 3.39) was of greater relevance than that between neighborhoods (MOR=1.65) for understanding variations in odds of households seeking care from private health facilities versus within the community.

Being a subsistence farmer, more than 60 minutes travel away from a private clinic, 15 to 60 minutes travel to a community health worker decreased the household odds of seeking care from the private health facility versus the community. In contrast, seeking healthcare the next or two days later, being less poor increased the odds of the household seeking care from the private health facility versus the community in South Western Uganda (See table 17).

Table 17. Predictors of and neighborhood effect on household care-seeking choice from private health facilities versus within the community in South Western Uganda.

	OR (95% CI)	P value	Neighbourhood effect		
			Neighbourhood level variance (SE)	Intra-neighbourhood correlation (%)	Median Odds Ratio
Empty model			0.210 (0.057)	6.0	1.55
Adjusted model					
Study arm					
Bushenyi (Comparison)					
Mbarara (Intervention)	0.46 (0.31, 0.69)	<0.001			
Study period					
Pre-intervention					
Post-intervention	0.31 (0.22, 0.44)	<0.001			
Interaction term between study arm and period	3.39 (2.24, 5.12)	<0.001			
U5 child presented with fever	1.17 (0.96, 1.42)	0.113			
Respondent's occupation					
Housewife					
Subsistence	0.69 (0.53, 0.90)	0.006			
Self employed	0.79 (0.57, 1.09)	0.158			
Civil servant	0.75 (0.37, 1.50)	0.423			
Time to private clinic					
15 mins or less					
15 – 60mins	0.81 (0.63, 1.03)	0.091	0.239 (0.069)	7.0	1.65
More than 60mins	0.68 (0.49, 0.94)	0.020			
No accessible private clinic	0.97 (0.62, 1.54)	0.910			
Time to community health worker					
15 mins or less					
15 – 60mins	0.66 (0.52, 0.88)	0.004			
> 60mins	0.74 (0.39, 1.40)	0.362			
No accessible CHW	1.01 (0.80, 1.30)	0.906			
Wealth quintile					
Poorest					
Poorer	1.07 (0.80, 1.43)	0.666			
Poor	1.11 (0.83, 1.48)	0.497			
Less poor	1.34 (0.99, 1.82)	0.059			
Least poor	1.24 (0.90, 1.70)	0.193			
Time to seek healthcare					
Same day					
Next day	1.38 (1.12, 1.70)	0.002			
Two days	1.41 (1.05, 1.88)	0.020			
> two days	0.87 (0.63, 1.20)	0.404			

A qualitative analysis of how the *AXEX* intervention was implemented to produce the effects observed

Using the theoretical market framework by bloom et al [8], five stakeholder categories who directly or indirectly influenced the retail health market were identified, namely; i) health providers (drug shop owners, sellers and CHWs; ii) beneficiaries (care-seekers); iii) Central government agencies MoH and NDA; iv) local government institution of Mbarara; and v) pharmaceutical supply chain actors (manufacturers and wholesalers). Other stakeholders were not-for-profit health providers, the health professional bodies (Pharmaceutical Society of Uganda (PSU) and allied health professional council), other private health providers outside the study and the global pharmaceutical supply chain. The theoretical market framework and Merton's theory on unanticipated consequences guided the qualitative analysis and discussion of the findings. The data was analysed into six themes as shown in Table 18.

Table 18. Themes and details of findings from study IV

Theme	Details or examples
Initial fears, perception and reactions	The initial attitude was that of fear of regulation on part of drug sellers, that of drug sellers' opportunistic behaviour on the part of government officials, that of loss of status in community on part of CHWs
Interface with the regulatory framework	<i>"...the problem is that we are constrained with the resources, both in terms of finances and human resources so there is a tendency of concentrating all our efforts to the government sector." (IDI, GO3) ...as mentioned by one government official.</i>
Information and dissemination	Key stakeholders (drug sellers, CHWs, care-seekers, government officials) reported receiving information about the <i>AXEX</i> intervention; most importantly that drug sellers had been trained on integrated case management of U5 febrile children.
Provide incentives	Drug sellers also stated that adding diagnostic-testing to their repertoire of services and insisting on face-to-face interaction with the care-seeker and sick child transformed them from "mere" sellers to " <i>ba-shaho</i> " loosely meaning "medical doctors" or "biomedicine experts" who appeared to make decisions based on some judgment. Care-seekers satisfied with drug shop fever-care recommended their friends and neighbours to seek care from drug shops, thereby increasing their customer numbers and sales.
Linkage to the formal health system	Both government officials and drug sellers mentioned that they favored a recognizable and formal linkage between drug shops and the nearest government health centres.
Perceived efficacy of the <i>AXEX</i> intervention	<i>"The drugs are also effective so it is helping people, most especially those (medicines) for fast breathing (pneumonia) and diarrhoea." IDI, DS1 ... as mentioned by one drug seller.</i> However, there were complaints about discrepancy between RDT results at the drug shops and malaria tests done at other private facilities. Overall, the drug sellers observed that the <i>AXEX</i> intervention had contributed to saving children's lives and requested for an extension of the project life and expansion of services to cover febrile illnesses in adults.

Discussion

Main findings

Drug seller interpretation has high concordance with laboratory scientist re-reading of the malaria RDT strips. Furthermore, the drug sellers' treatment recommendations were in compliance with the malaria RDT results. Overall, implementing an iCCM intervention at retail drug shops increases appropriate treatment for uncomplicated malaria, pneumonia symptoms and non-bloody diarrhoea, which implies that a higher proportion of U5 children receive the right medicine in the right dose, frequency and duration for the right indication in the intervention arm as compared to the comparison arm in South Western Uganda.

The *AXEX intervention* reduced the odds of households perceiving drug shop fever care quality as good. In contrast, it increased the household odds of choosing to seek fever care from private health facilities versus within the community. Stakeholders in the retail health market in rural South Western Uganda included community health workers, government health workers in health centres in study area, district health officials, and Ministry of Health officials, in addition to drug sellers and care-seekers. The drug sellers on the supply side provided health goods and services to care-seekers on the demand side in a dynamic relationship. This dynamic relationship was affected by interactions with the other stakeholders and existing norms, rules and regulations, whether informal or formal. The dynamic relationships between and among the stakeholders and the institutional² arrangements were also shaped by community values and beliefs. The fidelity and quality of *implementation* of the *AXEX intervention* was assessed by surrogate outcomes at different points of the *AXEX intervention* algorithm as discussed below.

² The term institutional here refers to rules, laws, norms and customs, and is distinct from its synonym organizational which refers to social settings

Drug seller interpretation of and compliance with the malaria RDT tests

First, study I reported a high concordance of drug seller interpretation with laboratory scientist re-reading of malaria RDT strips. This finding is similar to that of another Ugandan study [42] that reports 95% agreement between drug seller and research team reading of malaria RDT strips, despite a higher malaria transmission setting than that of this thesis. This is probably a result of the drug sellers having undergone training in the *AXEX intervention* study [155]. The *AXEX intervention* involved hands-on training of the drug sellers on the malaria RDT use to detect presence of malaria parasites, monthly support supervision by a clinical officer or pharmacist and an enhanced diagnostics and medicines supply mechanism [155]. Other studies among community health workers acknowledge that successive practice improves malaria RDT use [156].

Second, the high drug seller compliance with malaria RDT results is probably due to the implementation of co-interventions in the intervention drug shops. Supportive supervision, enhanced supply mechanism for the malaria RDTs and subsidized antimalarial medicines and community sensitization focusing on the importance of care-seekers accepting the malaria RDT test outcomes, were part of the iCCM intervention conducted from February 2014 to September 2015 [155, 157]. The high compliance observed was possibly a residual effect from the 20-month long period of *AXEX intervention*. These findings are consistent with those from similar studies among drug sellers [42, 155], especially for RDT-positive cases [92, 158-160]. Also studies among community health workers in Tanzania [161], Malawi, Senegal [162] report similarly high compliance levels to malaria RDT results. In contrast, some drug seller studies report variable inappropriate treatment of RDT-negative cases with antimalarial medicines: 45% [159], 10% [92], 1.5% [42] in each Ugandan study, 7% in Tanzania [160] and 3% in Ghana [158] of the RDT-negative cases are given antimalarial medicines, respectively. In community health worker studies, greater than 10% of the malaria RDT negative results [69, 74, 88, 163] and up to 20% [164], 30% [165] and 58% [166] were prescribed ACTs. Clinical judgement by community health worker is advanced to justify giving ACTs to test negative cases [165]. Also, compliance with observed malaria RDTs results in this thesis is higher than 83% (95% CI 80, 86) reported by Kabaghe *et al* in a systematic review that analyzed pooled findings from 14 studies involving clinicians and community health workers [167]. In that study, compliance among the malaria positive cases was higher 97% (95% CI 94, 99) while that among negative cases was lower 78% (95% CI 66, 89) [167] than reported in the current study, respectively. The difference in these findings is probably a result of less trained health cadres being more trusting in malaria RDT results while clini-

cians rely more on symptoms and past experience [168]. For instance, Kabaghe *et al* also reports a higher compliance, 95% (95% CI 92, 98) among malaria RDT negative cases among community health workers than 75% (95% 58, 89) among clinicians [167].

The results on the surrogate outcomes of proportions of children that were diagnostically-tested, prescribed any antimalarial or antibiotic and in the correct regimen demonstrate that overall the *implementation* quality and fidelity were high. However, these surrogate outcomes by nature of being in the pathway to effect of the *AXEX intervention*, they also explain the *mechanism of effect*, pointed out in the conceptual framework for this thesis (Figure 2).

Drug seller adherence to the iCCM guidelines

First, in study II, there was a higher increase from pre- to post-intervention in proportions of febrile children tested with malaria RDT, prescribed ACTs and in the correct regimen in the intervention arm as compared to the comparison arm, respectively. Second, in a similar pattern there was a higher increase in children with cough or fast breathing from pre- to post-intervention whose respiratory rate was counted, were prescribed any antibiotic, and among those prescribed DT Amoxycillin and in correct regimen in the intervention arm as compared to the comparison arm, respectively.

To understand the overall implication of the above surrogate outcomes on the quality of *AXEX intervention implementation* by the drug sellers, this thesis determined the appropriateness of the treatment for uncomplicated malaria, pneumonia symptoms and non-bloody diarrhea, as a composite variable. An increase in appropriate treatment for uncomplicated malaria, pneumonia symptoms and non-bloody diarrhea, in a relatively low malaria endemic setting [155] was observed. These findings are similar to those by Awor *et al.* in a higher malaria endemic setting in East Central Uganda. The observed higher malaria RDT positivity of 78% as compared to 47% reported in this thesis notwithstanding [41]. Meanwhile, the malaria RDT positivity rate of 47% was higher than what was expected, given values of 5% and 9.3% malaria prevalence reported in studies conducted in the same area [94, 106]. This difference in malaria prevalence could be explained by the difference in the populations of U5 children tested, this thesis tested sick children presenting at drug shops, while the 2014 malaria indicator survey [94] and the study by Kamya *et al.* [106] tested healthy children in their homes. It could also possibly be due to false malaria RDT positivity as a result of persistent HRP2 antigenaemia following malaria treatment [169, 170]. In contrast, the difference in malaria prevalence is unlikely to be due to falsifica-

tion of the malaria RDT results in the patient registries by drug sellers so as to increase the sales of ACT medicines as demonstrated in study II in this thesis.

Effect of implementing the *AXEX intervention* in drug shops on the perceived quality of drug seller fever care and care-seeking choice among households

Study III reported that the implementation of the *AXEX intervention* in drug shops decreased the household odds of perceiving drug seller fever care as good. In contrast, it increased the household odds of choosing to seek healthcare from private health facilities versus within the community and had no effect on household odds of choosing to seek healthcare from private health facilities as opposed to government health facilities. Except for household care-seeking choice from private health facilities versus within the community, the residual heterogeneity between neighbourhoods was of greater relevance than the impact of the *AXEX intervention* for understanding variations in odds of households perceiving drug seller fever care as good and choosing to seek care from private versus government health facilities.

Contrary to this thesis' hypothesis, the *AXEX intervention* had the opposite effect of decreasing the odds of perceiving drug seller fever care as good. This finding is probably a result of including many households that did not access or visit the drug shops that were implementing the *AXEX intervention* during the study period. However, measurement of a complex phenomenon like perceived quality of healthcare presents knotty issues; First, lack of an agreed upon tool for assessment given that research in this area is still in its infancy. This thesis for instance measured items in the domains of interpersonal relations, physical and financial barriers to access and healthcare delivery while other studies have include the same or other items. Existing instruments suffer ceiling effects and uncertainty about their reliability, validity and stability across cultures [171]. Although the tool used in this thesis was adapted from a validated World Health Organization instrument to measure access to and use of medicines in household surveys [172, 173], it may not have fitted in the context of the retail health market in a rural area.

Also, of importance to note, care-seeker perception of quality of healthcare is a complex phenomenon to define and thereby measure. It is known that care-seeker experiences and expectations contribute to their overall perception of quality of healthcare received [171] but there is often confusion between care-seeker satisfaction and perceptions. Additionally, it is not imme-

diately obvious if variations in care-seeker perceptions should be attributed to differences in expectations or actual experiences. Also, care-seeker perceptions of quality of healthcare develop over time as different characteristics of the service become available, clearer and better understood and their outcomes revealed [174]. The *AXEX intervention* at drug shops focused on technical quality for drug sellers to manage paediatric fever according to recommended guidelines. Therefore, it is possible that the assessment of perceived quality of drug seller fever care was done prematurely, before care-seeker perceptions had developed. Although, the perceptions take time to develop, they can also be rapidly lost on occasion of a single isolated event such poor staff attitude, or waiting time or stock out of medicines.

Factors that were associated with care-seeker perception of quality of care were as follows; households that participated in post-intervention surveys, were located in the intervention arm and within 60 minutes travel to the drug shop were more likely to perceive quality of drug shop fever care as good. In contrast, households that were 15 to 60 minutes travel or greater to a private clinic or community health worker or lacked routine access to a drug shop were less likely to perceive quality of drug shop fever care as good.

Qualitative analysis of causal mechanisms of the observed effects

Applying the health market system framework adapted from Bloom et al [8] to examine the role of contextual factors and AXEX intervention at drug shops and the effects observed, study IV demonstrated that the AXEX intervention is an example of a multi-component intervention towards creating a functioning health market. It provides equitable access to good quality, efficacious medicines to care-seekers (demand side) while maintaining transparency and accountability within the dynamic relationships and interactions among the actors. Care-seeker expectations of quality of fever care at drug shops were reconfigured, from trial and error to care that was based on definitive knowledge based on rapid tests. The medicines provided in the AXEX intervention had attributes that improved regulator – drug seller interaction, and care-seeking behaviour. The presence of quality-assured single-dose packaged, color-coded medicines that were easy to handle at drug shops and promoted patient adherence [175] to prescribed doses was justified to the regulators and care-seekers, albeit for different reasons. On the regulator's side, these products met medicine packaging standards and regulations [176] and encouraged dispensing of full treatment courses and maintaining good drug shop records. Care-seekers referred to the enhanced treatment experience due to the convenience of handling single dose pre-

packaged medicines and the palatable taste of medicines to the children as being important to children's adherence to treatment. This care-seeker experience and interpretation is consistent with observations by anthropological researchers who have inquired into the human dimension of medicine access, which goes beyond the product's efficacy and touches upon perceived quality and acceptability of treatment (including social and cultural dimensions) [177, 178].

Coupled with training, the provision of drugs and commodities and information, helped create incentives for drug shops to allow or cede to regulation. Taken together, this increased legitimacy and status and helped build trust, both between regulators and drug shops and between drug shops and care-seekers. This thesis portends that the approach to implementation of the *AXEX intervention*, which included analyzing relevant stakeholders and engaging them along with the multi-pronged character of the *intervention* led to conditions necessary to establish trust among the actors. Trust is an important ingredient for *cooperative relations* [179]. It is a precursor to aligning divergent interests among multiple actors towards a *collective action*. Above all, trust enables the actors to assimilate all evidence and secures *communication* and *dialogue* [179]. In the *context* of this thesis, the drug seller interpretation of the malaria RDTs and subsequent prescription or non-prescription of ACTs, or other recommended child medicines does not appear to have been substantially influenced by the drug seller motive to maximize sales. In study IV, this thesis argues that the drug sellers' primary interest for using the rapid diagnostics, child medicines and adhering to iCCM guidelines to high levels was the improved reputation within the community as a result of the increased trust in the healthcare provided to the U5 children.

Future research

As health systems in LMICs continue to face known challenges of lack of incentives to motivate health providers, and limited national ownership of the interventions [72], private sector outlets should be evaluated for their complementary source of healthcare going forward. Questions on how to construct supervision models for private sector interventions remain, as study-employed supervisors were used in this thesis and for most previous studies [41, 42, 159, 160]. A scalable supervision model integrated in district health services [41] is preferred. Addressing this question from a health systems perspective is important to determine if these interventions are reasonable at scale or not.

Study I in this thesis adds to already existing evidence on the variability in sensitivity and specificity of *P. falciparum* HRP2 RDTs [180-184], thus a larger scale examination of the magnitude of the misclassification with current malaria RDTs is warranted. Moreover, these field estimates are below the minimum WHO thresholds for sensitivity and specificity of 95 and 90% for all malaria species, respectively [185]. Possible explanatory factors for this variation include genetic variation in the histidine rich proteins, batch quality variations [186], *P. falciparum* HRP2 persistence in blood following parasite clearance [170], and *P. falciparum* HRP2 gene deletions [187-189]. Other predictors are parasite density, environmental and several host factors, inter-lot variability and performance deterioration, that could result from storage or transportation conditions [120, 186, 190]. Therefore, an external quality assurance scheme for malaria RDT use under field conditions, to detect any failures early and minimize adverse effects of misdiagnosis of malaria should urgently be tested for effect at population. And malaria RDT cassettes in routine practice can form the basis of such a scheme as they are an excellent source of *Plasmodium* DNA especially in the context of retail health markets [144, 191, 192].

In line with ongoing global debate on the importance of care-seeker perceptions of quality of healthcare to the achievement of UHC [193-195], research to develop reliable, valid and stable instruments to measure care-seeker perceptions of quality of healthcare in such contexts is required. Additionally, conceptual inquiry to adapt existing theoretical frameworks of care-seeker perceived quality of healthcare is imperative.

Methodological Considerations

Mixed-methods approach

Strength of this thesis is the use of both quantitative and qualitative methods in a mixed-method convergent parallel design. Quantitative methods in paper I, II and III isolated and identified correlates or variables important in drug seller adherence to the iCCM intervention while the qualitative techniques in paper IV and V provided insight in the underlying processes and events that lead to the observed variation. Qualitative methods allowed the thesis to expand the gaze onto key elements that had not been elucidated or even considered in the research protocol, thereby giving rise to unexpected insights. Some of these were addressed to keep the intervention implementation on track.

The iterative process involved was able to pick up from the unexpected insight and refocus the lens of inquiry towards it. This kind of flexibility and dynamism in mixed methods is often lacking in less comprehensive designs. The thesis was able to integrate, relate, and mix the quantitative and qualitative data. This led to deep descriptions and entry into the participant's lived realities from qualitative methods and also generalizability and statistical reliability from the quantitative methods. The mixed methods lend themselves to possibilities of data triangulation, transformation and instrument design.

Applying mixed methods in resource intensive, for instance, it requires the research team to pull expertise from different disciplines. A key consideration is the difference in the underlying assumptions, world view and epistemology between quantitative and qualitative methods. In contrast to the reductionist quantitative research, qualitative methods are generally inductive, starting with observation of reality, formulating hypotheses, and building theories. On the other hand, quantitative methods are generally deductive, starting with theories, constructing hypotheses grounded in those theories, and gathering data to prove or disprove them. In this way, in the quantitative paradigm, observations are often fit to prior ideas [196].

Quasi-experimental design

A second strength of this thesis was the use of the quasi-experimental design in studies II and III to assess causal inference. The intervention preceded assessment for its effect and the thesis was able to demonstrate the covariation between the cause and effect in analysis. However, the thesis did not use random assignment to ensure alternative explanations and confounding in the cause-effect relationship, were implausible. Instead, additional design elements of an untreated comparison arm and observation at a pre-intervention time point were added [128].

Since the groups are nonequivalent, selection bias may have been present. Pre-test measurements allowed for exploration of the possible size and direction of the bias [127, 128]. It also allowed close examination of the nature of attrition during the intervention implementation. Additionally, data collection and analysis was done carefully with detailed attention to identify and reduce the plausibility of alternative causal explanations.

Although, absence of pre-test difference in a quasi-experiment, is not adequate proof that selection bias is absent [127], this thesis observed pre-test differences in study II, increasing the possibility of selection combining with other threats additively or interactively. i) Selection maturation could have been present where drug sellers in one arm were got more experienced, tired or bored with U5 fever care that drug sellers in the other arm. ii) In study II, selection history could have been a threat when events of regulatory action and disruption in the availability of ACTs in the private supply chain occurred as a result of transition by Uganda MoH from AMFm to the private sector co-payment mechanism support by the Global Fund for AIDS, Tuberculosis and Malaria (GFATM). These events could have differentially affected treatment practices in the comparison arm, thereby making it impossible to know with confidence with observed differences in outcomes were caused by the intervention of by these other events.

To address the threat of selection bias and its potential to combine with other threats, this thesis used the DiD analytical technique in study II. Since, the DiD analysis adjusts for *time-invariant unobserved heterogeneity*, it requires testing the compliment of parallel paths of the outcome in the intervention and comparison arms [127]. However, this assumption could not be tested in this thesis because measurements were conducted at only two time points, pre- and post-intervention, respectively.

Instead, the thesis tested the balancing property of the intervention and comparison at baseline [131]. The balancing t-test [131] at baseline showed that there was no difference between appropriate treatment for pneumonia symp-

toms and diarrhoea, respectively, even after controlling for a given set of drug shop and care-seeker characteristics. In contrast, a difference in appropriate treatment for uncomplicated malaria in favor of the comparison arm at baseline was observed. Borrowing from the “parallel growth” extension of the balancing test, as advanced by Mora and Reggio [197], this thesis argues that in the absence of the intervention, this outcome variable is statistically independent to the intervention effect, given a set of extraneous variables. Since the parallel growth assumption is flexible and allows for differing trends before and after the intervention, the difference in appropriate treatment for uncomplicated malaria observed in the DID analysis is likely due to the intervention.

Measurement errors

Data for study II and III was collected using self-report questionnaires which are subject to social desirability and recall biases. For instance, drug sellers could have been reluctant to share information indicating less than desirable adherence to the iCCM guidelines in triage, diagnostic-testing or prescribing of medicines. Self-reports often lead to over-estimation of adherence [198].

This thesis eliminated social desirability bias in study II by assessing the drug seller treatment practices indirectly from the care-seekers in drug shop exit interviews. Recall bias is unlikely to have been problem in study II since the care-seeker interviews were conducted as they exited the drug shop shortly after the encounter with the drug seller. However, both social desirability and recall bias may have occurred in household surveys in study III. This thesis argues that social desirability bias was minimized to a substantial extent because the questionnaire items were neutral focusing on household health seeking behavior and it was not straightforward for the respondents to establish a direct link between the outcome variable and the raw data. The outcomes of perceived quality of drug seller fever care and care-seeking choice were derived variables after preliminary analysis.

For recall bias, care-seekers were asked questions about treatment seeking for the two most recent febrile illness episodes of the youngest U5 child. Analysis only focused on illness episodes that had occurred in the two weeks preceding the household survey. As reported in another study [199], it is possible there was an underestimate of disease rates in study III. However, in this thesis recall bias was minimized by limiting the required detail about the events, establishing logical flow to the questionnaire items to aid recall, training the interviewers and overall improving the quality of the structured questionnaire [200].

Clustering

Clustering was a concern in study II at drug shop level and in study III at village or neighborhood level, owing to the designs of the studies. Clustering was adjusted for at drug shop and village level in study II and III, respectively. Clustering if present leads to narrow confidence intervals and invalid standard errors [201, 202], if not adjusted for. Sample size calculation took in account the anticipated clustering. The number of clusters per study arm was small, between 10 and 12 clusters and they were not of equal size. For small cluster numbers, bootstrapping was done in 50 replications to improve inference with clustered standard errors [149]. And the adjustment for clustering in analysis used the intra cluster correlation estimated by large analysis of variance which applies a correction for imbalanced clusters [148].

Triangulation

To improve validity and provide a comprehensive understanding of the study findings, triangulation was applied. To triangulate means to consider or compare observations about the same or similar phenomenon using data from different sources [124]. Triangulation allows for greater accuracy and enriches the understanding of a phenomenon by allowing for newer and deeper dimensions to emerge [203]. The common approaches to triangulation include; methodological triangulation – use multiple methods to study a single problem; data triangulation – use of a variety of data sources in a study; investigator triangulation – use of different research assistants or evaluators and theory triangulation – use of multiple perspectives to interpret a single data set [204]. In this thesis, methodological and data triangulation were used majorly and investigator triangulation to a small extent.

Conclusion and Recommendations

Conclusions

1. Drug seller interpretation was in high agreement with laboratory scientist re-reading of malaria RDT strips and the drug sellers adhered to the diagnostic tests in prescribing antimalarials. The malaria RDTs in the field had moderate sensitivity (82%) and specificity (90%) against PCR detection of *Plasmodium* DNA.
2. Implementing the iCCM intervention at retail drug shops improved appropriate treatment for uncomplicated malaria, pneumonia symptoms and non-bloody diarrhea among U5 children in a relatively low malaria transmission setting.
3. The iCCM intervention in drug shops decreased the odds of households perceiving drug seller fever care as good. In contrast, it increased the odds of households choosing to seek healthcare from drug shops versus within the community in South Western Uganda.
4. Drugs shops are part of complex retail health systems with multiple actors. The actors and the system adapted. A multi-pronged intervention such as the *AXEX intervention* enacts realistic regulation to help increase and maintain quality, sustain provision of drugs and commodities as well as incentives to sellers to comply and users to come to licensed drug shops along with communication to enhance trust in drug shops among communities. Each of these, done alone cannot have similar effects. The *AXEX intervention* was thus more than the sum of its parts.

Recommendations to policy makers

1. To Ministry of Health, National Drug Authority and Health Professional authorities and their proxies³: Interventions to improve functioning of

³ Refers to health sector partner agencies such as UNICEF, WHO, GFTAM, BMGF and others that support government/MoH technically, financially and materially to implement its work plans

drug shops in retail health markets should comprise of components that target the multiple actors or influences that shape that market system.

For instance, the iCCM intervention discussed in this thesis improves drug seller management of children with malaria, pneumonia symptoms and diarrhea. It comprised of components that target inputs (medicines, rapid diagnostics and patient registries) into service delivery, consumer empowerment and demand generation, and modifications in regulatory permits or that create conditions for co-creation of regulation.

2. To National Malaria Control Program: Malaria control programmes in public as well as private sector should promote integrated case management of the sick child rather than single disease focus only.
3. To global health initiatives: Subsidies for medicines and diagnostics are necessary to ensure consistent availability and affordability. Support actions to the supply chain are necessary to eliminate perverse incentives or abuse of provider power.
4. To National Malaria Control Program and its proxies: Maintain and improve community and drug seller trust in malaria RDTs and other rapid diagnostics by ensuring the supply chain integrity of diagnostics and implementing a quality assurance scheme.

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