Community case management and referral of children with fever

within the primary health care system in Uganda.

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Declaration

I Sham Dharam Sain Lal, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Malaria remains a leading cause of under-five childhood morbidity and mortality in Sub-Saharan Africa and a third of febrile children lack prompt access to effective malaria case management services. Community health workers (CHW) provide an opportunity to deliver malaria diagnosis and treatment in primary health care settings closer to populations at risk. Recognising the potential of CHWs, many malaria endemic countries have national CHW programmes to provide case management services for malaria and other common childhood infections. However, for children that present to CHWs with signs and symptoms they are unable to manage current CHW guidelines indicate referral to the nearest health centre. Despite the scale-up of CHW programmes, there is little understanding of the referral processes and this thesis aimed to examine the processes as part of malaria case management trials with CHWs conducted in Rukungiri District, Uganda. The referral process was explored in four objectives that mirrored a child's continuum of care beginning at the CHW and ending at the public health centre. The first objective assessed CHWs adherence to the referral guidelines; the second examined the effect of CHWs using malaria rapid diagnostic tests (mRDT) on referrals; and the third examined caregiver's compliance to referral advice. Finally, the fourth objective described changes in outpatient department (OPD) visits and case-mix at health facilities over a 24-month period, before and after the start of the trials. The referral study was carried out as part of two cluster randomised trials which assessed the impact of CHWs using mRDTs on appropriate treatment of malaria when compared to presumptive diagnosis. Secondary analyses of routine CHW records revealed that two-thirds of children eligible for referral

were not referred, including children with severe malaria. Although, the use of mRDTs improved the odds of referral compared to presumptive diagnoses, almost 90% of caregivers failed to comply with CHW referral advice which was associated with factors such as distance from health facilities, seasonality and treatment seeking during the weekend. Compared to the pre-trial period, OPD visits at health facilities declined and case-mix changed following the start of the trial. Overall these findings show the referral processes can be monitored using routinely available data using appropriate indicators. Changes in the number and type of visits seen at health facilities, indicate that health resources could be allocated differently. Most importantly, these data show that the referral process intended to ensure the care of children with referral signs and symptoms did not perform well. Referral is key component of primary health care and the process requires strengthening to ensure a continuum of care in community case management settings. New interventions should be developed involving CHWs, caregivers and health facilities to overcome the referral barriers and consequently improve CHWs adherence to referral guidelines as well as caregivers compliance to referral advice.

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The research findings described in this thesis is a modest venture of an inexperienced science student who, with an ardent curiosity, set out to understand more about the role of communities providing primary health care, particularly for children under five years old at risk of malaria in rural Uganda. Throughout this quest, I have been privileged to interact with several people who have been a source of encouragement and wisdom and from whom I have learnt a great deal. Sincere appreciation goes to my PhD supervisors Dr Siân Clarke, who sparked my interest in malaria research and guided me through the challenges and rigours of scientific inquiry throughout the thesis and Dr Daniel Chandramohan who has been a constant source of encouragement and practical advice along this quest. I am also grateful to the support offered by my scientific advisory community, these members have lent their valuable time to listen and engage with my ideas, thoughts and reasoning and guided them throughout the research questions discussed in this thesis. These include Dr. Kristian S. Hansen, who nurture my interest in health economics; Lucy Paintain an admirable source of knowledge on community-based programmes in low and middle income countries, as well as a supportive colleague; Dr. Neal D. Alexander a remarkable statistician and writer who helped with much of the statistical methodological work and writing presented here. I would also like to thank the valuable input of Dr Kara Hansen and Dr David Schellenberg during the upgrading phase of this PhD, they actively engaged with my proposed thesis and provided critical and detailed input that shaped much of the research.

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ACT	Artemisinin-based combination therapy
AL	Artemether-lumefantrine
AMX	Amoxicillin
AQQ	Artesunate amodiaquine
AR	Adjusted residuals
ARIMA	Auto-regressive integrated moving average modelling
CBPR	Community based participatory research
CCM	Community case management
CCT	Conditional cash transfers
CDD	Community Drug Distributors
CHW	Community health worker
CMD	Community Medicine Distributors
CQ	Chloroquine
CQ-SP	Chloroquine and sulphadoxine-pyrimethamine
CRCT	Cluster randomised controlled trial
CRT	Cluster randomised trial
DFID	Department for International Development
EIR	Entomological inoculation rate
HBMF	Home Based Management of Fever
HC	Health Centres
HCII	Health centre II
HCIII	Health centre III
HCIV	Health centre IV
HMIS	Health management information systems
HMM	Home-based management of malaria
HT	Moderate to high transmission setting
iCCM	Integrated community case management
IMCI	Integrated management of childhood illnesses
IRS	Indoor residual spraying
ITN	Insecticide treated bednets
ITS	Interrupted time series
LT	Low transmission setting
MDG	Millennium Development Goals
MRC	Medical Research Council
mRDT	Malaria rapid diagnostic test
OPD	Outpatient department
PLA	Participatory learning and action
RBM	Roll Back Malaria
RRT	Respiratory rate timers

RTIs	Respiratory tract infections
SSA	Sub-Saharan Africa
TDR	WHO, the Special Programme for Research and Training in Tropical Diseases
UMIS	Uganda Malaria Indicator Survey
UNICEF	United Nations Children's Fund
VHT	Village health teams
WHO	World Health Organization

Preface

The scientific body of knowledge generated during these doctoral studies was conducted as part of two CHWs trials. The main aim of the trials was to examine the impact of introducing mRDT and ACTs on appropriate case management of children under-5 in two contrasting malaria transmission settings. Whilst the findings presented within here originated from data collection from the trials they cover a separate component of the trial which related to community referral system and its impact on health facilities.

In line with LSHTM Research Degrees Regulation each of the results chapters is presented as a series of peer-reviewed research manuscripts and are supplemented with additional material to explain how the thesis represents a coherent body of knowledge and follows a series of steps along the referral process. The introductory material describes the context of the work and the evidence on referral from CHWs treating uncomplicated childhood conditions. A final discussion chapter is also included to synthesise the findings of each of the results chapters and provide a broad overview of the thesis. It also explores limitations and strengths more generally of the thesis and suggests some implications for public health and policy. The presentation of the thesis in a series of manuscripts has inevitably resulted in repetition of background information and the methods used in this trial, in addition editorial standards between the journals may differ which may have resulted in some inconsistencies in formatting and terminology.

Chapter 1: Introduction

Background

Plasmodium falciparum infection continues to be a significant burden on health systems in sub-Saharan Africa. It causes up to 1 million childhood deaths each year and hinders childhood development (Kihara, Carter and Newton, 2006; Murray *et al.*, 2012). The public health impact of malaria has changed significantly over the past two decades, between the years 1990 and 2000 malaria mortality rates were increasing across SSA countries despite declines in mortality from other causes (Gething *et al.*, 2016). This rising mortality was predominantly due to the emergence and spread of plasmodium species resistant to first-line treatment chloroquine (CQ) which led to malaria treatment failures (Trape, 2001). The new millennium saw a change in the political commitment and effort to control malaria driven by the United Nations Millennium Development Goals (MDGs) and the Roll Back Malaria Partnership which aimed reverse the increasing incidence of malaria (United Nations, 2000). These efforts led to new international financing mechanisms such as the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002 and the US President's Malaria Initiative in 2005. Shortly after, financing for malaria control increased by 22% per year for control interventions including: insecticide-treated bednets (ITNs), indoor residual spraying (IRS), and treatment of clinical malaria with artemisinin-based combination therapy (ACT) (WHO, 2014, 2016). These multilateral control efforts have contributed to malaria mortality declines by an estimated 57% between 2000 and 2015, and an absolute decline in deaths from 1,007,000 to 631,000 during the same period (WHO, 2016). Whilst this represents remarkable progress, approximately 90% of the SSA population remains at risk of malaria and the burden of risk still remains greatest amongst children under-five, where 70% of all malaria cases occur. Furthermore, large proportions of the population lack coverage of malaria interventions, in 2015 nearly half of all households in SSA lacked either an ITN or IRS, and only 14% of children with confirmed malaria received first-line antimalarial treatment ACT (WHO, 2016). Many malaria endemic countries face challenges in addressing the poor coverage of malaria control measures as the disease becomes concentrated in countries with the weakest health systems (Cibulskis *et al.*, 2016).

In efforts to increase coverage of malaria programmes WHO's Global Malaria Programme developed the Global Technical Strategy for Malaria 2016-2030 to provide a framework for countries in their programmatic efforts towards greater malaria control and elimination, and set a target of reducing global malaria incidence and mortality rates by at least 90% by 2030 (WHO, 2015a). One of the three pillars of the strategy aims to ensure universal access to malaria prevention, diagnosis and treatment, and endorses the scale-up of community-based diagnostic testing and treatment, by training and deploying community health workers (CHWs) in remote areas. Populations that reside in rural areas are often beyond the catchment of formal health systems and it is envisaged that CHW programmes can increase access for malaria prevention and treatment services and serve to fill primary health care gaps, particularly for children under-five (WHO, 2015a).

A History of CHWs in Sub-Saharan Africa

Community health workers encompass a variety of persons recruited from a community and trained to provide healthcare services to the community they are from. In early 1989 the WHO defined CHWs as:

> "*…members of the communities where they work, should be selected by the communities, should be answerable to the communities for their activities, should be supported by the health system but not necessarily a part of its organization, and have shorter training than professional workers.*" (WHO, 1989)

CHWs may perform a variety of roles related to the delivery of healthcare in communities but are typically limited to the delivery of primary health care service. CHWs are not considered to be formally trained nurse aides, medical assistants or physician assistants and the training received by CHWs is often shorter than formal healthcare workers and is not considered part of a professional medical education.

Interest in CHWs grew between the 1970s and 1980s when many countries realised that services delivered through health centres failed to provide adequate coverage for the whole population at an affordable cost. Additionally, they also understood that medical nursing care and medications delivered through health centres did little to prevent the social, economic and cultural factors that caused poor health. In contrast, it was considered that

CHWs were socially and culturally acceptable by communities and therefore best placed to deliver primary health care in places that official health centres could not. CHWs programmes became the approach for primary health care in the 1970s and early 1980s after being enthusiastically adopted by UN member states and enshrined in the 1978 Alma-Ata declaration (Cueto, 2004). In the ensuing years, donors and governments supported large scale chemoprophylaxis programs for malaria, onchocerciasis and dracunculiasis (Kaseje, Sempebwa and Spencer, 1987; Adhanom Ghebreyesus *et al.*, 1996; Cairncross, Braide and Bugri, 1996; Richards Jr *et al.*, 1996). Some were highly successful whilst others were ineffective and became obsolete. The Onchocerciasis Control used communities to organise mass treatments schedules and it was successful in eliminating onchocerciasis in 10 countries (Coffeng *et al.*, 2013). Similarly, village health workers synonymous with CHWs formed the backbone of the guinea worm eradication program in 1981 (CDC, 2012). There was also well documented scale up of the use of CHWs for malaria chemoprophylaxis programmes. Early evaluations of these programmes had mixed and inconclusive results; Kenya and Zaire found no reductions in mortality, whilst Ethiopia reported an initial decline. Most of these studies were conducted in African countries emerging from post-independence civil wars and during economic and social upheaval. One of the earliest CHW programs implemented in Saradidi, Kenya aimed to provide prompt, appropriate treatment to each patient with malaria (Kaseje and Spencer, 1987). This resulted in high utilisation of services and delivered an average of 1.24 chloroquine phosphate treatments per person per year. Despite an increased utilisation of CHW services, there was no overall decline in parasitemia and malaria specific mortality rates (Spencer *et al.*, 1987). This was partly explained by already declining mortality rates but without reporting the causes of death (Spencer *et al.*, 1987). A similar community-based programme implemented in Tigray, Ethiopia from 1994 to 1997 treated an average of 489,378 patients per year. Malaria related mortality declined by 40% during the first two years, but rose during the last two years, which was largely due to increasing CQ resistance and labour migration to high malaria transmission areas (Ghebreyesus *et al.*, 2000). A study in Zaire found no changes in mortality, although malaria prevalence declined by 50% and they observed deficiencies in the provision of care. CHWs in this study sought to be acknowledged and formally recognised by the health system however they were poorly integrated with health centre staff, lacked the motivation and commitment for the role. Over time CHWs quality of care declined and they failed to presumptively treat a quarter of all malaria episodes during an outbreak (Delacollette, Van der Stuyft and Molima, 1996). The study also had insufficient statistical power to detect mortality and the sensitivity of verbal autopsies to detect malaria deaths were questioned. All these factors highlighted the complexities of implementing and evaluating the effectiveness of a CHW based programme.

Despite the poor effectiveness reported in early studies, an augmented community-based trial in The Gambia found the first reductions in malaria mortality and morbidity. Two intervention strategies were deployed by CHWs and compared with a control group. One group treated malaria with CQ and a second group provided fortnightly chemoprophylaxis with pyrimethamine/dapsone as well as treatment, whilst the control group administered a placebo (Greenwood *et al.*, 1988). Evaluations found a 34% reduction in overall mortality and 69% reduction in the incidence of clinical attacks of malaria. However, treatment alone had no effect on mortality or parasitemia, this may be attributed to the limited availability of CHWs when urgently needed by caregivers (Greenwood *et al.*, 1988).

The challenges faced by the early control programmes in Zaire and The Gambia highlighted some of the problems with implementing community primary health care services; which were also experienced by other countries after Alma-Ata. Programmes failed due to a lack of sustainable drug supplies, a lack of professional supervision, community acceptability of CHWs and their recognition from formal health services as well as the difficulty of retaining unpaid CHWs. Their service quality and motivation had diminished over time due to lack of incentives, support and recognition of their work. In Tanzania, CHWs were rejected by communities as they felt the government was mitigating state responsibilities by depending on village structures to sustain CHWs. Similarly, in Zambia and Thailand, CHW attrition rates of over 45% were reported (Walt, Perera and Heggenhougen, 1989). Four years after training 4,100 CHWs in Ethiopia only 62% were found to be active and less than 29% were performing their duties (Adhanom Ghebreyesus *et al.*, 1996). A study in Sri Lanka found strong institutional opposition to CHWs, as nurses and doctors felt they undermined professional services (Walt, Perera and Heggenhougen, 1989). These countries' experiences detail the early problems of implementing treatment community programs, despite promising results for onchocerciasis and guinea worm initiatives. The curative primary health care services provided by CHWs became underutilised by the community, programs suffered and some became obsolete. It is unsurprising therefore that many countries shifted away from primary health care in the early 1990s towards more selective vertical health programmes (Haines, Horton and Bhutta, 2007).

In 2004 strong advocates within the WHO, the Special Programme for Research and Training in Tropical Diseases (TDR) recommended the scale up and implementation of a new community-based strategy, the home-based management of malaria (HMM) (TDR, 2004). Two influential studies reported health gains to support this policy. A cluster randomised trial (CRT) in Tigray, Ethiopia that trained mothers to recognise the signs and symptoms of malaria and treat with CQ found a 41% reduction in mortality (Kidane and Morrow, 2000). A similar trial in Burkina Faso, found that using older mothers to presumptively treat their children's fevers with CQ reduced the risk of developing cerebral malaria by 50% (Sirima *et al.*, 2003). A common strategy of these two studies was to use mothers as service delivery agents to treat their own children as opposed to CHW treating children in their communities. The issues surrounding community acceptability, availability and utilisation of CHW, as described in Zaire, Ethiopia, Sri Lanka and The Gambia are largely obviated through mothers treating their own children compared to CHW treating children or patients in their community. The vested interests lie solely in the mother serving the needs of her child as opposed to the wider role of serving the community.

The success of community programs in Ethiopia and Burkina Faso prompted countries to scale-up activities to meet this target. This was facilitated by members of the African

Union signing the Roll Back Malaria Abuja Declaration in 2001, which committed countries to ensure that at least 60% of malaria cases have access to appropriate treatment with 24 hours of onset of symptoms by 2005 (WHO, 2003b). Uganda was an early proponent of HMM and launched a strategy in June 2002, which also coincided with a change in first line treatment policy from CQ monotherapy to combination therapy of chloroquine and sulphadoxine-pyrimethamine (CQ-SP).

The Home Based Management of Fever (HBMF) programme trained 3,983 CHW volunteers known as Community Drug Distributors (CDD) or Community Medicine Distributors (CMD), to deliver CQ-SP in two age-dependent and colour-coded packages; one for children 6 months to 2 years and another for the 2-5 year olds, known as HOMAPAK. CHWs also counselled caregivers on dosage, treatment duration and provided referral advice for children with severe illness to the nearest health centre (Fapohunda *et al.*, 2004). An evaluation study compared four intervention districts with HMBF with two control districts without HMBF over 1 year and found the odds of appropriate treatment to be 5 times higher in intervention districts when compared to control districts. Severe anaemia also declined from 19% to 13% in the control and intervention districts respectively (Fapohunda *et al.*, 2004). By 2005 HBMF had been implemented in 47 districts across the country, however shortly after implementation the programme suffered significant difficulties, such as sustaining an unpaid workforce, and vertical programme not adequately integrated with other community-based initiatives such as integrated management of childhood illnesses (IMCI). In addition, not long after the implementation of HBMF an increase in resistance strains of *P. falciparum* to CQ spread and led to a policy to change to from CQ to artemether-lumefantrine (AL), (Coartem®) an ACT, as the first line treatment for uncomplicated malaria and under WHO recommendations other malaria endemic countries followed suit (Malimbo *et al.*, 2006; Ikeoluwapo O Ajayi *et al.*, 2008). However, a few individuals within the public health community voiced concerns of the widespread use of ACTs in HMM, due to CHWs limited training. They argued that when ACTs are given unsupervised or with limited training it could also lead to resistance (Charlwood, 2004; D'Alessandro, Talisuna and Boelaert, 2005). Despite these concerns there was strong evidence to suggest CHW using ACTs could be scaled-up nationally and provide prompt appropriate treatment. A four site multi-country study found after CHWs treated 20,000 febrile episodes, 97% of CHWs gave correct doses with a PCR (polymerase chain reaction) adjusted cure rate of over 90% and concluded ACT use in HMM was safe, affordable and achievable (D'Alessandro, Talisuna and Boelaert, 2005; I O Ajayi *et al.*, 2008). These HMM strategies used the clinical signs and symptoms of malaria for diagnosis and routinely treated children with antimalarials in malaria endemic settings. Given that clinical features of malaria overlap with other common illnesses, overdiagnosis of malaria can delay care for fevers of different aetiologies and result in poor health outcomes (Chandramohan *et al.*, 2001; Reyburn *et al.*, 2004). Over prescription can also increase parasite selection pressure, encourage drug resistance and treatment failures.

Antigen based malaria rapid diagnostic tests (mRDT) allow ACT provision to be potentially limited to those with parasitologically confirmed malaria, in areas without light microscopy. They require simple training and less supplies compared to microscopy (Drakeley and Reyburn, 2009). There was early concerns and debates in the literature over the deployment of mRDTs in primary health care settings due to the increased complexity of diagnostic algorithms and the capability of CHWs to adhere to test results and manage children with mRDT negative test results (D'Acremont *et al.*, 2009; English *et al.*, 2009). However, with adequate training and supervision studies reported CHWs were able to interpret and adhere to mRDT results (Harvey *et al.*, 2008). CHW trials in Tanzania and Senegal reported 97% adherence to test results with only a small proportion of mRDT negative patients receiving an ACT and when compared to a signs and symptoms method of diagnosis, mRDTs reduced prescriptions of ACTs by 45% (Mubi *et al.*, 2011; Thiam *et al.*, 2012). These studies demonstrate the capacity of CHWs to adhere to clinical algorithms and emphasise the potential of CHWs for the case management of malaria with ACTs and mRDTs. High levels of mRDT adherence and ACT cure rates can be achieved with adequate training, and support supervision, additionally CHWs can extend malaria case management services to areas with poor access to health centres.

The evidence summarised here charts the development of community health programmes serving the needs of hard-to-reach populations. The successes of CHWs involvement in early disease specific prevention programs using mass drug administration and health education led to an expansion of their role into curative health care delivery. Early programmes failed show benefits, with inadequate service quality, poor retention and limited integration with existing health systems, these poor circumstances led to many

CHW programmes failing. Later renewed interest in CHW has led to scale-up of research and evaluation of implementing programs, building on the early challenges faced. Despite early concerns about the capacity of CHWs to deliver primary health care services, recent studies have documented their ability to follow increasingly complex clinical algorithms with diagnostic tools for common childhood illness.

Studies in Asia in the early 1990s also found CHWs could substantially reduce childhood mortality and morbidity due to uncomplicated pneumonia through adherence to a simplified clinical algorithm that involved prescribing antibiotics. A meta-analysis of 9 studies found CHWs could reduce pneumonia-specific mortality by 36% in children under-5 and by 2008 12 out of 16 countries with high burdens of child mortality had implemented pneumonia case management programmes (Sazawal *et al.*, 2006; Marsh *et al.*, 2008). The declines in mortality can be attributed to sustained supplies of commodities, development of training materials, supportive supervision by health facilities and adherence to clinical algorithms. Research comparing the agreement of CHWs to identify signs of uncomplicated pneumonia with a clinician's classification as a gold standard, have found good to high agreement identifying fast breathing signs (Kallander *et al.*, 2006; Mukanga *et al.*, 2011). A systematic review also found CHWs were able to give oral antibiotics to 80% of cases with correctly diagnosed with uncomplicated pneumonia (Druetz *et al.*, 2015). In contrast, the correct identification of severe pneumonia signs in particular lower chest in-drawing, by CHWs has tended to be poorer compared to clinicians, a study in Kenya found between 19% to 60% agreement and referral rates between 11% and 60% (Kelly *et al.*, 2001).

There is also strong evidence that CHWs can manage diarrhoea, randomised controlled trials from India and Bangladesh have found CHWs were able to correctly prescribe ORS and Zinc in at least 60% of cases and reduce diarrhoea mortality by 13% (Bhandari *et al.*, 2008; Yakoob *et al.*, 2011). The WHO now recommends low osmolarity ORS for the treatment of dehydration from diarrhoea, these solutions of sugar, salt, and water or other recommended fluids can reduce under-5 deaths by 69% when delivered by CHWs with supportive information on their use (Munos, Fischer Walker and Black, 2010). WHO and UNICEF also recommend the use of oral zinc for 10 – 14 days for the standard treatment of diarrhoea, which reduces the severity of diarrhoeal episodes. (WHO/UNICEF, 2004).

The evidence that well-trained and supervised CHWs are able to case manage single childhood illnesses and achieve reductions in morbidity and mortality have led to many influential global health actors advocating for an integrated approach to the management of malaria, pneumonia and diarrhoea, particularly in countries which have high burdens of all three illnesses (Ikeoluwapo O Ajayi *et al.*, 2008; Marsh *et al.*, 2008). Integrated community case management (iCCM) emerged in attempts to address some of the challenges found with Integrated Management of Childhood Illness (IMCI) which was designed to deliver curative and preventative interventions to manage the three main causes of under-5 mortality (malaria, pneumonia and diarrhoea) through an integrated case management approach (Tulloch, 1999). The justification for this approach was due to children frequently presenting with signs and symptoms that overlapped with more than one of these illnesses and that it might not be appropriate to diagnose and treat a single illness, rather an integrated approach was needed to improve child health (O'Dempsey *et al.*, 1993). IMCI was established in the early 1990s to manage common childhood illnesses to reduce under-5 child mortality and through the collaborative initiatives of WHO, UNICEF and other technical partners (WHO and UNICEF, 1997; Tulloch, 1999). IMCI comprised of three main components, first; case-management training of health centre staff with locally adapted guidelines, second; health system improvements for the management of childhood illnesses and third; improvements in family and community practices. Overall it aimed to reduce mortality and frequency of illnesses and disability. However, the effectiveness of IMCI was systematically reviewed in mid 2016 and found with low-certainty that IMCI may have reduced child mortality (Gera *et al.*, 2016). This was a less than satisfactory outcome and the underlying reasons for these results found that many countries had difficulties in ensuring the strength of IMCI implementation to ensure an adequate level of quality of care (Bryce *et al.*, 2005). Furthermore, technical medical guidelines for family and community members were not fully developed at the time of implementation. Consequently, countries faced difficulties in expanding critical inventions related to improving care seeking and care at home. The multi-country evaluation of IMCI concluded that the implementation of IMCI policies should include all health providers, not just health facilities and that community-based approaches should be used (Bryce *et al.*, 2005).

From 2004 onwards, SSA countries begun adopting national policies that included the management of malaria, pneumonia and diarrhoea at the community level with CHWs. This approach known as integrated community case management (iCCM) has been rapidly scaled up over the past decade, from 7 SSA countries in 2005 to 36 by 2013 (Young *et al.*, 2012; Rasanathan *et al.*, 2014). iCCM can be considered to be a successor to the household and community component of IMCI (HH/c-IMCI) which focused on health promotion at the household level and treatment at the community level with CHWs (Arifeen *et al.*, 2004; WHO, 2011b). The iCCM strategy primarily entails providing integrated case management services for two or more illnesses (diarrhoea, pneumonia and malaria) to children under-5 (Young *et al.*, 2012). Case management services include; using a simplified IMCI algorithm to assess a child's condition and refer complicated cases to the nearest health centre and treatment of non-severe pneumonia with oral antibiotics, treatment of non-severe diarrhoea with ORS and zinc and the treatment of uncomplicated malaria ACTs (WHO/UNICEF, 2012). As with other community programmes, iCCM aims to bring these free case management services closer to rural communities that have difficult access to health facilities. Despite the provision of free services closer to communities in countries that have scaled up iCCM, there is mixed evidence on the extent of its utilisation by the communities they are intended to serve (Doherty *et al.*, 2014).

There have been concerns that CHW's adherence to guidelines and performance may decline with the addition of clinical algorithms for the management multiple childhood illnesses (Cardemil *et al.*, 2012). The evidence evaluating CHW's performance suggest CHWs are able to adhere to guidelines for uncomplicated illnesses however, for management of 2 or more illness or complicated illnesses adherence might be lower. Including mRDTs and respiratory rate timers (RRTs) within CHW's case management algorithms provides the opportunity to discriminate malaria fevers from pneumonia fevers, theoretically leading to better case management for both illnesses. An evaluation of CHWs performance in Uganda found high agreement (≥85%) of normal or fast breathing with a paediatricians assessment using RRTs and perfect agreement in the interpretation of mRDTs (Mukanga *et al.*, 2011). Despite the correct use and interpretation of RRTs and mRDTs, CHWs found difficulties with translating these results into correct illness classifications for 13% of children. They also had difficulty with providing appropriate treatment for pneumonia in 40% of cases, compared with 87% of cases receiving appropriate treatment for malaria (Mukanga *et al.*, 2011). In a related study conducted in three countries (Burkina Faso, Ghana and Uganda) the authors found that despite training in the use of mRDT and RRTs, CHWs gave antibiotics to approximately 33% of mRDT negative children with normal respiratory rates and at least 27% mRDT negative children with high respiratory rates and did not receive antibiotics. In one of the countries, Burkina Faso, a third of mRDT positive children with normal respiratory rate received antibiotics (Mukanga *et al.*, 2012). Both these studies show that despite the providing training CHWs to use RRTs and mRDT for the case management of uncomplicate pneumonia and malaria respectively, there was still poor adherence to guidelines in the provision for appropriate treatment for pneumonia, in contrast there was good adherence to mRDT results leading to appropriate treatment for malaria with an ACT (Mukanga *et al.*, 2012). The authors concluded that the poor adherence to RRTs results could be due to poor CHW supervision in 2 of the countries (Burkina Faso and Ghana).

Evaluations have also been undertaken to assess CHWs performance in adhering to guidelines for more complicated illnesses. In Kenya, a study that carried out re-examinations of CHWs' assessments of sick children by clinicians (the gold-standard) found CHWs were able to adhere to an average of 80% of procedures for each child with uncomplicated signs, but were only able to adhere to an average of 30% of procedures per child when they had one or more severe signs of disease or diarrhoea (Rowe *et al.*, 2007). A study with a similar method of assessing CHW's performance was carried out in Malawi and made similar findings, between 24% and 40% of severe illnesses for fast breathing, fever and diarrhoea were correctly classified and treated by CHWs, this was lower than the proportion of cases that correctly classified and treated for uncomplicated illnesses 63% to 90%. In addition, as the number of uncomplicated illnesses increased per child, CHW's performance declined when attempting to correctly identify and treat each illness (Cardemil *et al.*, 2012). Failure to identify signs of severe illness could also reduce referral of caregivers to health facilities and prolong the delay in seeking treatment for potentially fatal conditions. In addition, the extent to which CHWs are able to identify and correctly manage severe illnesses when trained to use mRDTs and RRTs under an iCCM programme is unclear. Both studies in Malawi and Kenya were conceived before the use of diagnostics became a part of national iCCM policies and further research is needed to understand whether severe illnesses are correctly managed when CHWs use RRTs and mRDTs.

Care-seeking behaviours

The contemporary global health interest in community case management programmes can be partly ascribed to the limitations of existing health systems to provide accessible primary health care, universally to populations in need. CHWs provide an opportunity to expand primary health care to members of their communities and can be more acceptable than professional health services delivered through health centres (Singh, Cumming and Negin, 2015). In addition, acute childhood illnesses such as malaria can progress from a mild to a severe illness within 24 hours and deaths often occur shortly after the onset of symptoms (Greenwood *et al.*, 1987). Therefore, a key component of primary health care is the supply of timely health services that provide prompt diagnosis followed by quick effective treatment to avoid death. These case management strategies can be delivered to high risk populations through CHWs that are well trained and adequately equipped with first line treatments, such as ACTs and where necessary pre-referral treatment (Kidane and Morrow, 2000; Sirima *et al.*, 2003). Whilst the supply of these medical services are critical to achieving universal healthcare, demand has to be generated by the communities CHWs are intended to serve. Failure to seek care for proven health interventions such as iCCM may undermine the intended effectiveness of programmes and contribute to morbidity and mortality at home.

An evaluation of UNICEF supported iCCM implementation in 6 SSA countries (Ethiopia, Ghana, Malawi, Mali, Mozambique, Niger) found low utilisation of CHWs delivering iCCM between 2007 and 2013 (Doherty *et al.*, 2014). In five of the six countries less than 10% or more caregivers sought treatment for malaria, pneumonia and diarrhoea. Although there were substantial variations across the countries ranging from 3% in Ethiopia to 9% in Malawi (Doherty *et al.*, 2014). In contrast, Niger saw 16% of caregivers seeking treatment for all three illnesses. The low utilisation of iCCM was not related to the number of CHWs per child under-5 population, this ranged from 357 children per CHW in Ethiopia to 576 children per CHW in Niger. Similarly, most countries reported low-levels of stock-outs, conversely, expensive user fees may have been a barrier to accessing CHWs in Ghana and Mali (Daviaud *et al.*, 2017). These findings were further supported by a systematic review of care seeking behaviour in LMIC countries, care seeking from CHWs managing one or more childhood illness was low: 1% for malaria, 4% for pneumonia, 5% for diarrhoea (Geldsetzer *et al.*, 2014). Compared to CHWs, caregiver treatment seeking was greater at drug shops or pharmacies, 31% for malaria, 15% for pneumonia, 34% for cases of diarrhoea (Geldsetzer *et al.*, 2014). These studies did not explore in depth why utilisation was low, but it could be due to CHWs perceived low status within the community and caregivers poor recognition of signs and symptoms that require treatment seeking (Geldsetzer *et al.*, 2014; Amouzou *et al.*, 2016).

Treatment seeking behaviour is often related to the local cultural understandings about health and the decision to seek healthcare typically begins with the recognition of abnormal signs in children, often by the mother of the child (Tanner and Vlassoff, 1998; Oberländer and Elverdan, 2000). In many SSA countries, caregivers face difficulty recognising the signs that require medical treatment, for example in Ghana caregivers were unable to recognise nor report important symptoms such as sunken eyes, wheezing and swollen feet and pale face and palms, which corresponded to dehydration, malnutrition and respiratory infections respectively (Hill *et al.*, 2003). However, other symptoms were recognised and reported by caregivers but were considered unimportant because they normally would not seek treatment from a hospital for them. These symptoms included frequent stools, difficult or fast breathing and hot body, which may also correspond to malaria, pneumonia and diarrhoea (Hill *et al.*, 2003). Similar findings have also been made in East Africa where the local terminology used by caregivers which describes the identified symptoms that correspond closely to malaria are not considered important for seeking care. In Uganda, the word "*Omusujja*" often refers to a general feeling of being unwell and incorporates a range of symptoms, for which health centre care is only sought after traditional medicines have been used (Kengeya-Kayondo *et al.*, 1994). Authors in Kenya found that the word "*Homa"* refers to mild to severe febrile condition with symptoms ranging from general malaise, fever and headaches (Mwenesi, Harpham and Snow, 1995).

Research on caregiver's recognition of signs has often been conducted on uncomplicated malaria, pneumonia and diarrhoea and relatively less is understood about caregiver's recognition of the signs that manifest with severe disease that require referral and how their recognition relates to treatment seeking (McCombie, 1996; Warsame *et al.*, 2016). Severe pneumonia can be characterised by having both a high respiratory rate and lower chest indrawing (Benguigui and Stein, 2006; Druetz *et al.*, 2015). In studies that assessed caregiver's ability to recognise severe pneumonia signs, researchers in Ethiopia, Ghana and

Uganda found caregivers were often unable to correctly identify signs when shown a child with signs of severe pneumonia, furthermore there was no distinct word to refer to these symptoms and caregivers would delay seeking care (Denno *et al.*, 1994; Muhe, 1996; Hildenwall *et al.*, 2007). Uncomplicated malaria can progress to a severe form with neurological sequalae, organ failure and death within 16 hours, this rapid progression emphasises the need for early recognition of signs of severe malaria and seeking appropriate treatment (Crawley *et al.*, 2010). Current research suggests that caregivers are able to recognise signs of severe malaria (convulsions, altered consciousness, repeated vomiting, lethargy, inability to eat or drink), but may interpret these signs as the child being possessed by evil spirits or a victim of witchcraft (Kengeya-Kayondo *et al.*, 1994; Ahorlu *et al.*, 1997; Comoro *et al.*, 2003). These supernatural diagnoses often result in delayed treatment seeking from biomedical sources with caregivers preferring to seek treatment from spiritual or traditional healers in the first instance (Warsame *et al.*, 2016). In contrast to caregiver's poor recognition of severe malaria and pneumonia signs, some evidence suggests caregivers are able to recognise severe signs of diarrhoea (loose watery stools that have lasted 14 days or more or signs of blood in stools) (Ministry of Health, 2012; Geldsetzer *et al.*, 2014). In Burkina Faso and Pakistan, the authors of two studies found caregivers were correctly able to identify signs of severe diarrhoea as the number of loose watery stools increased and they were also able to correctly identify signs of severe dehydration (Wilson *et al.*, 2012; Geldsetzer *et al.*, 2014; Aftab *et al.*, 2018). Current iCCM guidelines recommend immediate referral for children with one or more signs of severe illness, however the current evidence suggests there is limited recognition of severe signs and understanding of their importance for a child's health by caregivers. Poor recognition and understanding of severe signs play a critical role in delaying seeking curative treatment once caregivers are referred for severe signs by CHWs. Thus, ensuring caregiver's awareness of severe illnesses that require urgent referral and the consequences of delayed treatment seeking are crucial to reducing under-5 child mortality and morbidity from malaria, pneumonia, and diarrhoea (Berkley, 2003; Colvin *et al.*, 2013). The importance of caregiver's treatment seeking has been recognised by the WHO and UNICEF and recommend strengthening the capacity of communities to recognise signs of severe illness and seek care promptly, as part of the Integrated Global Action Plan for the Control of Pneumonia and Diarrhoea (WHO/UNICEF, 2013).

As well as caregiver's recognition and understanding of signs that may affect accessing health services household financial barriers also play a substantial role. In Kenya, a study found nearly 50% of caregivers failed to seek care for common childhood illnesses due to insufficient finances to support the trip (Taffa and Chepngeno, 2005). In neighbouring Tanzania and Ethiopia a clear relationship between socio-economic status and treatment seeking was observed, caregivers from the poorest wealth quintile were less likely to seek care from health centres and had less knowledge about the signs of malaria, when compared to households in the higher wealth quintile (Schellenberg *et al.*, 2003; Deressa, Ali and Berhane, 2007). Direct household costs of treatment seeking, such as health centre user-fees, transport and prescriptions often account for more than 10% of a households annual income in SSA (McIntyre *et al.*, 2006). In Kenya, Nigeria and Pakistan direct annual costs of malaria or pneumonia ranged from 13% to 20% of a household's annual income, whilst indirect costs such as opportunity cost of caregiver time through loss of earnings for care seeking and child care, were often twice as much as direct costs (McIntyre *et al.*, 2006; Sadruddin *et al.*, 2012; Sicuri *et al.*, 2013). A 10% cut-off of household health care expenditure is suggested to reduce expenditure on other minimum living needs and may lead to a household's economic impoverishment (Russel, 2004). CHWs offer the possibility of reducing household's direct and indirect treatment seeking costs by providing treatment closer to caregiver's home (Matovu, Nanyiti and Rutebemberwa, 2014). There is limited evidence describing household costs as part of iCCM programmes and their potential impact on treatment seeking, additionally there have been calls for further evidence in this area (Collins *et al.*, 2014). In Ghana and Uganda economic evaluation of iCCM programmes found direct household costs were approximately half those incurred by households when they seek treatment from health centres (Matovu, Nanyiti and Rutebemberwa, 2014; Escribano Ferrer *et al.*, 2017). Despite the lower household costs borne from CHWs compared with health facilities, there is limited evidence to suggest that households costs for treatment seeking from CHWs differ according to the severity of illness. A three country study that evaluated the impact of training CHWs with ACTs and mRDTs, before iCCM became national policy, in Burkina Faso, Nigeria and Uganda, found evidence that the mean household costs of treatment seeking from CHWs were higher for complicated malaria episodes compared to uncomplicated malaria episodes in Burkina Faso and Nigeria (Castellani *et al.*, 2016). The authors did not explore reasons for this difference and did not capture caregivers' indirect costs, which may differ according to disease severity. Most studies examining household costs have been from community programmes managing a single uncomplicated childhood illness and it might be challenging to generalise these findings to integrated illness programmes such as iCCM, partly because households' costs may depend on the treatment services available in the community.

In circumstances where caregivers and their children are referred from one healthcare provider to another, caregivers often experience additional treatment seeking factors to consider when deciding whether to comply with referral advice. The availability of transport, cultural beliefs about illnesses and household costs are important factors to consider however, these factors may become more exacerbated when care seeking is lengthened or changed due to referral. For example, one study found that captured caregivers' direct and opportunity costs after a CHW referral found higher direct and opportunity costs of complying with referral advice compared with caregivers not complying with referral advice. However, it was not reported whether the costs played a role in whether caregivers complied to referral advice (Nanyonjo, Bagorogoza, *et al.*, 2015). Further research is needed to capture the treatment seeking costs along the continuum of care, from the initial visit to a CHW to caregivers requiring additional management, it presents an additional financial burden to households with limited finances to continue treatment seeking for essential case management.

Also, new factors may emerge, such as perceived quality of health services from referral health workers and the personal and social familiarity of different healthcare work that caregivers might not be accustomed to. These factors make compliance to referral advice complex and often challenging, which may result in treatment seeking delays. For example, studies in Guatemala and India found different factors associated with caregiver's compliance to referral advice from villages to hospitals. In Guatemala, severity of disease, duration of illnesses and absence from work were the key considerations when deciding to comply with the referral, whilst household costs, caregiver's education, age and gender were not associated with the referral (Weller, Ruebush II and Klein, 1997). In contrast in India, a gender bias was an important factor compared to others investigated in the study, caregivers were more likely to comply with the referral if they had sons when compared to daughters (Ganatra and Hirve, 1994).

Greater understanding of caregivers' treatment-seeking behaviours is important as they are related to the health outcome of children. Failure to recognise symptoms promptly and seek timely care are likely to undermine the effectiveness of clinically efficacious treatments and continue to contribute to greater child disability and mortality; approximately 70% to 85% of child deaths can be attributed to delayed treatment seeking in LMIC (Terra De Souza *et al.*, 2000; Hill *et al.*, 2003). The importance of care-seeking and the challenges of changing behaviours to promptly seek care have been noted since the early 1990s and more recently documented as part of evaluations of IMCI and iCCM programmes (Mwenesi, Harpham and Snow, 1995; Smith Paintain *et al.*, 2014).

However, there also remains a lack of clear interventions and recommendations that illustrate how care can be sought promptly to ensure access to life-saving interventions (Hill, Kirkwood and Edmond, 2004; Geldsetzer *et al.*, 2014). An example of poor utilisation of care despite the presence of appropriately trained and well-equipped health providers are CHWs. The low utilisation of CHWs is particularly concerning, the efficacy of CHWs in following clinical guidelines has been demonstrated in trials, but caregivers fail to seek care when CHW programmes are scaled-up nationally and the reasons for poor utilisation have not been investigated thoroughly. CHWs in recent years have become a cornerstone strategy for improving under-5 child survival and advocated for by influential global health actors such as UNICEF, WHO and Save the Children with substantial financial support. However, the current evidence suggests the utilisation of CHWs is less than expected and the causes of poor utilisation are not thoroughly understood.

Health systems

The role of CHWs in primary health care services for the management of malaria and related childhood illnesses have evolved substantially since WHO's Alma-Ata declaration on primary health care (Haines, Horton and Bhutta, 2007; Tulenko *et al.*, 2013). Leading global health actors such as WHO, UNICEF and Save the Children have underscored the interest in CHW programmes to increase the availability of primary health care services and tackle the acute shortage of health workers in some low and middle-income countries (Young *et al.*, 2012, 2014). For example, the lack of nurses and physicians is highlighted in Uganda with 1 per 1000 persons in 2010. These insufficient human resources for health are worsened by the geographic availability of health workers, with only 30% of physicians working in rural areas where 82% of the country's population reside (Ministry of Health, 2007; The World Bank, 2010). As well as Uganda, many other SSA countries are implementing CHW programmes at national scale to address the human resources problems and health actors have begun to acknowledge the beneficial health contributions of CHWs and begun formally accounting for them in health systems (WHO, 2015b).

Many health systems in SSA were inherited from the British, French and Spanish colonial administrations in the 1920s, where clinics, dispensaries and health centres were established in rural areas to deliver healthcare services where they were supported by larger central hospitals (King, 1966). These early african health systems were essentially imported from relatively wealthier European nations where the health systems had evolved after the social and economic upheavals during the 20th Century such as World War I and World War II.

Hospital and health centre based care remained the accepted model of delivering healthcare, where clinics and health centres provided local services for uncomplicated illnesses and referred more complex ones to central hospitals that had greater medical specialties and technologies (Bynum and Porter, 1993). This pyramidal system of care was the accepted model of healthcare delivery until the political and social aspects of healthcare were recognised and after many SSA countries attained independence from European powers, primary health care emerged partly in reaction to established centralised colonial health systems. The role of communities, community participation and CHWs were key features of the primary health care strategy that were articulated in the Alma Ata declaration in 1978 (Beard and Redmond, 1979). The declaration emphasised self-reliance and community ideals and values that resonated strongly with the newly independent, post-colonial African nations. During this time WHO also defined the role of hospitals as a back-up for the primary health care strategy with collaboration and coordination between different levels of hospitals and health centres in the form of referral care at higher levels and follow-up care in lower level health centres (WHO, 1987).

Despite the promise of CHWs many programmes failed to deliver 'health for all' partly due to a lack of donor support, but also due to poor community linkages with hospital care and a lack of implementation research in different country settings (Ebrahim, 1993). New global health initiatives were required to deliver primary health care, this included the Bamako Initiative in 1987, that delivered an integrated minimum healthcare package, including access to essential drugs through district hospitals (Kanji, 1989). This approach was financed through user fees and funds that were co-managed by communities and district hospitals that were decentralised from central government control. This decentralised approach to healthcare was supported and advocated by the World Bank with the additional emphasis of efficient allocation of resources at different levels of the health system to ensure limited medical resources were utilised in a cost-effective manner (The World Bank, 1993). It was also envisaged that the referral processes would strengthen the co-ordination and effectiveness of the health system at district level, through establishing a network of dialogues between different providers that exchanged information about referred patients as well as medical knowledge and skills. This would help to ensure patients continuum of care through the referral process, ultimately achieving patient satisfaction and beneficial health outcomes (The World Bank, 1993).

A simple referral process could involve a referral from a CHW to a health centre, and a caregiver would be expected to engage with this process and seek care from each of these health providers. Whilst this may appear relatively simple from the perspective of the health providers, a caregiver may face difficulties in seeking care from each provider. The evidence for the effectiveness of the district level organisation of health systems in LMIC countries is lacking, particularly for the care seeking practices of caregivers who are referred and are asked to seek care from one or more different health providers. The limited evidence highlights deficiencies in the performance of district level pyramidal health system, findings from Ethiopia, Namibia, Nigeria and Zimbabwe, suggest between (48% to 93%) of patients sought care directly from a hospital and bypassed primary health care centres (Sanders *et* *al.*, 1998; Low *et al.*, 2001; Akande, 2004; Abrahim *et al.*, 2015). Additionally, the authors of a Zimbabwe study found it was six times more expensive to manage patients at hospitals, when the medical resources were available for patients to be managed at lower level district hospitals (Sanders *et al.*, 1998).

To identify and address weaknesses experienced within the referral process a broader health systems perspective could be undertaken to monitor and evaluate the referral processes within health systems, involving key actors such as CHWs, caregivers, health workers within a primary health care setting. In addition, a key feature of CHWs since 1978 is the evolution of their roles and responsibilities, from relatively simple mass drug administration programmes the 1980s and 1990s, to more medically technical roles as part of community case management of common childhood illnesses in the 2000s. These more recent technical roles such as iCCM have required more extensive monitoring and evaluation of CHWs (Hamer *et al.*, 2012). In addition to the increased technical role, many SSA countries CHW programmes have reached national scale, which has required the management of programmes (co-ordination, retention, remuneration, performance, training and supervision) to be viewed through the lens of a health systems perspective.

WHO's definition for a health system include all the activities that aim to "*promote, restore or maintain health*" (WHO, 2000). To achieve this aim, WHO's health systems framework uses a "building blocks" approach to define a set of interconnected qualities of a health system, two key building blocks are; health services that deliver effective, safe, health interventions to populations in need and a health workforce that is fair, efficient and responsive to a populations requirements (WHO, 2007). CHWs and CHW programmes have typically been considered as a separate health workforce to address the shortage of health workers in rural communities and deliver targeted health interventions in primary health care settings. Whilst considering CHWs distinct from health systems may be important, a narrow view may limit the wider considerations of CHWs serving the needs of their community. These include relations and interactions with other community actors such as political organisations and religious based organisations and importantly the interactions with the formal health system that house medically certified personnel. A key moment of CHWs interaction with the formal health system occurs when CHWs encounter children with complex medical illnesses that are beyond their limited training to manage which require referral to higher level centres with health workers with more clinical experience and training. There have been longstanding concerns since the 1980s regarding CHWs referral of caregivers to higher level health centres with early studies suggesting CHWs were unable to identify the signs and symptoms in children that required referral and caregivers were unable to comply with referral advice, due to poor conditions of road and a lack of public transport, particularly during the rainy season (Berman, Gwatkin and Burger, 1987; Font *et al.*, 2002; Peterson *et al.*, 2004). In addition, many health centres were not equipped to manage referred cases and the quality of care is below caregivers expectations. (Muriel, 1984; English *et al.*, 2004).

A broader perspective would help improve the continuum of care from the community to the health centre for referrals and strengthen at least two of WHOs health system building blocks, first, the delivery of health interventions to populations in need and second, a well-performing workforce to achieve optimal health outcomes. This strengthening would subsequently improve the functioning of a health system that aims to "*promote, restore or maintain health*" (WHO, 2007).

CHW referral system

A key component of primary health care, community-based programmes and health systems is a well-functioning referral system, that allows patients to be managed at hospitals or formal health centres with specialist health workers and medical technologies (Don and Adam, 2009). Referral can be defined as a process in which CHWs at the lowest level of the health system, seek the assistance of healthcare providers who are specially trained and properly equipped to take over the responsibility for the management of the patient's clinical condition (Newbrander *et al.*, 2012).

A community-based referral process can be conceived of having three key components in order to function well (Figure 1.0); first CHWs should be trained to identify both patients that require referral and those who do not need referral and make an appropriate referral; second, when patients are referred, they should comply with the referral advice and visit health centres; third, health centres should be equipped and prepared to receive referred patients and treat them promptly and appropriately (Newbrander *et al.*, 2012). A patient's health and well-being could be at risk should one or more of these components be substandard.

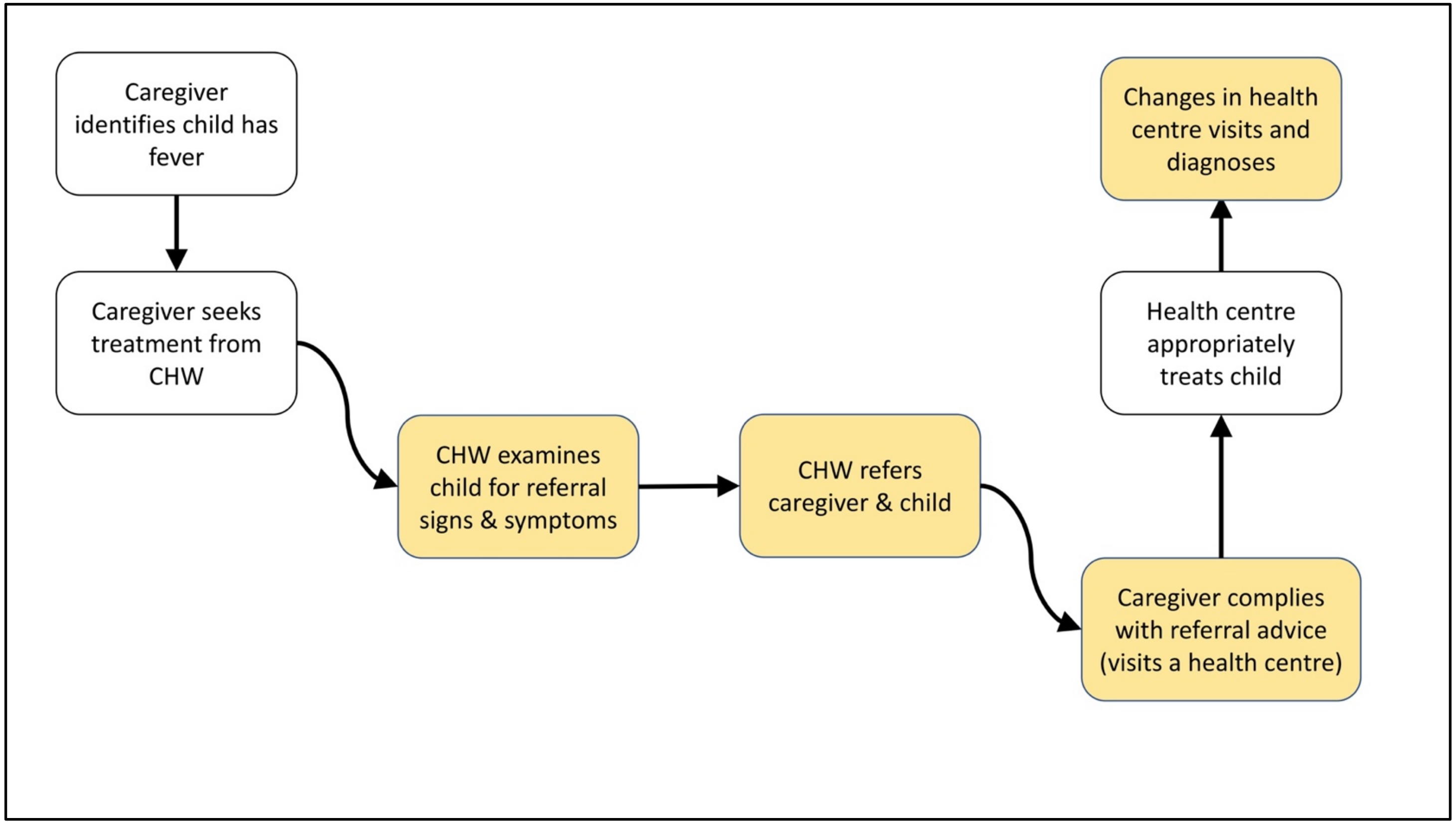

Figure 1.0 Components of a community-based referral process and impact on health centres.
Yellow filled components indicate topics explored in this thesis

CHW's ability to identify signs for referral and refer has been examined in single case management programmes as well as iCCM programmes. In Ghana, Chinbuah et al, undertook a review of CHWs' registers to identify which children reported signs for referral and children who were subsequently referred as part of home management of malaria programme (Chinbuah *et al.*, 2006). The authors found CHWs identified 17 children with signs for referral (very high temperature or persistent vomiting) but failed to refer 12 of these children (71%) to the nearest health centre. The team concluded that this poor adherence to referral advice might be due CHWs, preferring to follow-up and reassess children later and give referral advice during their follow-up visit. They also considered CHWs may have been reluctant to refer due to their belief that caregivers were unlikely to comply with referral due to the costs involved (Chinbuah *et al.*, 2006).

In community programmes where CHWs are trained to manage multiple childhood illnesses there is some evidence to suggest CHWs are reporting poorer adherence to referral guidelines compared to CHWs managing a single illness. In a later study by Chinbuah et al, the authors expanded CHWs training to include the management of suspected pneumonia with cotrimoxazole alongside the treatment of malaria with artesunate and amodiaquine (AAQ) (Chinbuah *et al.*, 2013). After a review of CHWs' registers they found CHWs reported 1758 visits with at least one referral sign failed to refer 89% of these. Compliance to referral guidelines for dangers signs was also poor, approximately 85% of episodes with at least one danger sign were not referred. Interestingly, the authors also found CHWs had a lower odds of adhering to the referral guidelines when CHWs were trained to treat malaria and pneumonia compared to CHWs who treated CHWs alone

(Chinbuah *et al.*, 2013). In a community case management study of malaria, pneumonia and diarrhoea in Malawi, CHW's performance was assessed using direct observations by clinicians. The authors found CHWs failed to refer up to 77% of cases with danger signs (Cardemil *et al.*, 2012). In Ethiopia a study also evaluating CHW's performance by re-examination of ill children with clinicians found CHWs failed to refer 66% of children classified as having at least one severe illness by a clinician (Miller *et al.*, 2014).

These studies suggest that further training and supervision of CHWs may be needed to ensure they are able to recognise signs that require referral and provide referral advice to caregivers, particularly with increasingly complex treatment algorithms. Training programmes of CHWs in these studies last between 3 and 7 days which may not be sufficient for CHWs to gain the required skills and experience to identify children who present will severe signs. CHW training materials could also emphasise the importance of referral and the potential poor outcomes if referral advice is not provided to caregivers. CHWs may also be discouraged to refer due to the additional treatment seeking costs involved with referral and may believe that caregivers are unlikely to comply with referral advice.

CHW referral rates and caregiver's compliance to referral advice have been discussed in the literature with reference to referrals from lower-level health centres and tertiary facilities such as hospitals (Font *et al.*, 2002; Bossyns *et al.*, 2006). In contrast, fewer studies have explored caregiver's compliance to CHW's referral advice as part of community-based programmes. In Western Uganda, a study during the HBMF programme found CHWs referred 8% (117/1454) of children to a health centre and a household survey of referred caregivers found 87% (67/77) complied with referral advice (Kallander *et al.*, 2006). Those with severe febrile illnesses were more likely to access care within 24 hours compared with non-urgent febrile referrals (69% vs. 39%). The main reasons for non-compliance were lack of money to seek further treatment and often the condition of the referred child improved. Poor compliance to CHW's referral advice was also found in a study in Mali, 42% of referrals actually attended a health centre and CHWs only recorded referrals when they knew the caregiver was likely to comply (Winch *et al.*, 2003). Those less likely to comply were excluded from the denominator thereby overestimating the proportion completing referral according to the CHW records. A key finding was that caregivers had a much higher odds of completing a referral from clusters where CHWs received extra IMCI training compared to CHWs without extra IMCI training (odds ratio (OR) 7.1, 95%CI 2.6-19.4)(Winch *et al.*, 2003).

With the introduction of mRDTs in community settings, a few studies have evaluated their effects on referral patterns when CHWs have been trained to use mRDTs. Research in Tanzania and Sierra Leone revealed overall referral rates of 12% and 15%, respectively, and mRDT negative children were more often referred than mRDT positive children (Mubi *et al.*, 2011; Thomson *et al.*, 2011). In Tanzania, referral was higher when CHWs used mRDTs compared to a presumptive diagnosis (OR 9.2, 95%CI: 5.8-14.5). The authors found that CHWs understood negative results could indicate other causes of diseases (abdominal pain, headaches, diarrhoea and breathing difficulties) and were likely to refer these (Mubi *et al.*, 2011) Caregiver's referral compliance was documented in Sierra Leone and this study found only 2% complied. mRDT positive patients with signs of severe malaria complied more often than mRDT negative patients (88% vs. 1%), and most complied within referral within 24 hours (Thomson *et al.*, 2011). This study combined both children under-5 and pregnant women who may have had different rates of compliance to referral. Also, the visits were to an NGO managed health centre where the quality of care may have been different to a government run health centre. Thus, the compliance results may not be fully generalizable to children under-5 or health systems where government run health centres are the main point of referral. This study was also conducted over a short 3-month period of data collection, and a retrospective study design was used which may have been subject to bias by changes in disease patterns in the environment.

CHW's ability to identify children with referral signs and refer are an important component of iCCM, it helps to ensure children who cannot be safely managed in the community are managed at health facilities. Two iCCM evaluation studies have examined caregiver's compliance to CHW's referral advice in Western Uganda, authors *Nanyonjo et al* and *English et al*, found 46% and 30% of caregivers complied with referral and visited a health centre, respectively(Nanyonjo, Bagorogoza, *et al.*, 2015; English *et al.*, 2016). The poor compliance in one study may partly be explained by the temporary resolution of symptoms in children who received rectal artesunate and caregivers interpreting this as a cure, thus deciding not to seek further care (Nanyonjo, Bagorogoza, *et al.*, 2015).

The current evidence on community referral is poor. Studies have small samples, mixed study age groups and have been carried out over a short time period in different transmission seasons. Many knowledge gaps for referred children still remain with the community rollout of ACTs and RDTs. The case management of those with positive mRDT results and with a non-febrile illness are not adequately documented. This thesis will seek to evaluate presenting disease patterns at health centres and reasons for referral. Key outcomes will include compliance and delay to referral uptake. Previous studies did not examine the predictors of referral uptake which will also be explored. Another area for further research is the capability of CHW to understand the severity of symptoms requiring referral; deficiencies in their ability to detect signs may miss children requiring referral.

CHW impact on health centres

Malaria poses a significant burden on existing health systems in SSA, accounting for an average 30% of all outpatient visits and between 20% and 50% of all hospital admissions (WHO, 2003a, 2006). High case fatality rates are often the result of late presentation, inadequate management and misdiagnoses. Community programs such as HBMF have the potential to reduce health centre caseloads by offering case management services close to patient's homes. This may release constrained health worker time to be spent on other work tasks, including longer contact time with patients, which has been shown to improve their treatment practices (Rowe *et al.*, 2000; Zurovac *et al.*, 2004). Despite the recent scale up of programmes, there are relatively few published studies documenting changes on health centre caseload and case-mix, and where there is available evidence, it presents mixed findings.

A review of the evidence so far, suggests a decline in the number of visits at health centres after community-based programmes have been implemented. Declines have been reported in Burkina Faso (83%), Rwanda (48%) and Southern Tigray, Ethiopia (46%) where CHWs also used mRDTs (Sievers *et al.*, 2008; Tiono *et al.*, 2008; Lemma *et al.*, 2010). In contrast, a 63% increase in visits was observed in Ethiopia over a 7 year period; the earliest study documenting changes in caseload (Ghebreyesus *et al.*, 2000). Although there was an increase in the number of outpatient department (OPD) visits, there was substantial variation across the 7 years. Shortly after the introduction of the community programme in 1992, there was an approximate halving (44%) until 1994, after which trends gradually reversed and reached a peak increase of 57% in 1997, compared with visits reported in 1992. These changing trends were due to additional ongoing malaria control programmes and other secular trends. Indoor residual spraying (IRS) was implemented alongside the community programme and the construction of dams and irrigation systems increased malaria transmission. There was also increased CQ resistance beginning in 1994 which contributed to treatment failures as part of the community programmes and also more visits to health centres. The authors of a study in Rwanda reported a 48% reduction in the number visits to a paediatric hospital, following the implementation of a community-based control programme. There was also a proportional rise in admissions of children over-5, which may have been due to the increased coverage of ITNs in children under-5 compared with children over-5. Whilst these are considerable reductions, the changes in utilisation could not directly be ascribed to the community programme, because ITNs were distributed to children under-5 in the year between the baseline and end-line surveys, which would have protected children under-5 from malaria (Sievers *et al.*, 2008). Due to these uncontrollable changes occurring throughout both studies in Ethiopia and Rwanda, the effects of a community-based programme on malaria admissions and OPD attendance were not clearly estimated. Interestingly, both these studies documented increases in non-malarial illnesses. In Ethiopia, non-malaria cases accounted for 86% and 96% in 1992 and 1994 respectively, whilst in Rwanda, a larger difference was found with non-malaria cases accounting for 11% and 35% of total admissions, pre and post intervention, respectively (Ghebreyesus *et al.*, 2000; Sievers *et al.*, 2008).

One method to account for these background changes over time is to compare parallel control groups with the intervention groups. The use of this design allows investigators to control allocation of an intervention and compare effects with those lacking the intervention, whilst ensuring both groups are comparable in all aspects other than the intervention. This provides stronger evidence that the observed effect is due to the intervention compared with observational study designs. The two studies in Burkina Faso and Southern Tigray had contemporary control groups and found reductions in malaria outpatient visits of 83% and 46% respectively, when the implementation of community-based programme was compared to standard health centre care (Tiono *et al.*, 2008; Lemma *et al.*, 2010). However, the intervention was not randomised in either study and there were differences in the control sites other than the intervention which may have affected OPD visits. In Southern Tigray, greater proportions of the control group lived at higher altitudes and geographically further (≥5KM) from the nearest health centre compared with the intervention group (Lemma *et al.*, 2010). These differences are likely to affect caseload reduction at health centres in a number of ways. First, those living at higher altitudes are at greater risk of severe malaria due to poor immunity to malaria, thus those presenting at centre are more likely to be correctly diagnosed as having malaria due to overt signs and symptoms (Reyburn *et al.*, 2004). Second, those living further away from a health centre are less likely to visit, and last, the authors reported that malaria control activities were carried out in the control group which may also reduce the number of visits at health centres. In contrast to these well documented study characteristics, the study in Burkina Faso reported on relatively few characteristics in each arm (Tiono *et al.*, 2008). Unmeasured confounding factors could affect the risk of health centre attendance. These include the location of communities from health centres, household wealth and the malaria risk in each arm. A common limitation amongst these studies is the method of malaria diagnosis, unless suspected malaria cases are parasitologically confirmed at health centres, the number of visits for malaria may be overestimated. In Southern Tigray, health centres used a mixture of clinical diagnosis based on the signs and symptoms of malaria, microscopy or mRDTs and it was not recorded which health centre had the capacity for a particular method of malaria confirmation (Ghebreyesus *et al.*, 2000). Whilst in Burkina Faso clinical signs of a hot body were used for malaria diagnoses at health centres (Tiono *et al.*, 2008). A clinical diagnosis based on signs and symptoms is less sensitive and less specific than microscopically confirmed malaria which would overestimate true malaria cases at health centres and underestimate reductions after the introduction of community-based programmes (D'Acremont *et al.*, 2009). A signs and symptoms method would also underestimate any changes in case-mix for non-malaria illnesses. In Rwanda the case definition of malaria excluded children who were blood slide positive but had an alternative febrile illness, which also underestimates true malaria admissions and overestimates the caseloads in suspected malaria admissions (Sievers *et al.*, 2008). Given these variations in diagnostic methods and case definitions, the effect of community-based programmes on health centre caseload and case-mix is not accurately known. At the community level most CHWs were trained on the signs and symptoms of malaria, however in Southern Tigray, half (16/32) the CHWs switched to RDT based diagnosis after one year of presumptive diagnosis. The effect of this dual community strategy on health centre caseload and case-mix was not reported. Given that this has not been evaluated in previous studies, this thesis will explore the effects of community-based strategies on case-mix and caseload at health centres.

The impact of CHW programmes on caseload and case-mix was also measured at different levels of the health system in each study. In Burkina Faso changes were captured at first level health centres (Tiono *et al.*, 2008). Both studies in Ethiopia captured data from hospitals, health centres, health stations and health posts (Ghebreyesus *et al.*, 2000; Lemma *et al.*, 2010). The capacity of services and their catchment population were not apparent from these studies nor was it possible to assess changes in caseload at each level due to the aggregation of caseload data from providers. The Rwandan study collected data from one hospital and the effects at peripheral health centres were not captured (Sievers *et al.*, 2008). Therefore, the variation in attendance at various levels has not been accounted for or documented. Such data limits the generalisations and conclusions that can be made on impacts of CHW programmes on health centres and their impacts on caseload may vary between outpatients and admissions.

In malaria endemic countries, febrile illnesses presenting at health centres are often treated as malaria. This can result in further complications for patients with other aetiologies of fever. As well as influencing caseload, the implementation of community-based programmes may have potential impacts on patient management in health centres. For example, if more malaria cases are treated in the community the majority of febrile patients attending a health centre may have some other cause of fever. Should overdiagnosis of malaria continue in light of this change in case-mix, patients may be misdiagnosed and inappropriately treated. In addition, community programmes often incorporate a referral process for the continued care of severe patients, beyond the capabilities of CHW. Additional training at health centres might be required to ensure appropriate diagnosis and treatment of other non-malarial diseases and to ensure health workers have the capacity to treat severe illnesses. In the broader context of planning health care, fewer uncomplicated malaria cases observed at HFs would reduce the demand for antimalarials but increase the demand for drugs to treat the rise in other illnesses, having implications for stock management. Also given the reductions in their caseloads, health workers would have additional time available to spend on other tasks or more time consulting per patient.

Theoretical framework

Many influential global health actors have advocated SSA countries to adopt and expand community-based health care programmes. This is partly driven by the understanding that caregivers with sick children will be able to access appropriate and acceptable health care, promptly from providers in their community compared to providers in health facilities. Health care access can be defined as the ease of opportunity with which individuals or communities are able to utilise appropriate services according to their needs (Daniels, 1982; Whitehead, 1991). However, access to health care is a complex construct with limited international standardisation and the challenges in ascribing a common understanding may partly be due to how access is conceived both from the perspective of individuals seeking care and the individuals involved in delivering care. Various authors have operationalised this definition of health care access with different frameworks to analyse and evaluate programmes, that aim to improve health care access.

Health seeking frameworks attempt to explain the process of seeking care, the means by which it is sought and when it is sought. Studies on accessing healthcare are typically dominated by two different approaches to understanding the process. The first focuses on the steps of therapeutic actions taken by individuals in the utilisation of the formal health system, in response to perceived ill health, often referred to health seeking behaviours (Ahmed *et al.*, 2000). The second approach considers health care seeking behaviours, these can be understood in terms of an individual's perception of their social environment, which may include a mixture of social, economic, demographic, emotional, personality and cognitive factors, as well as their perceived symptoms (Mackian, Bedri and Lovel, 2004).

Two common models used to explain the first approach, health seeking behaviours, are known as the Health Belief Model and the Theory of Reasoned Action. The Health Belief Model was developed to explain which behaviours could be targeted to cause positive health behaviours. It explains that an individuals' behaviours are more likely if they; a) perceive a negative health outcome to be severe, b) that they perceive themselves to be susceptible to the outcome, c) that there are good benefits to taking up behaviours that mitigate the risk of the outcome and d) the are limited barriers to adopting new behaviours (Rosenstock, 1966). It has been used in to increase the uptake screening for TB, immunisation and adherence to drug regimens. However, critics argue that the Health Belief Model is poorly explained and the available evidence suggests it has weak power to predict behaviours in most areas of health (Armitage and Conner, 2000).

The Theory of Reasoned Action attempts to explains behaviours by an individual's intention to perform a behaviour. This intention is product of an individual's attitude towards the behaviour, the social pressure around the behaviour and their readiness to perform the behaviour (Ajzen and Fishbein, 1975). This has been widely used in sexual health and AIDs related research however weaknesses of this model to explain behaviour, relate to focusing on the individual's intentions. It also does not consider the interpersonal and social relations of individuals in which they act nor the broader social structures that may influence behaviours (Kippax and Crawford, 1993).

In contrast to the models that explain health seeking behaviours, the three delays model has been suggested as model to explain health care seeking behaviours. This model has been used in reproductive health research as a model for identifying the factors that affect the time taken to receive appropriate care. It argues there are three main factors which can delay access to care, the first relates to the delays in deciding to seek care, delay in reaching a health centre and lastly delays in receiving adequate care (Thaddeus and Maine, 1994). However, health care seeking behaviour is an on-going inherited process driven by personal, cultural, societal and structural factors. A broader framework ought to consider the individuals perception of illness and their interaction with the formal health system.

Obrist and colleagues conceptualise access to health care through livelihood insecurity in low-income countries and consider access from three different perspectives (Obrist *et al.*, 2007). The first describes the influence that structures such as institutions, policies, organisations have on the delivery of health care through health providers. For example, these could include the national health strategic plans for resource allocation or national treatment guidelines. These structures directly affect the access of services available from health service providers. The second perspective considers the availability of health services from providers, and it includes studying factors to improve services, including availability of health facilities, equipment, qualified staff, protocols of diagnosis, treatment, and quality of care. The last access perspective considers individuals seeking care from health providers. Individuals need to be able to recognise and understand the signs that require treatment seeking from health services. Evaluations from this perspective often seek to increase treatment seeking from individuals through information, education and behaviour change interventions. Obrist, et al also consider in depth the intersection between the last two perspectives of access, the availability of health services and the individuals that seek care, through 5 dimensions of access; availability, accessibility, affordability, adequacy, and acceptability. The availability dimension refers to the understanding the types of health services available, whether there are sufficient skilled personnel and whether the services cater to individuals' needs. Accessibility is defined as the geographic location of health services and their proximity to individuals seeking care. This definition of accessibility also describes the transport means available and the time taken to reach a health care provider. The third dimension of affordability pertains to both the cost of health services and the individual's ability to pay in terms of direct and indirect costs. The adequacy dimension relates to how the health care services are organised, such as the types of services available at health centres the opening days and hours. The last and fifth dimension, acceptability relates to whether the health services are culturally appropriate for the individuals seeking care. For example, the health advice and treatment should be given in a format which takes into consideration local illness concepts and social values, other aspects of acceptability could include whether the individuals feel respected and welcome and whether individuals trust the competency of the providers (Obrist *et al.*, 2007).

The framework proposed by Obrist *et al* offers a more comprehensive and inclusive approach to investigate health care access. It was also developed in view of the social, economic and public health circumstances that may be evident in SSA contexts. Therefore, this thesis will apply the framework proposed by Obrist et al to examine the referral process in a CHW setting. This framework may limit the other possible perspectives of care, such as treatment seeking from traditional healers, drug shops, private providers or faith healers. However, focusing on the interaction of caregivers with CHWs and health facilities will allow the results and analyses to provide recommendations for existing community programmes with referral systems. In addition, other health care access frameworks exist, they often consider health care from a single perspective, either from the health care provider to inform the improvement care or from the perspective of individuals seeking care.

The community referral process has been outlined previously and involved CHWs making referral decisions, caregiver's complying with referral decisions and health facilities receiving caregivers and their children. The thesis will attempt to evaluate the CHW programme from two different perspectives, first from the perspective of the CHWs providing referral advice and secondly from the perspective of the caregiver complying with referral advice. In addition, the thesis will seek to examine the 5 dimensions of access as framed by Obrist et al, and the extent to which they may influence access from either perspective, this has been conceptualised in Figure 1.1. In this framework once caregivers recognise the need to seek treatment, their ability to utilise CHWs and public health facilities upon receiving any referral advice from CHWs is mediated by the 5 dimensions of care. In Figure 1.1 the pathway of care that caregivers may follow in a community-based programme is indicated by the large arrow and the 5 dimension of access they might experience at each provider is indicated by the green boxes. Availability of CHWs and referred caregivers, relates to understanding whether there are sufficient CHWs trained to follow guidelines, manage malaria and refer complicated cases they were not trained to manage to the nearest health facility. Similarly, at health facilities, health workers should be trained to receive and mange referred cases from the community. The accessibility of CHWs and health facilities may also be explored through their location relative to caregivers who seek care or are referred by CHWs to public health facilities. Affordability relates to the direct costs of seeking care from both providers such as user fees or treatment charges and the indirect costs such as the opportunity costs of time spent while travelling to and waiting for CHWs or at health centres. The ability of caregivers to access CHWs and health facilities can also be mediated by the adequacy of services, such as the opening hours and working hours for caregivers. The acceptability of health providers can also be explored to understand whether CHWs and health workers are able to receive caregivers in an approachable manner and provide treatment and referral advice in a culturally sensitive format. The framework presented in this thesis will allow a structured analysis of the different dimensions of access from both CHWs and public health facilities. This will aim to identify key barriers to access and provide recommendations for access.

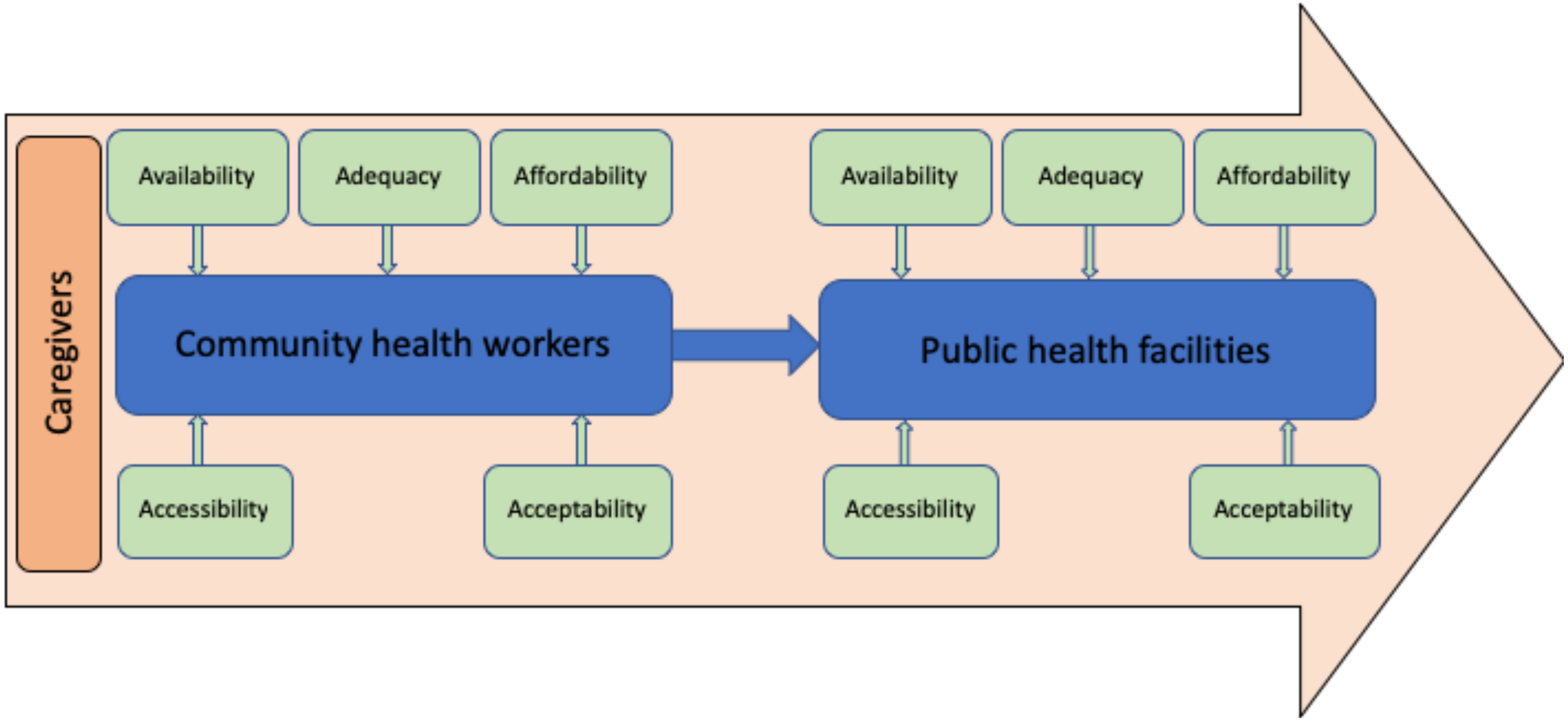

Figure 1.1. Theoretical framework to explore referral access in community-based programmes
Caregivers envisaged treatment seeking pathway within a programme is indicated in orange and the 5 access barriers they may encounter are shaded in green for each type of provider.

Thesis aim and objectives

Overall aim

This thesis aims to examine the effects of introducing a community case management programme with mRDTs on the public health system in Uganda.

Objective 1

To investigate the CHWs adherence to the referral guidelines and explore the factors related to adherence when CHWs were trained to use mRDTs and prescribe ACTs (Chapter 3).

Objective 2

To examine the effect of mRDTs on referrals made by CHWs and explore the factors associated with referral when CHWs diagnosed based on just clinical symptoms (presumptive) or on mRDT-results (Chapter 4).

Objective 3

To investigate caregivers compliance to CHWs referral advice and describe the barriers to referral compliance (Chapter 5).

Objective 4

To examine the effects of introducing a CHW programme for appropriate management of malaria on health centre utilisation by children under-5 (Chapter 6).

Chapter 2: Research Context

This thesis explores each of the referral objectives as caregivers and their children encounter CHWs, become referred and seek treatment as part of a case management trial in South western Uganda. Investigating the referral process requires a broader understanding of the context within which CHWs were operating, this includes the health system within which CHWs are expected to refer, the case management guidelines for malaria and the epidemiology of malaria and other common childhood illnesses. Each of these components are may influence caregivers treatment seeking and CHWs capacity to refer.

The Ugandan health system

In 1981 Uganda began a process of decentralising all political and administrative power and authority from central government to locally elected government authorities. This process was completed in 1997 with the ratification of the Local Governments Act of 1997 (Uganda Legal Information Institute, 1997). Thus, the role of the central government became focused towards planning, policy development and monitoring. The delivery of health services followed a similar process and is currently co-ordinated at the district level, whilst the role of the Ministry of Health is to set national guidelines and budgets, health policies and ensure quality and standards (Ministry of Health, 2007).

Public healthcare is delivered through different levels of health facilities; National Referral Hospitals and Regional Referral Hospitals, General Hospitals and Health Centres (HCs)

HCIVs, HCIIIs, HCIIs, and HCIs. Health Centre I are village health teams (VHTs) that are typically 5 to 7 lay persons elected by the community to operate as community health workers (Table 2.0) (Ministry of Health, 2014). VHTs promote healthcare and mobilise communities for health campaigns such as immunisation, sanitation and bed net distributions. They also serve as the first link between the communities and professional healthcare providers at HCIIs and HCIIIs. The HCIIs are primary rural health posts typically staffed with an enrolled nurse, a midwife and a nursing assistant and only provide outpatient services, including treatment of common illnesses, immunisation and referrals to higher health facilities. HCIIIs provide both inpatient and outpatient care and have laboratory diagnostic services, they also supervise HCIIs within their catchment area and offer the first referral cover for a sub-county. HCIVs serve large health sub-districts with approximately 100,000 people and offer inpatient outpatient services alongside delivery care and minor surgeries. Hospitals offer a wide range of inpatient, outpatient and laboratories and services. They serve as the referral units in the districts. National Referral hospitals and regional hospitals provide comprehensive specialist services and offer medical educational programmes also engage in research activities (Ministry of Health, 2014).

Table 2.0: Structure of the national health service of Uganda

Health facility level	Health service provision	Location	Catchment population
Health Centre I (VHTs)	Health promotion, community mobilisation and participation.	Village	500
Health Centre II	Community outreach, outpatient	Parish	5,000
Health Centre III	Outpatient, maternity, general ward and laboratory	Sub-county	25,000
Health Centre IV	Outpatient, inpatient, maternity, general ward and laboratory, surgical theatre	County	100,000
District Hospital	All as above and radiology services	District	100,000 – 1,000,000
Regional Hospital	All services, specialised care, research and medical education.	Regional	5,000,000
National Referral Hospital	Comprehensive specialised care, research and teaching	National	35,000,000

Malaria case management guidelines

The malaria diagnosis and treatment guidelines in Uganda have changed substantially due to the emergence of drug resistance and due to developments of diagnostic testing. Until 2000, chloroquine (CQ) was the first-line treatment for uncomplicated malaria, however by this time treatment failures had reached an average of 33% amongst under-5 (Talisuna *et al.*, 2014). This led to the first treatment change from CQ to a combination of CQ-SP as the first line treatment for uncomplicated malaria. The policy was implemented in 2002 after new training materials had been developed and health staff had been trained on the new guidelines. CQ-SP was used at all levels of the health system including the CHWs as part of HBMF programme and at primary health centres (HCIIs, HCIIIs), whilst quinine was the treatment for severe malaria and for cases resistant to CQ at health centres. At the time CQ-SP was implemented it had a treatment failure rate of 7%, but shortly after its widespread use treatment failures reached an average of 16% (Talisuna *et al.*, 2004). In response Uganda changed its treatment guidelines a second time to the ACT, AL in 2004 due to a good safety profile and the long-life expectancy of the drug. However, there were delays in obtaining funding for the procurement of AL and developing training materials. The revised policy was eventually implemented in all health facilities by the end of 2006 (Nanyunja *et al.*, 2011).

In 2008 Uganda adopted a parasite-based malaria diagnosis policy, where the National Malaria Control Programme (NMCP) recommended that a parasitological malaria diagnosis should be made either by testing blood using a light microscope where laboratory facilities existed or by using mRDTs at primary health facilities (HCII and HCIIs), between 2009 and 2010 21 districts had implemented mRDTs (Altaras, Streat and Nuwa, 2014; Talisuna *et al.*, 2014). Towards the end of 2010, the use of mRDTs by CHWs was launched under an iCCM strategy in mid-western and central Uganda (Nanyonjo *et al.*, 2012).

Later in April 2010, the WHO Global Malaria Programme also advocated for universal testing of all suspected cases of malaria, before receiving anti-malarial treatment. They also recommended that patients with severe malaria should be given a single dose of rectal artesunate as pre-referral treatment in situations where parenteral administration is not feasible (WHO, 2010). The rationale for this change was largely due to the imprecise method of using a presumptive clinical signs and symptoms to diagnose malaria. Parasitological confirmation of suspected malaria cases would ensure only those with confirmed malaria received an ACT and those without malaria would receive the correct treatment for their non-malarial illness. This rational algorithmic approach also reduces unnecessary expenditure on ACTs for non-malarial cases and delays the onset of resistance to ACTs (Wongsrichanalai *et al.*, 2007).

Epidemiology of malaria in Uganda

Uganda experiences year-round (perennial) malaria transmission with relatively little seasonal variability in most areas, due to a stable temperature and rainfall pattern. Subsequently malaria is endemic in approximately 95% of the country and nearly 33 million, or 90% of the population is at risk (PMI, 2017). The remaining 5% of the country consists of unstable and epidemic prone malaria transmission in the highland mountainous areas of south-west and the east along the border with Kenya. The number of infective bites per person, the entomological inoculation rate (EIR), is high in many parts of the country, >100 in 70% of the country (UBOS, 2014). The prevalence of malaria mirrors these transmission patterns. The 2009 Uganda Malaria Indicator Survey (UMIS) estimated malaria prevalence between 38-63% in all regions except Kampala and in the South-Western highland region, where it ranged between 5-10% (Macro., 2010). The prevalence is also particularly high amongst children under-5 in whom it ranges between 30 to 50% and anaemia is also common with haemoglobin <11 g/dl in at least 50% of children. *P. falciparum* is responsible for 90 to 98% of diagnosed malaria cases, and the most common cause of severe malaria. In contrast, *P. vivax* and *P. ovale* are rare causing 10% of the total number of malaria cases (Macro., 2010) .

Whilst fever in children is the primary symptom of uncomplicated malaria, it is also a commonly occurring symptom for pneumonia and meningitis (Gwer, Newton and Berkley, 2007; Hildenwall *et al.*, 2016). The fever symptom overlap across both malaria and non-malarial fever illnesses (NMFIs) is challenging. In countries with limited diagnostic capacity children are commonly treated presumptively depending on the symptom presentation. For example, in malaria endemic settings, a febrile child is often diagnosed with malaria and treated with an antimalarial and a child with difficulty breathing and an increased respiratory rate is often diagnosed with pneumonia and treated accordingly. However, these symptoms are not mutually exclusive and malaria may also present with an increased respiratory rate and fever is a common presentation in children with pneumonia (O'Dempsey *et al.*, 1993). Some studies found 37 to 80% of children under-5 that met the case definition of malaria also met the pneumonia definition and approximately 93% of child cases that met the pneumonia definition also met the malaria definition (English *et al.*, 1996; Källander, Nsungwa-Sabiiti and Peterson, 2004). The introduction of mRDTs offer a parasite based method of diagnosis to discriminate malaria from pneumonia in areas with limited laboratory infrastructure for diagnosis. A randomised trial in Zambia found a much lower proportion of febrile children diagnosed with pneumonia when CHWs used mRDTs compared (intervention arm) to when they used a presumptive diagnosis (control arm). In the intervention arm 28% were classified as pneumonia whilst in the control arm 87% were classified as pneumonia (Yeboah-Antwi *et al.*, 2010).

In contrast to the abundance of epidemiological information on malaria there is relatively limited detailed epidemiological data on non-malarial fevers. This data could be particularly important to inform case-management guidelines for febrile children who present to CHWs and who may get referred. Country level epidemiological data on fever cases are often elicited through household interviews with the mothers of children under-5, where interviewers ask if a child had a fever in the two weeks preceding the interview.

The 2011 Demographic and Health Survey (DHS) of Uganda found a 40% prevalence of fever amongst children under-5, this was lowest in the Southwest region (13%) and highest in the Eastern and East Central region, 56% and 69% respectively (UBOS, 2012). However, the use of verbal confirmation of fever is unlikely to be an accurate measure of fever and may be prone to recall bias. The DHS survey was also conducted at the end of the rainy season which coincides with increases in malaria prevalence, thus a high proportion of the reported cases of fever are likely to be malaria rather than NMFIs (UBOS, 2012). A more detailed study in Kampala, Uganda found 68% of fevers were NMFIs in children aged between 1 and 10, with the most common causes of NMFI being upper respiratory tract infections (47%), common cold (29%), non-specified fever (15%), pharyngitis/tonsillitis (12%), diarrhoea (10%), skin infections/wounds (4%) and pneumonia (4%) (Njama-Meya *et al.*, 2007). In the absence of reliable data, modelling studies have estimated the relative proportion of fever cases caused by malaria and non-malaria fevers. *Dalrymple et al* found increases in the proportion NMFIs causing fevers across 43 African countries from 83% in 2006 to 90% in 2014 and in Uganda the prevalence of NMFI increased from 65% to 91% during the same period (Dalrymple *et al.*, 2017). The changing trends of malaria and NMFIs may have implications for both the case-management of febrile illnesses and the impact on health systems. The IMCI guidelines for febrile illnesses currently recommend an antibiotic if there are signs of a bacterial co-infection with malaria. This signs and symptoms approach to a co-infection may lead to a misdiagnosis and inappropriate treatment. The limited capacity of primary health facilities to manage NMFIs may cause greater referrals to tertiary health facilities which may have greater capacity to manage

NMFIs. Although the ability of caregivers to recognise the NMFI signs and symptoms that require referral is largely unknown it may influence their treatment seeking and compliance to referral advice. Lastly, the increase in cases of NMFIs at health facilities may cause changes in the resources needed to manage cases, such as appropriately trained and skilled personnel, diagnostics and antibiotics. Despite these important data on the epidemiology of NMFI, further primary data at sub-national levels are needed to assess a health systems capacity and to inform case-management guidelines.

Epidemiology of pneumonia and diarrhoea in Uganda

Acute respiratory infections (ARIs) are the most common childhood illnesses in SSA, amongst these lower respiratory infections (LRTIs) such as pneumonia are the most severe and account for a large majority of hospital attendances and admissions (Fischer Walker *et al.*, 2013). In 2011, pneumonia caused approximately 36.4 million episodes and half a million deaths in SSA amongst children under 5 (Fischer Walker *et al.*, 2013). The aetiological causes of severe pneumonia and pneumonia deaths were predominantly due to bacteria *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* (HiB). Uganda sits amongst the top 10 high burden countries with an estimated incidence of 1,750 pneumonia episodes per 1,000 child years and 21,200 deaths amongst under-5. Mortality is mainly concentrated amongst the youngest age groups with 53% of episodes occurring in children under 2 years and slightly greater in males compared to females (Fischer Walker *et al.*, 2013). The 2011 Demographic and Health Survey of Uganda found considerable regional variation in the prevalence of pneumonia ranging from 22% in the North region and 9% in the Central 1 region, in Southwest region the prevalence in 2011 was 11%. Prevalence of pneumonia was more frequent amongst children in the poorest wealth quintile (20%) compared to children in the highest quintile (12%) (UBOS, 2012). The survey estimates should be interpreted with caution because the case definition of pneumonia is defined as the mother's recall of pneumonia signs and symptoms (a cough with short, rapid breathing) in children under 5, two weeks preceding the survey. The mother's ability to identify signs and symptoms of pneumonia during an interview may be in accurate and their ability to recall illness episodes with may be subject to recall bias (Hazir *et al.*, 2013).

Alongside pneumonia, diarrhoea is a major cause of morbidity and mortality amongst under-5 , it caused an estimated 700,000 deaths in children under-5 in 2011. Uganda has a high burden of diarrhoea accounting for an estimated 12,200 deaths in 2011 and ranks 10th amongst countries with the highest number of deaths (Fischer Walker *et al.*, 2013). Uganda's demographic health survey in 2011, 23% of the under-5 population had diarrhoea whilst 4% had severe diarrhoea, and nearly 50% of cases occurred in children under 24 months. Diarrhoea prevalence was also lower amongst households with an improved, un-shared toilet compared with households without an improved toilet. Additional variation was found across the regions of Uganda, children living in the Southwest region had the lowest prevalence of diarrhoea (14%) and the Eastern region had the highest with 33% prevalence. There was no variation in diarrhoea by the child's sex or source of drinking water (UBOS, 2012).

ACT Consortium

The referral studies in this thesis were conducted with in a larger research consortium that aimed to inform the implementation of mRDTs and ACTs in SSA and Asia. It was established in early 2009 and undertook 25 studies in 10 countries.

As part of this consortium, a community-based project aimed to examine the role of CHWs in improving access to ACTs, and the feasibility and cost-effectiveness of interventions at the community-level to improve malaria diagnosis and appropriate treatment. The trial was designed in late 2009 before Uganda changed the national guidelines malaria case-management with mRDTs and ACTs in early 2010. The trial also intended to fill the gaps in the evidence at the time, where it was unclear whether the use of mRDT improves the targeting of ACTs to malaria in children in communities, especially in low malaria transmission settings.

A cluster-randomised controlled trial was designed to compare the impact of mRDTs, used by CHWs, on the proportion of children under-5 years of age receiving appropriately targeted treatment with ACT, *vs.* presumptive, signs and symptoms based management. The trial took place in two contrasting malaria transmission settings in rural Uganda to provide evidence to optimise use of ACTs and mRDTs within CHW programmes.

My role in the trial was the data manager, I was responsible for designing and implementing the data collection tools and databases. I was also responsible for monitoring data quality of the trial and the routine reporting. Later, I undertook all the primary and secondary statistical analyses of the trial and contributed to the interpretation of data and the writing of the manuscripts. My role in the main trial provided an opportunity to conceive distinct research questions and design separate studies set within the trial. These studies included investigating the referral process from the community level to health facilities as well as examining the impact of introducing a community health worker programme on the health system.

Trial design and methods

Trial setting

The trial was carried in Rukungiri District in South Western Uganda and lies at an altitude ranging from 615m and 1864m above sea level. The administrative headquarters and local council offices are based in Rukungiri Town that are approximately 400km from the capital city Kampala. The district can be categorised into three topographical zones, the highland area, characterised by hills and steep slopes and includes Nyarushanje and Nyakishenyi sub-counties; the plateau area with undulating plains that merge into Lake Edward; the Rift Valley area which can be described as having broad flat tracts of clay swamps which feature heavily in Bwambara sub-county and Queen Elizabeth National Park (Rukungiri District Local Government, 2009). The climate is characterised by a long rainy season between February and May and short rainy season between September and November each year. The annual rainfall ranges between 700m and 1200mm and daytime temperatures range from 15°C to 20°C. The district was chosen for its diverse malaria transmission patterns which is partly contributed by the wide topographical altitudinal range from 980m to 2157m above sea level.

Each of the two trials conducted as part of this study were implemented in either Bwambara (980–1200m above sea level) or Nyakishenyi sub-counties (1064–2157m above sea level) due to their contrasting malaria transmission patterns. Population projections during the conduct of the study indicated 28,900 people in Bwambara and 32,200 in Nyakishenyi. In both sub-counties more than 52% of the land is dedicate to farming and subsistence agriculture was 79% of the population's primary occupation. Approximately 16% of the population lived below the international poverty line ($1.90) and life expectancy was estimated at 50 years (Rukungiri District Local Government, 2009).

Trial design

Two, two arm cluster-randomised trials were designed to compare two alternative malaria case management strategies, the intervention arm consisted of training CHWs to use mRDTs and treat malaria with an ACT after a positive test result, whilst the control arm consisted of CHWs diagnosing and treating malaria based on a presumptive signs and symptoms approach. Villages within each sub-county were randomised to either the intervention arm or the control arm using a random number table in Epi-Info.

CHW training

In January 2010, 318 CHWs (192 and 189 in Bwambara sub-county and Nyakishenyi, respectively) attended a series of training workshops on malaria case management. These were participatory that included, presentations, role-plays and demonstrations carried out over 3-4 days. The training included topics, on how to receive caregivers and their children, how to take a clinical history, managing stocks of consumables such as ACTs, gloves, cotton wool, and mRDTs (intervention arm only). All CHWs were trained on how to receive a child with a fever or a recent history of fever, administer antimalarial treatment and when to refer. CHWs in the intervention arm received additional training on how to perform an mRDT, interpret test results and treat with an ACT after a positive test result. Members of the District Health Office, research staff and health centre staff conducted the workshops. At the end of their training, CHWs were provided with pictorial job aids for reference, bicycles, project t-shirts and certificates of training completion. A small monthly allowance (15,000 Uganda Shilling, approximately 4.50 USD) were also given to purchase paraffin and soap locally, both of which could support safe hygiene practices and help with working after sunset.

Chapter 3: Community Health Workers Adherence to Referral Guidelines

Adapted from: Sham Lal, Richard Ndyomugenyi, Lucy Paintain, Neal D. Alexander, Kristian S. Hansen, Pascal Magnussen, Daniel Chandramohan, Siân E. Clarke. 2016. "*Community Health Workers Adherence to Referral Guidelines: Evidence from Studies Introducing RDTs in Two Malaria Transmission Settings in Uganda.*" Malaria Journal.

Abstract

Background

Many malaria-endemic countries have implemented national community health worker (CHW) programmes to serve remote populations that have poor access to malaria diagnosis and treatment. Despite mounting evidence of CHWs' ability to adhere to malaria rapid diagnostic tests (RDTs) and treatment guidelines, there is limited evidence whether CHWs adhere to the referral guidelines and refer severely ill children for further management. In southwest Uganda, this study examined whether CHWs referred children according to training guidelines and described factors associated with adherence to the referral guideline.

Methods

A secondary analysis was undertaken of data collected during two cluster-randomized trials conducted between January 2010 and July 2011, one in a moderate-to-high malaria transmission setting and the other in a low malaria transmission setting. All CHWs were trained to prescribe artemisinin-based combination therapy (ACT) and recognize symptoms in children that required immediate referral to the nearest health centre. Intervention arm CHWs had additional training on how to conduct an RDT; CHWs in the control arm used a presumptive diagnosis for malaria using clinical signs and symptoms. CHW treatment registers were reviewed to identify children eligible for referral according to training guidelines (temperature of ≥38.5°C), to assess whether CHWs adhered to the guidelines and referred them. Factors associated with adherence were examined with logistic regression models.

Results

CHWs failed to refer 58.8% of children eligible in the moderate-to-high transmission and 31.2% of children in the low transmission setting. CHWs using RDTs adhered to the referral guidelines more frequently than CHWs not using RDTs (moderate-to-high transmission: 50.1 vs 18.0%, $p = 0.003$; low transmission: 88.5 vs 44.1%, $p < 0.001$). In both settings, fewer than 20% of eligible children received pre-referral treatment with rectal artesunate. Children who were prescribed ACT were very unlikely to be referred in both settings (97.7 and 73.3% were not referred in the moderate-to-high and low transmission settings, respectively). In the moderate-to-high transmission setting, day and season of visit were also associated with the likelihood of adherence to the referral guidelines, but not in the low transmission setting.

Conclusions

CHW adherence to referral guidelines was poor in both transmission settings. However, training CHWs to use RDT improved correct referral of children with a high fever compared to a presumptive diagnosis using sign and symptoms. As many countries scale up CHW programmes, routine monitoring of reported data should be examined carefully to assess whether CHWs adhere to referral guidelines and take remedial actions where required.

Introduction

In many sub–Saharan African countries where malaria is endemic, community health workers (CHWs) have received renewed interest to deliver primary health care in areas with poor access to public health services, and CHW programmes to treat common childhood infections of malaria, pneumonia and diarrhoea (known as integrated community case management; iCCM) have been introduced in over 25 countries with the aim to reduce under-five mortality (M Young et al. 2012; Rasanathan et al. 2014). Previous studies have shown that adequately trained CHWs can correctly diagnose and treat children with uncomplicated malaria resulting in mortality reductions (Yeboah-Antwi et al. 2010; Sirima et al. 2003). Although CHW training usually includes guidance on when children should be referred to be seen by a fully qualified health worker, few studies have examined CHW adherence to these referral guidelines (WHO 2011a; Save the Children 2011; CORE Group et al. 2010; Yeboah-Antwi et al. 2010). Guidelines can serve to: (1) support CHWs to make appropriate referral decisions, (2) encourage caregivers to seek further care from health facilities, (3) ensure CHWs do not risk managing illnesses they are not trained for, and thus limit adverse outcomes that may arise if children do not receive attention from qualified health workers.

In contrast to the growing literature on CHW adherence to treatment guidelines, there is much less describing adherence to referral guidelines, and findings are mixed with referral ranging from 9%-83% (Kelly et al. 2001; A. M. Chinbuah et al. 2006; M. A. Chinbuah et al. 2013). Provision of guidelines to CHWs on which illnesses should be referred to health centres is the start of a complex process involving CHWs, caregivers and health workers in health facilities (Newbrander et al. 2012). First, CHWs need to have the skills to identify and distinguish children with severe signs and symptoms from those who do not, and refer them promptly. Second, when referrals are made, caregivers need to adhere to the advice. Last, health facilities need to be prepared to receive, assess and treat referred cases promptly and effectively. The lack of evidence on referral has been highlighted as a priority for further research to inform the implementation and scale-up of iCCM globally (Smith Paintain et al. 2014; Mark Young et al. 2014; Wazny et al. 2014; Hamer et al. 2012). Previous studies on adherence to referral were small-scale evaluations involving a few CHWs, conducted in the context of a presumptive clinical diagnosis for malaria, before WHO recommended parasitological testing with malaria rapid diagnostics tests (mRDTs) at all levels of the health system, including the community (WHO 2011b). There is urgent need for contemporary data, based on larger samples to be representative of the range of referral practices amongst CHWs. In this analysis, we examine data on CHWs adherence to referral guidelines, collected during trials conducted in Uganda to evaluate the effect of a CHW intervention using mRDTs on malaria treatment (Ndyomugyenyi et al. 2016). These two trials provided an opportunity to describe CHWs adherence to referral guidelines and explore the factors related to adherence when CHWs were trained to use mRDTs and prescribe artemisinin-based combination therapy (ACTs).

Methods

Study context

The two cluster-randomised trials were conducted in Rukungiri District, South-western Uganda, one trial was conducted in villages in a moderate-to-high malaria transmission setting, Bwambara sub-county (980m-1200m above sea level) and another was conducted in villages in a low transmission highland setting, Nyakishenyi sub-county (1064m-2157m above sea level) (Lal et al. 2015). More than 85% of the population in both settings lived in rural areas and the main occupation of Bahororo and Bakiga ethnic groups was subsistence agriculture (Rukungiri District Local Government 2009). The climate is characteristic of East African tropics with two rainy seasons, March-May and September-December, and annual temperatures ranging between 16°C-25°C. Malaria transmission is perennial with peaks in incidence shortly after the rains. The public health system in each sub-county comprises of three health centres, two are classed as public health centre IIs (HCII) and one is classed as a health centre III (HCIII). HCIIs provide outpatient and community outreach services, whilst HCIIIs provide both inpatient and outpatient services and supervise lower level HCIIs; they also act as the first referral cover for the sub-county (Ministry of Health 2014; Rutebemberwa et al. 2009).

Prior to the trials starting, community meetings were held to select CHWs for training and sensitise local communities on diagnostic testing for malaria. The key messages were: not all fevers are malaria and a diagnostic test was advisable before treatment with an ACT (artemether-lumefantrine); that a quick malaria test (mRDT) could test for malaria, and tests were available from CHWs in villages in the intervention arm. In January 2010, 381 CHWs (192 CHWs in moderate-to-high transmission setting, 189 CHWs in the low transmission setting) were trained to diagnose and treat malaria, including: a) receiving children presenting with fever and their caregivers, b) taking a history of a child's symptoms and diagnosing malaria, c) treating uncomplicated malaria, and d) recording basic information, including treatment decisions and drugs prescribed. All CHWs were provided with digital thermometers and trained to measure axillary temperature in children with a history of fever. CHWs in the intervention arm of each trial (93 moderate-to-high transmission setting, 96 low transmission setting) received training on how to perform an mRDT and prescribe an age-dependent oral dose of ACT after a positive mRDT result. In contrast, mRDT negative children were not prescribed an ACT, and referred if the CHW identified any of the listed signs and symptoms for referral (Figure 3.0). CHWs in the control arm were trained to prescribe an ACT based on a presumptive diagnosis of malaria if a child had an axillary temperature >37.5°C. CHWs in both arms were trained to administer rectal artesunate if a child presented with one or more severe signs and symptoms including high fever (temperature of ≥38.5°C) and refer the child to the nearest health centre for further management.

The training also covered the identification of signs and symptoms of other illnesses that CHWs were not trained to manage and that required referral to health centres for investigation. Severe signs and symptoms for immediate referral included: convulsions or fits, extreme weakness, coma, loss of consciousness and high temperature of 38.5°C or more;

whilst non-severe referral signs and symptoms included: wounds or burns, ear infections, sticky or red eyes, and vomiting and diarrhoea (Figure 3.0). The danger signs for urgent referral were chosen to identify severe forms of malaria, cerebral malaria, meningitis, pneumonia and/or severe bacterial infections. Other signs and symptoms for referral typically identified less serious illnesses that required management at a health centre, including gastrointestinal infections, skin infections, otitis media, and conjunctivitis and/or respiratory tract infections. The referral criteria were based on our clinical experience and national treatment guidelines in Uganda at the time (Uganda Ministry of Health 2010). CHWs were only trained to treat malaria, had limited case management experience before this study, and the criteria for referral thus veered on the side of caution, aiming to ensure children with danger signs and/or non-malarial illnesses were treated at a health centre. The job aids summarising the decisions CHWs were trained to make in each arm are shown in Figure S3.0 (further details of the trial are available from: www.actconsortium.org/RDThomemanagement).

Figure 3.0: List of severe and non-severe signs and symptoms that community health workers (CHWs) were trained to identify and refer in children

Severe sign and symptoms for urgent referral	Nonsevere sign and symptoms for referral
Refer using emergency referral form if child shows any of the following symptoms: 1. Illness in child below 2 months 2. Convulsions or fits now or within the past 2 days 3. Coma/loss of consciousness 4. Patient is confused or very sleepy-cannot be woken 5. Extreme weakness-unable to stand or sit without support 6. Very Hot-with temperature of 38.5°C or more 7. Very Cold-with temperature of 35.0°C or less 8. Vomiting everything-cannot keep down food or drink 9. Not able to drink or breast feed 10. Severe anaemia-very pale palms, fingernails, eyelids 11. Yellow eyes 12. Difficulty in breathing 13. Severe dehydration	*Refer using ordinary referral form if child shows any of the following symptoms:* 1. Fever in babies less than 4 months old 2. Fever that has last for more than 7 days 3. Fever with measured temperatures of 37°C or more and mRDT negative 4. Vomiting and diarrhoea 5. Blood in faeces or blood in urine 6. Pain when passing urine or frequent urination 7. Wound or burns 8. Skin abscess 9. Painful swelling or lumps in the skin 10. Ear infection (runny ear or child pulling at the ear) 11. Sticky or red eyes
If RDT result is positive: Treat child (if older than 2 months) with rectal artesunate suppository prior to referral.	***If RDT result is positive:*** Treat child (if older than 4 months) with artemether-lumefantine tablets prior to referral.

The CHWs began treating children in May 2010 in the moderate-to-high transmission setting and in June 2010 in the low transmission setting. CHW training was reinforced through close-support supervision for the first few months, with weekly visits by a field co-ordinator to review and collect CHWs treatment records, referral forms and stock cards, and to discuss concerns or difficulties of carrying out their roles. From January 2011, supervision of CHWs was scaled back and limited to monthly meetings to reflect typical levels of supervision under programmatic conditions.

The aim of both trials was to evaluate the effectiveness of training CHWs to use mRDTs to diagnose and treat malaria with ACTs compared with CHWs using a presumptive diagnosis for the management of malaria. The primary trial endpoint was the proportion of febrile children with malaria receiving appropriately targeted treatment with an ACT (Ndyomugyenyi et al. 2016). In this secondary analysis, we assessed whether CHWs adhered to the referral guidance and decided to refer children, by examining adherence to one of the criteria for urgent referral: high fever with an axillary temperature ≥38.5°C.

Evaluation of referral

This analysis examined whether CHWs in each transmission setting adhered to referral guidance in children who presented with a high fever (temperature ≥38.5°C); this indicator of adherence to referral guidelines was selected because axillary temperature was the only sign routinely recorded by CHWs for all children. Therefore, we could use the recorded temperature to identify children who should, irrespective of the mRDT result, have been referred according to the training guidelines and examine whether these children were actually referred by CHWs (Figure 3.1). We did not have an independent assessment of the other 11 severe signs and symptoms for referral. We analysed data from the treatment registers completed by CHWs between January 2011 and July 2012, after CHW supervision was scaled back.

Data analysis

All data were double entered and verified using Microsoft Access 2007 (Microsoft Corporation, Redmond, Washington), village distances to the nearest health centre were calculated using ArcGIS Desktop 10.3 (Environmental Systems Research Institute Inc., Redlands, CA). All data were analysed using STATA version 14.1 (STATA Corporation, College Station, Texas).

The outcome for this analysis was CHWs adherence to the referral guideline, defined as the proportion of children presenting with high fever (temperature ≥38.5°C) that were referred by CHWs. We also undertook an exploratory analysis of the trial datasets available to identify factors associated with adherence to referral guideline in which child visits to CHW were grouped into three categories (1) children who visited CHWs using a presumptive diagnosis for malaria [without mRDT]; (2) children who tested mRDT positive; (3) children who tested mRDT negative. Additional factors routinely recorded in CHW treatment registers which were considered as potentially affecting CHWs adherence to the referral guidelines included; child's age, sex, duration of fever and the use of an insecticide-treated net (ITN) the previous night. Time of visit (weekday or weekend) was derived from the date of the child's visit; and rainy season visits were defined as visits in March-May and September-December. Finally, Euclidean (straight-line) distance was estimated from the centre of a village to the nearest health centre.

For each transmission setting, an explanatory model for the outcome of referral was developed using logistic regression; odds ratios (OR) and 95% confidence intervals (95% CI) were calculated with random effects to account for clustering at the village level (Hayes and Moulton 2009). An unadjusted analysis was used to identify factors associated with CHWs referral of children with a high fever. To examine CHWs adherence to the referral guideline and identify independent factors associated with referral, all factors identified a priori were included in the adjusted model. In both the unadjusted and adjusted models factors associated with referral were assessed using a log-likelihood ratio test.

Results

Child characteristics

During the 19-month study period (January 2011–July 2012), 18,497 children with a history of fever were seen by 180 CHWs in the moderate-to-high transmission setting, of whom 8.0% (1,473/18,497) were eligible for referral with a high fever (temperature ≥38.5°C) according to the referral guidelines (Figure 3.1a). In the low transmission setting, 13.3% (428/3,223) of children visiting the 189 CHWs had a temperature ≥38.5°C (Figure 3.1b). The characteristics of children with high fever were broadly similar in both transmission settings: nearly half were aged between 1-3 years and similar proportions were males and females (Table 3.0). A large proportion of caregivers reported their child had slept under a net the previous night, and >80% had sought care within 24 hours of onset of fever. Most children were seen on a weekday, with more visits occurring during the two rainy seasons compared to the dry seasons (Table 3.0). There were a few differences between the two transmission settings: a higher proportion of children were tested with an mRDT in the moderate-to-high transmission setting compared to the low transmission setting (72% and 55%, respectively), and villages in the low transmission setting were located further away from the nearest public health centre than villages in moderate-to-high transmission setting (Table 3.0).

Figure 3.1a: Profile of children analysed in the moderate-to-high transmission setting

*Referral outcome missing for 10 children

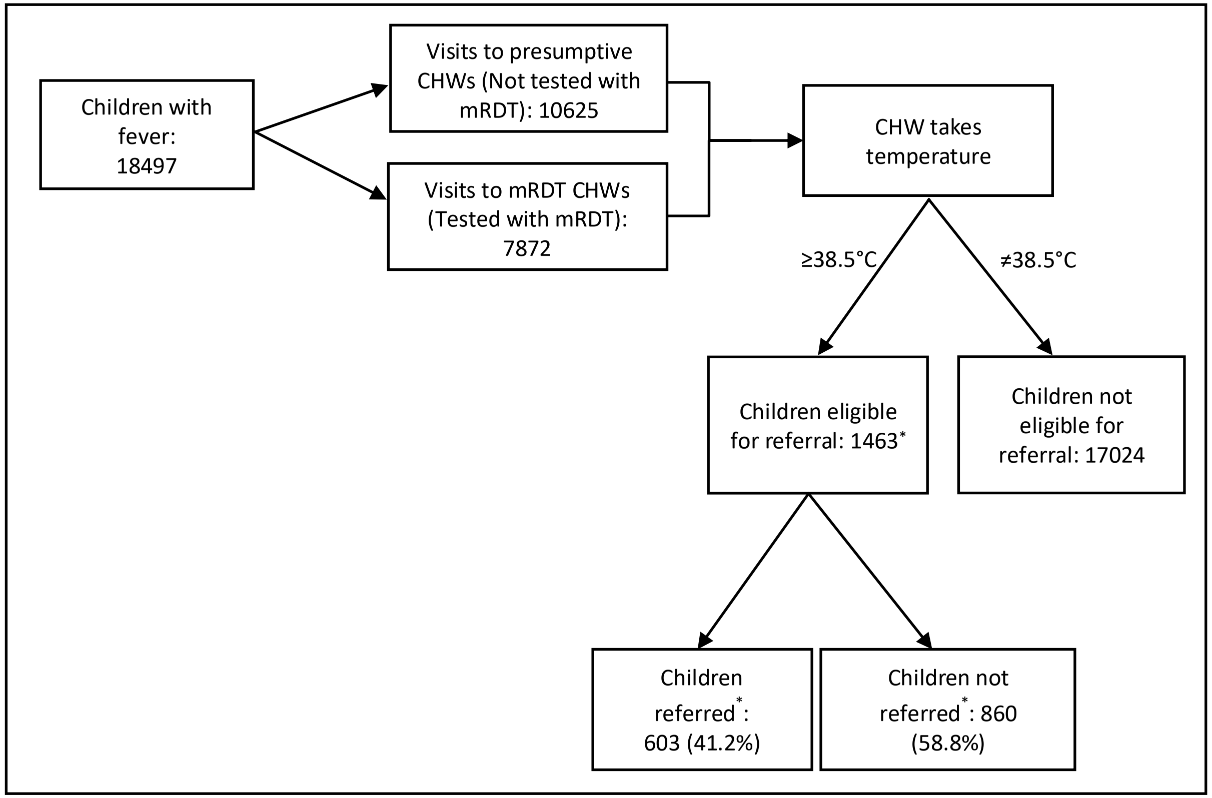

Figure 3.1b: Profile of children analysed in the low transmission setting

*Referral outcome missing for 8 children

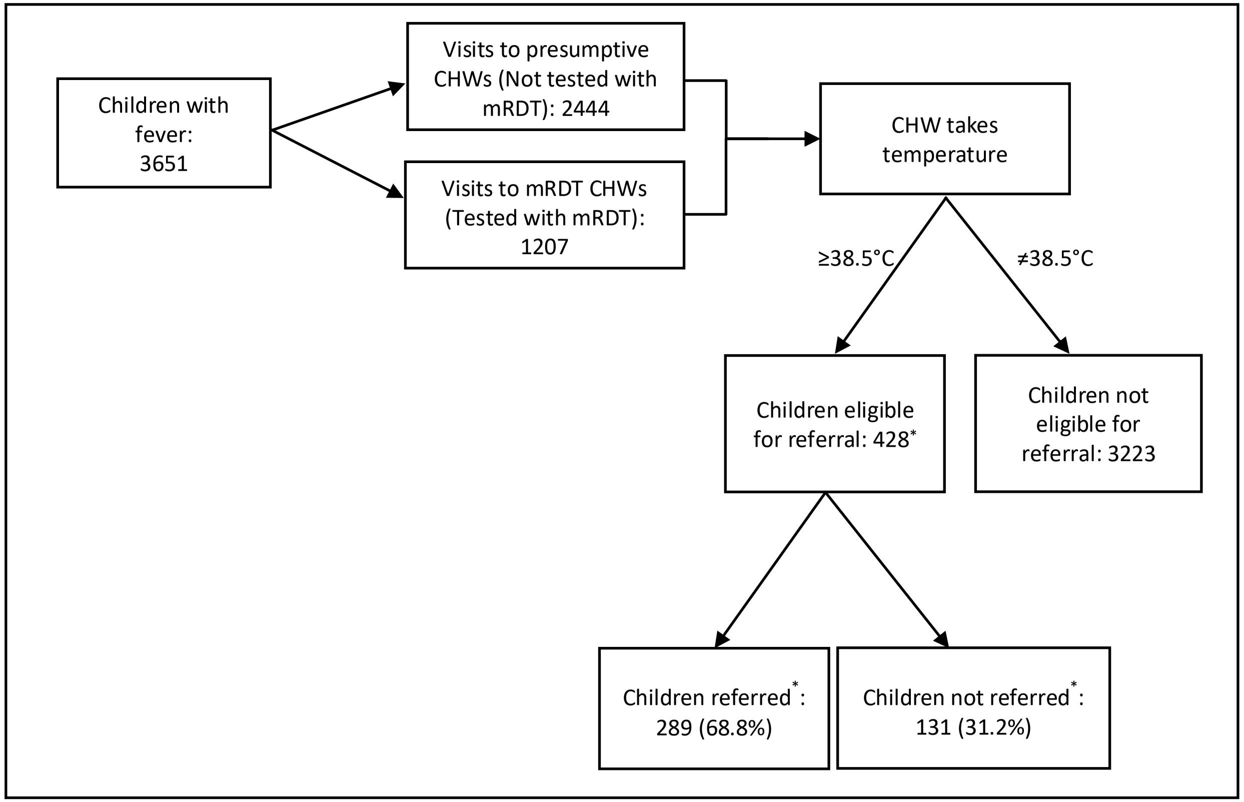

Table 3.0: Characteristics of children who visited CHWs and were eligible for referral (presented with a temperature ≥38.5°C)

	Moderate-to-high transmission setting (%)[a] N=1473	Low transmission setting (%)[b] N=428
Age group (years)		
<1.0	296 (20.2)	116 (27.4)
1.0-2.9	630 (43.0)	179 (42.3)
3.0-4.9	530 (36.2)	128 (30.3)
5.0-15.0	8 (0.5)	0 (0.0)
Sex		
Male	761 (52.0)	209 (48.8)
Female	703 (48.0)	219 (51.2)
Slept under a net the previous night		
No	141 (9.7)	50 (11.9)
Yes	1312 (90.3)	371 (88.1)
Resident in the same village as a CHW		
No	123 (8.4)	73 (17.1)
Yes	1345 (91.6)	355 (82.9)
Time of visit to CHW after onset of symptoms		
>24hrs	181 (12.5)	65 (15.6)
Within 24hrs	1266 (87.5)	352 (84.4)
Tested with mRDT		
Not Tested	406 (27.6)	192 (44.9)
Tested	1067 (72.4)	236 (55.1)
Day of visit to a CHW		
Weekday	1054 (71.6)	312 (72.9)
Weekend	419 (28.4)	116 (27.1)
Season of visit to a CHW		
Dry	512 (34.8)	162 (37.9)
Wet	961 (65.2)	266 (62.1)
Village distance to nearest health centre (km)		
0.0-2.4	690 (47.0)	97 (24.0)
2.5-4.9	727 (49.5)	159 (39.3)
5.0-7.4	51 (3.5)	103 (25.4)
7.5-8.9	0 (0.0)	46 (11.4)

[a]Data missing in the moderate-to-high transmission setting, for age: 9; sex: 9; net use: 20; resident in the same village: 5; onset of symptoms 26.

[b]Data missing in the low transmission setting, for age: 5; sex: 0; net use: 7; resident in the same village: 0; onset of symptoms 11.

CHWs adherence to referral guideline

In both transmission settings, CHWs did not always adhere to the guideline and refer all children that were eligible for referral (temperature ≥38.5°C). In the moderate-to-high transmission setting, CHWs failed to refer 58.8% (860/1463) of eligible children; this was higher than the low transmission setting, where 30.6%, 131/420 of eligible children were not referred (Figure 3.1a, Figure 3.1b). Table 3.1 shows the proportion of eligible children who were referred, categorised by whether CHWs tested with an mRDT or not, their mRDT result and whether ACTs were prescribed. In both settings, CHWs adhered to the referral guideline more often when children were tested with an mRDT compared to those who were not tested (moderate-to-high transmission: 50.1% vs. 18.0%, p=0.003, Table 3.1a; low transmission: 88.5% vs. 44.1%, p<0.001, Table 3.1b). In both settings, CHWs also adhered to the referral guideline more frequently when children were mRDT negative as opposed to test positive. The frequency of CHWs adherence to the referral guideline was generally higher among children seen in the low transmission setting than among children seen in moderate-to-high transmission setting, across all categories (tested/untested; RDT-positive/RDT-negative; ACT prescribed/not prescribed).

Referral of eligible children also varied by whether CHWs prescribed an ACT and was less frequent when ACTs were prescribed. In the moderate-to-high transmission setting only 2.3% of eligible children prescribed an ACT were referred, while 75.8% of children not prescribed an ACT were referred (Table 3.1a). In the low transmission setting, 26.7% of children who were prescribed an ACT were referred whilst 89.3% who were not prescribed

ACT were referred (Table 3.1b). Use of rectal artesunate was generally low; in total 47 and 37 children with high fever in the moderate-to-high transmission and low transmission setting respectively received rectal artesunate during the 19-month trial; all of whom were subsequently referred according to the guideline. CHWs not testing with an mRDT rarely prescribed rectal artesunate: only 7.2% (27/374) and 16.6% (27/163) of children with high fever not tested received rectal artesunate in the moderate-to-high transmission and low transmission sites respectively. Similarly, CHWs using RDT tests gave rectal artesunate in only 4.3% (17/397) of mRDT positive children with high fever in the moderate-to-high transmission setting, and in 11.1% (1/9) of eligible children in the low transmission setting.

Table 3.1: CHWs referral practices amongst eligible children (temperature ≥38.5°C) by mRDT result and ACT prescription in each transmission setting.

a) Moderate-to-high transmission setting

	Total	Referred (%)	Not referred (%)
Overall[a]	1463	603 (41.2)	860 (58.8)
mRDT			
Not tested	405	73 (18.0)	332 (82.0)
Tested	1058	530 (50.1)	528 (49.9)
Within those tested with mRDT			
mRDT Negative	657	497 (75.6)	160 (24.4)
mRDT Positive	401	33 (8.2)	368 (91.8)
ACT Prescription[b]			
ACT Not prescribed	665	504 (75.8)	161 (24.2)
ACT Prescribed	709	16 (2.3)	693 (97.7)
Rectal artesunate prescribed	47	47 (100.0)	0 (0.0)

[a]10 missing referral status, [b]42 missing treatment prescription

b) Low transmission setting

	Total	Referred (%)	Not referred (%)
Overall[c]	186	82 (44.1)	104 (55.9)
mRDT			
Not tested	186	82 (44.1)	104 (55.9)
Tested	234	207 (88.5)	27 (11.5)
Within those tested with mRDT			
mRDT Negative	225	202 (89.8)	23 (10.2)
mRDT Positive	9	5 (55.6)	4 (44.4)
ACT Prescription[d]			
ACT Not prescribed	225	201 (89.3)	24 (10.7)
ACT Prescribed	146	39 (26.7)	107 (73.3)
Rectal artesunate prescribed	37	37 (100.0)	0 (0.0)

[c]8 missing referral status, [d]12 missing treatment prescription

Factors associated with CHWs adherence to referral guideline: moderate-to-high transmission setting

CHWs in the moderate-to-high transmission setting were less likely to adhere to the referral guideline (referring all children with a temperature ≥38.5°C) when ACTs were prescribed (adjusted odds ratio, AOR 0.0025; 95%CI 0.00061-0.0099; p<0.001); when a child visit occurred on the weekend compared to a weekday (AOR 0.62; 95%CI 0.41-0.95; p=0.027); and during the wet season compared to the dry season (AOR 0.65; 95%CI 0.42-0.99; p=0.043) (Table 3.2). After controlling for other variables, the adjusted analysis found no association between the likelihood of CHWs adherence to referral guideline and the child's age or mRDT result.

Factors associated with CHWs adherence to referral guideline: low transmission setting

In the low transmission setting the adjusted analysis found that CHWs had a 7 fold higher odds of adherence to the referral guideline and refer when children were mRDT negative, compared to those not tested (OR 7.14; 95%CI 1.99-25.59; p=0.010; Table 3.3); and more than a 3 times greater odds of adherence when children tested positive (OR 3.19; 95%CI 0.38-26.87; p=0.010). There was also an association with malaria treatment, independent of mRDT result: CHWs had a lower odds of adherence to the referral guideline if they prescribed an ACT compared to not prescribing an ACT (OR 0.07; 95%CI 0.02-0.26; p<0.001). Unlike the moderate-to-high transmission setting, there were no associations between adherence to the referral guideline and distance to the nearest health centre, day or season of the visit.

Table 3.2: Factors associated with CHWs adherence to the referral guideline among children eligible for referral (temperature ≥38.5°C) in the moderate-to-high transmission setting

Variables	Eligible for referral (≥38.5°C)	Referrals made (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Test result						
Not Tested	405	73 (18.0)	1		1	
mRDT Negative	657	497 (75.6)	6.93 (3.45-13.92)	<0.001	0.54 (0.16-1.79)	0.567
mRDT Positive	401	33 (8.2)	0.11 (0.05-0.24)		1.03 (0.29-3.61)	
Age group (years)						
<1.0	292	155 (53.1)	1		1	
1.0-2.9	628	258 (41.1)	0.55 (0.39-0.78)		0.98 (0.59-1.63)	
3.0-4.9	527	184 (34.9)	0.39 (0.27-0.56)	<0.001	1.11 (0.64-1.91)	0.805
5.0-15.0	8	3 (37.5)	0.38 (0.07-1.98)		0.45 (0.64-1.91)	
Sex						
Male	756	306 (40.5)	1		1	
Female	698	290 (41.5)	0.94 (0.73-1.21)	0.626	1.05 (0.71-1.56)	0.795
Slept under a net the previous night						
No	138	65 (47.1)	1		1	
Yes	1305	523 (40.1)	1.35 (0.84-2.17)	0.211	1.39 (0.66-2.92)	0.382
Resident in the same village as a CHW						
No	122	73 (59.8)	1		1	
Yes	1336	526 (39.4)	0.73 (0.46-1.16)	0.184	0.59 (0.28-1.25)	0.169
Time of visit to CHW after onset of symptoms						
>24hrs	181	90 (49.7)	1		1	
Within 24hrs	1256	496 (39.5)	0.77 (0.53-1.13)	0.189	0.70 (0.39-1.27)	0.244
ACT Prescription						
No ACT	665	504 (75.8)	1		1	
ACT	709	16 (2.3)	0.004 (0.002-0.009)	<0.001	0.003 (0.001-0.010)	<0.001
Day of visit to a CHW						
Weekday	1046	451 (43.1)	1		1	
Weekend	417	152 (36.5)	0.74 (0.56-0.98)	0.033	0.62 (0.41-0.95)	0.027
Season of visit to a CHW						
Dry	508	235 (46.3)	1	0.004	1	
Wet	955	368 (38.5)	0.68 (0.52-0.88)		0.65 (0.42-0.99)	0.043
Village distance to nearest health centre (km)						
0.0-2.4	686	337 (49.1)	1		1	
2.5-4.9	721	251 (34.8)	0.52 (0.28-0.97)	0.093	0.39 (0.18-0.86)	0.060
5.0-7.4	51	14 (27.5)	0.41 (0.08-2.12)		0.93 (0.12-7.07)	
7.5-8.9	n/a	n/a	n/a		n/a	

Table 3.3: Factors associated with CHWs adherence to the referral guideline among children eligible for referral (temperature ≥38.5°C) in the low transmission setting

Variables	Eligible for referral (≥38.5°C)	Referrals made (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Test result						
Not Tested	186	82 (44.1)	1		1	
mRDT Negative	225	202 (89.8)	17.00 (6.53-44.26)	<0.001	7.14 (1.99-25.59)	0.010
mRDT Positive	9	5 (55.6)	1.23 (0.20-7.53)		3.19 (0.38-26.87)	
Age group (years)						
<1.0	113	82 (72.6)	1		1	
1.0-2.9	174	128 (73.6)	0.95 (0.46-1.96)		1.47 (0.59-3.69)	
3.0-4.9	128	76 (59.4)	0.55 (0.26-1.16)	0.195	0.64 (0.25-1.63)	0.158
5.0-15.0	0	0 (0.0)				
Sex						
Male	203	137 (67.5)	1		1	
Female	217	152 (70.0)	1.26 (0.70-2.27)	0.436	1.63 (0.78-3.42)	0.193
Slept under a net the previous night						
No	50	38 (76.0)	1		1	
Yes	363	244 (67.2)	0.69 (0.29-1.64)	0.398	1.70 (0.51-5.64)	0.389
Resident in the same village as a CHW						
No	72	49 (68.1)	1		1	
Yes	348	240 (69.0)	1.89 (0.83-4.31)	0.131	3.05 (0.94-9.92)	0.064
Time of visit to CHW after onset of symptoms						
>24hrs	63	51 (81.0)	1		1	
Within 24hrs	346	232 (67.1)	0.44 (0.18-1.07)	0.072	0.67 (0.23-1.89)	0.445
ACT Prescription						
No ACT	225	201 (89.3)	1		1	
ACT	146	39 (26.7)	0.03 (0.01-0.07)	<0.001	0.07 (0.02-0.26)	<0.001
Day of visit to a CHW						
Weekday	307	213 (69.4)	1		1	
Weekend	113	76 (67.3)	1.42 (0.74-2.75)	0.295	1.21 (0.53-2.74)	0.649
Season of visit to a CHW						
Dry	158	96 (60.8)	1		1	
Wet	262	193 (73.7)	2.24 (1.24-4.06)	0.008	1.67 (0.77-3.60)	0.191
Village distance to nearest health centre (km)						
0.0-2.4	96	61 (63.5)	1		1	158
2.5-4.9	158	116 (73.4)	1.29 (0.27-6.29)		0.78 (0.22-2.79)	0.200
5.0-7.4	100	63 (63.0)	1.41 (0.27-7.41)	0.846	0.55 (0.14-2.14)	
7.5-8.9	43	34 (79.1)	3.11 (0.27-7.41)		5.41 (0.68-42.80)	

Other symptoms in children referred for high fever

A supplementary analysis was undertaken to describe the other signs and symptoms recorded by CHWs amongst children referred with a high fever (temperature ≥38.5°C). Nearly all CHWs who referred children with a high fever correctly reported this as a symptom for referral on the form for urgent referrals (moderate-to-high transmission setting, 51/54, Table S3.0; low transmission setting, 22/23, Table S3.1). Among severe signs and symptoms for referral, the most frequently reported were "difficulty in breathing" and "not able to drink or breastfeed", in both settings (Tables S3.0, S3.1). Less frequent severe signs and symptoms included convulsions and extreme weakness. Although all children should have been given a severe referral form because they had a high fever, CHWs also referred children using the form for non-severe signs and symptoms, most commonly for "fever with measured temperature of >37°C and mRDT negative". Other symptoms, included "fever that had lasted for 7 days", "vomiting and diarrhoea", "pain when passing urine" and "wounds or burns". In the moderate-to-high transmission setting, high fever was reported as the exclusive sign for referral in 29.6% (16/54) of referrals, and alongside other severe signs and symptoms in 70.4% (38/54) of all severe referral forms (Table S3.0). In the low transmission setting CHWs reported high fever exclusively on 6 of the 23 severe referral forms, and alongside other severe signs and symptoms on 17 forms (Table S3.1).

In both transmission settings, there was a discrepancy between the number of referrals recorded in the CHWs treatment register and the number of referral forms (used to analyse the reasons for referral, summarised above). In the moderate-to-high transmission setting 603 referrals were recorded, but referral forms were only available for 74 (12.3%) of these. In the low transmission setting, 420 referrals were recorded, but only 34 (8.1%) referral forms were available.

Discussion

These results indicate that CHWs failed to refer up to 60% of children who should have been referred according to the referral guideline (high fever temperature ≥38.5°C). However, we found that CHWs using mRDTs in the low transmission setting more frequently adhered to referral guidance compared to CHWs using presumptive diagnosis based solely on signs and symptoms, with both mRDT negative and positive children more likely to be referred compared to CHWs not testing with an mRDT. CHWs adherence to ACT treatment guidelines was not any better: all children with a high fever who were mRDT positive (or not tested with an mRDT) should have received rectal artesunate pre-referral treatment, but fewer than 20% of these children received the correct treatment. Failure to prescribe pre-referral treatment (rectal artesunate) and refer is a concern because not referring these children for further management has the potential to worsen their condition.

Children with high fevers who were not referred were often mRDT positive and prescribed an ACT, suggesting CHWs may have overlooked the need for referral once an ACT was given. In contrast, mRDT negative children not prescribed ACT were more likely to be referred to the nearest health centre for further management. These results also show poor CHW adherence to rectal artesunate prescribing guidelines, the WHO guidance for the management of severe malaria in primary care recommends pre-referral treatment with rectal artesunate and referral (WHO 2012). Children with high fevers who visited CHWs using a presumptive diagnosis and those who were mRDT positive should all have received rectal artesunate and been referred according to the study guidelines, due to their increased risk of severe malaria (Figure S3.0). However, in both settings children with a high fever who were mRDT positive or not tested were frequently prescribed an ACT and not referred. Despite the low use of rectal artesunate overall, it is reassuring that when CHWs did prescribe rectal artesunate, they always referred.

In addition to malaria test result and treatment, the CHWs decision to refer also differed according to both the day and season of visit, in one study area. This could possibly be due to CHWs knowing that local health centres (HC II and III) would be closed during the weekend and that access would be difficult due to the poor condition of roads during the rainy season, factors which might affect whether the caregiver would take their child to a health centre. In contrast, in the other transmission setting we found no evidence for an association between the day or season of visit and referral. This difference could have been due to the existence of a nearby mission-run hospital open during the weekend, enabling CHWs to refer in the belief that caregivers would be likely to seek further care. There is also the possibility that CHWs did not refer because caregivers influenced the decision to refer. Although this was not captured systematically, ad-hoc evidence from the open-text comments section of the CHWs treatment record forms confirm instances where caregivers refused referral and CHWs did not refer them (3% of all comments made). Similar observations were made by Winch et al, who found CHWs were more likely to make a referral when they knew caregivers would comply with their advice (Winch et al. 2003).

Adherence to the referral guideline by CHWs was generally higher in the low transmission setting compared to the moderate-to-high transmission setting. This may be due to differences between the two trial sites. First, CHWs in the low transmission setting saw fewer children than CHWs in the moderate-to-high transmission setting, and may have been less trusting in the malaria test and/or their competence in deciding when to refer. CHWs who are less confident in their role may prefer to refer according to the guidelines and not risk further complications in the child. In contrast, CHWs in the moderate-to-high transmission experienced higher number of visits, will have obtained case management experience more rapidly, and may have made their own judgements on when to prescribe rectal artesunate or refer. Similar patterns have been reported in other community-based studies in Uganda, where drug shop vendors became increasingly confident in their skills to manage clients and were reluctant to refer clients (Hutchinson et al. 2015). Second, the low transmission setting is historically prone to epidemics, children develop acquired immunity more slowly due to reduced malaria exposure, and may be more likely to develop severe malaria if not treated (Reyburn et al. 2005; White et al. 2014). CHWs may have been aware of this risk and more inclined to refer. Finally, the presence of a nearby mission-run hospital with an insurance scheme in the low transmission setting may have enabled CHWs to refer knowing care would be available; no such hospital or insurance scheme was present in the moderate-to-high transmission setting.

In this analysis, adherence to referral guidelines was assessed through review of treatment records kept by CHWs; temperature was used as an indicator of whether a referral should have been made, because it was routinely recorded for all children. There are potential limitations to this approach. First, direct observation with re-examination by a medical professional is an established method to assess health workers adherence to case management guidelines in hospitals and would have enabled evaluation of all referral criteria (Hermida, Nicholas, and Blumenfeld 1999; Franco et al. 2002). Our analysis was limited to the data available from the two trials, which did not use this method of evaluation. However, prior studies which have used direct observation to evaluate CHWs performance have found evidence of the Hawthorne effect, where CHWs may have followed guidelines more accurately under observation in a clinical setting compared to their community environment (Cardemil et al. 2012; Kelly et al. 2001). Register review has previously been found to approximate results from a medical professional directly observing CHWs performance (Cardemil et al. 2012; Franco et al. 2002), and can offer a number of advantages: we were able to screen and analyse approximately 22,000 records in less time, with fewer resources compared to a direct observation method, without having to remove CHWs or health centre workers from their normal work. Second, our analysis was limited to data that were routinely recorded, but other unrecorded factors could also have influenced a CHW's decision to refer or not, including perceptions of the availability and quality of care available at local facilities, caregivers demands, and interpersonal relationships. Since CHW supplies were regularly provided as part of the trial, we can be confident that non-adherence to the guideline was not due to stock-outs of rectal artesunate or referral forms. Finally, the single criterion (temperature ≥38.5°C) used in our analysis is not necessarily representative of all criterial for referral, of all children needing referral, or adherence to referral guidelines for other symptoms. Indeed, when children with high fever were referred CHWs often reported additional severe signs and symptoms for referral alongside the temperature criterion, suggesting that CHWs may have thought that high fever on its own did not justify a referral. It is conceivable that other severe signs and symptoms may have had higher referral rates; also that referral might be lower for non-severe signs and symptoms.

Despite these limitations our findings are consistent with two earlier studies in Ghana where CHWs used a presumptive malaria diagnosis, which found similar patterns of low referral (Chinbuah et al. 2006;. Chinbuah et al. 2013). Chinbuah et al 2006, reported 5 out of 17 children with signs of severe disease requiring referral were referred with a form; the authors thought this might reflect CHWs limited confidence in their diagnosis and a preference to reassess later the need for referral. Being resident in the same village as patients, CHWs are in a position to follow-up and monitor the child's condition. This may mean that unlike other health workers, CHW's decision to refer is not always made at the time of first contact with the patient but later. It is possible in our study that CHWs may have also followed-up and reassessed severely ill children for referral, however this was not systematically recorded.

To our knowledge this is one of the first studies to investigate CHWs adherence to referral guidelines when mRDTs have been implemented as part of a community case management programme, and although CHWs in these trials were only trained to treat malaria, the findings may also have relevance for referral guidance within iCCM programmes. The use of mRDTs in any programme will identify some children that the CHW is not equipped to treat, and guidance for managing RDT-negative children is needed. In both settings we found CHWs referred eligible children more frequently when they were mRDT negative compared to when they were mRDT positive or not mRDT tested. Nonetheless, it is probably impractical that all children who test RDT-negative should be referred without consideration of other sign or symptoms. CHWs in this study were trained to identify more than 20 signs and symptoms for referral. Is this too many, and can inclusion of non-severe signs diminish the perceived importance of adherence to referral guidelines? More worrying, there was strong evidence that children treated by the CHW were not referred. Treatment for one condition can thus increase the risk that CHWs overlook other signs and symptoms requiring referral; underlining the emphasis that needs to be placed on the referral criteria during CHW training. Although children with a high fever are at increased risk of febrile convulsions, it is possible that in the absence of other symptoms high-fevers were not perceived by CHWs and caregivers to be serious enough to justify referral. Caregivers may prefer to observe the progression of the child's fever at home and may not comply with CHWs referral advice to visit a health centre. Poor compliance to referral by caregivers has been reported in studies in Uganda and Sierra Leone (Thomson et al. 2011; Nsibande et al. 2013). There is considerable heterogeneity in national and iCCM guidelines on the referral criteria used in the countries that are currently scaling up iCCM (Friedman and Wolfeim 2013). Some, but not all, include high fever as a criterion for referral. Although the findings presented here are not necessarily generalizable to other referral criteria, the results highlight the need to understand how CHWs make decisions on when to refer, and the factors that influence these decisions. Failure to refer may result in delayed treatment seeking and poorer child health, which would partly undo the benefits of increasing access to primary health care afforded by using CHWs (Who/Unicef 2012; E Rutebemberwa et al. 2012).

Conclusion

In this study, CHWs tended not to refer children presenting with high fever (temperature ≥38.5°C) if they had confirmed malaria diagnosis with mRDT and prescribed an ACT. This practice was inconsistent with the CHW training guidelines that recommend to refer children presenting with one or more severe symptoms. In other settings where CHW interventions are being implemented, further research is required to fully understand when and how CHWs decide to refer children, and the factors that influence their decision, in order to refine the guidelines and improve management of febrile illness in children.

Ethics approval and consent to participate

The trials were approved by the Uganda National Council for Science and Technology (Ref no. HS 555) and London School of Hygiene & Tropical Medicine Ethics Committee (Ref no. 5595). Written informed consent was obtained from village leaders and CHWs to participate in the trials. At the time of consultation with a CHW, children refusing an mRDT blood test received presumptive treatment for malaria. The trial was registered with ClinicalTrials.gov identifier NCT01048801, 13th January 2010.

Consent for publication

Not applicable

Availability of data and materials

A complete dataset for this study, reflecting the results and supporting the conclusions will be available in the LSHTM and ACTc open access institutional repository: https://actc.lshtm.ac.uk/

Competing interests

We declare no competing interests.

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Authors' contributions

SL conceived the idea for this work, conducted the analysis and wrote the first draft of the paper. All authors reviewed and provided substantial input to the final version of the paper.

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Table S3.0: Signs and symptoms for referral amongst children eligible for referral (temperature ≥38.5°C) and referred in the moderate-to-high transmission setting

	Moderate-to-high transmission setting[a]		
	Not tested with an mRDT Frequency (%)	**mRDT Negative** Frequency (%)	**mRDT Positive** Frequency (%)
Non-severe signs and symptoms for referral			
Fever in babies less than 4 months old	0 (0.0)	0 (0.0)	0 (0.0)
Fever that has lasted more than 7 days	0 (0.0)	3 (4.5)	0 (0.0)
Fever with measured temperature of >37°C and mRDT Negative	0 (0.0)	42 (63.6)	0 (0.0)
Vomiting and diarrhoea	0 (0.0)	4 (6.1)	1 (33.3)
Blood in faeces or urine	0 (0.0)	0 (0.0)	0 (0.0)
Pain when passing urine, or frequent urination	0 (0.0)	2 (3.0)	0 (0.0)
Wounds or Burns	0 (0.0)	2 (3.0)	0 (0.0)
Skin abscess	0 (0.0)	1 (1.5)	0 (0.0)
Painful swellings or lumps in the skin	0 (0.0)	1 (1.5)	0 (0.0)
Ear infection (runny ear or child pulling at ear)	0 (0.0)	1 (1.5)	0 (0.0)
Sticky or red eyes	0 (0.0)	3 (4.5)	1 (33.3)
Other non-severe signs and symptoms (free text)[b]	0 (0.0)	7 (10.6)	1 (33.3)
Total number of non-severe signs and symptoms reported	**0**	**66**	**3**
Total number of non-severe referrals forms	0	17	3
Mean number of signs and symptoms reported per non-severe referral form	0.0	3.9	1.0
Severe signs for referral			
Illness in child below 2 months	0 (0.0)	0 (0.0)	0 (0.0)
Convulsions or fits now or within the past 2 days	0 (0.0)	4 (3.8)	2 (16.7)
Coma / Loss of consciousness	0 (0.0)	2 (1.9)	0 (0.0)
Patient is confused or very sleepy - cannot be woken	1 (11.1)	0 (0.0)	0 (0.0)
Extreme weakness unable to stand or sit without support	1 (11.1)	4 (3.8)	1 (8.3)
Very Hot with temperature of 38.5°C or more	3 (33.3)	45 (42.5)	3 (25.0)
Very Cold with temperature of 35.0°C or less	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting everything-cannot keep down food or drink	0 (0.0)	5 (4.7)	1 (8.3)
Not able to drink or breastfeed	0 (0.0)	16 (15.1)	2 (16.7)
Severe anaemia very pale palms, fingernails, eyelids	0 (0.0)	2 (1.9)	0 (0.0)
Yellow eyes	0 (0.0)	2 (1.9)	1 (8.3)
Difficulty in breathing	3 (33.3)	19 (17.9)	2 (16.7)
Severe dehydration	0 (0.0)	0 (0.0)	0 (0.0)
Other severe signs and symptoms (free text)[c]	1 (11.1)	7 (6.6)	0 (0.0)
Total number of severe signs and symptoms reported	**9**	**106**	**12**
Total number of severe referral forms	3	47	4
Mean number of signs and symptoms reported per severe referral form	3.0	2.3	3.0
Total number of severe and non-severe signs and symptoms reported	9	172	15
Total non-severe and severe referral forms[d]	3	64	7
Total referrals made	73	497	33

[a] Percentages are calculated based on the total number of signs and symptoms reported.

[b] Other non-severe signs and symptoms for referral included: mRDT negative; cough & flu (5), diarrhoea (1), dysentery (1); not tested; cough flu (1).

[c] Other severe signs and symptoms included: mRDT negative; very high temperature but mRDT negative (5), cough flu, mRDT negative (1); worms (1); mRDT positive; very high temperature (1).

[d] 529 referral forms were missing when a referral was made (70 not tested, 433 mRDT negative and 26 mRDT positive)

Table S3.1: Signs and symptoms for referral amongst children eligible for referral (temperature ≥38.5°C) and referred in the low transmission setting

	Low transmission setting[a]		
	Not tested with an mRDT	**mRDT Negative**	**mRDT Positive**
	Frequency (%)	Frequency (%)	Frequency (%)
Non-severe signs and symptoms for referral			
Fever in babies less than 4 months old	0 (0.0)	0 (0.0)	0 (0.0)
Fever that has lasted more than 7 days	0 (0.0)	2 (6.5)	0 (0.0)
Fever with measured temperature of >37°C and mRDT Negative	0 (0.0)	16 (51.6)	0 (0.0)
Vomiting and diarrhoea	0 (0.0)	2 (6.5)	0 (0.0)
Blood in faeces or urine	0 (0.0)	0 (0.0)	0 (0.0)
Pain when passing urine, or frequent urination	0 (0.0)	2 (6.5)	0 (0.0)
Wounds or Burns	0 (0.0)	1 (3.2)	0 (0.0)
Skin abscess	0 (0.0)	0 (0.0)	0 (0.0)
Painful swellings or lumps in the skin	0 (0.0)	0 (0.0)	0 (0.0)
Ear infection (runny ear or child pulling at ear)	0 (0.0)	0 (0.0)	0 (0.0)
Sticky or red eyes	0 (0.0)	1 (3.2)	0 (0.0)
Other non-severe signs and symptoms (free text)[b]	0 (0.0)	7 (22.6)	1 (0.0)
Total number of non-severe signs and symptoms reported	**0**	**31**	**0**
Total number of non-severe referrals forms	0	10	0
Mean number of signs and symptoms reported per non-severe referral form	0.0	3.1	0.0
Severe signs for referral			
Illness in child below 2 months	0 (0.0)	0 (0.0)	0 (0.0)
Convulsions or fits now or within the past 2 days	0 (0.0)	1 (2.9)	0 (0.0)
Coma / Loss of consciousness	1 (5.0)	0 (0.0)	0 (0.0)
Patient is confused or very sleepy - cannot be woken	1 (5.0)	0 (0.0)	0 (0.0)
Extreme weakness unable to stand or sit without support	0 (0.0)	1 (2.9)	0 (0.0)
Very Hot with temperature of 38.5°C or more	10 (50.0)	11 (32.4)	1 (50.0)
Very Cold with temperature of 35.0°C or less	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting everything-cannot keep down food or drink	1 (5.0)	3 (8.8)	0 (0.0)
Not able to drink or breastfeed	0 (0.0)	5 (14.7)	0 (0.0)
Severe anaemia very pale palms, fingernails, eyelids	1 (5.0)	1 (2.9)	0 (0.0)
Yellow eyes	0 (0.0)	0 (0.0)	0 (0.0)
Difficulty in breathing	5 (25.0)	8 (23.5)	1 (50.0)
Severe dehydration	0 (0.0)	1 (2.9)	0 (0.0)
Other severe signs and symptoms (free text)[c]	1 (5.0)	3 (8.8)	0 (0.0)
Total number of severe signs and symptoms reported	**20**	**34**	**2**
Total number of severe referral forms	10	12	1
Mean number of signs and symptoms reported per severe referral form	2.0	2.8	2.0
Total number of severe and non-severe signs and symptoms reported	20	65	2
Total non-severe and severe referral forms[d]	10	22	1
Total referrals made	186	225	9

[a] Percentages are calculated based on the total number of signs reported.

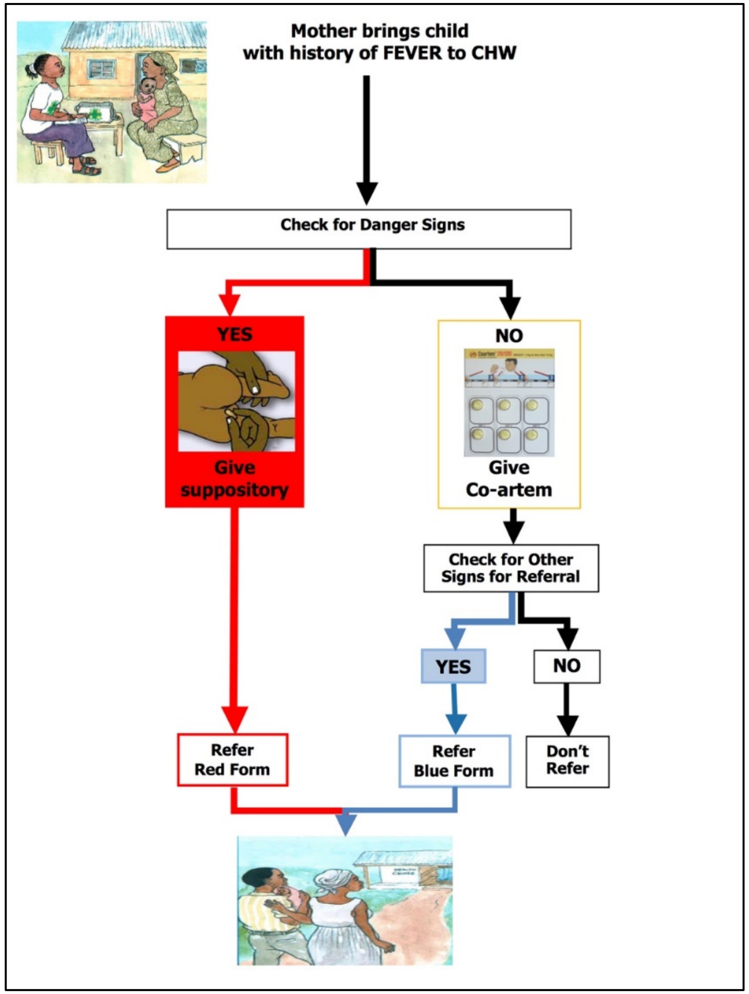
[b] Other non-severe signs included: mRDT negative; very high temperature but mRDT negative (5); doesn't feed well (1), vomiting and loss of appetite (1); mRDT positive; cough (1).

[c] Other severe reasons for referral included: mRDT negative; cough & problem with eyes (1), abdominal pain (2); not tested; cough (1);

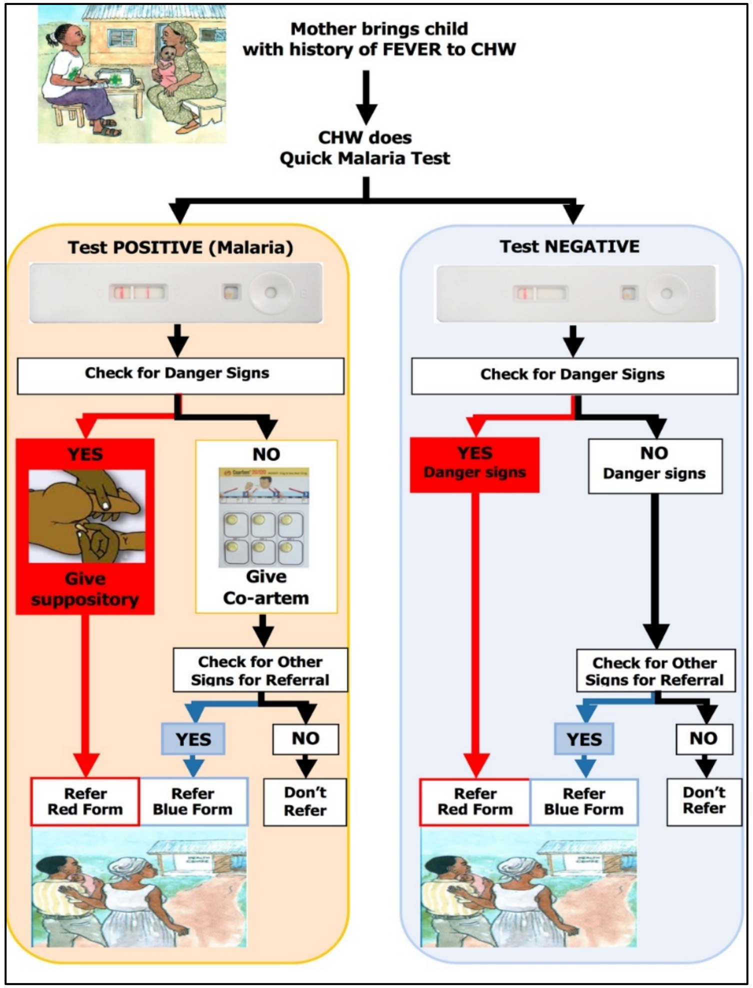
[d] 255 referral forms were missing when a referral was made. (71 not tested, 180 mRDT negative and 4 mRDT positive.

Figure S3.0: Job aid for CHWs in a) control (presumptive) arm, b) intervention (mRDT) arm

a) Control arm



b) Intervention arm



Chapter 4: Community health workers referral patterns for malaria

Adapted from: Sham Lal, Richard Ndyomugenyi, Pascal Magnussen, Kristian S Hansen, Neal D Alexander, Lucy Paintain, Daniel Chandramohan, and Siân E Clarke. 2016. *"Referral Patterns of Community Health Workers Diagnosing and Treating Malaria: Cluster-Randomized Trials in Two Areas of High- and Low-Malaria Transmission in Southwestern Uganda."* The American Journal of Tropical Medicine and Hygiene.

Abstract

Malaria endemic countries have implemented community health worker (CHW) programmes to provide malaria diagnosis and treatment to populations living beyond the reach of health systems. However, there is limited evidence describing the referral practices of CHWs. We examined the impact of malaria rapid diagnostic tests (mRDTs) on CHW referral in two cluster randomised trials, one conducted in a moderate-to-high malaria transmission setting and one in a low-transmission setting in Uganda, between January-2010-July-2012. All CHWs were trained to prescribe artemisinin-based combination therapy (ACT) for malaria and recognise signs and symptoms for referral to health centres. CHWs in the control arm used a presumptive diagnosis for malaria based on clinical symptoms, whilst intervention arm CHWs used mRDTs. CHWs recorded ACT prescriptions, mRDT results and referral in patient registers. An intention-to-treat analyses was undertaken using multivariable logistic regression. Referral was more frequent in the intervention arm vs. the control arm (moderate-to-high transmission; $p<0.001$, low-transmission; $p<0.001$). Despite this increase, referral advice was not always given when ACTs or pre-referral rectal artesunate were prescribed: 14% prescribed rectal artesunate in the moderate-to-high setting were not referred. Additionally, CHWs considered factors alongside mRDTs when referring. Child visits during the weekends or the rainy season were less likely to be referred, while visits to CHWs more distant from health centres were more likely to be referred (low-transmission only). CHWs using mRDTs and ACTs increased referral compared to CHWs using a presumptive diagnosis. To address these concerns, referral training should be emphasised in CHW programmes as they are scaled-up.

Introduction

Early diagnosis and effective treatment for malaria is an essential strategy to reduce the high under-5 child morbidity and mortality associated with malaria in sub-Saharan Africa (SSA).(Liu et al. 2012; WHO 2013) To address the disease burden, UNICEF, WHO and Save the Children have supported SSA countries to implement national community-based programmes such as integrated community case management (iCCM) for the diagnosis and treatment of malaria, pneumonia and diarrhoea.(Nsona et al. 2012; Young et al. 2012) The programmes typically train laypersons with limited medical education, as community health workers (CHWs) that are able to provide case management services in communities with poor access to public health facilities.

Early community studies found CHWs were able to reduce malaria morbidity and mortality using a presumptive diagnosis based on clinical symptoms.(Kidane and Morrow 2000; Sirima et al. 2003) However, WHO now recommends all suspected cases of malaria should be tested with a malaria rapid diagnostic test (mRDT) and upon confirmation, treated with an artemisinin-based combination therapy (ACT).(World Health Organization 2015) Following WHO recommendations, and supported by strong evidence that CHWs can effectively treat uncomplicated malaria and adhere to mRDT results, (Harvey et al. 2008; Elmardi et al. 2009) many SSA countries have begun to introduce mRDTs and ACTs at the community level. Community programmes usually also train CHWs to refer children who present with complicated illnesses to a health centre for further management. A referral pathway is an important element of primary healthcare that ensures the continuity of a child’s care from the community to health centre. It helps to ensure that professional healthcare workers manage complex illnesses in medically equipped health facilities, whilst CHWs manage the uncomplicated illnesses in the community. Failure to refer or failure to comply with referral advice may increase the risk of medical complications. Despite the large body of evidence on implementing and scaling up national CHW programmes, currently there is relatively little evidence on referral practices by CHWs using both mRDTs and ACTs. Two small-scale studies in Tanzania and Sierra Leone found CHWs referred between 5% and 15% of children and very few children completed referral.(Thomson et al. 2011; Mubi et al. 2011) Filling the evidence gap on referral was identified as important component to improve the effectiveness, implementation and scale-up of community-based programmes by the international taskforce on iCCM. (Wazny et al. 2014)

We undertook an exploratory examination of referrals made by CHWs as part of two large trials that evaluated the impact of mRDTs on appropriately targeted ACTs: one trial was conducted in a moderate-to-high malaria transmission setting and the other in a low-transmission setting.(Ndyomugyenyi et al. 2016) The trials provided an opportunity to yield insights on how referral patterns can change following the introduction of mRDTs and the objective of this referral study was to examine the referrals made by CHWs and explore the factors associated with referral when CHWs diagnosed malaria using either a presumptive or mRDT-based diagnosis.

Methods

Study area and participants

Both trials were conducted in Rukungiri District, Western Region, Uganda, one in a moderate-to-high malaria transmission setting in Bwambara sub-county (980m-1200m above sea level), the other in a low-transmission setting in Nyakishenyi sub-county (1064m-2157m above sea level). The 2002 census for Uganda reported a population of 28,900 in the moderate-to-high transmission setting and 32,000 in the low-transmission setting, with more than 85% living in rural areas in both settings. (Rukungiri District Local Government 2009) The main occupation in both settings was subsistence agriculture and the majority of the population belonged to either Bahororo or Bakiga ethnic groups. The climate in the area is characteristic of East African tropics with mean annual temperatures between 16°C-25°C and a pronounced bimodal pattern of annual rainfall with a long rainy season between September to December and a short rainy season from March to May. Malaria transmission is perennial with peaks in incidence shortly after the rains.

The public health system in each transmission setting comprises of three health centres: two are classed as public Health Centre IIs (HCII), which only provide outpatient and community outreach services, and the third is a Health Centre III (HCIII) that provides basic preventive and curative care and supervises lower level health centre IIs. Health centre IIIs also have services for diagnosis, maternity care and act as the first referral cover for the sub-county (Ministry of Health 2014).

Trial design

A two-arm cluster randomized controlled trial (CRCT) design was used to evaluate the primary outcome of the main trials, to compare the effectiveness of CHWs using mRDTs versus CHWs using a presumptive diagnosis to treat malaria with an ACT. In each transmission setting a series of community meetings were held to explain the purpose of the research and to elect three adults per village for CHW training. All elected CHWs provided written and informed consent to take part in the trial and in each setting villages (clusters) were randomised in 1:1 ratio to either the intervention arm (mRDT diagnosis) or control arm (presumptive diagnosis) using Epi-Info. In the moderate-to-high transmission setting 63 villages were randomised (Figure 4.0), and in the low-transmission setting 64 were randomised (Figure 4.1). In addition, shortly before the trials began, community sensitisation was carried out in both transmission settings. Key messages included: not all fevers are malaria and a diagnostic test is advisable before treatment with an ACT; that a quick malaria test (mRDT) could test for malaria; and these tests were available from CHWs in the intervention arm.

Figure 4.0: Trial profile for the moderate-to-high transmission setting

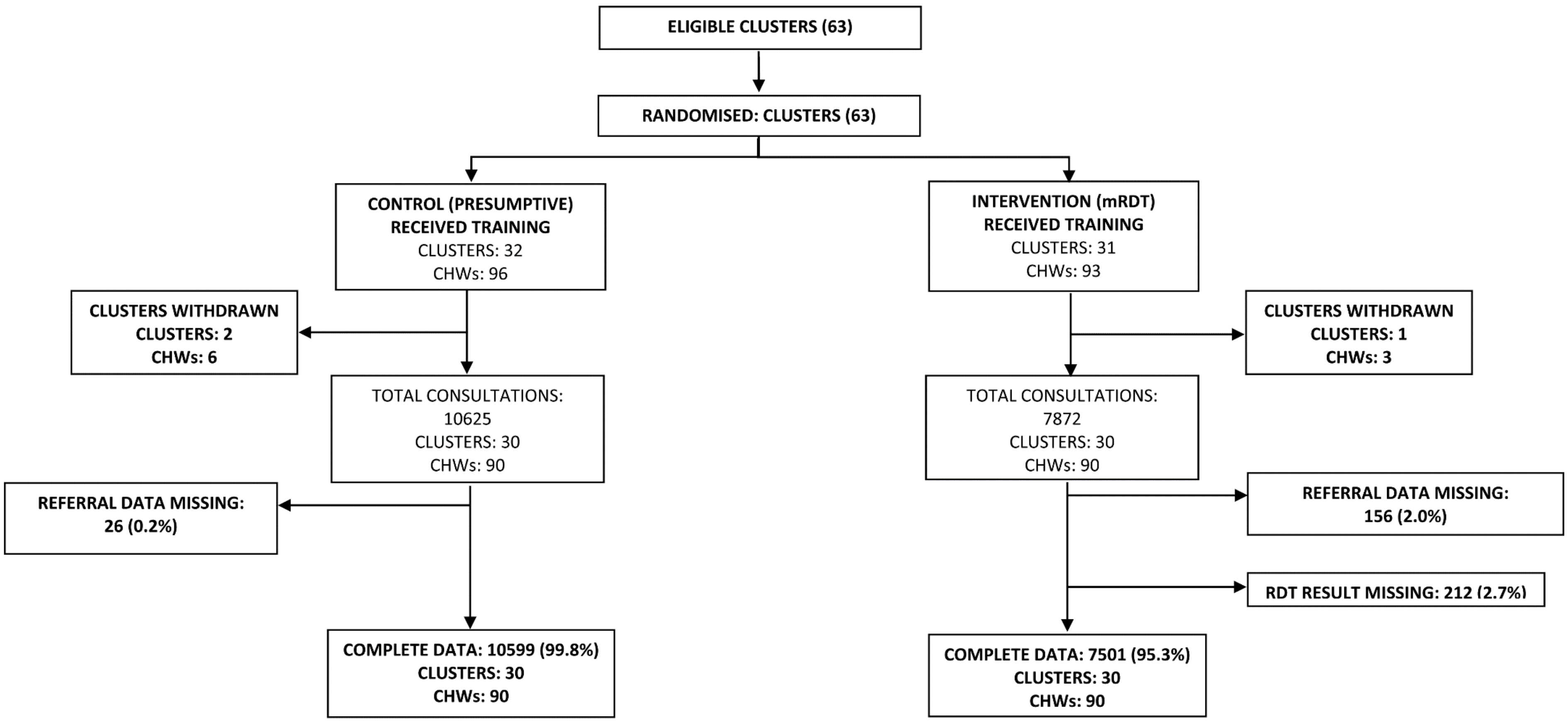
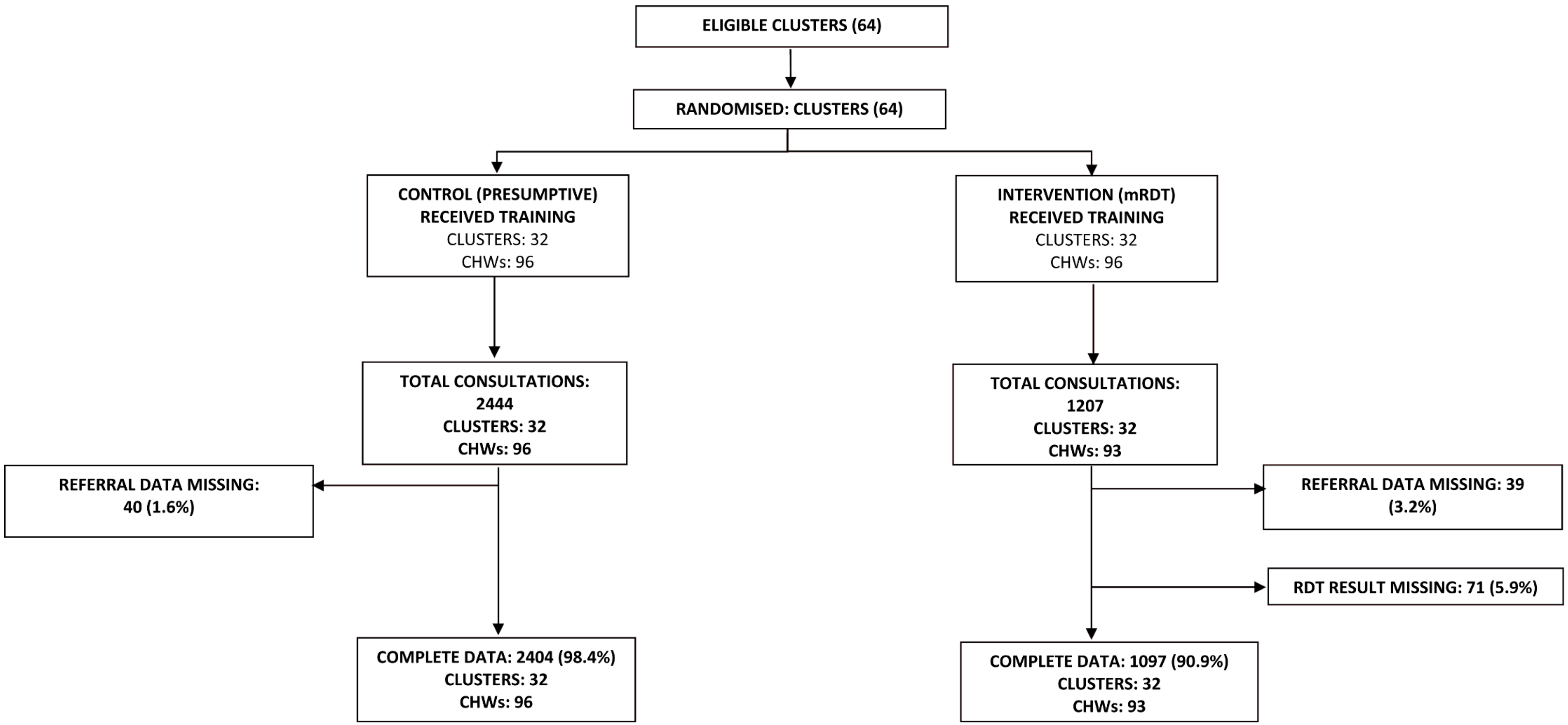


Figure 4.1: Trial profile for the low-transmission setting



CHW intervention

In January 2010, 381 CHWs received training (192 and 189 in the moderate-to-high and low transmission settings, respectively) in the management of febrile children during 3-4 day workshops. The training was based on a manual with simplified pictorial treatment algorithms (job aids) to help with malaria diagnosis (Figure S4.0). The key topics included: how to take a basic clinical history, physical examination skills, and counselling caregivers. All CHWs were also trained on how to identify non-severe and severe signs and symptoms, which would require immediate referral to the nearest health centre for further management. Severe signs and symptoms included convulsions or fits, extreme weakness, coma, loss of consciousness and very hot body temperature of 38.5°C or more, whilst non-severe signs and symptoms included wounds or burns, ear infections, sticky or red eyes and vomiting and diarrhoea (Figure 4.2). Members of the District Health Office, research staff and health centre workers conducted the workshops. These were interactive and included presentations, role-plays, demonstrations and supervised clinical practice at health centres.

Figure 4.2: List of severe and non-severe signs and symptoms that community health workers (CHWs) were trained to identify and refer in children

Severe sign and symptoms for urgent referral	Nonsevere sign and symptoms for referral
Refer using emergency referral form if child shows any of the following symptoms: 1. Illness in child below 2 months 2. Convulsions or fits now or within the past 2 days 3. Coma/loss of consciousness 4. Patient is confused or very sleepy-cannot be woken 5. Extreme weakness-unable to stand or sit without support 6. Very Hot-with temperature of 38.5°C or more 7. Very Cold-with temperature of 35.0°C or less 8. Vomiting everything-cannot keep down food or drink 9. Not able to drink or breast feed 10. Severe anaemia-very pale palms, fingernails, eyelids 11. Yellow eyes 12. Difficulty in breathing 13. Severe dehydration	*Refer using ordinary referral form if child shows any of the following symptoms:* 1. Fever in babies less than 4 months old 2. Fever that has last for more than 7 days 3. Fever with measured temperatures of 37°C or more and mRDT negative 4. Vomiting and diarrhoea 5. Blood in faeces or blood in urine 6. Pain when passing urine or frequent urination 7. Wound or burns 8. Skin abscess 9. Painful swelling or lumps in the skin 10. Ear infection (runny ear or child pulling at the ear) 11. Sticky or red eyes
If RDT result is positive: Treat child (if older than 2 months) with rectal artesunate suppository prior to referral.	***If RDT result is positive:*** Treat child (if older than 4 months) with artemether-lumefantine tablets prior to referral.

CHWs in the intervention arm were trained to diagnose uncomplicated malaria with an mRDT (First Response Malaria© -HRP2, Premier Medical Corp) and prescribe test-positive children with an age-dependent dose of ACT (artemether-lumefantrine, Lumartem®). CHWs were also trained to prescribe pre-referral treatment, rectal artesunate to children who visited with signs and symptoms of severe malaria and to refer them immediately to the nearest health centre. CHWs were trained not to prescribe ACT to children who were mRDT negative, and to refer those who had signs and symptoms of severe or non-severe illnesses (Figure S4.0). In contrast, CHWs in the control arm were trained to make a presumptive diagnosis based on the clinical symptoms of malaria if a child had a fever or history of fever without any other obvious cause of fever and prescribe an ACT, if there were severe signs and symptoms of disease they were trained to prescribe rectal artesunate and refer them immediately to the nearest health centre (Figure S4.0).

CHWs were also trained on how to manage stocks of consumables such as ACTs, gloves, cotton wool and mRDTs (intervention arm only). They recorded basic demographic details about the child, such as age, sex, their village of residence and the head of household's name on treatment recording forms. CHWs also reported the clinical history of the febrile illness such as the child's temperature, how long ago the fever started, and whether the child slept under a net the previous night. Finally, CHWs recorded whether an ACT or rectal artesunate was prescribed, the test result (intervention arm only) and whether they referred the child. In the event of a referral, CHWs were asked to classify it as a severe or non-severe referral and subsequently complete a referral form and mark the signs and symptoms they identified. The research team collected treatment recording forms and referral forms during monthly meetings. (Further details of the trial and training materials are available from www.actconsortium.org/RDThomemanagement).

Data collection

The trials in the moderate-to-high and low transmission settings started in May 2010 and June 2010 respectively. Between May/June 2010 and December 2010 CHWs were visited by field co-ordinators at least once per week to discuss concerns or difficulties in carrying out their roles and collected CHWs treatment recording forms, referral forms and stock cards for ACTs. From January 2011 to the end of the trial in July 2012, this supervision of CHWs was scaled back and limited to monthly meetings to reflect an operational programme.

To examine the patterns of referrals CHW made, we collected data from the treatment recording and referral forms for the 19-month "operational" intervention period (January 2011–July 2012). Previous studies suggested a number of characteristics that may influence referral patterns, these included the child's age, sex, net use the previous night, and the duration of fever. (Winch et al. 2003) In addition, the day of consultation (weekday/weekend) was derived from the date of the child's visit and a rainy season variable was defined to coincide with the rains that occurred in the months September-December and March-May. Finally, GPS coordinates were taken in the centre of each village and at the health centre to measure Euclidean (straight-line) distance from the centre of a village to the nearest health centre.

Statistical methods

All data were double entered and verified using Microsoft Access 2007 (Microsoft Inc., Redmond, Washington). Village distances to the nearest health centre were calculated using ArcGIS Desktop 10.3 (ESRI). All data were analysed using STATA version 14.1 (STATA Corporation, College Station, Texas).

The primary outcome for this analysis was the proportion of children that were referred by CHWs and a different method of analysis was undertaken for each trial. In the moderate-to-high transmission setting, 3 clusters (2 control arm and 1 intervention arm) withdrew from the trial after randomisation and contributed no data to the analyses, therefore a modified intention to treat analysis was undertaken with 30 clusters in each arm (Figure 4.0). In the low-transmission setting no clusters withdrew after randomisation and all clusters contributed data to the primary outcome analysis, allowing an intention-to-treat analysis (Figure 4.1).

We present child and cluster characteristics of the study population in each arm using descriptive statistics (proportions, means). We also assessed whether there were important differences between the arms by examining the size of any child- or cluster-level imbalances between the study arms after randomisation. Unadjusted and adjusted analyses were undertaken for each trial and clustering of data at the village level was accounted for using logistic regression models with random effects. (Hayes and Moulton 2009) To understand the aetiology of referral and identify a set of independent factors associated with referral, all factors identified a priori were included in multivariable models. In both the univariable and multivariable models the significance of factors was compared using a likelihood ratio test.

Ethics statement

The main trial was approved by the Uganda National Council for Science and Technology (Ref no. HS 555) and London School of Hygiene & Tropical Medicine Ethics Committee (Ref no. 5595). Prior to randomisation, meetings were held with community leaders in each village to explain the study objectives and procedures. Written informed consent was obtained from village leaders and CHWs to participate in the trial. At the time of visit with a CHW, children refusing an mRDT received presumptive treatment. The study was registered with ClinicalTrials.gov. Identifier NCT01048801, 13th January 2010. An independent data safety and monitoring board reviewed the protocol and the analytical plan.

Results

Study population

During the 19-month intervention period (January 2011-July 2012) 18,100 child visits were reported by CHWs in 60 villages in the moderate-to-high transmission setting (7,501 control arm, 10,599 intervention arm) (Figure 4.0). In the low-transmission setting, CHWs saw 3,501 children in 64 villages; 2,404 and 1,097 in the control and intervention arms respectively (Figure 4.1). There were similarities in both transmission settings and trial arms: the majority of children were aged between 1 and 5 years, approximately half were female, more than 86% had slept under a net the previous night, and nearly all (>82.0%) resided in the same village as the CHW (Table 4.0). We also examined characteristics that were different between the arms after randomisation and found a larger proportion of children visited control arm villages within 24 hours after the onset of fever symptoms, compared to the intervention arm (moderate-to-high transmission setting; 94.4% vs. 85.1%, low-transmission setting; 88.3% vs. 78.4%, control and intervention arms respectively). Similarly, a greater proportion of visits occurred during the rainy season in the intervention arm villages compared to the control arm (moderate-to-high transmission setting; 63.2% vs. 56.3%, low-transmission setting; 65.5% vs. 59.7%). The notable difference between the transmission settings was that children in the low-transmission setting lived more than 5 km away from the nearest public health centre compared to children in the moderate-to-high transmission setting (Table 4.0).

Table 4.0: Characteristics of children visiting community health workers (CHWs)

	Moderate-to-high transmission setting		Low-transmission setting	
	Control arm	**Intervention arm**	**Control arm**	**Intervention arm**
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
Number of participating villages (clusters)	30	30	32	32
Number of CHWs	90	90	96	93
Total number of child visits to CHWs	10599	7501	2404	1097
Age group (years)				
<1.0	2042 (19.4)	1528 (20.6)	587 (24.6)	297 (27.6)
1.0-2.9	3982 (37.7)	3113 (41.9)	970 (40.7)	478 (44.4)
3.0-4.9	4506 (42.7)	2751 (37.1)	817 (34.3)	295 (27.4)
5.0-15.0	21 (0.2)	33 (0.4)	11 (0.5)	6 (0.6)
Sex				
Male	5329 (50.6)	3907 (52.3)	1264 (52.6)	550 (50.1)
Female	5207 (49.4)	3559 (47.7)	1137 (47.3)	544 (49.6)
Slept under a net the previous night				
No	919 (8.7)	738 (9.8)	222 (9.2)	145 (13.2)
Yes	9507 (89.7)	6687 (89.1)	2146 (89.3)	938 (85.5)
Resident in the same village as CHW				
No	785 (7.4)	690 (9.2)	311 (12.9)	191 (17.4)
Yes	9751 (92.0)	6792 (90.5)	2085 (86.7)	901 (82.1)
Mean body temperature (°C)	37.43 (37.42-37.44)	37.38 (37.35-37.40)	37.42 (37.39-37.46)	37.21 (37.13-37.30)
Time of visit to CHW after onset of symptoms				
>24hrs	586 (5.6)	1089 (14.9)	271 (11.7)	232 (21.6)
Within 24hrs	9799 (94.4)	6222 (85.1)	2050 (88.3)	844 (78.4)
Day of visit to a CHW				
Weekday	7267 (68.6)	5219 (69.6)	1632 (67.9)	743 (67.7)
Weekend	3332 (31.4)	2282 (30.4)	772 (32.1)	354 (32.3)
Season of visit to a CHW				
Dry	4630 (43.7)	2761 (36.8)	969 (40.3)	378 (34.5)
Rainy	5969 (56.3)	4740 (63.2)	1435 (59.7)	719 (65.5)
Village distance to nearest health facility (km)				
0.0-2.4	4179 (39.8)	3995 (53.7)	793 (34.6)	204 (19.8)
2.5-4.9	5099 (48.6)	3234 (43.5)	667 (29.1)	487 (47.3)
5.0-7.4	1220 (11.6)	207 (2.8)	696 (30.3)	250 (24.3)
7.5-8.9	0 (0.0)	0 (0.0)	139 (6.1)	89 (8.6)

Data missing in the moderate-to-high transmission setting for: Age 124 (48 control, 76 intervention), sex 98 (63 control, 35 interventi under a net the previous night 249 (173 control, 76 intervention), Resident in the same village as CHW 82 (63 control, 19 interventic temperature (°C) 267 (187 control, 80 intervention), time of visit to CHW after of onset of symptoms 404 (214 control, 190 intervent
Data missing in the low-transmission setting for: Age 40 (19 control, 21 intervention), sex 6 (3 control, 3 intervention), slept under a previous night 50 (36 control, 14 intervention), resident in the same village as CHW 13 (8 control, 5 intervention), mean body tempe (23 control, 3 intervention), time of visit to CHW after of onset of symptoms 104 (83 control, 21 intervention).

Referral and treatment practices

CHWs in the low-transmission setting referred a greater proportion of child visits than CHWs in the moderate-to-high transmission setting (31.3% (1096/3501) vs. 15.2% (2,760/18,100)). Within each transmission setting CHWs referred more frequently in the intervention arm compared to the control arm (moderate-to-high transmission setting; 35.3% *vs.* 1.0% p<0.001, low-transmission setting; 71.3% *vs.* 13.1%, p<0.001, Table 4.1a, Table 4.1b). An examination of referrals according to mRDT results in the intervention arms, found 61.7% (2,558/4,147) of mRDT negative children were referred compared with 2.8% (93/3,355) of mRDT positive children in the moderate-to-high transmission setting (Table 4.1a). Whilst in the low-transmission setting 72.4% (770/1,064) of mRDT negative children were referred compared with 38.2% (13/34) mRDT positive children in the low-transmission setting (Table 4.1b).

CHWs ACT prescribing patterns and their referral practices are shown in Table 4.1a and Table 4.1b. Referral was more frequent when an ACT was not prescribed compared to when an ACT was prescribed in both settings (moderate-to-high transmission setting: 61.1% vs. 0.6%; low-transmission setting: 74.3% vs. 9.0%). In both settings the use of pre-referral rectal artesunate was low with less than 2% of all visits receiving rectal artesunate (0.4% (70/18,100) and 1.7% (59/3,501) in moderate-to-high and low-transmission setting, respectively). Not all children receiving rectal artesunate were referred: in the moderate-to-high transmission setting 14.3% (10/70) of children prescribed rectal artesunate were not referred; in contrast, in the low-transmission setting this figure was 1.7% (1/59).

CHWs classified referrals as non-severe or severe depending on the signs and symptoms they identified (Table 4.1a and 4.1b). Children visiting with severe signs and symptoms were more common in the low-transmission compared with the moderate-to-high transmission setting (11.5% vs. 5.5%). Non-severe signs and symptoms for referrals were more likely to be referred in intervention arm compared with control arm (62.6% vs. 24.7%, $p<0.001$) in the moderate-to-high transmission setting. There was no difference between the trial arm and the type of referrals CHWs made in the low-transmission setting ($p=0.120$).

Table 4.1: Children referred in each arm, their mRDT test result and ACT treatment received

a) Moderate-to-high transmission setting

	Total visits	**Number referred (%)**	*Number non-severe referrals (%)+*	*Number severe referrals (%)+*
Trial arm				
Control (Presumptive arm)	10599	109 (1.0)	*20 (24.7)*	*61 (75.3)*
Intervention (mRDT arm)	7501	2651 (35.3)	*1562 (62.6)*	*932 (37.4)*
Within intervention arm				
mRDT Negative	4147	2558 (61.7)	*1536 (63.3)*	*892 (36.7)*
mRDT Positive	3355	93 (2.8)	*26 (39.4)*	*40 (60.6)*
ACT Prescription§				
ACT Not prescribed	4039	2495 (61.8)	*1478 (62.7)*	*878 (37.3)*
ACT prescribed	13785	78 (0.6)	*25 (53.2)*	*22 (46.8)*
Rectal artesunate prescribed	70	60 (85.7)	*5 (9.8)*	*46 (90.2)*

§206 missing ACT Prescription

+ Percentage of type of referral (severe or non-severe) of those who were referred, 185 visits missing type (severe or non-severe) of referral

b) Low-transmission setting

	Total visits	**Number referred (%)**	*Number non-severe referrals (%)+*	*Number severe referrals (%)+*
Trial arm				
Control (Presumptive arm)	2404	314 (13.1)	*180 (67.7)*	*86 (32.3)*
Intervention (mRDT arm)	1097	782 (71.3)	*444 (58.3)*	*317 (41.7)*
Within intervention arm				
mRDT Negative	1064	770 (72.4)	*439 (58.4)*	*313 (41.6)*
mRDT Positive	34	13 (38.2)	*5 (50.0)*	*5 (50.0)*
ACT Prescription§				
ACT Not prescribed	1053	782 (74.3)	*454 (59.8)*	*305 (40.2)*
ACT prescribed	2328	209 (9.0)	*138 (79.8)*	*35 (20.2)*
Rectal artesunate prescribed	59	58 (98.3)	*12 (23.5)*	*39 (76.5)*

§206 missing ACT Prescription

+ Percentage of type of referral (severe or non-severe) of those who were referred, 185 visits missing type (severe or non-severe) of referral

Referral signs and symptoms

The specific signs and symptoms for referring a child were collected using a referral form separate to the treatment recording form and Table 4.2 lists the signs and symptoms CHWs identified using this referral form. On average CHWs recorded three or more signs and symptoms for referral on each referral form. However, it is important to note that unfortunately, despite the number of referrals made and recorded in the treatment recording form, CHWs returned very few referral forms to the research team. In the moderate-to-high transmission setting only 260 (9.4%) referral forms were collected despite CHWs reporting 2,760 referrals on the treatment recording form, similarly in the low-transmission setting only 204/1,096 (18.6%) forms were collected. The reason for this disparity is unknown, though it is possible that CHWs only informed patients verbally that additional treatment from a health facility was advisable.

In the intervention arm of each transmission setting, the most frequently reported non-severe signs and symptoms related to referral were; “fever and mRDT negative”, “vomiting/diarrhoea” and “pain when passing urine” (Table 4.2a). In contrast, the most frequent severe signs and symptoms related to referral were; “high fever”, “difficulty in breathing” and the “inability to drink or breastfeed” (Table 4.2b). When the signs and symptoms of referral were examined according to mRDT test result, there were generally very few signs and symptoms recorded for mRDT positive referrals compared to mRDT negative referrals, in both transmission settings (Table S4.0, Table S4.1).

Table 4.2a: Non-severe referral signs and symptoms of children visiting community health workers (CHWs)

	Moderate-to-high transmission setting		Low transmission setting	
	Control arm	**Intervention arm**	**Control arm**	**Intervention arm**
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
Non-severe signs and symptoms for referral				
Fever in babies less than 4 months old	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever that has lasted more than 7 days	0 (0.0)	16 (4.8)	1 (6.7)	3 (3.1)
Fever with measured temperature of >37°C and mRDT Negative	0 (0.0)	214 (64.3)	0 (0.0)	37 (38.1)
Vomiting and diarrhoea	1 (100.0)	30 (9.0)	7 (46.7)	13 (13.4)
Blood in faeces or urine	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Pain when passing urine, or frequent urination	0 (0.0)	7 (2.1)	1 (6.7)	3 (3.1)
Wounds or Burns	0 (0.0)	8 (2.4)	0 (0.0)	2 (2.1)
Skin abscess	0 (0.0)	3 (0.9)	0 (0.0)	0 (0.0)
Painful swellings or lumps in the skin	0 (0.0)	3 (0.9)	1 (6.7)	1 (1.0)
Ear infection (runny ear or child pulling at ear)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Sticky or red eyes	0 (0.0)	15 (4.5)	0 (0.0)	1 (1.0)
Other non-severe signs and symptoms #	0 (0.0)	34 (10.2)	5 (33.3)	37 (38.1)
Total number of non-severe signs and symptoms reported	1	333	15	97
Total number of non-severe referrals forms	1	108	16	24
Mean number of signs and symptoms reported per non-severe referral form	1.0	3.1	0.9	4.0

Other non-severe signs and symptoms in the moderate-to-high transmission setting intervention arm included; cough and flu (14), difficulty in breathing (1), swollen legs and eyes (1), headache (1), worms (1), high temperature (17), no fever (1)

Other non-severe signs and symptoms in the low-transmission setting intervention arm included; cough and flu (11), difficulty in breathing (1), high temperature (19), unable to breast feed (1), mouth wounds (1), control arm; cough (5).

Table 4.2b: Severe referral signs and symptoms of children visiting community health workers (CHWs)

	Moderate-to-high transmission setting		Low transmission setting	
	Control arm	**Intervention arm**	**Control arm**	**Intervention arm**
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
Severe signs and symptoms for referral				
Illness in child below 2 months	0 (0.0)	2 (0.6)	0 (0.0)	1 (1.7)
Convulsions or fits now or within the past 2 days	0 (0.0)	21 (5.9)	0 (0.0)	2 (3.4)
Coma / Loss of consciousness	0 (0.0)	6 (1.7)	1 (3.0)	0 (0.0)
Patient is confused or very sleepy - cannot be woken	1 (16.7)	4 (1.1)	1 (3.0)	1 (1.7)
Extreme weakness unable to stand or sit without support	1 (16.7)	10 (2.8)	1 (3.0)	2 (3.4)
Very Hot with temperature of 38.5°C or more	2 (33.3)	78 (22.0)	13 (39.4)	18 (30.5)
Very Cold with temperature of 35.0°C or less	0 (0.0)	10 (2.8)	1 (3.0)	2 (3.4)
Vomiting everything-cannot keep down food or drink	0 (0.0)	36 (10.2)	3 (9.1)	5 (8.5)
Not able to drink or breastfeed	0 (0.0)	52 (14.7)	1 (3.0)	7 (11.9)
Severe anaemia very pale palms, fingernails, eyelids	0 (0.0)	18 (5.1)	1 (3.0)	1 (1.7)
Yellow eyes	0 (0.0)	9 (2.5)	1 (3.0)	0 (0.0)
Difficulty in breathing	2 (33.3)	69 (19.5)	8 (24.2)	14 (23.7)
Severe dehydration	0 (0.0)	7 (2.0)	0 (0.0)	1 (1.7)
Other severe signs and symptoms ¶	0 (0.0)	32 (9.0)	2 (6.1)	5 (8.5)
Total number of severe signs and symptoms reported	6	354	33	59
Total number of severe referral forms	2	149	16	24
Mean number of signs and symptoms reported per severe referral form	3.0	2.4	2.1	2.5
Total number of severe and non-severe signs and symptoms reported	7	687	48	156
Total non-severe and severe referral forms*	3	257	31	78
Total referrals made	109	2651	314	782

$ Percentages are calculated based on the total number of signs and symptoms reported, ¶ Other severe signs and symptoms included in the moderate-to-high transmission setting intervention arm; cough and flu (19), diarrhoea (4), dysentery (2), burns (1), eye problems (2), painful ear (3), eating problem (1), yellow skin (1), vomiting (1), ¶Other severe signs and symptoms included in the low-transmission setting intervention arm; abdominal pain (1), constipation (1), cough (1), difficulty in breathing (1), eye problems (1), control arm; abdominal pain (1), eye problems (1)

Factors associated with referral

The results of the logistic regression analyses to explore child factors associated with referral are presented in Table 4.3 and Table 4.4 for the moderate-to-high and low-transmission settings respectively. In the adjusted analysis of both transmission settings we found an independent relationship between ACT prescription and referral. Children who were prescribed ACTs had a lower odds of referral when compared to children who were not prescribed ACTs (moderate-to-high transmission setting: OR 0.003; 95%CI 0.002-0.004; p<0.001, low-transmission setting: OR 0.03; 95%CI 0.01-0.05; p<0.001). The adjusted analysis also showed CHWs in the intervention arm using mRDTs had a greater odds of referring visits compared with CHWs using a presumptive diagnosis, however this finding was not statistically significant (moderate-to-high transmission setting OR 2.07; 95%CI 0.97-4.41; p=0.06, low-transmission setting; OR 2.07; 95%CI 0.90-4.79; p=0.09). Associations were found in the moderate-to-high transmission setting (Table 4.3), children who visited on a weekday compared to the weekend had a lower odds of referral (OR 0.76; 95%CI 0.65-0.89; p=0.01), as were children who visited during the rainy season compared to the dry season (OR 0.85; 95%CI 0.73-0.99; p=0.04). Children who visited within 24 hours of their symptom onset also had a lower odds of referral (OR 0.76; 95%CI 0.61-0.94; p=0.01) and the odds of referral was greater when children slept under a net the previous night compared to children not sleeping under a net (OR 1.41; 95%CI 1.08-1.85; p=0.011). In the low-transmission setting, the only factor in addition to ACT prescription independently associated with referral was distance. Children residing in villages further away from health centres had a lower odds of being referred (p=0.001) compared to children living closer to health centres (Table 4.4).

Table 4.3: Odds ratios for referral of children in the moderate-to-high transmission setting

Variables	Total visits	Referrals made (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Study arm						
Control	10599	109 (1.0)	1		1	
mRDT intervention	7501	2651 (35.3)	61.90 (38.40-99.77)	<0.0001	2.07 (0.97-4.41)	0.060
Age group (years)						
<1.0	3570	804 (22.5)	1		1	
1.0-2.9	7095	1148 (16.2)	0.55 (0.48-0.62)	<0.0001	0.88 (0.73-1.05)	
3.0-4.9	7257	771 (10.6)	0.31 (0.27-0.36)		0.79 (0.65-0.97)	0.140
5.0-15.0	54	10 (18.5)	0.43 (0.19-0.95)		0.68 (0.18-2.53)	
Sex						
Male	9236	1430 (15.5)	1		1	
Female	8766	1309 (14.9)	0.93 (0.84-1.02)	0.1330	0.95 (0.82-1.11)	0.528
Slept under a net the previous night						
No	1657	263 (15.9)	1		1	
Yes	16194	2450 (15.1)	1.52 (1.27-1.83)	<0.0001	1.41 (1.08-1.85)	0.011
Resident in the same village as CHW						
No	1475	310 (21.0)	1		1	
Yes	16543	2442 (14.8)	1.03 (0.87-1.22)	0.7510	0.91 (0.69-1.21)	0.531
Time of visit to CHW after onset of symptoms						
>24hrs	1675	399 (23.8)	1		1	
Within 24hrs	16021	2281 (14.2)	0.80 (0.69-0.92)	0.0020	0.76 (0.61-0.94)	0.011
ACT Prescription						
No ACT	4039	2495 (61.8)	1		1	
ACT	13785	78 (0.6)	0.003 (0.002-0.004)	<0.0001	0.003 (0.002-0.004)	<0.001
Day of visit to a CHW						
Weekday	12486	1977 (15.8)	1		1	
Weekend	5614	783 (13.9)	0.86 (0.77-0.95)	0.0050	0.76 (0.65-0.89)	0.001
Season of visit to a CHW						
Dry	7391	1110 (15.0)	1		1	
Rainy	10709	1650 (15.4)	0.79 (0.71-0.87)	<0.0001	0.85 (0.73-0.99)	0.042
Village distance to nearest health centre (km)						
0.0-2.4	8174	1548 (18.9)	1		1	
2.5-4.9	8333	1116 (13.4)	1.15 (0.84-1.59)		1.28 (0.81-2.03)	
5.0-7.4	1427	72 (5.0)	0.97 (0.37-2.52)	0.647	1.24 (0.44-3.49)	0.579
7.5-8.9	n/a	n/a	n/a		n/a	

Table 4.4: Odds ratios for referral of children in the low-transmission setting

Variables	Total visits	Referrals made (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Study arm						
Control	2404	314 (13.1)	1		1	
mRDT intervention	1097	782 (71.3)	28.45 (15.41-52.49)	<0.001	2.07 (0.90-4.79)	0.090
Age group (years)						
<1.0	884	313 (35.4)	1		1	
1.0-2.9	1448	467 (32.3)	0.75 (0.59-0.95)	0.002	0.90 (0.68-1.20)	
3.0-4.9	1112	291 (26.2)	0.64 (0.49-0.83)		0.74 (0.54-1.01)	0.285
5.0-15.0	17	9 (52.9)	2.23 (0.61-8.15)		0.74 (0.13-4.32)	
Sex						
Male	1814	564 (31.1)	1		1	
Female	1681	527 (31.4)	0.93 (0.77-1.13)	0.463	0.94 (0.74-1.18)	0.579
Slept under a net the previous night						
No	367	124 (33.8)	1		1	
Yes	3084	951 (30.8)	1.04 (0.76-1.43)	0.788	1.12 (0.77-1.64)	0.552
Resident in the same village as CHW						
No	502	177 (35.3)	1		1	
Yes	2986	916 (30.7)	1.11 (0.85-1.47)	0.440	1.19 (0.81-1.73)	0.372
Time of presentation to CHW after onset of symptoms						
>24hrs	503	212 (42.1)	1		1	
Within 24hrs	2894	851 (29.4)	0.83 (0.63-1.09)	0.180	0.89 (0.64-1.22)	0.464
ACT Prescription						
No ACT	1053	782 (74.3)	1		1	
ACT	2328	209 (9.0)	0.02 (0.01-0.03)	<0.001	0.03 (0.02-0.05)	<0.001
Day of visit to a CHW						
Weekday	2375	763 (32.1)	1		1	
Weekend	1126	333 (29.6)	0.82 (0.67-1.01)	0.058	0.88 (0.69-1.13)	0.321
Season of visit to a CHW						
Dry	1347	403 (29.9)	1		1	
Rainy	2154	693 (32.2)	1.01 (0.82-1.23)	0.960	0.98 (0.77-1.25)	0.859
Village distance to nearest health centre (km)						
0.0-2.4	997	285 (28.6)	1		1	
2.5-4.9	1154	384 (33.3)	0.75 (0.34-1.66)		0.42 (0.21-0.83)	
5.0-7.4	946	236 (24.9)	1.36 (0.52-3.58)	0.111	0.98 (0.46-2.12)	0.001
7.5-8.9	228	124 (54.4)	3.66 (0.88-15.19)		3.23 (1.01-10.38)	

Discussion

This study demonstrates that CHWs trained to use mRDTs for malaria diagnosis refer children to health centres more frequently than CHWs using a presumptive clinical diagnosis. In both arms of the trials CHWs were trained to refer based on the child's presenting signs and symptoms and thus referral rates were expected to be similar across the two arms, however we found the mRDT result and prescription of an ACT affected the pattern of referral. In both transmission settings, almost all children who were diagnosed presumptively without an mRDT received an ACT and very few were referred. Similarly, children who were mRDT positive and treated with an ACT were rarely referred for other conditions. In contrast, referral was more likely in mRDT negative children, who usually did not receive an ACT. These data suggest that although mRDT use can result in more referrals overall, the possibility of co-infections and other illnesses may be still overlooked in mRDT positive children and the opportunity for early detection and referral is missed. Since the presence of referral signs and symptoms in children and their environment is unlikely to be affected by the method of diagnosis used by CHWs, this suggests that use of mRDTs encourages CHWs to consider alternative diagnoses if an ACT was not prescribed.

There were some observed differences between the two transmission settings. Referral was more frequent in the mRDT arm of the low-transmission setting compared with the mRDT arm of the moderate-to-high transmission setting. CHWs were trained to refer all children receiving pre-referral treatment rectal artesunate, despite this only 14% of children receiving rectal artesunate in the moderate-to-high transmission setting were not referred. In contrast, almost all children receiving rectal artesunate in the low-transmission setting were referred. Poor adherence to the guidelines regarding the use of rectal artesunate in a community-based setting is a concern. Failure to refer children immediately to the nearest health centre for further management when they are mRDT positive have severe malaria signs and symptoms and given rectal artesunate increases the child's risk of health complications, morbidity and death.

The tendency of CHWs to report very few signs and symptoms on the referral form for children diagnosed presumptively or mRDT-positive, compared to the greater range reported for children who were mRDT negative, may be partially explained by ACT prescription. Nearly all children in these two groups (presumptive and mRDT positive) received an ACT and CHWs may have considered the child as treated and they may therefore have been less likely to observe and record other signs and symptoms requiring referral. In contrast, when the child is mRDT negative and the CHW decides not to give the child an ACT, CHWs may attempt to identify more signs and symptoms of disease. It is also possible that children who were mRDT negative, may have presented with a more complex and obvious set of clinical signs and symptoms, compared to mRDT positive and presumptively diagnosed children who may have only presented with one or two discrete referral signs and symptoms. CHWs may increase the risk of further complications when ACTs are prescribed to children who are mRDT positive but fail to identify other clinical symptoms requiring referral. Unfortunately, in this study we cannot know if CHWs were more likely to have missed signs and symptoms for referral in mRDT positive children, because we did not directly observe CHWs practice of identifying referral signs and symptoms in these children. Nevertheless, the data presented here are suggestive of a possible concern, and further research, which includes observation of the clinical encounters at community-level, is needed.

Although the factors independently associated with referral differed between the two transmission settings, prescription of an ACT was negatively associated with referral in both settings. Indeed, once ACTs were entered into multivariable model differences according to the method of diagnosis (presumptive or mRDT) were reduced and no longer reached statistical significance. In the moderate-to-high transmission setting, other factors associated with a lower likelihood of referral included visits to CHWs during the weekend compared with a weekday, and during the rainy season compared with the dry season. These findings might be explained by perceived barriers to accessing healthcare in the area; during the weekend, health centres were often not open nor were they staffed with health workers and during the rainy season, roads and paths may become difficult to use to access the health centres. Given these barriers, CHWs may have been reluctant to refer. The multivariable analysis also found some evidence that children who presented within 24 hours of their symptoms starting were less likely to be referred. This could indicate that CHWs were waiting to see if the child's signs and symptoms worsened over the course of a day and only referred them after 24 hours if they worsened. Paradoxically, there was also some evidence to suggest that sleeping under a mosquito net the previous night increased the chance of being referred; the reasons for which are unclear. In the low-transmission setting, we also found the main driver of referral to be the prescribing pattern of ACTs and the only additional factor associated with referral was the distance of the village to the nearest health centre. CHWs living in villages further away from public health centres were more likely to refer children than those living in villages closer to health centres. This observation might also have been affected by the presence of a privately run mission hospital that was located at the outskirts of the sub-county and further away from the more centrally located public health facilities in the low-transmission sub-county.

This and a number of other contextual factors differed between transmission settings which may partly explain the tendency for CHWs in the low-transmission setting to refer more frequently than CHWs in the moderate-to-high transmission setting. Firstly, the type of signs and symptoms that children presented with may differed between the two transmission settings. More children in the low-transmission setting were reported to have signs and symptoms of severe illness compared to children in the moderate-to-high transmission setting, which may have resulted in CHWs in the low-transmission setting referring more frequently than CHWs in the moderate-to-high transmission. The higher frequency of severe signs and symptoms in the low-transmission setting could reflect a lack of acquired immunity to malaria amongst young children living in this epidemic-prone area of the Ugandan highlands. Secondly, CHWs in the moderate-to-high transmission setting experienced a high number of visits and through experience they may have judged that they knew when it was safe not refer a child visit. In contrast CHWs in the low-transmission experienced substantially fewer visits than CHWs in the moderate-to-high transmission setting and may have felt less confident in their diagnostic competence and/or ability to make judgements about when it might be safe not to refer a child. Finally, in the low-transmission setting CHWs were also able to refer patients to a large privately run mission hospital, which also co-ordinated a community-based health insurance scheme in the area. The scheme may have facilitated CHWs tendency to refer, being more confident knowing that health services and drugs would be available and that caretakers would comply with the referral advice.

When interpreting these findings there are limitations that ought to be considered. CHWs often did not report the signs and symptoms for referral and very few referral forms were collected from CHWs compared to the treatment recording forms. CHWs reported child characteristics, fever history, treatment and referral decisions (including whether it was a severe or non-severe referral) on the treatment recording forms, whilst the referral forms captured the specific signs and symptoms for referral and were given to the caretaker to take to the health centre. There is no obvious reason why very few referral forms were completed by CHWs, but some qualitative evidence from comments recorded by CHWs on the treatment forms suggests caretakers often refused referral forms and did not want be referred to health centres. It is thus possible that CHWs only informed patients verbally that additional treatment from a health facility was advisable. Therefore, the data on referral signs and symptoms recorded on the forms may not be representative of all children who were referred by CHWs. Finally, in this analysis we did not examine whether CHWs made the appropriate decision to refer. An analysis of referral in children with measured temperature >38°C (an eligibility criterion for urgent referral) in this study, suggests that CHW adherence to referral guidelines was poor and CHWs failed to refer children who were eligible for referral (Lal *et al.*, 2016). Therefore, the combination of under-reporting of referrals and failure to refer children who were eligible for referral, may underestimate the true number of children who should have been referred (Chinbuah *et al.*, 2013). In addition to the data reporting practices by CHWs, there were also differences in the statistical analyses of each trial. In the moderate-to-high transmission setting, a modified-intention to treat analysis was undertaken because after randomisation, 3 of the 63 clusters (9/189 CHWs) withdrew from the study and did not provide data for the final analysis. Post-randomisation withdrawal of clusters that were not included in the analysis may bias the results because CHWs in the clusters that withdrew from the study may have differed from those that did not withdraw. Therefore, some of the differences in referrals CHWs made between the two arms may not have been due to the intervention, but due to the differences between CHWs in each trial that remained in the study. However, in low-transmission setting trial, CHWs in all clusters contributed data to the primary outcome and an intention-to-treat analysis was used. Due to the different analytical approaches used, findings from the trial in the moderate-to-high transmission setting may not be directly comparable with the findings from the low-transmission trial. Although this study had limitations, similar patterns of referral and a strong relationship between prescription of ACT and referral were observed in both trials.

Despite the limitations, these results are consistent with previous studies that compared referral practices from CHWs trained to use either an mRDT or a presumptive diagnosis for malaria. A randomised crossover trial in Tanzania found CHWs trained to use mRDTs were more than 4 times more likely to refer children compared to CHWs trained to use a presumptive diagnosis. (Mubi *et al.*, 2011) However, this previous study did not report whether the proportion of referrals differed by mRDT positive or negative results. Our results were also consistent with a study in Sierra Leone that found referral was more common amongst mRDT negative patients compared with mRDT positive children. (Thomson *et al.*, 2011) Our study expands on these previous works by describing CHWs referral patterns over a larger time span, in two contrasting malaria transmission settings and exploring other factors in addition to the diagnosis method that might affect the CHW's decision to refer.

These trials were designed and conducted before iCCM became national policy for many SSA countries and the training in this study related to malaria, thus all the findings may not be generalizable to iCCM programmes which also include the management of pneumonia and diarrhoea in addition to malaria. However, there are a number of referral findings presented here that are of direct relevance to iCCM programmes. Firstly, routinely available data can be used to monitor and evaluate CHWs referral practices. Secondly, CHW training packages should emphasise the provision of referral advice to all children upon the identification of signs and symptoms requiring referral, and finally training should strongly state that all children prescribed rectal artesunate should be referred for further management. Referral patterns and the reasons CHWs take to refer children should be examined in further studies along with the health outcomes of children referred.

Conclusion

During the course of two years we observed low referral rates in two contrasting malaria transmission settings, but training CHWs to use mRDTs and ACTs increased the referral of children compared to CHWs trained to use a presumptive clinical diagnosis for malaria. Despite the increase, referral advice was not always given when rectal artesunate was prescribed as a pre-referral treatment. We also found CHWs considered other factors alongside mRDTs and ACTs when considering to give referral advice. These findings suggest training on referral should be emphasised in iCCM programmes being scaled-up in SSA and that additional research is required to examine whether CHWs referral decision making is appropriate as well as the final health outcomes of referred children.

Contributors

SL RN, PM, KSH and SC conceived the idea for this research. SL conducted the analysis and wrote the first draft of the paper. All authors reviewed and provided substantial input to the manuscript.

Competing interests

We declare no competing interests.

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Table S4.0: Referral signs and symptoms of children visiting community health workers (CHWs) by mRDT results, in the moderate-to-high transmission setting

	Moderate-to-high transmission setting[¢]		
	Intervention arm Frequency (%)	*mRDT Negative* Frequency (%)	*mRDT Positive* Frequency (%)
Non-severe signs and symptoms for referral			
Fever in babies less than 4 months old	0 (0.0)	0 (0.0)	0 (0.0)
Fever that has lasted more than 7 days	16 (4.8)	16 (4.9)	0 (0.0)
Fever with measured temperature of >37°C and mRDT Negative	214 (64.3)	214 (65.0)	0 (0.0)
Vomiting and diarrhoea	30 (9.0)	29 (8.8)	1 (25.0)
Blood in faeces or urine	2 (0.6)	2 (0.6)	0 (0.0)
Pain when passing urine, or frequent urination	7 (2.1)	7 (2.1)	0 (0.0)
Wounds or Burns	8 (2.4)	8 (2.4)	0 (0.0)
Skin abscess	3 (0.9)	3 (0.9)	0 (0.0)
Painful swellings or lumps in the skin	3 (0.9)	3 (0.9)	0 (0.0)
Ear infection (runny ear or child pulling at ear)	1 (0.3)	1 (0.3)	0 (0.0)
Sticky or red eyes	15 (4.5)	13 (4.0)	2 (50.0)
Other non-severe signs and symptoms[∞]	34 (10.2)	33 (10.0)	1 (25.0)
Total number of non-severe signs and symptoms reported	333	329	4
Total number of non-severe referrals forms	108	103	5
Mean number of signs and symptoms reported per referral form	3.1	3.2	0.8
Severe signs and symptoms for referral			
Illness in child below 2 months	2 (0.6)	2 (0.6)	0 (0.0)
Convulsions or fits now or within the past 2 days	21 (5.9)	19 (5.7)	2 (10.0)
Coma / Loss of consciousness	6 (1.7)	5 (1.5)	1 (5.0)
Patient is confused or very sleepy - cannot be woken	4 (1.1)	4 (1.2)	0 (0.0)
Extreme weakness unable to stand or sit without support	10 (2.8)	9 (2.7)	1 (5.0)
Very Hot with temperature of 38.5°C or more	78 (22.0)	73 (21.9)	5 (25.0)
Very Cold with temperature of 35.0°C or less	10 (2.8)	10 (3.0)	0 (0.0)
Vomiting everything - cannot keep down food or drink	36 (10.2)	35 (10.5)	1 (5.0)
Not able to drink or breastfeed	52 (14.7)	48 (14.4)	4 (20.0)
Severe anaemia very pale palms, fingernails, eyelids	18 (5.1)	17 (5.1)	1 (5.0)
Yellow eyes	9 (2.5)	8 (2.4)	1 (5.0)
Difficulty in breathing	69 (19.5)	65 (19.5)	4 (20.0)
Severe dehydration	7 (2.0)	7 (2.1)	0 (0.0)
Other severe symptoms[≠]	32 (9.0)	32 (9.6)	0 (0.0)
Total number of signs and symptoms reported	354	334	20
Total number of severe referral forms	149	142	7
Mean number of symptoms reported per severe referral form	2.4	2.4	2.9
Total number of severe and non-severe symptoms reported	687	663	24
Total non-severe and severe referral forms	257	245	12
Total referrals made	2651	2558	93

¢ Percentages are calculated based on the total number of signs and symptoms reported

∞ Other non-severe signs and symptoms in children mRDT negative included; cough and flu (14), difficulty in breathing (1), swollen legs and eyes (1), headache (1), worms (1), high temperature (15)

∞ Other non-severe symptoms in children mRDT positive included; cough and flu (1)

≠ Other severe signs and symptoms included in children mRDT negative included; cough and flu (17), diarrhoea (4), dysentery (2), burns (1), eye problems (2), painful ear (3), eating problem (1), yellow skin (1), vomiting (1)

Table S4.1: Referral signs and symptoms of children visiting community health workers (CHWs) by mRDT results, in the low-transmission setting

	Low-transmission setting[@]		
	Intervention arm Frequency (%)	*mRDT Negative* Frequency (%)	*mRDT Positive* Frequency (%)
Non-severe signs and symptoms for referral			
Fever in babies less than 4 months old	0 (0.0)	0 (0.0)	0 (0.0)
Fever that has lasted more than 7 days	16 (4.8)	16 (4.9)	0 (0.0)
Fever with measured temperature of >37°C and mRDT Negative	214 (64.3)	214 (65.0)	0 (0.0)
Vomiting and diarrhoea	30 (9.0)	29 (8.8)	1 (25.0)
Blood in faeces or urine	2 (0.6)	2 (0.6)	0 (0.0)
Pain when passing urine, or frequent urination	7 (2.1)	7 (2.1)	0 (0.0)
Wounds or Burns	8 (2.4)	8 (2.4)	0 (0.0)
Skin abscess	3 (0.9)	3 (0.9)	0 (0.0)
Painful swellings or lumps in the skin	3 (0.9)	3 (0.9)	0 (0.0)
Ear infection (runny ear or child pulling at ear)	1 (0.3)	1 (0.3)	0 (0.0)
Sticky or red eyes	15 (4.5)	13 (4.0)	2 (50.0)
Other non-severe signs and symptoms^	34 (10.2)	33 (10.0)	1 (25.0)
Total number of non-severe signs and symptoms reported	333	329	4
Total number of non-severe referrals forms	108	103	5
Mean number of signs and symptoms reported per referral form	3.1	3.2	0.8
Severe signs and symptoms for referral			
Illness in child below 2 months	2 (0.6)	2 (0.6)	0 (0.0)
Convulsions or fits now or within the past 2 days	21 (5.9)	19 (5.7)	2 (10.0)
Coma / Loss of consciousness	6 (1.7)	5 (1.5)	1 (5.0)
Patient is confused or very sleepy - cannot be woken	4 (1.1)	4 (1.2)	0 (0.0)
Extreme weakness unable to stand or sit without support	10 (2.8)	9 (2.7)	1 (5.0)
Very Hot with temperature of 38.5°C or more	78 (22.0)	73 (21.9)	5 (25.0)
Very Cold with temperature of 35.0°C or less	10 (2.8)	10 (3.0)	0 (0.0)
Vomiting everything - cannot keep down food or drink	36 (10.2)	35 (10.5)	1 (5.0)
Not able to drink or breastfeed	52 (14.7)	48 (14.4)	4 (20.0)
Severe anaemia very pale palms, fingernails, eyelids	18 (5.1)	17 (5.1)	1 (5.0)
Yellow eyes	9 (2.5)	8 (2.4)	1 (5.0)
Difficulty in breathing	69 (19.5)	65 (19.5)	4 (20.0)
Severe dehydration	7 (2.0)	7 (2.1)	0 (0.0)
Other severe symptoms~	32 (9.0)	32 (9.6)	0 (0.0)
Total number of signs and symptoms reported	354	334	20
Total number of severe referral forms	149	142	7
Mean number of symptoms reported per severe referral form	2.4	2.4	2.9
Total number of severe and non-severe symptoms reported	687	663	24
Total non-severe and severe referral forms	257	245	12
Total referrals made	2651	2558	93

@ Percentages are calculated based on the total number of signs and symptoms reported

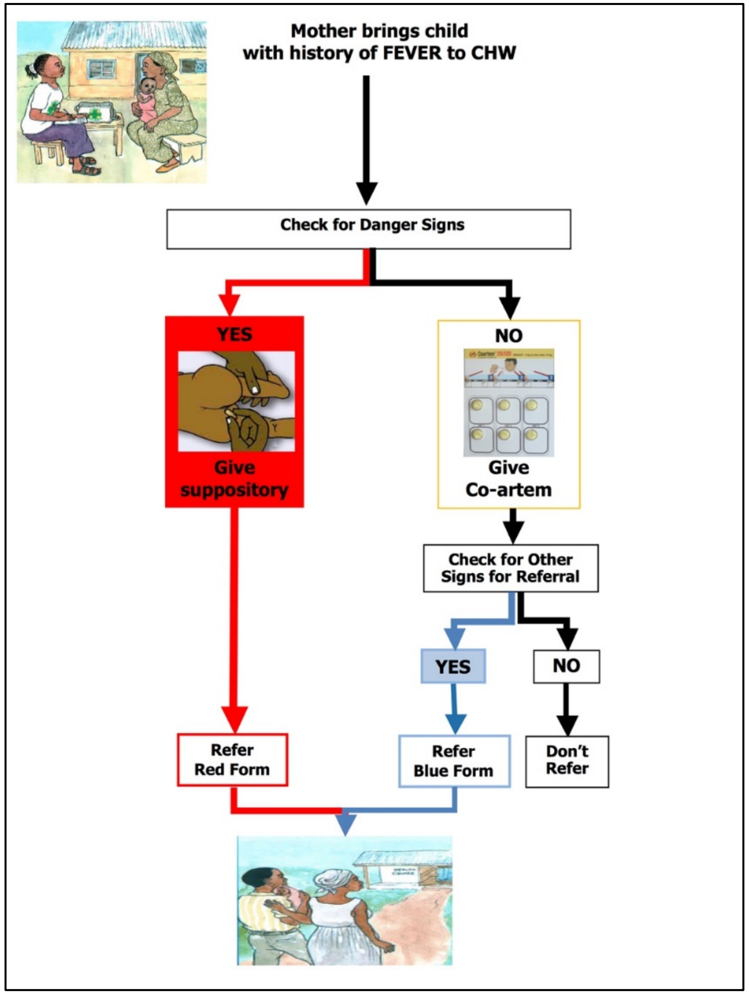
^ Other non-severe signs and symptoms of mRDT negative children included; cough and flu (8), vomiting (1), high temperature (20) difficulty in breathing (2), eating problem (1), headache (2), worms (1)

^ Other non-severe signs and symptoms of mRDT positive children included; cough and flu (1), headache (1)

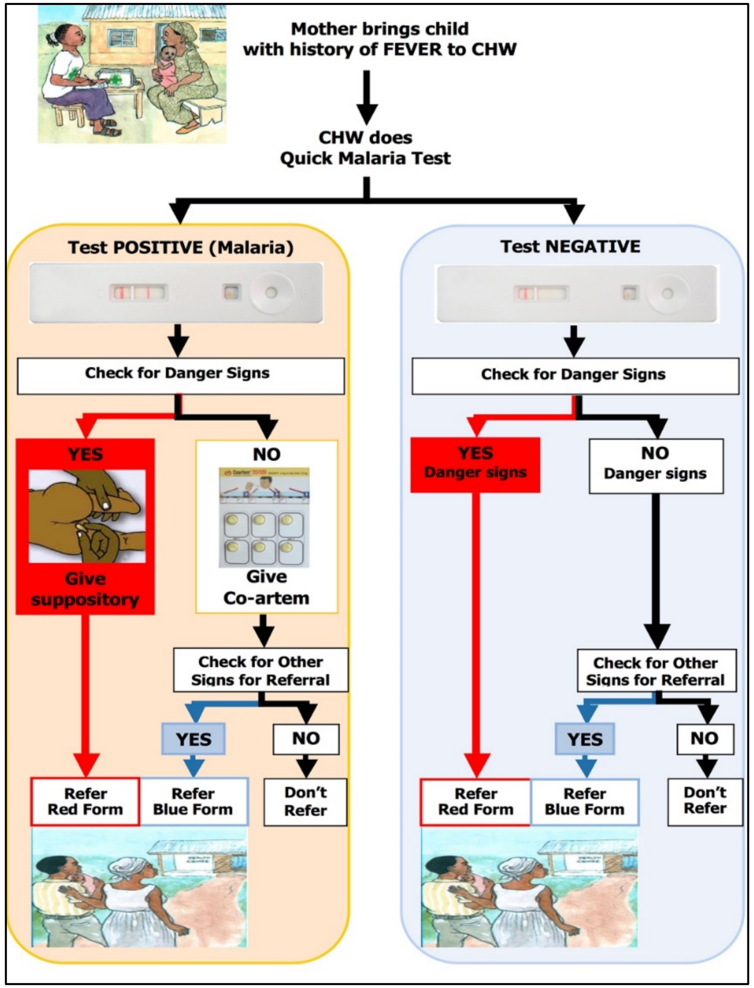
~ Other severe signs and symptoms of children in the intervention arm included; abdominal pain (1), constipation (1), cough (1), difficulty in breathing (1), eye problems (1)

Figure S4.0: Job aid for CHWs in a) control (presumptive) arm, b) intervention (mRDT) arm

a) Control arm



b) Intervention arm



Chapter 5: Caregivers' compliance with referral advice

Adapted from: Sham Lal, Richard Ndyomugenyi, Lucy Paintain, Neal D. Alexander, Kristian S. Hansen, Pascal Magnussen, Daniel Chandramohan, Siân E. Clarke. 2018. "*Caregivers' compliance with referral advice: evidence from two studies introducing mRDTs into community case management of malaria in Uganda*" BMC Health Services Research (accepted, in press).

Abstract

Background

Several malaria endemic countries have implemented community health worker (CHW) programmes to increase access to populations underserved by health care. There is considerable evidence on CHW adherence to case management guidelines, however, there is limited evidence on the compliance to referral advice and the outcomes of children under-5 referred by CHWs. This analysis examined whether caregivers complied with CHWs referral advice.

Methods

Data from two cluster (village) randomised trials, one in a moderate-to-high malaria transmission setting, another in a low-transmission setting conducted between January 2010-July 2011 were analysed. CHW were trained to recognise signs and symptoms that required referral to a health centre. CHW in the intervention arm also had training on; malaria rapid diagnostic tests (mRDT) and administering artemisinin based combination therapy (ACT); CHW in the control arm were trained to treat malaria with ACTs based on fever symptoms. Caregivers' referral forms were linked with CHW treatment forms to determine whether caregivers complied with the referral advice. Factors associated with compliance were examined with logistic regression.

Results

CHW saw 18,497 child visits in the moderate-to-high transmission setting and referred 15.4% (2,815/18,315, 182 missing data) of all visits; in the low-transmission setting, 31.8%

(1,135/3,572, 72 missing data) of all visits were referred. Compliance to referral was low, in both settings <10% of caregivers complied with referral advice. In the moderate-to-high transmission setting compliance was higher if children were tested with mRDT compared to children who were not tested with mRDT. In both settings, nearly all children treated with pre-referral rectal artesunate failed to comply with referral and compliance was independently associated with factors such as health centre distance and day of referral by a CHW. In the moderate-to-high transmission setting, time of presentation, severity of referral were also associated with compliance, whilst in the low-transmission setting, compliance was low if an ACT was prescribed.

Conclusions

This analysis suggests there are several barriers to comply with CHWs referral advice by caregivers. This is concerning for children who received rectal artesunate. As CHW programmes continue scale-up, barriers to referral compliance need to be addressed to ensure a continuum of care from the community to the health centre.

Introduction

Globally there have been considerable declines in malaria mortality rates during the past decade, but progress has been slowest in countries where the burden of malaria is highest and where access to primary healthcare is most limited (Cibulskis et al., 2016). In Uganda, where malaria accounts for approximately 18% of all deaths in children under-5 years, approximately 65% of the population lived more than 5 km from the nearest government health centre (Murray et al., 2014; UBOS, 2014b). To address the disease burden and increase access to healthcare, community health worker (CHW) programmes such as integrated community case management (iCCM), have been extensively supported by WHO, UNICEF and The Global Fund since 2012 (Young et al., 2012). Studies suggest that when CHW are appropriately trained, supplied and supported, they can increase access to healthcare and reduce under-5 mortality by providing primary healthcare closer to homes of children at risk of malaria (Yeboah-Antwi et al., 2010; Kidane and Morrow, 2000; Das et al., 2013).

A CHW is typically a member of the community with little or no previous professional medical experience, but are trained to diagnose and treat a small number of specific diseases, often including malaria (Olaniran et al., 2017). A crucial component of CHW training programmes is to identify and refer children who require the attention of higher-level healthcare professionals who are better equipped and trained to manage a wider range of clinical conditions (Hensher et al., 2006). For a community-based referral system to function optimally, the CHW should first be able to identify children requiring referral based on signs and symptoms and to advise caregivers to take the child to a referral centre;

second the caregivers should comply with CHWs referral advice and seek care from health centres; and third health centres should be equipped and ready to manage appropriately the referred children (Newbrander et al., 2012). Progression through each of these stages is essential to help avoid treatment delays and possibly death.

iCCM has become national healthcare policy in thirty-three sub-Saharan African (SSA) countries, informed by an ever growing evidence base on how to implement and scale-up this approach. In comparison, data on the effectiveness of referral systems remains limited, despite being an integral component of primary healthcare (Rasanathan et al., 2014; WHO, 1987). Prior studies have usually reported low compliance with referral advice for example, studies of CHW using mRDTs for only malaria case management in Sierra Leone and Zambia found that 98% and 70% of caregivers respectively, did not comply with referral advice (Chanda et al., 2011; Thomson et al., 2011). Poor compliance has also been reported in recent iCCM programmes, with less than 46% of all caregivers complying with referral (English et al., 2016; Nanyonjo et al., 2015). Yet relatively few studies have examined the barriers that hinder caregivers' compliance with referral advice. The limited evidence base on referral has been highlighted as a priority research area by the international task force on iCCM (Wazny et al., 2014). In this analysis, we explored caregivers' compliance to CHW referral advice in relation to the demographic, geographical and temporal barriers that might affect compliance, using data collected during two cluster randomised trials to introduce malaria rapid diagnostic tests (mRDT) in community case management in rural Uganda.

Methods

Study area and participants

The two trials were conducted in two sub-counties in Rukungiri District, South-west Uganda; one trial in a moderate-to-high malaria transmission setting (Bwambara sub-county, 980m-1200m above sea level) and the other in an epidemic-prone low transmission setting (Nyakishenyi sub-county, 1064m-2157m above sea level). In each setting, approximately 20% of the population were aged under 5 years (UBOS, 2014a). Both settings were characterised by hilly terrain, where 86% of the population lived in rural areas, the predominant livelihood was subsistence farming, and walking was often the main form of transport (Bank, 2005; Rukungiri District Local Government, 2009). The public health system in each setting was comprised of three government health centres: two classed as Health Centre II (HCII) and one classed as Health Centre III (HCIII). HCIIs are typically staffed by two enrolled nurses providing basic outpatient care and community outreach services, while HCIIIs also have the capacity to admit patients and supervise the lower level HCIIs. Both HCIIs and HCIIIs serve as a referral point for CHW (Ministry of Health, 2014).

Detailed information on the design and procedures of each trial is available elsewhere (Ndyomugyenyi et al., 2016; Lal, Ndyomugenyi, Paintain, et al., 2016; Lal, Ndyomugenyi, Magnussen, et al., 2016). In brief, within each sub-country, CHWs were randomised to either a current practice or intervention arm; the latter receiving training in mRDT-based diagnosis of malaria. In all other respects, the training received by CHWs was identical in both arms. This training included how to treat uncomplicated malaria in children and how to recognise symptoms of other febrile illnesses that should be referred to the nearest health centre. All 381 CHWs (192 in the moderate-to-high transmission setting, 189 in the low-transmission setting) were thus trained to identify severe and non-severe signs and symptoms for referral in children presenting with fever (Figure 5.0). Severe signs and symptoms requiring urgent referral included convulsions or fits, extreme weakness, coma/loss of consciousness and very hot body temperature of 38.5°C; these symptoms were chosen to ensure children with indications compatible with meningitis, severe malaria, pneumonia, or severe bacterial infections were referred and managed at health centres as quickly as possible. Non-severe signs and symptoms included wounds, ear infections, sticky or red eyes, and vomiting and diarrhoea without signs of dehydration; selected to identify common and readily detectable conditions in children requiring management at health centres. These referral criteria were based on Uganda's national treatment guidelines and the research team's clinical experience (Uganda Ministry of Health, 2010).

As well as the training on referral guidelines, CHWs in the intervention arm of each trial (93 in the moderate-to-high transmission setting, 96 in the low-transmission setting) were trained to diagnose malaria by using mRDTs and to only treat with antimalarials after a positive mRDT result. In contrast, control arm CHWs were trained to diagnose malaria based on a child's presenting signs and symptoms. In both arms, all CHWs were trained to treat uncomplicated malaria with an oral age-dependent dose of an ACT (artemether-lumefantrine) and to administer pre-referral rectal artesunate when children presented with signs or symptoms of severe malaria and to refer them to the nearest health centre for further management. The job aids summarising the decisions CHW were trained to make in each arm are shown in Figure S5.0 (further details of the trial and CHW training materials are available from: http://www.actconsortium.org/publications.php/83/training-manuals-use-of-artemisinin-based-combination-therapies-and-rapid-diagnostic-tests-for-home-.html

Data collection

The trials in the moderate-to-high and low transmission settings began in May 2010 and June 2010 respectively. For the first six months of the trial (May/June 2010-December 2010) CHW were supervised frequently by field coordinators to discuss concerns or difficulties in carrying out their new roles. From January 2011 until trial completion in July 2012 supervision of CHWs was scaled back and limited to monthly group meetings to reflect operational programme conditions.

For every child that presented with a fever or a history of fever, the CHW recorded the history of illness including the child's temperature, when the fever started, and whether the child had slept under a net the previous night, together with demographic details on name, age, gender, and village of residence, on a treatment recording form (TRF). Finally, CHWs recorded the mRDT result (intervention arm only), whether an ACT or rectal artesunate was prescribed and whether they had advised the caregiver to take the child to the nearest health facility. CHWs were asked to classify referrals as severe or non-severe referrals according to the symptoms and to complete either a severe referral form or a non-severe referral form accordingly. Both referral forms listed the referral signs and symptoms identified by the CHW; as well as the RDT test result (where applicable), and any malaria treatment given by the CHW. Caregivers were asked to report to health centres as soon as possible and a copy of the referral form was given to them to present at the health centre; with a duplicate carbon copy of the referral form kept by CHW for their records. At the health centre, health workers received the caregiver and their child and recorded their final diagnosis and treatment decisions on the referral form. Referral forms completed by the CHW and health centre staff were collected from the health centres on a regular basis by the research team.

Figure 5.0: List of severe and non-severe signs and symptoms that community health workers (CHW) were trained to identify and refer in children

Severe sign and symptoms for urgent referral	**Non-severe sign and symptoms for referral**
Refer using emergency referral form if child shows any of the following symptoms: 1. Illness in child below 2 months 2. Convulsions or fits now or within the past 2 days 3. Coma/loss of consciousness 4. Patient is confused or very sleepy-cannot be woken 5. Extreme weakness-unable to stand or sit without support 6. Very Hot-with temperature of 38.5˚C or more 7. Very Cold-with temperature of 35.0˚C or less 8. Vomiting everything-cannot keep down food or drink 9. Not able to drink or breast feed 10. Severe anaemia-very pale palms, fingernails, eyelids 11. Yellow eyes 12. Difficulty in breathing 13. Severe dehydration	Refer using ordinary referral form if child shows any of the following symptoms: 1. Fever in babies less than 4 months old 2. Fever that has last for more than 7 days 3. Fever with measured temperatures of 37˚C or more and mRDT negative 4. Vomiting and diarrhoea 5. Blood in faeces or blood in urine 6. Pain when passing urine or frequent urination 7. Wound or burns 8. Skin abscess 9. Painful swelling or lumps in the skin 10. Ear infection (runny ear or child pulling at the ear) 11. Sticky or red eyes
If RDT result is positive: Treat child (if older than 2 months) with rectal artesunate suppository prior to referral.	***If RDT result is positive:*** Treat child (if older than 4 months) with artemether-lumefantine tablets prior to referral.

To examine caregiver compliance to CHW referral advice, data were collected over an 18-month period after the end of close support supervision (January 2011-July 2012). Caregiver's compliance was determined by record linkage between the CHW treatment record form, which captured whether a referral was made, and either the severe or non-severe referral form completed by health workers at public health centres, both forms were linked in the database using the child's unique identification number. The analysis examined factors found to influence referral compliance in previous studies (Kallander et al., 2006; Peterson et al., 2004), such as child's age, gender and the reported duration of fever. In addition, the analysis also examined whether the day of referral (weekday/weekend) and the season (wet/dry) were associated with differences in the caregiver's referral compliance. These data were derived from the date of referral, and the season indicator variable was defined as the months that coincided with the two rainy seasons (March-May and September-December). The number of days taken to complete referral was also calculated from the date of referral and the date a caregiver visited the health centre. Finally, GPS coordinates were taken to measure Euclidean (straight-line) distance from the centre of a village to the nearest health centre.

Statistical methods

All data were double entered and verified using Microsoft Access 2007 (Microsoft Inc., Redmond, Washington). Data were analysed using STATA version 14.1 (STATA Corporation, College Station, Texas). The outcome for this analysis was the proportion of caregivers that complied with CHW referral advice out of all caregivers who were referred by CHW. The denominator for the proportion was defined as the total number of referrals CHWs reported on their treatment recording forms. The numerator for compliance was defined as the number of caregivers visiting a public health centre with a severe or non-severe referral form. Since perceptions of the severity of malaria might differ between the two transmission areas, potentially influencing compliance with referral, data were analysed separately for the two sub-counties. Analysis of each trial dataset was analysed to examine whether caregiver compliance to CHW referral advice differed in relation to malaria testing with mRDTs or other factors (age, gender, net use, ACT prescribed, day of referral, season, distance to nearest health facility, severity of referral, time the since first onset of symptoms). For each child visit to a CHW, mRDT testing was defined as one of three mutually exclusive categories; (1) visits where CHW did not use a mRDT and diagnosis was presumptive; (2) visits where CHW used a mRDT and the mRDT result was positive; (3) visits where CHW tested with a mRDT and mRDT result was negative. For each trial, an explanatory model for the outcome of referral compliance was developed using logistic regression and odds ratios (OR) with 95% confidence intervals (95%CI) were calculated using random effects to account for clustering at the village level (Hayes and Moulton, 2009). Factors identified *a priori* were included in the adjusted analysis and likelihood ratio tests were used.

Results

Study population

Between January 2011 and July 2012, CHWs in the moderate-to-high transmission setting recorded 18,497 children with fever, of whom they referred 15.4% (2,815/18,315, 182 missing referral status) of all child visits (Figure 5.1). Over the same period, CHWs in the low transmission setting saw fewer children but referred more frequently, with 31.8% (1,135/3,572, 72 missing referral status) of all visits being referred (Figure 5.1). The characteristics of referred children were broadly similar in both transmission settings, most were aged 1-3 years, approximately half were female, 80.0% or more had slept under a bed net the previous night, 83.5% lived in the same village as the CHW, 80.0% had visited a CHW within 24 hours of fever onset however distance from the nearest health facility was greater for children referred in the low transmission setting (Table 5.0). In both settings, more referrals occurred on a weekday (70%) than during the weekend (30.0%), and around 60% of referrals were made in the wet season.

Figure 5.1: Flowchart of children analysed in the moderate-to-high malaria transmission setting (HT) and the low-transmission setting (LT).

*Referral status missing for 182 child visits in the HT setting and 79 visits in the LT setting

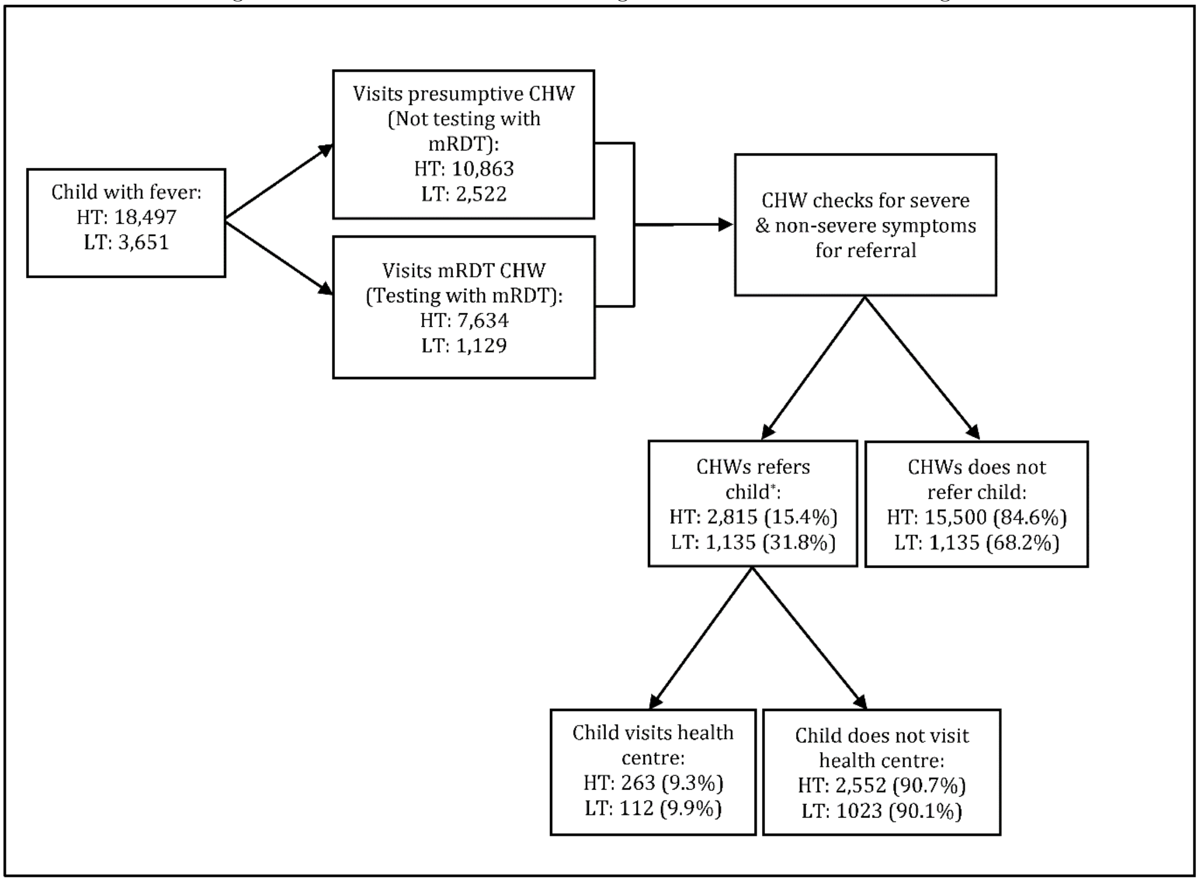


Table 5.0: Characteristics of children who were referred by CHWs

	Number of referrals by CHWs in the moderate-to-high transmission setting (%)[a] N=2815	**Number of referrals by CHWs in the low-transmission setting (%)**[b] N=1135
Age (years)		
<1.0	820 (29.4)	324 (29.0)
1.0-2.9	1169 (41.9)	483 (43.2)
3.0-4.9	788 (28.3)	302 (27.0)
5.0-15.0	10 (0.4)	9 (0.8)
Gender		
Male	1463 (52.4)	585 (51.8)
Female	1330 (47.6)	544 (48.2)
Slept under a net the previous night		
No	267 (9.6)	129 (11.6)
Yes	2500 (90.4)	984 (88.4)
Came from same village		
No	317 (11.3)	187 (16.5)
Yes	2490 (88.7)	945 (83.5)
Duration of fever (hours) since onset of symptoms		
>24hrs	408 (15.0)	220 (20.0)
Within 24hrs	2321 (85.0)	879 (80.0)
Tested with mRDT		
Not tested	164 (5.8)	352 (31.0)
Tested	2651 (94.2)	783 (69.0)
Type of referral		
Severe referral signs	1013 (36.0)	421 (37.1)
Non-severe referral signs	1607 (57.1)	636 (56.0)
Day of referral		
Weekday	2022 (71.8)	791 (69.7)
Weekend	793 (28.2)	344 (30.3)
Season		
Dry	1139 (40.5)	419 (36.9)
Wet	1676 (59.5)	716 (63.1)
Village distance to nearest health facility (km)		
0.0-2.4	1578 (56.5)	296 (27.9)
2.5-4.9	1141 (40.9)	395 (37.2)
5.0-7.4	72 (2.6)	241 (22.7)
7.5-8.9	0 (0.0)	130 (12.2)

a Data missing on the number of referrals in the moderate-to-high transmission setting, for age: 28; sex: 22; net use: 48; resident in the same village: 8; onset of symptoms 86.

b Data missing on the number of referrals in the low transmission setting, for age: 17; sex: 6; net use: 22; resident in the same village: 3; onset of symptoms 36.

Compliance to referral advice

Caregivers' compliance to referral advice was low, with only 9.3% (263/2,815) and 9.9% (112/1,135) of referred children subsequently seen at a government health centre in the moderate-to-high transmission (Table 5.1a) and low transmission (Table 5.1b) settings respectively. The majority of caregivers in the low transmission setting who complied with referral did so on the same day as being referred by CHW (65.7% (69/105, 7 missing information)), but this was less frequent in the moderate-to-high transmission setting (49.4% (127/257, 6 missing information)). In both settings, caregivers who did not comply the same day, took between 2 to 10 days to visit a health centre. There were no differences in the days taken to complete referral in relation to whether a child was referred with severe or non-severe signs or symptoms (data not shown).

The relationship between caregiver's compliance and the diagnosis and treatment characteristics the child had received from the CHW (mRDT testing, ACT prescription and severity of illness) was also examined. In the moderate-to-high transmission setting, compliance was greater when children were tested for malaria using mRDTs compared children who were not tested (9.7% vs. 4.3%, p=0.025) and more frequent amongst children with severe signs or symptoms compared with children with non-severe signs or symptoms (15.0% vs. 6.9%, p<0.001, Table 5.1a). However, there was no significant difference in compliance between mRDT positive or negative children, or whether a CHW prescribed an ACT. In contrast, in the low transmission setting there was no evidence to suggest compliance was associated with mRDTs or the severity of illness (Table 5.1b). However, in this setting caregivers complied more frequently when an ACT was not prescribed compared to when it was prescribed (10.7% vs. 4.6%, p=0.031, Table 5.1b).

Table 5.1a: Caregivers' compliance to referral, in relation to mRDT results and ACT prescribing in moderate-to-high transmission setting

	Referrals by CHWs	Complied with referral (%)	Did not comply with referral (%)	p-value
Total	**2815**	**263 (9.3)**	**2552 (90.7)**	
mRDT result				
Not tested	164	7 (4.3)	157 (95.7)	
Tested	2651	256 (9.7)	2395 (90.3)	0.025
Within those tested with an mRDT				
mRDT negative	2558	244 (9.5)	2314 (90.5)	
mRDT positive	93	12 (12.9)	81 (87.1)	0.319
ACT prescription by CHW[a]				
ACT not prescribed	2538	242 (9.5)	2296 (90.5)	
ACT prescribed	82	8 (9.8)	74 (90.2)	0.961
Rectal artesunate prescribed	63	3 (4.8)	60 (95.2)	
Type of referral[b]				
Non-severe signs or symptoms	1607	111 (6.9)	1496 (93.1)	
Severe signs or symptoms	1013	152 (15.0)	861 (85.0)	<0.001

a 132 missing ACT prescription data

b 195 missing type of referral

Table 5.2b: Caregivers' compliance to referral, in relation to mRDT results and ACT prescribing in low transmission setting

	Referrals by CHWs	Complied with referral (%)	Did not comply with referral (%)	p-value
Total	**1135**	**112 (9.9)**	**1023 (90.1)**	
mRDT result				
Not tested	352	34 (9.7)	318 (90.3)	
Tested	783	78 (10.0)	705 (90.0)	0.923
Within those tested with an mRDT				
mRDT negative	770	75 (9.7)	695 (90.3)	0.147
mRDT positive	13	3 (23.1)	10 (76.9)	
ACT prescription[c]				
ACT not prescribed	805	86 (10.7)	719 (89.3)	
ACT prescribed	218	10 (4.6)	208 (95.4)	0.031
Rectal artesunate prescribed	61	10 (16.4)	51 (83.6)	
Type of referral[d]				
Non-severe signs or symptoms	636	71 (11.2)	565 (88.8)	0.082
Severe signs or symptoms	421	41 (9.7)	380 (90.3)	

a 51 missing ACT prescription data

b 78 missing type of referral

Factors associated with compliance to referral advice

Tables 5.3 and 5.4 present a multivariable adjusted analyses of the factors associated with caregivers compliance to CHW referral advice in the two transmission settings respectively. In the moderate-to-high transmission setting, compliance with referral was less likely when children visited a CHW within 24 hours of symptoms onset, compared to later (OR 0.50; 95%CI 0.37-0.69; p<0.001). Compliance was also 37% less likely for children presenting with non-severe signs or symptoms for referral compared to children with severe signs and symptoms for referral (OR 0.63; 95%CI 0.44-0.90; p<0.012) (Table 5.3). After controlling for other factors in the adjusted analyses, there was no association between referral compliance and the mRDT result, age or gender; however, it was found that compliance was less likely when children were referred during a weekend compared to a weekday and when referrals occurred during the wet season compared to the dry season. We also found compliance with referral advice declined with increasing distance from the nearest health centre in the moderate-to-high transmission setting (Table 5.3).

In the low transmission setting, caregivers of female children were more likely to comply with referral compared to males (OR 1.88; 95%CI 1.12-3.15; p=0.018) and the likelihood of compliance was 76% (OR 0.24; 95%CI 0.09-0.65; p=0.005) less amongst children prescribed an ACT compared to children not prescribed an ACT (Table 5.4). Several of the factors associated with referral compliance in the moderate-to-high transmission setting were also associated with referral in the low transmission setting. Referral during a weekend compared to a weekday was less likely to result in compliance (OR 0.35; 95%CI 0.18-0.68;

p=0.002) and increasing village distance from the nearest health centre was significantly associated with referral compliance (Table 5.4).

A supplementary analysis of these referral forms was undertaken to examine caregivers referral compliance according to the specific signs and symptoms reported by CHWs in each transmission setting (Table S5.0, Table S5.1). Caregivers in both settings nearly always complied with referral when either a non-severe or a severe sign or symptom was reported. The sole exception to this pattern was when a measured temperature of >37°C and mRDT negative test results were recorded as the reason for referral (Table S5.0, Table S5.1).

Health centre management of referred cases

The case management decisions taken by health workers at health centres when caregivers complied with CHW referral advice were reported on referral forms and these were examined to describe the final child diagnoses. In both transmission settings, most children were diagnosed and treated the same day in health centre outpatient departments, however a few children were admitted (moderate-to-high transmission setting: 18/208, 36 missing data, low-transmission setting: 2/89, 23 missing data) and one child in the moderate-to-high transmission setting was referred from a health centre to a hospital. No deaths were reported in either setting. The diagnoses made by health workers in both transmission settings were broadly similar. Children tested with a mRDT by CHWs in the moderate-to-high transmission setting were frequently diagnosed with respiratory tract infections (RTI) (32.9%), helminths (24.3%), malaria (18.1%) and diarrhoea (10.7%), and in the low transmission setting, RTI (66.7%), malaria (9.7%) and diarrhoea (8.3%) were the most frequent diagnoses (Table S5.2, Table S5.3). The frequency and types of diagnoses reported by health workers among mRDT tested children were predominantly due to children who were mRDT negative by CHW and compliant with the referral. In the moderate-to-high transmission setting, 21 different diagnoses were reported amongst mRDT negative children whilst only 3 diagnoses were reported for mRDT positive children. There was consistent agreement between the diagnoses made by CHW and health workers, in the moderate-to-high transmission setting 156/169 found by CHW to be mRDT negative were also found to mRDT negative by health workers. However, 8/169 (4.7%) children found to mRDT negative by health workers were given a malaria diagnosis, suggesting health workers did not agree with the negative test result. The agreement was also consistent in the low transmission setting, 23/27 mRDT negative children were also found negative by health workers whilst, 4/27 (14.8%) were mRDT positive and given a malaria diagnosis.

Table 5.3: Caregiver factors associated with referral compliance in the moderate-to-high transmission setting

Variables	Referrals by CHWs	Complied with referral (%)	Unadjusted odds Ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Test result						
Not tested	164	7 (4.3)	1		1	
mRDT negative	2558	244 (9.5)	2.32 (0.97-5.54)	0.151	2.50 (0.84-7.44)	0.144
mRDT positive	93	12 (12.9)	2.61 (0.90-7.63)		3.70 (0.94-14.56)	
Age group						
<1.0	820	73 (8.9)	1		1	
1.0-2.9	1169	119 (10.2)	1.05 (0.76-1.44)		1.13 (0.80-1.61)	
3.0-4.9	788	69 (8.8)	0.95 (0.66-1.37)	0.951	1.04 (0.70-1.55)	0.768
5.0-15.0	10	0 (0.0)	n/a		1.00 (0.70-1.55)	
Gender						
Male	1463	134 (9.2)	1		1	
Female	1330	126 (9.5)	1.07 (0.82-1.40)	0.628	1.04 (0.78-1.39)	0.778
Slept under a net the previous						
No	267	27 (10.1)	1		1	
Yes	2500	232 (9.3)	0.87 (0.54-1.41)	0.579	1.04 (0.61-1.74)	0.897
Resident in the same village as a CHW						
No	317	23 (7.3)	1		1	
Yes	2490	239 (9.6)	1.43 (0.89-2.30)	0.137	1.17 (0.71-1.92)	0.536
Time of presentation to CHW after the onset of symptoms						
>24 hrs	408	54 (13.2)	1		1	
Within 24 hrs	2321	202 (8.7)	0.68 (0.48-0.96)	0.030	0.50 (0.37-0.69)	<0.001
Type of referral						
Severe referral	1013	152 (15.0)	1		1	
Non-severe referral	1607	111 (6.9)	0.47 (0.35-0.64)	<0.001	0.63 (0.44-0.90)	0.012
ACT prescription						
No ACT	2538	242 (9.5)	1		1	
ACT	82	8 (9.8)	1.01 (0.45-2.25)	0.978	1.70 (0.54-5.41)	0.368
Day of visit to CHW						
Weekday	2022	211 (10.4)	1	0.002	1	
Weekend	793	52 (6.6)	0.60 (0.44-0.84)		0.63 (0.45-0.89)	0.009
Season of visit						
Dry	1139	142 (12.5)	1	<0.001	1	
Wet	1676	121 (7.2)	0.58 (0.44-0.76)		0.56 (0.42-0.74)	<0.001
Village distance to nearest health facility (km)						
0.0-2.4	1578	189 (12.0)	1		1	
2.5-4.9	1141	74 (6.5)	0.46 (0.25-0.85)		0.49 (0.25-0.94)	
5.0-7.4	72	0 (0.0)	n/a	0.013	n/a	0.019
7.5-8.9	0	0 (0.0)	n/a		n/a	

Table 5.4: Caregiver factors associated with referral compliance in the low-transmission setting

Variables	Referrals by CHWs	Complied with referral (%)	Unadjusted odds Ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Test result						
Not tested	352	34 (9.7)	1		1	
mRDT negative	770	75 (9.7)	0.95 (0.44-2.05)	0.735	0.50 (0.21-1.18)	0.249
mRDT positive	13	3 (23.1)	1.87 (0.30-11.70)		1.30 (0.09-18.35)	
Age group						
<1.0	324	29 (9.0)	1		1	
1.0-2.9	483	49 (10.1)	1.02 (0.60-1.74)		1.41 (0.76-2.62)	
3.0-4.9	302	30 (9.9)	1.00 (0.55-1.82)	0.996	1.08 (0.54-2.18)	0.490
5.0-15.0	9	1 (11.1)	0.74 (0.06-9.38)		1.00 (0.54-2.18)	
Sex						
Male	585	45 (7.7)	1		1	
Female	544	64 (11.8)	1.78 (1.14-2.77)	0.011	1.88 (1.12-3.15)	0.018
Slept under a net the previous night						
No	129	15 (11.6)	1		1	
Yes	984	93 (9.5)	0.92 (0.48-1.78)	0.815	0.63 (0.29-1.36)	0.237
Resident in the same village as a CHW						
No	187	12 (6.4)	1		1	
Yes	945	100 (10.6)	1.51 (0.74-3.09)	0.254	1.94 (0.68-5.52)	0.215
Time of presentation to CHW after the onset of symptoms						
>24 hrs	220	20 (9.1)	1		1	
Within 24 hrs	879	83 (9.4)	1.22 (0.70-2.14)	0.483	0.94 (0.53-1.66)	0.827
Type of referral						
Severe referral	421	41 (9.7)	1		1	
Non-severe referral	636	71 (11.2)	0.81 (0.50-1.31)	0.392	1.33 (0.70-2.52)	0.391
ACT prescription						
No ACT	805	86 (10.7)	1		1	
ACT	218	10 (4.6)	0.30 (0.12-0.72)	0.007	0.24 (0.09-0.65)	0.005
Day of visit to CHW						
Weekday	791	94 (11.9)	1	0.001	1	
Weekend	344	18 (5.2)	0.39 (0.22-0.69)		0.35 (0.18-0.68)	0.002
Season of visit						
Dry	419	40 (9.5)	1	0.938	1	
Wet	716	72 (10.1)	0.98 (0.63-1.54)	0.938	0.93 (0.55-1.58)	0.798
Village distance to nearest health facility (km)						
0.0-2.4	296	20 (6.8)	1		1	
2.5-4.9	395	10 (2.5)	0.37 (0.15-0.94)		0.32 (0.11-0.89)	
5.0-7.4	241	44 (18.3)	2.81 (1.30-6.07)	<0.001	2.94 (1.19-7.24)	<0.001
7.5-8.9	130	32 (24.6)	5.10 (2.05-12.71)		3.25 (1.15-9.21)	

Discussion

In these studies, less than 10% of caregivers in rural Uganda adhered to the referral advice given by CHW trained to identify referral signs and symptoms in children under-5 in two different malaria transmission settings. There was a trend suggesting that testing for malaria with mRDTs in the moderate-to-high transmission setting increased caregivers compliance to referral advice compared with a presumptive diagnosis. However, there was no association between compliance and the mRDT result or ACT treatment in the multivariable analyses. The study also found compliance was greater when children presented with severe referral signs and symptoms compared with non-severe signs and symptoms in the moderate-to-transmission setting. Whilst there was some evidence of an association between mRDT testing and compliance in the moderate-to-high transmission setting, there was no association in the low transmission setting. Also, there was evidence that caregivers of children who were not treated with an ACT were more likely to comply with referral advice compared to caregivers of children treated by the CHW. The difference in compliance according to the severity of signs or symptoms might suggest that caregivers also applied their own judgement in deciding which symptoms required higher level management at health centres. Despite the poor overall compliance in both settings, there was evidence to suggest that amongst caregivers who complied with referral advice, many did so within one day of being referred.

CHWs in the study were also trained to give pre-referral rectal artesunate to children presenting with signs and symptoms of severe malaria. However, nearly all children treated with rectal artesunate failed to comply with the referral advice. This might be explained by an immediate improvement of signs and symptoms after administering pre-referral treatment and caregivers perceiving there is no longer a necessity to seek treatment. This is particularly concerning, because the failure to seek further curative treatment after pre-referral artesunate may lead to severe disease or a recrudescence of malaria because approximately one-third of children can still be parasitemic after receiving rectal-artesunate (Hinton et al., 2007; Gomes et al., 2008). To improve compliance to referral advice amongst this high-risk group, training materials of CHW should emphasise more strongly that rectal artesunate is not a full curative treatment for malaria and that further care should be sought from health centres.

In both transmission settings, caregivers were less likely to comply when referred during the weekend compared to on weekdays. In the moderate-to-high transmission setting children living in villages further away from health centres were less likely to comply with referral advice, whilst in the low transmission setting caregivers living further away from a health facility were more likely to comply. This counterintuitive finding in the low transmission setting may partly be explained by a health insurance scheme run by a private hospital in the low-transmission setting, this may have facilitated timely use of healthcare services compared to the moderate to high transmission setting that lacked an insurance scheme. There may also have been differences in caregivers' perceptions of the seriousness of a malaria diagnosis, in this high-altitude epidemic-prone setting where acquired immunity to malaria can be lower and malaria can be deadlier compared to an endemic setting.

In the moderate-to-high setting caregivers who visited CHWs within twenty-four hours of symptoms starting were less likely to comply with referral advice compared to children who visited CHW more than twenty-four hours and children referred during the wet season were less likely to comply compared with children referred during the dry season. By contrast, in the low-transmission setting, there was no association between compliance and the time of fever symptom onset or season. There was a trend that female children had a higher odds of referral compliance compared to males and compliance was lower when children were prescribed ACT compared to when an ACT was not prescribed. This suggests that having received a malaria treatment from the CHW, caregivers decided not to seek further care from health centres, despite being referred by CHW for other symptoms. This may also be a concern because ACTs only treat uncomplicated cases of malaria and management should still be sought for the other conditions which require different treatments.

Reviewing and linking referral forms completed by CHW and health centre workers, was advantageous as it enabled an assessment of referral compliance on a large sample of referred children and allowed an exploration of several geographical and temporal factors likely to be associated with compliance, such as age, sex, distance and seasonality. However, there are some disadvantages to this method of record linkage. For example, the CHWs reported that caregivers sometimes refused to accept referral forms upon being referred by CHW, indicating that the CHW may not always have issued a referral form. It is also possible that caregivers might leave the forms at home, or that health workers misplaced the forms of children taken to a health centre. In any of these situations, the absence of referral forms at the health centre would be interpreted as the caregiver failing to comply with the referral advice, which may underestimate actual compliance, for example if caregivers had visited without a form. Secondly, routinely available data from the treatment recording forms were used to examine factors likely to be associated with referral. However, these forms did not capture data on several other potentially relevant factors such as socio-economic and educational status of caregivers that may also be associated with compliance. Due to logistical constraints it was not possible to conduct follow-up household visits with all referrals which could have provided more information related to referral compliance, such as education, socio-economic status and attitudes and perceptions towards medicines (Nanyonjo et al., 2015). A related cost-effectiveness study reported the household costs for caregivers complying with the referral, which might suggest increased household costs for referral may be a consideration when deciding to comply with referral (Hansen et al., 2017). Finally, this study did not follow-up caregivers who did not comply with the referral advice and therefore the health outcomes of these children were not assessed. Neither did it seek to examine whether CHW's decision to refer caregivers was correct. It is possible that CHWs referred children who did not require referral and the caregivers' non-compliance to referral advice had no negative consequence in terms of health outcomes. Further research is required to understand the reasons for poor compliance and the health outcomes of children who do not comply with referral. A qualitative investigation of attitudes towards referral from the perspectives of the caregiver and CHW may help to further understand referral and care seeking behaviours and inform future intervention strategies.

Despite the challenges of tracking referrals in this analysis, the results are consistent with other previous studies investigating referral compliance from community settings which also report low compliance. Studies in Sierra Leone and Zambia with CHW-managed malaria with mRDTs and ACTs found caregivers' compliance ranged from 2% to 46% respectively (Chanda et al., 2011; Hinks et al., 2011). More recent iCCM referral studies also found suboptimal compliance ranging from 30% to 46% with both iCCM studies also identifying distance to the health centre and household costs of referral to be barriers to access (Nanyonjo et al., 2015; English et al., 2016).

The findings from these studies in Uganda and elsewhere show that community-based referral systems operate less than optimally at each stage of the referral process. In the first stage, CHW often do not refer children with referral signs and symptoms to the nearest health centre (Kelly et al., 2001; Chinbuah et al., 2013; Lal, Ndyomugenyi, Paintain, et al., 2016). In the second stage, caregivers often fail to comply with CHW referral advice and do not seek care from health centres (Chanda et al., 2011; Thomson et al., 2011; English et al., 2016; Nanyonjo et al., 2015). The combined effect of both the failure of CHWs to refer eligible children and the poor compliance to referral advice by caregivers risks undermining the full effectiveness of community-based treatment programmes that aim to reduce child mortality by providing primary healthcare services closer to populations with poor access to health centres.

A functional and appropriately managed referral system is an essential component of primary healthcare yet remains poorly understood. In acknowledgement of the current evidence gaps regarding referral the international task force on iCCM has highlighted this as a global research priority (Maher and Cometto, 2016; Wazny et al., 2014). The evidence presented here provides some evidence that CHWs can make appropriate referrals and caregivers comply with referral advice. It also raises additional research questions requiring further investigation to better inform recommendations and guidelines for countries implementing community programmes. First, our findings indicate that referral compliance may differ depending on the sign or symptom, and referral guidelines and communication with caregivers may thus need to address both clinical priorities and local caregivers' perceptions of the severity of symptoms. Second, better coordination and monitoring of referrals from the CHW to health centres is required to track caregivers' compliance and the health outcomes of children. Second, CHWs play an important role in advising caregivers on further treatment options. CHW training could include counselling caregivers about the importance of complying with referral and discussing alternative solutions to overcome barriers to seeking further care. This is particularly important for caregivers who fail to comply with referral advice after their child receives pre-referral rectal artesunate. Third, further research is needed on barriers and enablers of caregiver's compliance with referral advice. Fourth, better coordination and monitoring of referrals from the CHW to health centres is required to track caregivers' compliance and the health outcomes of children. Finally, health centres should be equipped and managed to receive referred cases effectively. For example, priority could be given to referral cases upon arrival allowing them to bypass waiting in outpatient departments. Finally, health centres should be equipped and managed to receive referred cases effectively. For example, priority could be given to referral cases upon arrival allowing them to bypass waiting in outpatient departments.

The referral challenges faced by community-based programmes may be similar to the challenges to access and utilisation of health services faced by other health programmes. Interventions developed to improve attendance at health centres for pregnant women and utilisation of antenatal care and new-born health, could also be relevant to iCCM programmes to improve health seeking behaviour amongst referred caregivers (Z.S. et al., 2010). Findings from this field may also be adapted to iCCM programmes to improve health seeking behaviour amongst referred caregivers. For example, interventions that involve regular home visits by CHWs to prepare pregnant women for birth and immediate new-born care could also be adapted to iCCM programmes where CHWs regularly follow-up referred caregivers to encourage compliance and offer further support and counselling on the importance of referral. An important barrier to accessing public health centres are the household costs associated with seeking care (Puchalski Ritchie et al., 2016). Financial incentives such as conditional cash transfers (CCTs) aim to offset some of the household financial burden associated with health seeking and CCT interventions have shown to increase the use of health centres for ANC services in Latin American and South East Asian countries (Bassani et al., 2013). Further research could explore whether particular models of CCTs within iCCM programmes could also improve caregiver's compliance with referral advice.

Conclusion

In two randomised controlled trials that evaluated the effectiveness of training CHWs to diagnose malaria using mRDT in Uganda, the majority of caregivers of children with a febrile illness did not comply with the referral advice given by CHW. This is particularly concerning for children with signs of severe disease, including children with severe malaria who received pre-referral treatment with rectal artesunate. Such children are beyond the capacity of CHW and lack of follow up treatment increases the risk of recrudescence, health complications and possible death. The findings also identified multiple geographical and temporal treatment seeking barriers associated with poor compliance. As countries in sub-Saharan Africa continue the scale-up of community-based programmes, interventions to diminish barriers to accessing first level referral services are needed to ensure the continuum of care from the community to the health centre.

Over the past decade Uganda and 33 SSA countries have implemented community case management programmes as part of national healthcare strategies and despite the considerable literature on addressing the bottlenecks to scaling-up programmes there has been relatively limited evidence on strengthening referral systems as part of community programmes. The referral system is an important part of primary healthcare to improve access to appropriate care for children with conditions that cannot be managed by CHW. However, unless the barriers to comply with referral advice are understood and overcome the full potential of community-based programmes may not be achieved.

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Supplementary information

Table S5.0: Referral compliance according to child's signs and symptoms recorded on referral forms in the moderate-to-high transmission setting[a]

	Total[a]	Complied with referral Frequency (%)	Did not comply with referral Frequency (%)
Severe signs and symptoms for referral			
Illness in child below 2 months	2	2 (100.0)	0 (0.0)
Convulsions or fits now or within the past 2 days	22	21 (95.5)	1 (5.5)
Coma / Loss of consciousness	6	6 (100.0)	0 (0.0)
Patient is confused or very sleepy - cannot be woken	5	5 (100.0)	0 (0.0)
Extreme weakness unable to stand or sit without support	12	12 (100.0)	0 (0.0)
Very Hot with temperature of 38.5°C or more	81	80 (98.8)	1 (1.2)
Very Cold with temperature of 35.0°C or less	10	10 (100.0)	0 (0.0)
Vomiting everything - cannot keep down food or drink	36	36 (100.0)	0 (0.0)
Not able to drink or breastfeed	53	52 (98.1)	1 (1.9)
Severe anaemia very pale palms, fingernails, eyelids	19	19 (100.0)	0 (0.0)
Yellow eyes	9	9 (100.0)	0 (0.0)
Difficulty in breathing	73	72 (98.6)	1 (0.4)
Severe dehydration	7	7 (100.0)	0 (0.0)
Other severe signs and symptoms[b]	34	34 (100.0)	0 (0.0)
Total number of severe signs and symptoms reported	369	365	338
Total number of severe referral forms	151	150 (99.3)	1 (0.7)
Mean number of signs and symptoms reported per severe referral form	2.4	2.4	338
Non-severe signs and symptoms for referral			
Fever in babies less than 4 months old	0	-	-
Fever that has lasted more than 7 days	16	16 (100.0)	0 (0.0)
Fever with measured temperature of > 37.0°C and mRDT Negative	214	0 (0.0)	214 (100.0)
Vomiting and diarrhoea	32	31 (96.9)	1 (3.1)
Blood in faeces or urine	2	2 (100.0)	0 (0.0)
Pain when passing urine, or frequent urination	8	8 (100.0)	0 (0.0)
Wounds or Burns	8	8 (100.0)	0 (0.0)
Skin abscess	3	3 (100.0)	0 (0.0)
Painful swellings or lumps in the skin	3	3 (100.0)	0 (0.0)
Ear infection (runny ear or child pulling at ear)	1	1 (100.0)	0 (0.0)
Sticky or red eyes	16	16 (100.0)	0 (0.0)
Other non-severe signs and symptoms[c]	35	35 (100.0)	0 (0.0)
Total number of non-severe signs and symptoms reported	338	123	215
Total number of non-severe referrals forms	313	98 (31.3)	215 (68.7)
Mean number of signs and symptoms reported per referral	1.1	1.3	1.0

a The number of reported signs and symptom is lower than the referrals reported in the main tables. This is because not all referrals reported on the treatment recording forms were accompanied with the separate referral forms.

b Other severe signs and symptoms included: complied with referral; cough and flu (20), diarrhoea (5), eye problems (2), burns (1), painful ear (1), unable to eat or drink (2), yellow skin (1), dysentery (1), severe headaches (1)

c Other non-severe signs and symptoms for referral included: complied with referral; cough and flu (15), high temperature (17), worms (1), swollen legs and eyes (1), Unknown (1); Did not comply with previous referral; cough flu (1).

Table S5.1: Referral compliance according to child's signs and symptoms recorded on referral forms in the low transmission setting[a]

	Total[a]	Complied with referral Frequency (%)	Did not comply with referral Frequency (%)
Severe signs and symptoms for referral			
Illness in child below 2 months	1	1 (100.0)	0 (0.0)
Convulsions or fits now or within the past 2 days	2	2 (100.0)	0 (0.0)
Coma / Loss of consciousness	1	1 (100.0)	0 (0.0)
Patient is confused or very sleepy - cannot be woken	2	2 (100.0)	0 (0.0)
Extreme weakness unable to stand or sit without support	3	3 (100.0)	0 (0.0)
Very Hot with temperature of 38.5°C or more	32	32 (100.0)	0 (0.0)
Very Cold with temperature of 35.0°C or less	3	3 (100.0)	0 (0.0)
Vomiting everything - cannot keep down food or drink	8	8 (100.0)	0 (0.0)
Not able to drink or breastfeed	8	8 (100.0)	0 (0.0)
Severe anaemia very pale palms, fingernails, eyelids	2	2 (100.0)	0 (0.0)
Yellow eyes	1	1 (100.0)	0 (0.0)
Difficulty in breathing	22	22 (100.0)	0 (0.0)
Severe dehydration	1	1 (100.0)	0 (0.0)
Other severe signs and symptoms[b]	7	7 (100.0)	0 (0.0)
Total number of severe signs and symptoms reported	93	114	114
Total number of severe referral forms	41	41	0
Mean number of signs and symptoms reported per severe referral form	0.0	2.3	0.0
Non-severe signs and symptoms for referral			
Fever in babies less than 4 months old	0	-	-
Fever that has lasted more than 7 days	4	4 (100.0)	0 (0.0)
Fever with measured temperature of > 37.0°C and mRDT Negative	37	0 (0.0)	37 (100.0)
Vomiting and diarrhoea	21	21 (100.0)	0 (0.0)
Blood in faeces or urine	0	0 (0.0)	0 (0.0)
Pain when passing urine, or frequent urination	4	4 (100.0)	0 (0.0)
Wounds or Burns	2	2 (100.0)	0 (0.0)
Skin abscess	0	0 (0.0)	0 (0.0)
Painful swellings or lumps in the skin	2	2 (100.0)	0 (0.0)
Ear infection (runny ear or child pulling at ear)	0	0 (0.0)	0 (0.0)
Sticky or red eyes	1	1 (100.0)	0 (0.0)
Other non-severe signs and symptoms[c]	43	43 (100.0)	0 (0.0)
Total number of non-severe signs and symptoms reported	114	77	37
Total number of non-severe referrals forms	98	61 (62.2)	37 (37.8)
Mean number of signs and symptoms reported per referral	1.2	1.3	1.0

a The number of reported signs and symptom is lower than the referrals reported in the main tables. This is because not all referrals reported on the treatment recording forms were accompanied with the separate referral forms.

b Other severe signs and symptoms included: complied with referral; cough and flu (20), diarrhoea (5), eye problems (2), burns (1), painful ear (1), unable to eat or drink (2), yellow skin (1), dysentery (1), severe headaches (1)

c Other non-severe signs and symptoms for referral included: complied with referral; cough and flu (15), high temperature (17), worms (1), swollen legs and eyes (1), Unknown (1); Did not comply with previous referral; cough flu (1).

Table S5.2: Diagnoses of children made at health centres for children complying with CHW referral advice in the moderate-to-high transmission setting

Diagnoses made by health centre staff	Total Frequency (%)[a]	Not tested with mRDT at health centre Frequency (%)	Tested with mRDT at health centre Frequency (%)	*mRDT test result: Positive Frequency (%)*	*mRDT test result: Negative Frequency (%)*
Abscess	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Anaemia	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Bacterial conjunctivitis	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Burns	2 (0.0)	0 (0.0)	2 (100.0)	*0 (0.0)*	*2 (100.0)*
Diarrhoea	28 (0.1)	2 (7.1)	26 (92.9)	*0 (0.0)*	*26 (100.0)*
Ear wound	-	-	-	-	-
Epilepsy	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Epistaxis	-	-	-	-	-
Eye infection	2 (0.0)	1 (50)	1 (50)	*0 (0.0)*	*1 (100.0)*
Flu	80 (0.3)	0 (0.0)	80 (100.0)	*2 (2.5)*	*78 (97.5)*
Gastroenteritis	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Helminths	60 (0.2)	1 (1.7)	59 (98.3)	*0 (0.0)*	*59 (100.0)*
Malaria	45 (0.2)	1 (2.2)	44 (97.8)	*6 (13.6)*	*38 (86.4)*
Mumps	3 (0.0)	1 (33.3)	2 (66.7)	*0 (0.0)*	*2 (100.0)*
Oral candidiasis	0 (0.0)	-	-	-	-
Otitis media	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Pneumonia	11 (0.0)	0 (0.0)	11 (100.0)	*3 (27.3)*	*8 (72.7)*
Scalp infection	0 (0.0)	-	-	-	-
Skin infection	5 (0.0)	0 (0.0)	5 (100.0)	*0 (0.0)*	*5 (100.0)*
Toe wound	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Trachoma	2 (0.0)	0 (0.0)	2 (100.0)	*0 (0.0)*	*2 (100.0)*
Trauma	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Ulcer	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Urinary tract infection	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Vomiting	1 (0.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Total diagnoses	**249**	**6 (2.4)**	**243 (97.6)**	**11 (4.5)**	**232 (95.5)**

a Column percentages are reported for the totals.

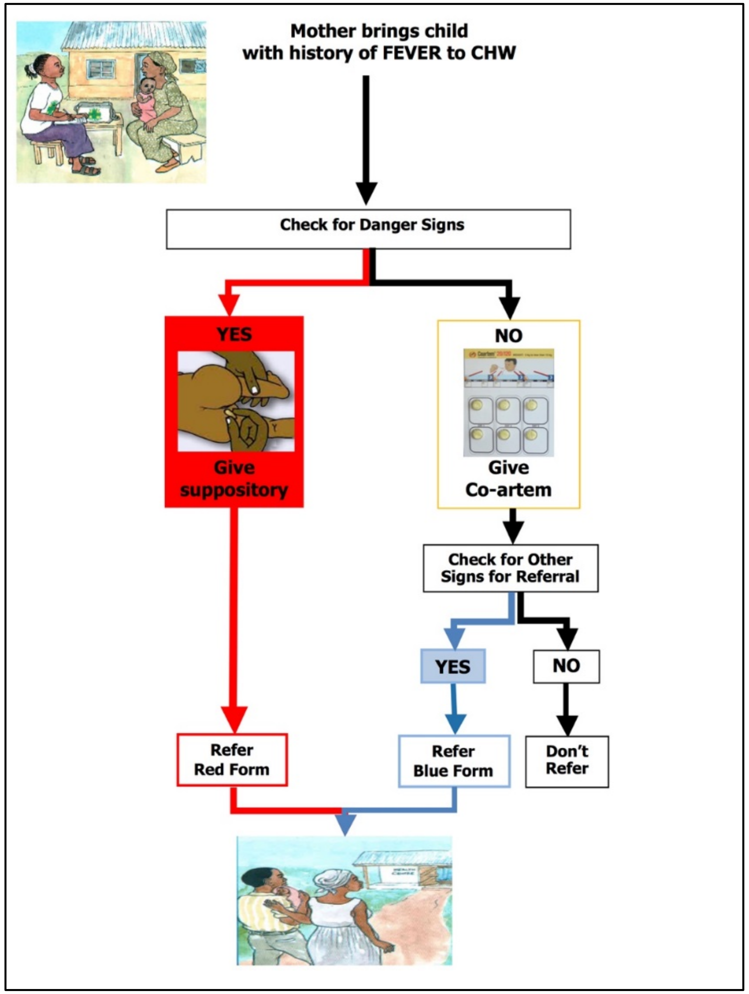
Table S5.3: Diagnoses of children made at health centres for children complying with CHW referral advice in the low transmission setting

Diagnoses made by health centre staff	Total Frequency (%)[a]	Not tested with mRDT at health centre Frequency (%)	Tested with mRDT at health centre Frequency (%)	*mRDT test result: Positive Frequency (%)*	*mRDT test result: Negative Frequency (%)*
Abscess	(0.0)	-	-	-	-
Anaemia	(0.0)	-	-	-	-
Bacterial conjunctivitis	(0.0)	-	-	-	-
Burns	(0.0)	-	-	-	-
Diarrhoea	10 (10.0)	4 (40.0)	6 (60.0)	*0 (0.0)*	*6 (100.0)*
Ear wound	1 (1.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Epilepsy	(0.0)	-	-	-	-
Epistaxis	1 (1.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Eye infection	(0.0)	-	-	-	-
Flu	63 (63.0)	15 (23.8)	48 (76.2)	*1 (2.1)*	*47 (97.9)*
Gastroenteritis	1 (1.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Helminths	1 (1.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Malaria	9 (9.0)	2 (22.2)	7 (77.8)	*2 (28.6)*	*5 (71.4)*
Mumps	(0.0)	-	-	-	-
Oral candidiasis	1 (1.0)	1 (100.0)	0 (0.0)	-	-
Otitis media	1 (1.0)	0 (0.0)	1 (100.0)	*0 (0.0)*	*1 (100.0)*
Pneumonia	8 (8.0)	2 (25.0)	6 (75.0)	*0 (0.0)*	*6 (100.0)*
Scalp infection	(0.0)	-	-	-	-
Skin infection	1 (1.0)	1 (100.0)	0 (0.0)	-	-
Toe wound	(0.0)	-	-	-	-
Trachoma	(0.0)	-	-	-	-
Trauma	(0.0)	-	-	-	-
Ulcer	(0.0)	-	-	-	-
Urinary tract infection	3 (3.0)	3 (100.0)	0 (0.0)	-	-
Vomiting	(0.0)	-	-	-	-
Total diagnoses	**100**	**28 (28.0)**	**72 (72.0)**	***3 (4.2)***	***69 (95.8)***

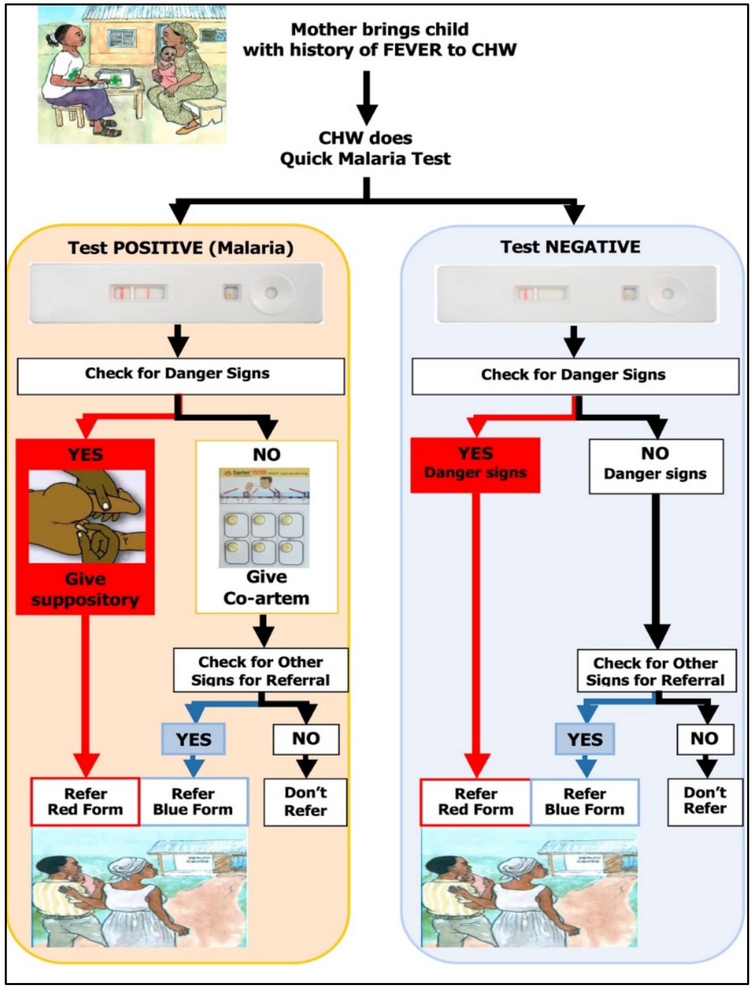
a Column percentages are reported for the totals.

Figure S5.0: Job aid for CHWs in a) control (presumptive) arm, b) intervention (mRDT) arm

a) Control arm



b) Intervention arm



Abbreviations

ACT: Artemisinin-based combination therapy; CHW: Community health worker; HCII: Health centre II; HCIII: Health centre III; iCCM: Integrated community case management; ITN: insecticide treated net; mRDTs: Malaria rapid diagnostic tests; 95% CI: 95% confidence intervals; OR: Odds ratio; AOR: Adjusted odds ratio.

Declarations

Ethics approval and consent to participate

The main trials were approved by the Uganda National Council for Science and Technology (Ref no. HS 555) and London School of Hygiene & Tropical Medicine Ethics Committee (Ref no. 5595). Meetings were held with community leaders in each village to explain the study objectives and procedures. Written informed consent was obtained from village leaders and CHW to participate in the trial. At the time of consultation with a CHW, children refusing an mRDT received presumptive treatment. The study was registered with ClinicalTrials.gov. Identifier NCT01048801, 13th January 2010.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are publicly available from http://datacompass.lshtm.ac.uk/

Competing interests

We declare no competing interests.

Funding

The trials were funded by the ACT Consortium through a grant from the Bill & Melinda Gates Foundation to the London School of Hygiene and Tropical Medicine (www.actconsortium.org). NDA receives salary support from the MRC Tropical Epidemiology Group, award reference number MR/K012126/1. This award is jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 programme supported by the European Union. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' Contributions

The randomised trials, and associated referral study, were designed and implemented by SL, RN, KSS, PM and SEC. SL conducted the statistical analyses and wrote the first draft of the manuscript. NDA, DC, NL and SEC all provided substantial statistical advice and ideas for this paper. All authors reviewed and revised the manuscript in preparation for submission and approved the final manuscript.

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Supplementary analysis

Table S5.4: Characteristics of referred caregivers given and not given a completed referral form, moderate-to-high transmission setting

	Total referrals (%)	Given completed referral form (%)	Not given completed referral form (%)
	N=2815	N=464	N=2351
Age (years)			
<1.0	820 (29.4)	135 (29.3)	685 (29.4)
1.0-2.9	1169 (42.0)	210 (45.7)	959 (41.2)
3.0-4.9	788 (28.3)	115 (25.0)	673 (28.9)
5.0-15.0	9 (0.3)	0 (0.0)	10 (0.4)
Sex			
Male	361 (52.2)	239 (52.0)	1224 (52.5)
Female	331 (47.8)	221 (48.0)	1109 (47.5)
Slept under a net the previous night			
No	267 (30.0)	43 (9.4)	224 (9.7)
Yes	624 (70.0)	416 (90.6)	2084 (90.3)
Came from same village			
No	317 (33.4)	38 (8.2)	279 (11.9)
Yes	631 (66.6)	425 (91.8)	2065 (88.1)
Duration of fever (hours) since onset of symptoms			
>24hrs	408 (41.6)	74 (16.3)	334 (14.7)
Within 24hrs	573 (58.4)	379 (83.7)	1942 (85.3)
Tested with mRDT			
Not Tested	164 (19.5)	7 (1.5)	157 (6.7)
Tested	676 (80.5)	457 (98.5)	2194 (93.3)
Type of referral			
Severe referral signs	1013 (69.6)	151 (32.5)	862 (40.0)
Non-severe referral signs	442 (30.4)	313 (67.5)	1294 (60.0)
Day of referral			
Weekday	522 (39.7)	356 (76.7)	1666 (70.9)
Weekend	793 (60.3)	108 (23.3)	685 (29.1)
Season			
Dry	1139 (74.6)	219 (47.2)	920 (39.1)
Wet	388 (25.4)	245 (52.8)	1431 (60.9)
Village distance to nearest health facility (km)			
0.0-2.4	400 (24.8)	270 (58.2)	1308 (56.2)
2.5-4.9	1141 (70.7)	179 (38.6)	962 (41.3)
5.0-7.4	72 (4.5)	15 (3.2)	57 (2.4)
7.5-8.9	0 (0.0)		

[a]Data missing amongst those with a referral form, for age: 4; sex: 9; net use: 5; resident in the same village: 1; onset of symptoms 11.

[b]Data missing amongst those without a referral form, for age: 24; sex: 18; net use: 43; resident in the same village: 7; onset of symptoms 75; type of referral: 195.

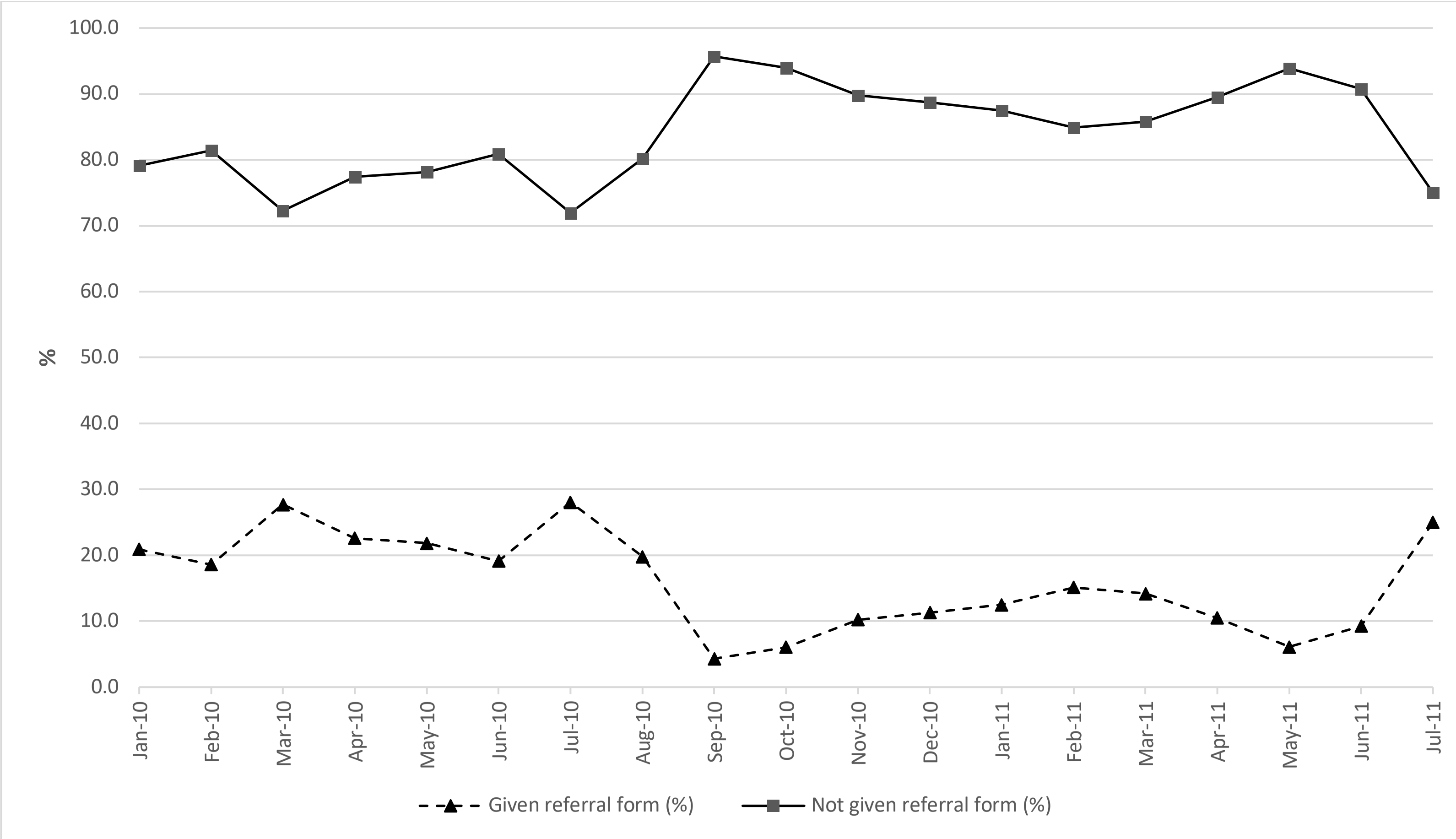


Figure S5.1: Percentage of referred caregivers given and not given a completed referral form during the period of evaluation January 2010 to July 2011 – moderate-to-high transmission setting.

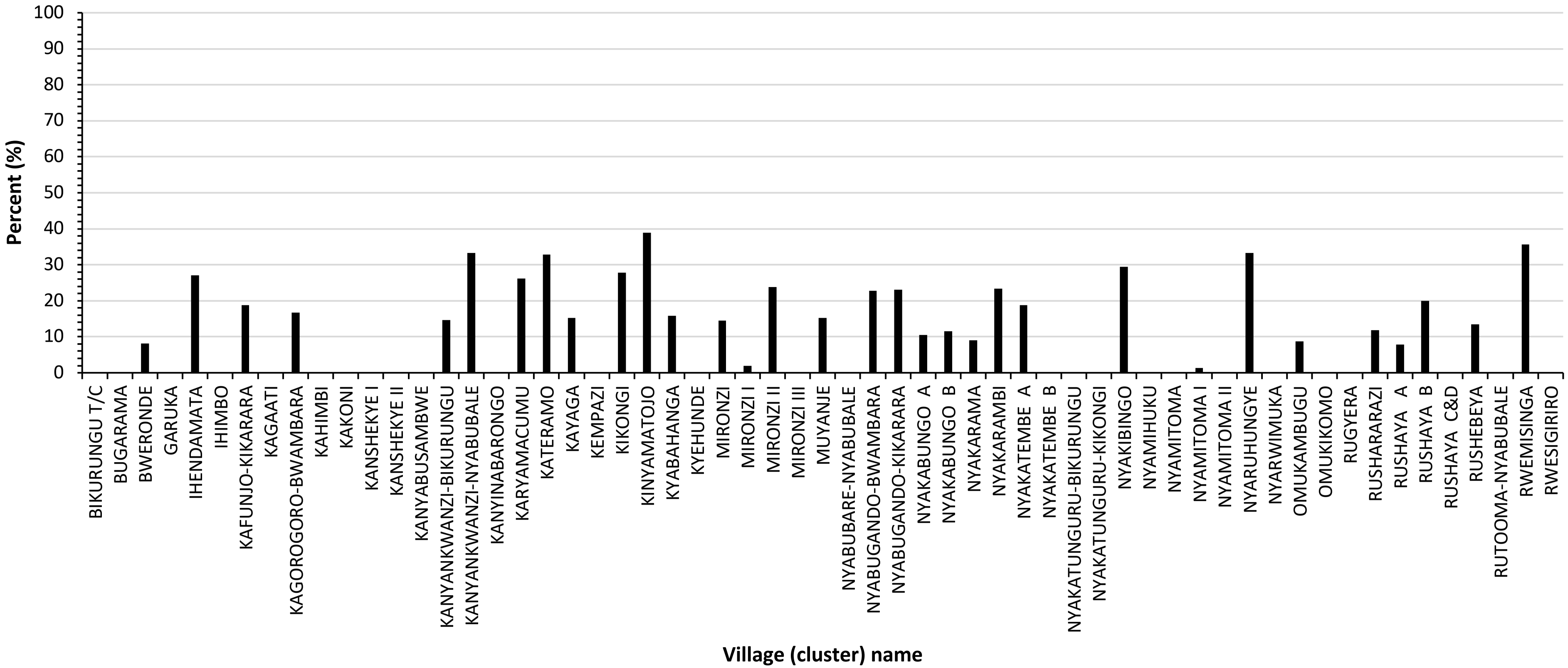


Figure S5.2: Percentage of referred caregivers not given a completed referral form by village (cluster) – moderate-to-high transmission setting.

Table 5.5: Characteristics of referred children given and not given a completed referral form - low transmission setting

	Total referrals (%) N=1315	Given completed referral form (%) N=139	Not given completed referral form (%) N=996
Age (years)			
<1.0	324 (29)	38 (28.4)	286 (29.1)
1.0-2.9	483 (43.2)	57 (42.5)	426 (43.3)
3.0-4.9	302 (27)	38 (28.4)	264 (26.8)
5.0-15.0	9 (0.8)	1 (0.7)	8 (0.8)
Sex			
Male	585 (51.8)	59 (43.4)	526 (53.0)
Female	544 (48.2)	77 (56.6)	467 (47.0)
Slept under a net the previous night			
No	129 (11.6)	17 (12.5)	112 (11.5)
Yes	984 (88.4)	119 (87.5)	865 (88.5)
Came from same village			
No	187 (16.5)	19 (13.7)	168 (16.9)
Yes	945 (83.5)	120 (86.3)	825 (83.1)
Duration of fever (hours) since onset of symptoms			
>24hrs	220 (20.0)	24 (18.3)	196 (20.2)
Within 24hrs	879 (80.0)	107 (81.7)	772 (79.8)
Tested with mRDT			
Not Tested	352 (31.0)	31 (22.3)	321 (32.2)
Tested	783 (69.0)	108 (77.7)	675 (67.8)
Type of referral			
Severe referral signs	421 (39.8)	41 (29.5)	380 (41.4)
Non-severe referral signs	636 (60.2)	98 (70.5)	538 (58.6)
Day of referral			
Weekday	791 (69.7)	112 (80.6)	679 (68.2)
Weekend	344 (30.3)	27 (19.4)	317 (31.8)
Season			
Dry	419 (36.9)	50 (36.0)	369 (37.0)
Wet	716 (63.1)	89 (64.0)	627 (63.0)
Village distance to nearest health facility (km)			
0.0-2.4	296 (27.9)	23 (17.4)	273 (29.4)
2.5-4.9	395 (37.2)	33 (25.0)	362 (38.9)
5.0-7.4	241 (22.7)	44 (33.3)	197 (21.2)
7.5-8.9	130 (12.2)	32 (24.2)	98 (10.5)

[a]Data missing amongst those with a referral form, for age: 5; sex: 3; net use: 3; resident in the same village: 0; onset of symptoms 8.

[b]Data missing amongst those without a referral form, for age: 12; sex: 3; net use: 19; resident in the same village: 0; onset of symptoms 28; type of referral: 78.

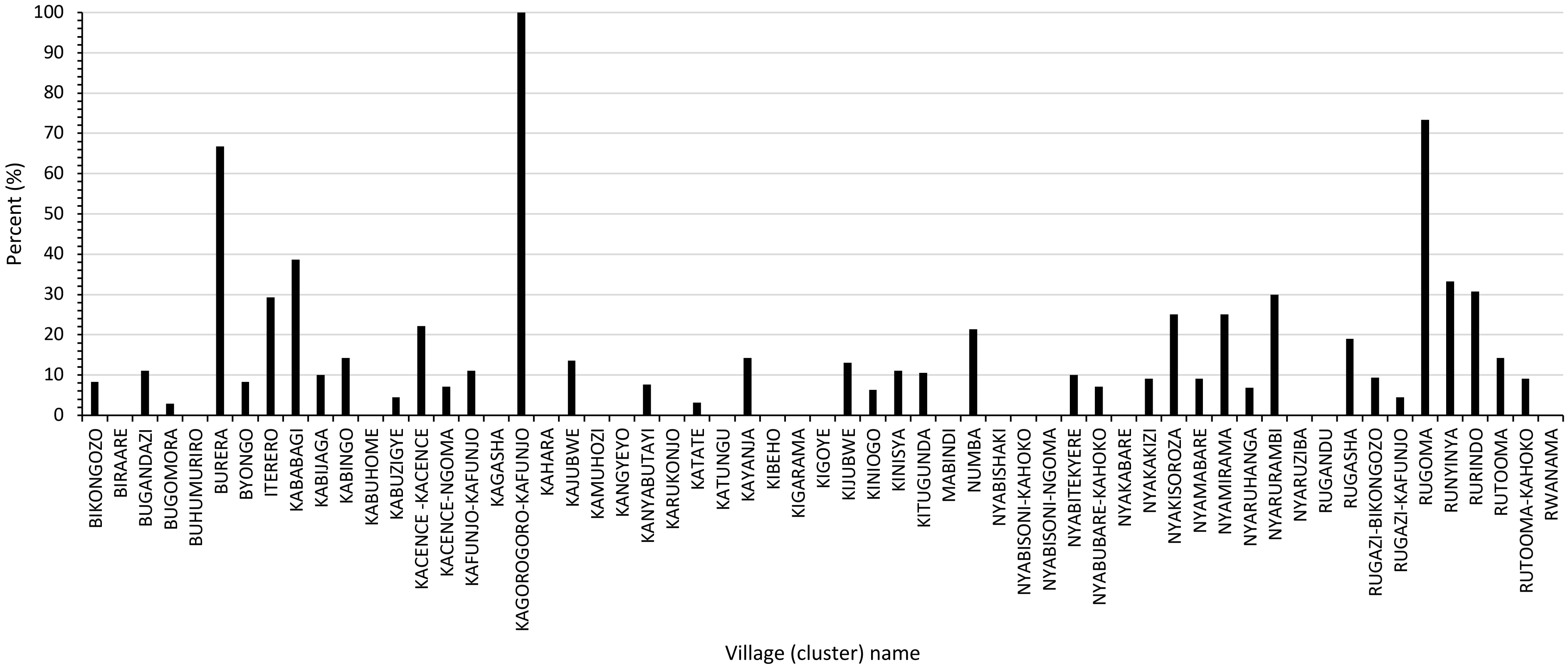


Figure S5.3: Percentage of referred caregivers not given a completed referral form by village (cluster) – low transmission setting.

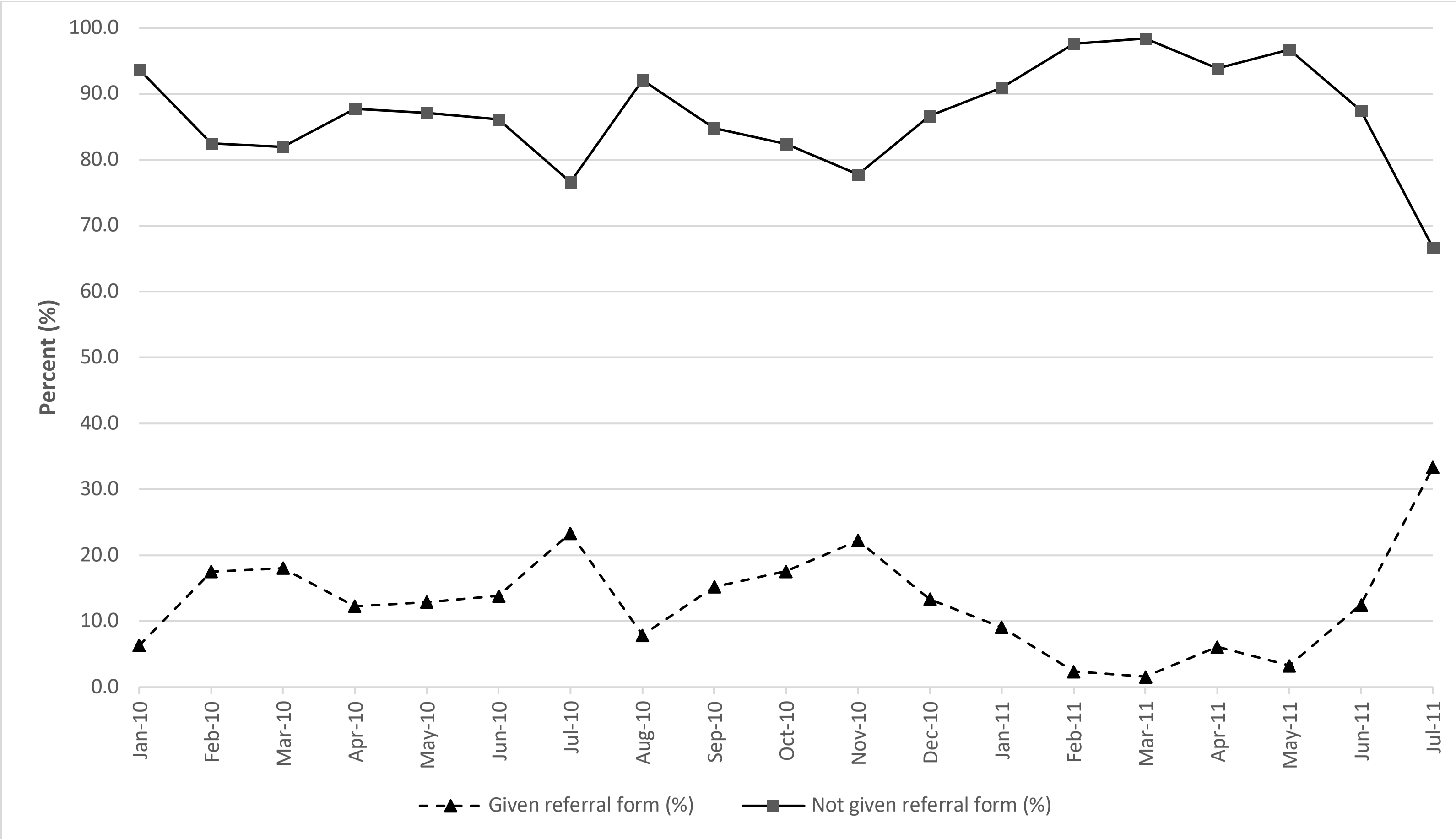


Figure S5.4: Percentage of referred caregivers given and not given a completed referral form during the period of evaluation January 2010 to July 2011 – low transmission setting

Chapter 6: Changes in Health Facility Utilisation

Adapted from: Sham Lal, Richard Ndyomugenyi, Neal D. Alexander, Mylene Lagarde, Lucy Paintain, Pascal Magnussen, Daniel Chandramohan, Siân E. Clarke. 2015. "*Health Facility Utilisation Changes during the Introduction of Community Case Management of Malaria in South Western Uganda: An Interrupted Time Series Approach*" PLOS ONE

Abstract

Background

Malaria endemic countries have scaled-up community health worker (CHW) interventions, to diagnose and treat malaria in communities with limited access to public health systems. The evaluations of these programmes have centred on CHW's compliance to guidelines, but the broader changes at public health centres including utilisation and diagnoses made, has received limited attention.

Methods

This analysis was conducted during a CHW–intervention for malaria in Rukungiri District, Western Uganda. Outpatient department (OPD) visit data were collected for children under-5 attending three health centres one year before the CHW-intervention started (pre-intervention period) and for 20 months during the intervention (intervention-period). An interrupted time series analysis with segmented regression models was used to compare the trends in malaria, non-malaria and overall OPD visits during the pre-intervention and intervention-period.

Results

The introduction of a CHW-intervention suggested the frequency of diagnoses of diarrhoeal diseases, pneumonia and helminths increased, whilst the frequency of malaria diagnoses declined at health centres. In May 2010 when the intervention began, overall health centre utilisation decreased by 63% compared to the pre-intervention period and the health centres saw 32 fewer overall visits per month compared to the pre-intervention period ($p<0.001$). Malaria visits also declined shortly after the intervention began and there were

27 fewer visits per month during the intervention-period compared with the pre-intervention period ($p<0.05$). The declines in overall and malaria visits were sustained for the entire intervention-period. In contrast, there were no observable changes in trends of non-malarial visits between the pre-intervention and intervention-period.

Conclusions

This analysis suggests introducing a CHW-intervention can reduce the number of child malaria visits and change the profile of cases presenting at health centres. The reduction in workload of health workers may allow them to spend more time with patients or undertake additional curative or preventative roles.

Introduction

Malaria is one of the leading causes of under-5 child morbidity and mortality in low income countries where children have limited access to public healthcare (Liu et al. 2012). In order to increase access to prompt effective treatment for malaria, many countries have implemented community health worker (CHW) strategies as part of national malaria control programmes (Rasanathan et al. 2014). They have been effective in reducing under-5 mortality by 40% and reducing the incidence of severe malaria by 50% (Sirima et al. 2003; Kidane and Morrow 2000; Okwundu et al. 2013). Recently CHWs have been endorsed by the World Health Organization (WHO), United Nations Children's Fund (UNICEF) and international donors as a strategy to meet the fourth Millennium Development Goal (MDG) of reducing under-5 mortality from 1990 levels by two-thirds by 2015.

In many Sub-Saharan African (SSA) countries without CHW interventions, malaria accounts for an average of 50% of all outpatient department (OPD) visits and between 20% to 90% of all hospital admissions (WHO 2003a; WHO 2006a; Steinhardt et al. 2014; Uganda Ministry of Health 2011). When malaria treatment is available in the community, there may be a shift in treatment seeking away from health centres to CHWs within a child's community (Tiono et al. 2008). This may partly arise by the closer proximity of the treatment provider in the child's area compared to a health centre. Secondly, there may be reduced household costs associated with seeking treatment closer to home and finally, CHWs are often elected by the community and might be more trusted and accepted providers compared to health centre staff. We hypothesise that changes in treatment seeking may affect the conditions that present at health centres. For example, if a large proportion of febrile visits are treated in the community, the proportion of non-malaria fever visits may increase among children attending health centres.

Many SSA countries are scaling up CHW interventions, specifically integrated community case management (iCCM). The primary evaluations of these programmes have been on CHW's compliance to guidelines and disease-specific impacts whilst the effects of the CHW programmes on public health centres have not been widely documented (Wazny et al. 2014). The aim of this paper is to examine the effects of introducing a CHW intervention for malaria on health centre utilisation by children under-5 in South Western Uganda.

Materials and Methods

Ethical approval

Data analysed comes from routinely available, anonymised health management information systems (HMIS) captured from three public health centres in the study area. Ethical approval for the collection and analysis of the anonymised HMIS data was approved by institutional review boards at the Uganda National Council of Science and Technology, Ministry of Health, Uganda and the London School of Hygiene & Tropical Medicine. Local approval to collect and analyse the HMIS data was also sought from the district health officer and health centre staff.

Study context

This study was conducted in parallel to an on-going CHW-intervention which examined the impact of malaria rapid diagnostic tests (mRDTs) on the proportion of children under-5 years receiving appropriately targeted artemisinin based combination therapy (ACT) ((Ndyomugyenyi *et al.*, 2016)). The intervention was conducted in a moderate-to-high malaria transmission setting within Bwambara Sub-county, Rukungiri District, South Western Uganda (Sserwanga et al. 2011). Bwambara lies 400km west of the capital Kampala with a population of approximately 28,900 with more than 85% living in rural areas (Rukungiri District Local Government 2009). The area experiences a bimodal pattern of annual rainfall with a long rainy season between September and December and a short rainy season from March to May. Malaria transmission is perennial with peaks in incidence shortly after the rains. The public health system has three health centres that serve the sub-county's population. Two are classified as public health centre II and are limited to outpatient services. There is one health centre III and in addition to outpatient services, it has maternity services, an inpatient ward and microscopy for diagnosing malaria, it also acts as a referral centre for both lower level II health centres (Table 6.0) (Ministry of Health 2014).

Table 6.0: The structure of the Uganda National Health system in Bwambara Sub-county

Health Centre	Services	Number of Health Centres	Catchment	Population Served	Method of malaria diagnosis
Health Centre II	Outpatient	2	Parish	5,000	mRDT
Health Centre III	Outpatient, maternity services, inpatient ward, microscopy	1	Sub-county + Parish	20,000	mRDT + light microscopy

Adapted from Government of Uganda, Health Sector Strategic Plan III, 2010/11 – 2014/15(Ministry of Health, 2014)

Community health worker intervention

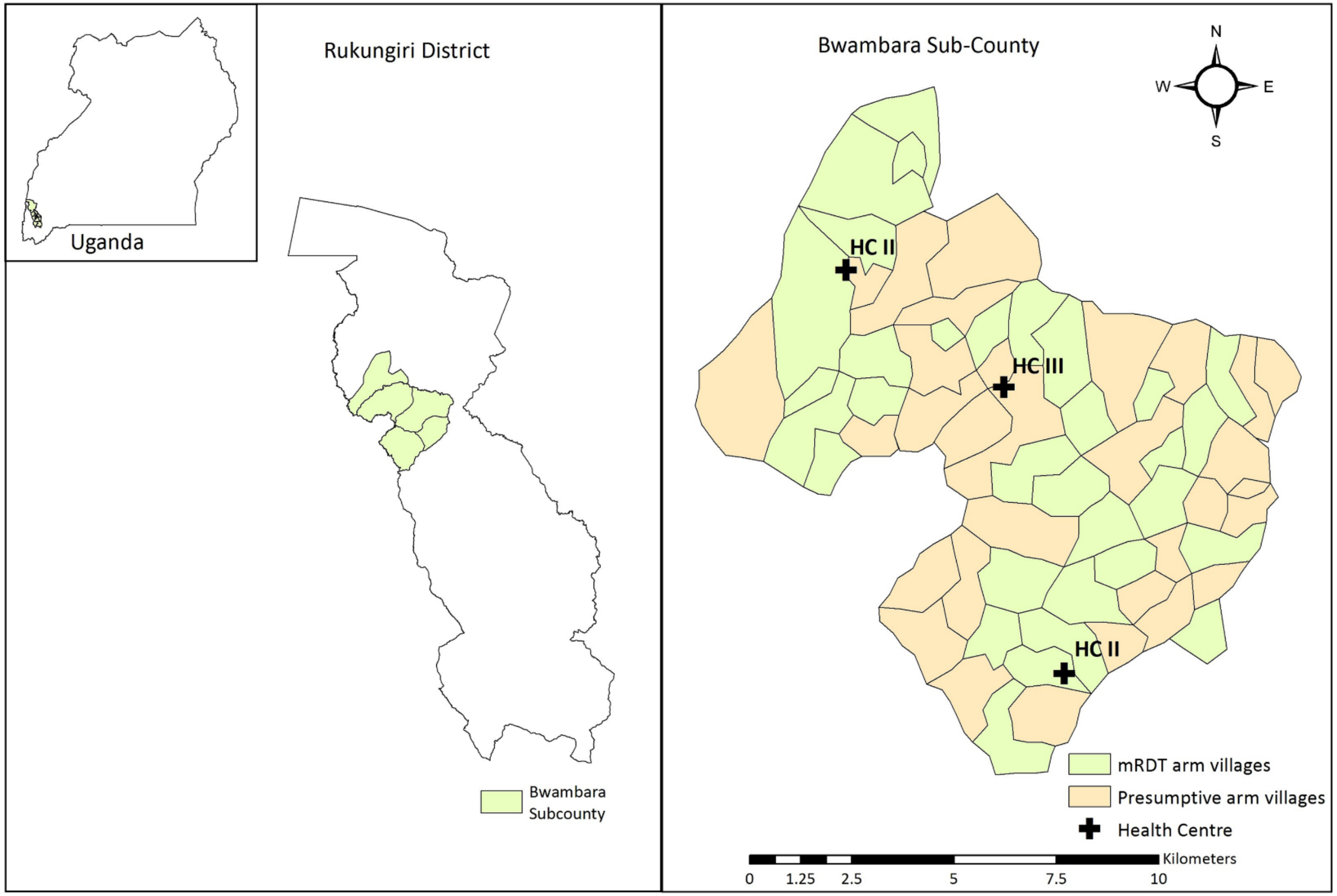
The primary objective of the CHW-intervention was to evaluate the effectiveness of mRDTs used to diagnose and treat only malaria with ACTs compared with the presumptive diagnosis and treatment of malaria. The intervention was implemented at the village level, where 63 clusters were randomised to either the mRDT diagnosis arm or the presumptive diagnosis arm. In total 189 CHWs were trained (3 per village) between January and February 2010, with separate training sessions for each arm. All CHWs were trained on how to examine the febrile children, take their history and record basic patient details on treatment registers. CHWs were also taught how to recognise children with severe malaria and symptoms of other illnesses and how to refer them to the nearest public health centre for further management. The 31 villages in the mRDT arm received additional training in malaria diagnosis using mRDTs and to only prescribe ACTs after a positive test result (further trial details available at www.actconsortium.org/RDThomemanagement). In February 2010, public meetings were held with participating villages to disseminate key messages that included, a) not all fevers are malaria, b) a diagnostic test was advisable before treatment with an antimalarial and c) tests were available from CHWs in the intervention arm. After CHWs completed training, the intervention was implemented in all villages during the first week of May 2010. Immediately prior to the trial there were no other community case management services operating in the sub-county.

Data collection

To analyse the impact of the CHW-intervention on the changes in health centre visits before and after the introduction of the intervention, we reviewed OPD records on children under-5 from the three health centres. Data were extracted from OPD treatment registers maintained by the health centre staff for the 12 months prior to the commencement of the CHW-intervention (May 2009 to April 2010, the "pre-intervention period") and for the full 20 months of the intervention (May 2010 to December 2011, the "intervention-period"). The intervention did not introduce changes in the practice of OPD data collection or recording at any of the three health centres. The routinely available OPD data captured demographic data on age, sex, village of residence, diagnosis and date of visit. Malaria diagnosis at health centres in Uganda was based on a presumptive diagnosis until 2009, when the National Malaria Control Programme adopted the WHO recommendation of universal parasitological testing at all levels of the health care system (Uganda Ministry of Health 2011). Diagnosis of malaria at the health centres varied by the type of health centre: the primary method of malaria diagnosis at the two level II health centres was mRDT, whilst at the level III health centre the main method of malaria diagnosis was either by light microscopy or mRDTs. When neither of these methods were possible, for example due to a stock-out of mRDTs, a presumptive diagnosis was made. However, the method of diagnosis for malaria or other conditions was not routinely recorded in the registers by health centre staff.

This analysis of health centre OPD visits was conducted within the context of a cluster randomised trial (CHW-intervention) and the locations of each health centre in relation to the randomised villages (clusters) are shown in Figure 6.0. The aim of this analysis was to examine the changes in the mean number of visits at health centres when a CHW-intervention for malaria was implemented in the health centre's catchment area.

Figure 6.0: Map of study area Bwambara Sub-county. The Map was generated by authors in Arc GIS 10.3. Sub-county boundaries were sourced from Global Administrative Areas (http://gadm.org).



Statistical methods

The diagnoses recorded in OPD registers by health centre staff were categorised into commonly occurring childhood conditions (malaria, respiratory tract infections (RTIs), pneumonia, diarrhoea, helminths and other infections) during the pre-intervention and intervention-period for each health centre and collectively for all three health centres. Statistical chi-square tests were calculated to test the null hypothesis that there were no differences in the age, sex and diagnoses made between the pre-intervention and intervention-period. In addition, we calculated standardised differences, the adjusted residuals (ARs) between the observed and expected frequencies. These were calculated by dividing the residual (observed minus the expected frequency) by the standard error of all the residuals. They measure the number of standard errors the residual falls from zero and follow a standard normal distribution that allows hypothesis testing (Haberman 1973; Agresti 2007).

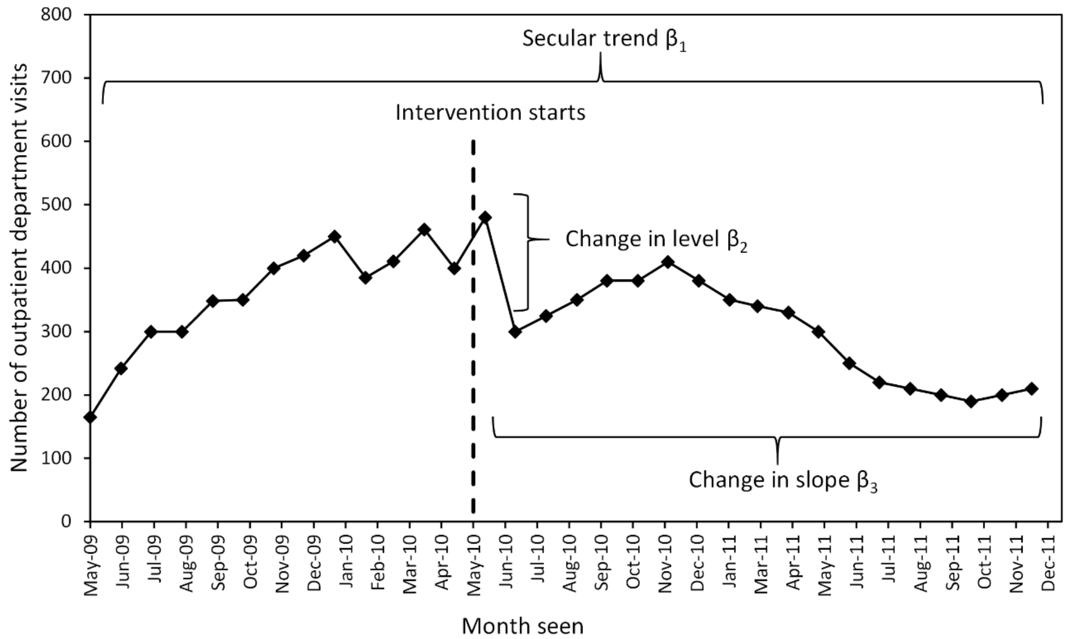
An interrupted time series (ITS) approach was used to analyse the longitudinal OPD visit data and evaluate the impact of introducing a CHW-intervention on health centre utilisation, taking into account background secular trends (Penfold and Zhang 2013). In an ITS approach, each unit of analysis acts as its own control and one compares changes in the outcome of interest (here monthly OPD visits) before and after the start of the CHW-intervention (Penfold and Zhang 2013). To undertake the ITS analysis, segmented linear regression was used to estimate the effect of the intervention on three outcomes at the health centres (malaria visits, non-malaria visits and overall visits) before and after the introduction of the CHW-intervention. The specification of the linear regression model to be analysed for each outcome is:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention_t + \beta_3 \times time\ after\ intervention_t + \varepsilon_t \qquad (1)$$

Where Y_t denotes the number of child visits (outcome) in month t at a health centre for malaria, non-malaria or overall visits; *time* is a continuous variable indicating the time in months at time t over the entire period; *trial* is a dichotomous indicator variable for the CHW-intervention, equal to zero before the start of the intervention and equal to one after the start of the intervention; *time after intervention* is a continuous variable counting the number of months after the CHW-intervention starts, and equal to zero before the intervention starts. Finally, ε_t is an error term at time t that represents random variability not explained by the model.

With the variables defined as above, β_0 estimates the number of visits per month at time 0 (baseline level of visit); β_1 estimates the secular trend in the number of visits per month over the entire period; β_2 estimates the level change in the number of visits per month immediately after the trial (the immediate effect of the intervention on the outcome of interest); β_3 is the coefficient that captures the change in trend in the number of visits after the start of the intervention. The sum of $\beta_1$and β_3 is the intervention-period slope. By controlling for baseline level and trend, the model estimates level and trend changes associated with the start of the intervention. The coefficients are illustrated graphically in Figure 6.1 and describe the analysis undertaken using equation 1.

Figure 6.1: Graphical representation of the parameters in the segmented regression equation 1 using artificial data.



The Durbin-Watson statistic was used to test for the presence of autocorrelation on the error term ε_t. When this was detected, regression coefficients were estimated using a Prais-Winsten estimator (Lagarde 2012).

Finally, assuming that the changes in trend would remain the same in the future, we used the estimated regression coefficients to predict changes in each outcome at 3, 6, 12 and 18 months after the introduction of the intervention (Wagner et al. 2002). These estimates were compared with a simulated counterfactual, to project expected values in the absence of the intervention. This assumes the trends continue along the same trajectory as in the pre-intervention period (β_3=0). Percentage changes were calculated for any visit and malaria-specific visits for each health centre separately and for all three combined.

Data were entered using Microsoft Access 2007 (Microsoft Inc., Redmond, Washington), cleaned and analysed using STATA version 13.1 and the 'prais' package (STATA Corporation, College Station, Texas).

Results

Throughout the 12-month pre-intervention and 20-month intervention-period, a total of 11,422 visits were reported from all health centres and 97% of these came from the same sub-county where the CHW-intervention was implemented. Approximately 3% of visits originated from neighbouring sub-counties and were excluded from the analysis. The utilisation of all three health centres was higher during the pre-intervention period (509 visits per month) compared to the intervention-period (265 visits per month).

The age distribution of visits at health centres was statistically different between the two periods (χ^2=66.6, df=4, p<0.001). The ARs revealed the largest changes in age frequencies were in children aged <1 year (AR=6.7, p<0.001), 1.0–2.9 years (AR=-5.5, p<0.001) and there were no significant changes for children aged between 3.0–4.9 years (AR=0.2, p<0.195) or 5.0–11.0 years (AR=0.4, p=0.363) (Table 6.1). The change in age frequencies suggests visits of infants (<1 year) increased during the intervention-period compared to the pre-intervention period, whilst there were decreases in visits from children aged between 1.0–4.9 years. There were no significant differences between the frequencies of male or female visits between the two time periods (Table 6.1).

Table 6.1: Characteristics and diagnoses made of children attending all three health centres.

	12 month Pre-intervention period (%)	20 month Intervention-period (%)	Adjusted Residual	p-value
Total number of visits	6110	5312		
Age in years [$]				
<1.0	1650 (27.3)	1737 (33.1)	6.7	<0.001
1.0 – 2.9	3252 (53.7)	2548 (48.5)	-5.5	<0.001
3.0 – 4.9	1124 (18.6)	942 (17.9)	-0.9	0.195
5.0 – 11.0	25 (0.4)	24 (0.5)	0.4	0.363
Sex [*]				
Male	2792 (46.2)	2441 (47.1)	-1.0	0.456
Female	3257 (53.8)	2740 (52.9)	1.0	0.456
Total diagnoses made [€]	9721	8708		
Diagnosis [%]				
Malaria	4400 (45.3)	1845 (21.2)	-37.4	<0.001
Respiratory tract infection	2644 (27.2)	2735 (31.4)	6.3	<0.001
Pneumonia	59 (0.6)	123 (1.4)	5.5	<0.001
Diarrhoea	538 (5.5)	593 (6.8)	3.6	<0.001
Helminths	428 (4.4)	771 (8.9)	12.2	<0.001
Other	1652 (17.0)	2641 (30.3)	21.4	<0.001
Average number of diagnoses per visit	1.5	1.5		

[$]Age missing 59 pre-intervention period, 61 intervention-period; *Sex missing 61 pre-intervention period and 131 intervention-period; € It was possible for children attending health centres, to have more than one diagnosis; [%]RTI includes cough, cold, flu, excludes pneumonia, TB and asthma. A child can have more than one diagnosis. Other diagnoses pre-intervention include: Skin infections (1.9%), burns, wounds, injuries (0.3%), eye infections (2.2%), epilepsy (0.2%), ear conditions (1.4%), gastro intestinal infections (0.6%), STIs (0.03%), fungal infections (0.2%), viral infections (0.07%). Other diagnoses trial period include: Skin infections (4.5%), burns, wounds, injuries (0.9%), eye infections (5.3%), epilepsy (0.7%), ear conditions (2.6%), gastro intestinal infections (0.8%), STIs (0.1%), fungal infections (0.7%), viral infections (0.6%)

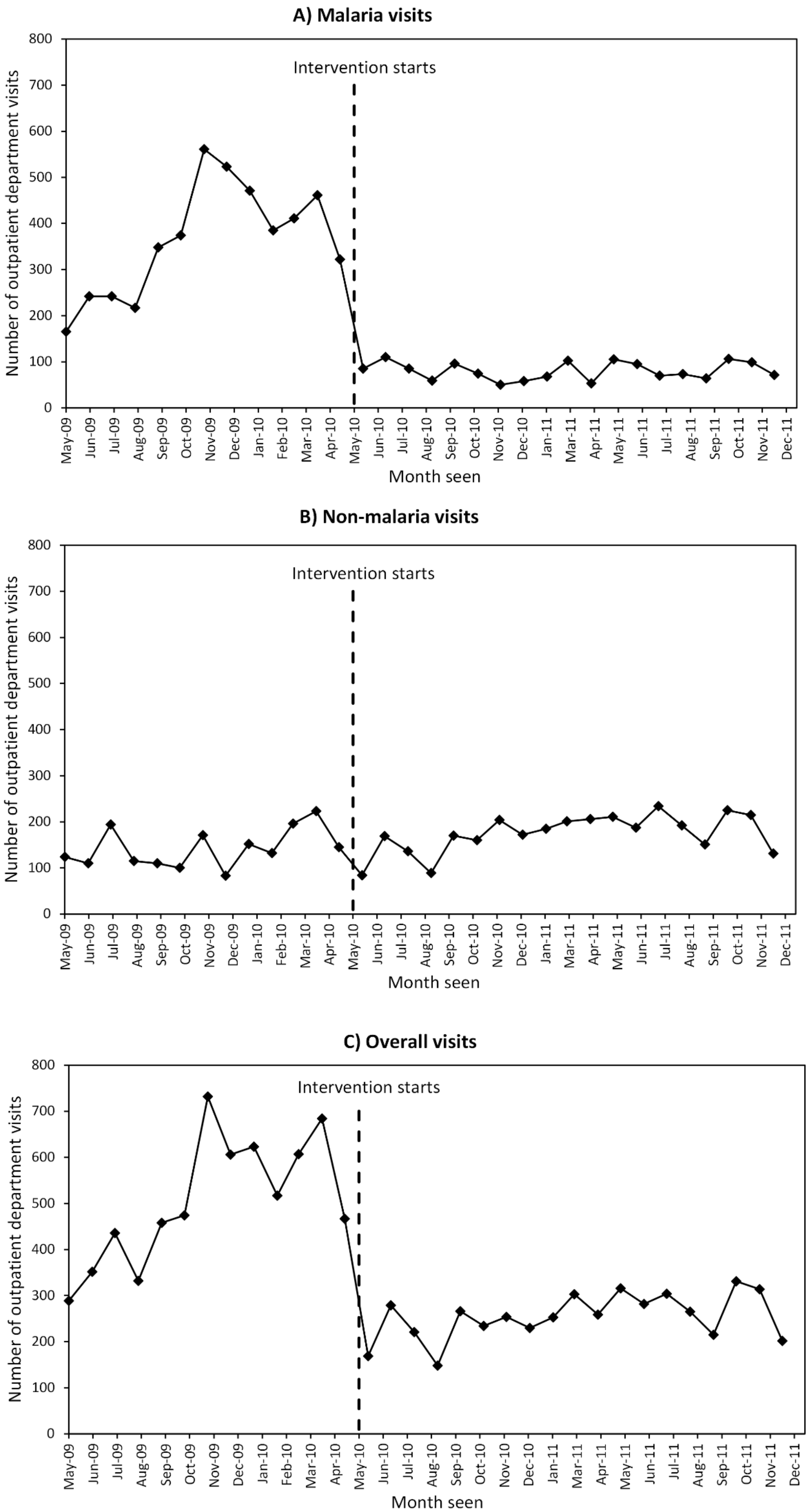
OPD Diagnoses

Table 6.1 also shows the combined childhood diagnoses made by health centre staff at the three health centres. Malaria contributed to approximately 45% of all diagnoses made during the pre-intervention period, followed by RTIs (27%), diarrhoea (6%), helminth infections (4%), pneumonia (1%) and other diagnoses (17%). During the intervention-period the frequencies of diagnoses at the three health centres changed significantly when compared to the pre-intervention period (χ^2=1346.4, df=4, $p<0.001$). There was a significant decline in malaria diagnoses observed between the two time periods (AR=-37.4, $p<0.001$), whilst the frequency of other diagnoses (AR=21.4, $p<0.001$), helminths (AR=12.2, $p<0.001$), RTIs (AR=6.3, $p<0.001$), pneumonia (AR=5.5, $p<0.001$) and diarrhoea (AR=3.6, $p<0.001$) all increased from the pre-intervention to the intervention-period.

Trends in malaria, non-malaria and overall visits

The graphs in Figure 6.2 show the trends of a) malaria, b) non-malaria and c) overall visits at the three health centres combined. During the pre-intervention period there were seasonal peaks of malaria visits during the two rainy seasons between October-December 2009 and between March-April 2010. When the intervention started in May 2010, a drop in malaria visits was observed, with no seasonal variation in visits during the intervention-period (Figure 6.2a). In contrast, the patterns of non-malaria visits did not change substantially between the two periods (Figure 6.2b). Finally, the trends of overall visits during the pre-intervention and intervention-period are shown in Figure 6.2c. Collectively, the health centres saw similar patterns of visits as those for malaria, with two large peaks of visits coinciding with the rainy seasons. Shortly after these peaks the health centres saw a sharp drop in visits when the CHW-intervention began and there appeared to be substantially fewer visits during the intervention-period compared with pre-intervention period (Figure 6.2c).

Figure 6.2: Trends in visits during the pre-intervention and intervention-period at all health centres. a) Malaria visits, b) Non-malaria visits and c) Overall visits



Segmented regression results

Table 6.2 shows the segmented regression results for malaria, non-malaria and overall visits for the three health centres combined. The regression coefficient β_1 estimates the average number of visits during the pre-intervention period and indicates health centres saw an increase of approximately 20 malaria visits per month. The average difference between pre-intervention trend and the intervention-period slope is estimated by β_3 and after the intervention began there were 27 fewer malaria visits per month compared with the pre-intervention period (Table 6.2). The health centres saw a sharp change in malaria visits in May 2010 within one month after the start of the intervention, and an estimate of the percentage change was calculated using the regression coefficients estimated from Table 6.2. These suggest that in May 2010 there was an average of 261.7 visits per month, whilst in the absence of the intervention 722.0 malaria visits per month would have been observed. This suggests the absolute effect of the intervention was a sharp drop of 63.8% in malaria visits in May 2010. Despite the clear changes in trends for malaria visits, there was poor evidence to indicate changes in non-malaria visits. The results in Table 6.2 indicate an increase in the mean number of non-malaria visits during the pre-intervention period and that these declined by 40 visits per month when the intervention started, however these changes did not reach significance.

The results of the segmented regression analysis for overall visits in Table 6.2 reflect similar findings as those presented in Figure 6.2c. At the beginning of the period of observation (May 2009) 296 consultations were reported from all three health centres and during the pre-intervention period the average number of visits increased by 33 per month. These increases at health centres were reversed with a drop shortly after the start of the intervention with 428 fewer monthly visits compared to the pre-intervention period, which represents a 63% decrease in the mean number of overall visits at health centres between the two time periods ($p<0.001$). The average difference between pre-intervention trend and the intervention-period slope found that health centres received 32 fewer visits per month compared with the pre-intervention period (Table 6.2). The number of visits during the intervention-period remained constant throughout the period because there was no change in trend during the intervention-period (Figure 6.2c).

The adjusted segmented regression models incorporated an indicator variable to capture the effects of the rainy seasons on visits (Table 6.2). When compared to the unadjusted results, there was no longer evidence for an increasing trend in malaria visits at health centres during the pre-intervention period, and the magnitude of decline in malaria visits when the intervention began was slightly smaller (219 visits per months) compared with the unadjusted results (245 visits per month). In addition, malaria visits peaked by approximately 52 visits per month during the rainy seasons. There were no substantial changes in non-malaria visits and overall visits between the adjusted and unadjusted results (Table 6.2).

Table 6.2: Changes in level and trend of malaria, non-malaria and overall visits at three health centres combined, results from a segmented linear regression model, unadjusted and adjusted results.

	Unadjusted			Adjusted^		
	Malaria visits$	Non-malaria visits	Overall visits	Malaria visits$	Non-malaria visits	Overall visits
Constant (β_0)	207.7** (70.9)	106.0*** (23.3)	296.3*** (46.5)	204.0** (70.8)	106.3*** (23.7)	294.4*** (45.5)
Secular trend (β_1)	19.2* (8.9)	5.6 (3.2)	32.7*** (6.3)	15.7 (8.9)	6.0 (3.4)	29.8*** (6.5)
Change in level after intervention starts (β_2)	-245.0*** (65.9)	-39.8 (27.1)	-427.9*** (54.0)	-218.7** (62.9)	-42.6 (28.3)	-408.3*** (54.3)
Change in slope after intervention starts (β_3)	-27.1* (11.0)	-1.8 (3.5)	-32.3*** (7.0)	-24.7* (11.1)	-2.1 (3.6)	-30.0*** (7.0)
Rainy season (β_4)				51.8* (23.7)	-6.1 (14.6)	42.8 (28.1)

Standard errors in parenthesis *p<0.05, p<0.01**, p<0.001***; $model includes an adjustment for autocorrelation, ^adjusted for bimodal rainy seasons.

Table 6.3 uses the coefficients presented in Table 6.2 to calculate the simulated counterfactual visits that would have occurred in the absence of the CHW-intervention. At all the health centres these were calculated for malaria, non-malaria and overall visits at 3, 6, 12 and 18 months after the start of the intervention. Three months after the intervention began malaria and overall visits declined by 68% and continued to decline throughout the course of the intervention and there were no significant changes in non-malaria visits.

The declines in overall health centre are plotted alongside all visits to CHWs as part of the intervention. The data in Figure 6.3 shows when the intervention began in May 2010 there was a sharp rise in visits at CHWs which gradually declined in subsequent months, except for a peak in visits from October to December 2011. The average number of visits at the CHW-intervention was 1,267 per month, which exceeded the average number of malaria visits at health centres (80 per month) during the months of the intervention-period.

Figure 6.3. Trends in malaria visits at health centres and visits to the community health worker intervention, during the pre-intervention and intervention-period.

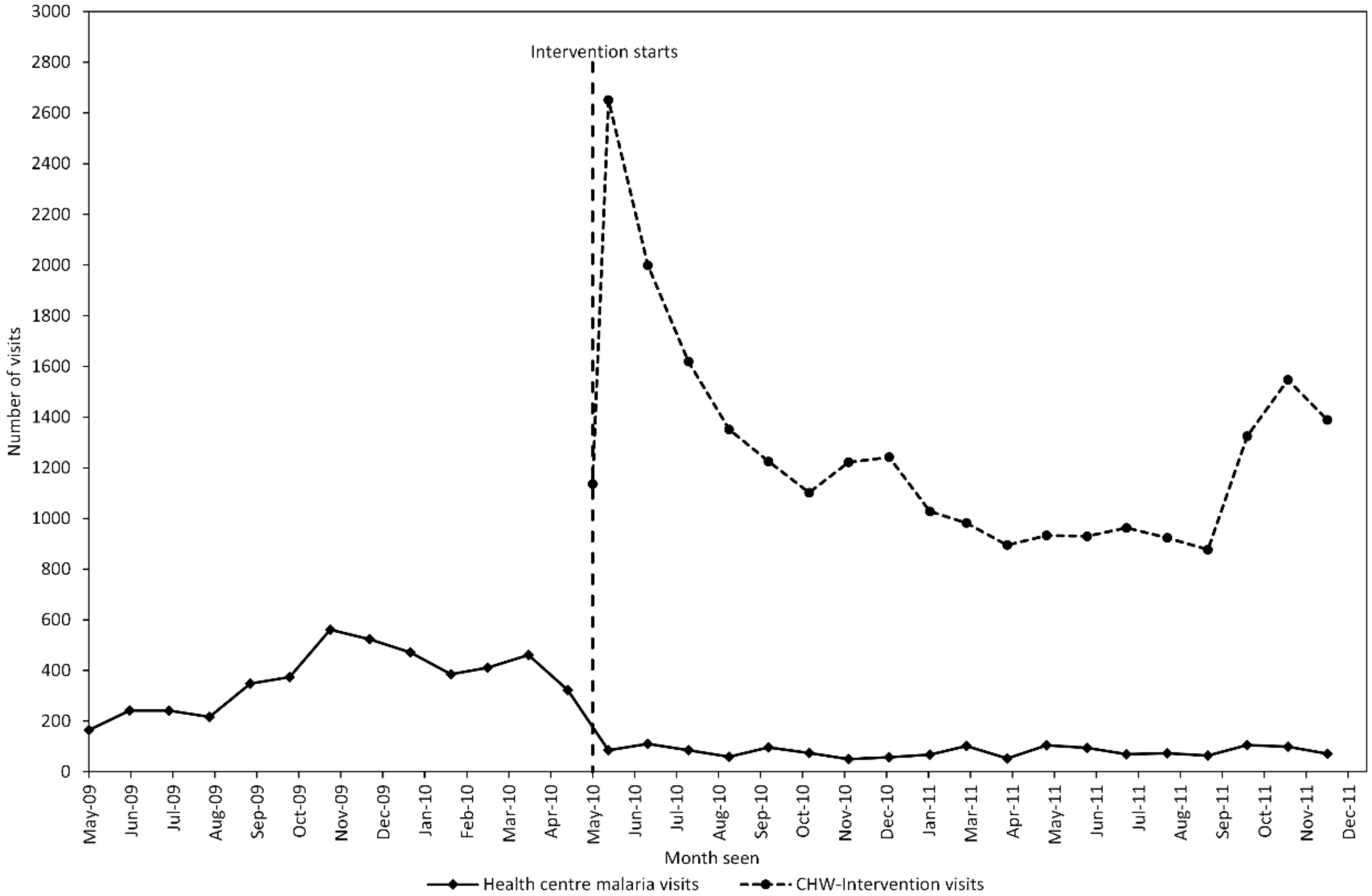


Table 6.3: Percentage change in health centre visits for malaria, non-malaria visits and overall visits over time unadjusted and adjusted results.

	Unadjusted			Adjusted^		
	Malaria visits[$]	Non-malaria visits*	Overall visits	Malaria visits	Non-malaria visits*	Overall visits*
% Change 3 months after intervention starts	-68.6	-24.1	-67.9	-69.7	-25.2	-68.6
% Change 6 months after intervention starts	-75.8	-24.7	-71.2	-77.9	-26.1	-72.0
% Change 12 months after intervention starts	-86.8	-25.8	-76.1	-90.4	-27.4	-77.0
% Change 18 months after intervention starts	-94.5	-26.5	-79.5	-99.5	-28.4	-80.5

[$]Model includes an adjustment for autocorrelation, *Percentage changes not significantly different from zero, ^adjusted for bimodal rainy seasons.

Supplementary analyses

An additional analysis was undertaken to compare the age distributions and diagnoses between two equal time periods, a 12-month pre-intervention period and a 12-month intervention-period (Table S6.0). This found the same changes in age visits as the analysis with a 20-month intervention-period. Children <1 year increased during the 12-month intervention-period, whilst children aged between 1.0-2.9 years decreased and no significant changes were seen with children aged 3 years or greater (Table S6.0).The analysis of diagnoses found similar changes: as the frequency of malaria diagnoses during the 12-month intervention-period decreased, RTIs, pneumonia, diarrhoea, helminths and other diagnoses all increased during the intervention-period (Table S6.0).

The aggregated results mask some of the heterogeneity seen at the individual health centres, and to examine patterns of visits at each individual health centre a further set of analyses were undertaken (Table S6.1). During the pre-intervention period, level II health centres saw a monthly increase in malaria and overall visits, ranging between 9 and 18 visits per month. One month after the start of the intervention, both level II health centres saw a drop in visits that ranged from 127 to 142 fewer visits per month (Table S6.1). Shortly after the drop, in the intervention-period health centres IIs saw between 8 and 20 fewer visits per month compared to the pre-intervention period. Despite the changes seen at each individual health centre for malaria and overall visits, there were no obvious changes at each health centre for non-malaria visits (Table S6.2). The higher level health centre III saw no significant change in the number of monthly malaria or overall visits during the pre-intervention period, however there was a significant drop in overall visits when the intervention began (Table S6.5).

The regression results adjusted for the rainy seasons were broadly similar compared to the unadjusted results for each health centre. However, health centre III saw a large reduction of 129.2 malaria visits compared with a non-significant reduction of 44.2 visits in the unadjusted model (Table S6.1). The adjusted results also showed an increase of between 15-18 malaria and overall visits per month at Kikongi Health Centre II during the rainy seasons (Table S6.1, Table S6.5).

The percentage change in visits at each health centre was also calculated using a simulated counterfactual. Both health centre IIs saw an estimated 90% decline in malaria visits and both centres followed similar patterns of decline 18 months after the intervention started (Table S6.2). There was little difference between the adjusted and unadjusted percentage changes, suggesting the rainy season did not affect the results.

Discussion

This interrupted time series analysis shows a decline in health centre utilisation for malaria and overall visits shortly after the introduction of a CHW-intervention for malaria diagnosis and treatment. This decline did not occur gradually over the study period, rather there was a clear drop in visits that coincided with the introduction of the intervention to the surrounding communities. Three months after the invention began malaria and overall visits declined by an average of 70% across the three health centres, however there was little evidence to suggest any change in the average number of non-malaria visits at the health centres. The reductions in both malaria visits and overall visits were sustained beyond an initial three-month period, after 18 months malaria visits had decreased by 95% and overall visits by 80% when compared to the pre-intervention period. In relation to these changes a marked increase in utilisation of CHWs (1,267 visits per month) was reported, when compared with malaria-visits at health centres (Figure 6.3). This suggests there was a shift in caretaker treatment seeking from public health centres to CHWs during the intervention-period and that access to malaria diagnosis and treatment also increased when compared to the pre-intervention period. Both the shift in treatment seeking and the increased access suggest a greater utilisation of case management services for those in rural areas. These findings are similar to household cross-sectional surveys where 27%-59% of caretakers first sought treatment from CHWs treating malaria (Kalyango et al. 2012; Nsungwa-Sabiiti et al. 2007; Ikeoluwapo O Ajayi et al. 2008).

In this study, CHWs only treated malaria and saw the proportion of malaria diagnoses approximately halved at health centres between the pre-intervention and intervention-periods. The diagnoses made for RTIs, pneumonia, diarrhoea, helminth and other diagnoses all increased during the intervention-period. There could be a number of explanations for this change. Firstly, there were more overall visits to CHWs by caretakers and a larger number of non-malaria visits may have been referred to health centres, which would have been unlikely in the absence of a CHW-intervention. Secondly, the change in diagnoses could be due to health workers being more alert and aware to the possibility of other diagnoses, knowing that CHWs in their health centre catchment area are diagnosing and treating malaria, and therefore tend to diagnose other conditions over malaria. However, previous studies report a low frequency of referral making by CHWs and a low compliance to referral advice by caretakers (Thomson et al. 2011; Kallander et al. 2006). This was also confirmed in this study by examining CHW's and health centre worker's treatment registers from the intervention trial, which suggested that only 13% of children referred from a CHW to a health centre actually went (i.e. completed the referral) (Lal *et al.*, 2018). Thus referral may explain only a small fraction of visits attending for non-malaria diagnoses, whilst the change in clinical decision-making by health workers may be an explanation that accounts for the increase in the diagnoses of non-malarial conditions.

There are a number of limitations that need to be considered when interpreting the findings from this analysis. The impacts of new healthcare programmes are ideally evaluated using experimental study designs such as cluster randomised controlled trials. However, when programmes begin to scale up at a district or national level they are not randomised and evaluating impacts on health systems can be achieved using routinely available health centre data. Therefore a non-experimental interrupted time series approach was used with segmented regression models and these are becoming more commonly used to assess impacts of health programmes or policies (Lagarde 2012; Ramsay et al. 2003). Another approach to analyse the routinely available visit data would be to use auto-regressive integrated moving average modelling (ARIMA) (McCleary et al. 1980). However, ARIMA modelling-based approaches require a large number of data points over time and much of the routinely available data from low and middle-income countries are not available for long periods of time and can be irregularly reported. As with all non-randomised studies, causal inference from the interrupted time-series approach is limited because it is impossible to rule out alternative explanations for observed changes in visits at health centres. For example, one explanation for the observations found could be a change in data recording practices, however the study did not introduce data collection tools at the health centres to systematically collect data over the entire period of the analysis and no other changes in routine reporting took place during the period of this analysis. Another explanation for the decrease in malaria visits could be the misclassification of diagnoses as malaria instead of other non-malaria febrile illness. During the pre-intervention period if health centres experienced stock-outs of mRDTs and continued with a presumptive diagnosis of malaria this may have resulted in a practice of over diagnosing visits as malaria. In contrast, during the intervention-period health centres were supported by the project with regular supplies of mRDTs, and the increased stock and use of mRDTs during this period may have improved the accuracy of malaria diagnoses compared to the pre-intervention period.

Another explanation for the changes in utilisations observed between the two periods could be the changes in individual demographic or socio-economic characteristics of caretakers visiting health centres. These may have changed between the pre-intervention period and the intervention-period and may have led to different patterns of health centre utilisation. However, as the unit of analysis in the segmented regression model was the monthly number of visits, it was not possible to undertake an analysis with individual-level covariates nor was it possible to determine whether there was a change in characteristics visiting between the two periods. Regardless, routine OPD data does not include detailed characteristics or socio-economic information on each visit. Individual level characteristics, such as child age or sex, would only confound the time series results if they were associated with the outcome and changed in relation to the timing of the intervention.

Another set of factors to be considered is whether malaria risk declined over the time period of this study. Rainfall is a predictor of malaria admissions to hospitals and may have changed between the pre-intervention and intervention-period (Hay, Snow, and Rogers 1998). Rainfall affects vector density by providing breeding sites for vectors and their development during the immature stages of the mosquito (Martens et al. 1999). We estimated monthly rainfall in South-Western Uganda from the National Oceanic and Atmospheric Administration satellite, and did not change between the pre-intervention and intervention-period (32mm and 31mm, respectively), suggesting it is unlikely rainfall affected the changes in health centre visits found in this analysis (NOAA 2010). Similarly parasitological malaria surveillance data collected from a neighbouring district suggested prevalence was comparable during pre-intervention period (43.4%) and intervention-period (43.9%) (Sserwanga et al. 2011). Finally, during the intervention-period CHWs were also mobilised to distribute insecticide-treated nets (ITNs) to all villages and other studies have found net distribution may play a role in decreased utilisation of health services for malaria (Okiro et al. 2007). Four months after the start of the CHW-intervention in May 2010 ITNs were distributed to all villages. Therefore, ITN distribution could not have explained the immediate decline in malaria visits the subsequent declines 3 months after the intervention. However, it is plausible that ITNs may have supported the continued reductions in malaria trends during the intervention-period in parallel with the CHW-intervention. Unfortunately it is not possible to separate effects of ITNs and the CHW-intervention on health centre visits in this study. Another explanation for the abrupt decrease in visits during the intervention-period could be a sharp decline in the population under-5 years within the sub-country. However, this seems unlikely and was not reported by the project or health staff.

Despite these potential limitations and the relatively short period of observation, it is unlikely that the sharp declines in malaria and overall visits observed would be seen in a short time frame in the absence of our CHW-intervention. We are thus confident that the changes we observed can be attributed to the intervention operating within the population catchment area of the three health centres. This is further supported by the timing of the dramatic decreases in malaria and overall visits reported by health centres that coincided with the same month as the start of the intervention. Data from the CHW treatment registers suggest that all CHWs in the sub-county were reporting management of malaria visits in the first month of the intervention.

These findings are consistent with all previous observational studies that have documented the effects of health centre utilisation during the introduction of a community case management programme. Studies in Burkina Faso, Rwanda and Southern Tigray, Ethiopia reported reductions in overall visits to public health centres of 83%, 48%, and 46% respectively (Tiono et al. 2008; Sievers et al. 2008; Lemma et al. 2010). It is important to note that methodological differences between these studies, in terms of study design, length of the CHW-intervention, case definitions for malaria and multiple CHW activities, restrict cross country comparisons. The study in Rwanda by Sievers et al was the only study to capture changes in diagnoses, finding a 24 percentage point increase in non-malaria admissions between the pre and post-intervention period (Sievers et al. 2008). However, ITNs were also distributed in addition to training CHWs to diagnose malaria presumptively, therefore it is not possible to discern the relative contribution of the two control activities to the reduction in admissions in Rwanda (Sievers et al. 2008).

In SSA countries where malaria poses a considerable burden on the health system and where there is a shortage of healthcare workers, our analysis suggests CHW-interventions can alleviate the often overwhelming caseload at health centres. Many of these countries, including Uganda face a shortage of qualified healthcare workers and WHO recommends a ratio of 2.3 healthcare workers per 1,000 population as a minimum to meet the MDGs and Uganda's ratio remains below the target level at 1.8 per 1,000 (WHO 2006b; Uganda Ministry of Health 2010; Uganda Ministry of Health,Health Systems 20/20, Makerere University School of Public Health 2011). A low healthcare worker to patient ratio results in greater caseload and poorer quality of care due to time pressures that affect their ability to follow guidelines and best practices, which in turn results in poor patient outcomes such as readmissions and increased mortality (Needleman et al. 2002). From our study, we found visits can be reduced by 63% immediately after the introduction of a CHW-intervention and the reduction can be sustained throughout the duration of the intervention. Shifting workload from health workers to CHWs suggests more consulting time would be available for patients at health centres, which has shown to improve patient diagnoses and treatment in low and middle income countries (Dubois and Singh 2009; Zurovac et al. 2004). It may also allow the role of health workers to be expanded to include other ameliorative tasks, outreach services or the supervision of CHWs.

Conclusion

The introduction of CHWs can reduce the number of patient visits presenting as malaria and change the profile of cases seen at health facilities. As malaria endemic countries begin to scale up community-based treatment interventions such as iCCM, there may be reductions in the utilisation of health services as caretakers use CHWs instead. There is a need for further research to document the impact these changes may have on health services and healthcare financing. Priorities for future research should include estimating changes in caretaker's treatment seeking behaviour, allocation of health worker's time, quality of care and the diagnoses being made at health centres when CHWs are implemented. This evidence would help plan how available healthcare resources can be distributed more efficiently in countries with high patient caseloads and constrained healthcare budgets.

Author Contributions

SL conceived the idea for this research and designed the study. SL did the analysis and wrote the first draft of the paper. NDA and ML provided input into the analysis and interpretation of the time series data. All authors reviewed and provided substantial input to revisions.

Declaration of interests

We declare no competing interests.

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Supplementary information

Table S6.0: Characteristics and diagnoses made of children attending all three health centres

	12 month Pre-intervention period (%)	12 month Intervention-period (%)	Adjusted Residual	P-value
Total number of visits	6110	3083		
Age in years$				
<1.0	1650 (27.3)	998 (32.8)	5.4	<0.001
1.0 – 2.9	3252 (53.7)	1495 (49.2)	-4.2	<0.001
3.0 – 4.9	1124 (18.6)	541 (17.8)	-1.0	0.171
5.0 – 11.0	25 (0.4)	13 (0.4)	0.1	0.464
Sex*				
Male	2792 (46.2)	1493 (49.1)	1.6	0.06
Female	3257 (53.8)	1551 (51.0)	-1.5	0.07
Total diagnoses made€	9721	5148		
Diagnosis%				
Malaria	4400 (45.3)	1162 (23.3)	-27.2	<0.001
Respiratory tract infection	2644 (27.2)	1569 (30.5)	4.2	<0.001
Pneumonia	59 (0.6)	72 (1.4)	4.9	<0.001
Diarrhoea	538 (5.5)	361 (7.0)	3.6	<0.001
Helminths	428 (4.4)	437 (8.5)	10.1	<0.001
Other	1652 (17.0)	1547 (30.1)	18.4	<0.001
Average number of diagnoses per visit	1.6	1.7		

$Age missing 59 pre-intervention period, 36 intervention-period, *Sex missing 61 pre-intervention period and 39 intervention-period.

€ It was possible for children to have more than one diagnosis, %RTI includes cough, cold, flu, excludes pneumonia, TB and asthma.

Other diagnoses pre-intervention include: Skin infections (1.9%), burns, wounds, injuries (0.3%), eye infections (2.2%), epilepsy (0.2%), ear conditions (1.4%), gastro intestinal infections (0.6%), STIs (0.03%) fungal infections (0.2%), viral infections (0.07%), Other diagnoses intervention-period include: Skin infections (3.9%), burns, wounds, injuries (1.0%), eye infections (9.0%), epilepsy (0.9%), ear conditions (2.8%), gastro intestinal infections (0.8%), STIs (0.1%), fungal infections (1.1%), and viral infections (1.0%)

Table S6.1: Changes in level and trend of malaria visits at three health centres, results from a segmented linear regression model, unadjusted and adjusted results.

	Malaria visits unadjusted			Malaria visits adjusted^		
	Kikongi Health Centre II	**Kikarara Health Centre II**	**Bwambara Health Centre III$**	**Kikongi Health Centre II**	**Kikarara Health Centre II**	**Bwambara Health Centre III**
Constant (β_0)	33.9***	8.3	141.6***	33.1**	7.3	147.5***
	(11.8)	(16.5)	(43.6)	(10.6)	(16.4)	(21.2)
Secular trend (β_1)	9.4***	12.7***	1.7	8.1***	12.0***	3.5
	(1.6)	(2.2)	(5.3)	(1.5)	(2.3)	(3.0)
Change in level after intervention starts (β_2)	-126.8***	-125.7***	-44.2	-118.4***	-121.2***	-129.2***
	(13.7)	(19.8)	(35.0)	(12.6)	(20.1)	(25.3)
Change in slope after intervention starts (β_3)	-9.5***	-14.1***	-6.4	-8.5***	-13.5***	-5.3
	(1.8)	(2.5)	(6.8)	(1.6)	(2.5)	(3.2)
Rainy season (β_4)				18.3**	11.5	21.0
				(6.5)	(10.2)	(13.1)

Standard errors in parenthesis *p<0.05, p<0.01**, p<0.001***; $Model includes an adjustment for autocorrelation, ^adjusted for bimodal rainy seasons.

Table S6.2: Percentage change at each health centre for malaria visits over time unadjusted and adjusted results.

	Malaria visits decrease unadjusted			Malaria visits decrease adjusted^		
	Kikongi Health Centre II	**Kikarara Health Centre II***	**Bwambara Health Centre III$***	**Kikongi Health Centre II**	**Kikarara Health Centre II***	**Bwambara Health Centre III***
% Change 3 months after intervention starts	-89.4	-89.4	-69.7	-93.6	-87.9	-73.8
% Change 6 months after intervention starts	-91.0	-92.8	-77.9	-95.0	-91.7	-77.5
% Change 12 months after intervention starts	-93.0	-97.1	-90.4	-97.0	-96.5	-84.0
% Change 18 months after intervention starts	-94.3	-97.7	-99.5	-98.3	-99.5	-89.4

$Model includes an adjustment for autocorrelation, *Percentage changes not significantly different from zero, ^adjusted for bimodal rainy seasons.

Table S6.3 Changes in level and trend of non-malaria visits at each health centre, results from a segmented linear regression model, unadjusted and adjusted results.

	Non-malaria visits unadjusted			Non-malaria visits adjusted^		
	Kikongi Health Centre II	**Kikarara Health Centre II**	**Bwambara Health Centre III$**	**Kikongi Health Centre II**	**Kikarara Health Centre II**	**Bwambara Health Centre III**
Constant (β_0)	40.7*** (10.2)	-8.0 (14.3)	70.2*** (10.8)	41.4*** (9.5)	-8.3 (14.9)	70.4*** (11.0)
Secular trend (β_1)	-0.5 (1.4)	5.7** (1.9)	1.3 (1.5)	-0.5 (1.3)	5.6** (2.0)	1.5 (1.6)
Change in level after intervention starts (β_2)	0.1 (11.7)	-23.4 (15.2)	-31.4 (12.6)	0.5 (11.3)	-23.4 (15.7)	-32.8* (13.1)
Change in slope after intervention starts (β_3)	2.0 (1.5)	-6.3** (2.2)	2.3 (1.6)	2.0 (1.5)	-6.2* (2.3)	2.1 (1.7)
Rainy season (β_4)				-1.0 (5.8)	3.1 (6.6)	-3.2 (6.8)

Standard errors in parenthesis *p<0.05, p<0.01**, p<0.001***; $model includes an adjustment for autocorrelation, ^adjusted for bimodal rainy seasons.

Table S6.4: Percentage change at each health centre for non-malaria visits over time unadjusted and adjusted results.

	Non-malaria visits unadjusted*			Non-malaria visits adjusted^*		
	Kikongi Health Centre II$	**Kikarara Health Centre II$**	**Bwambara Health Centre III$**	**Kikongi Health Centre II**	**Kikarara Health Centre II$**	**Bwambara Health Centre III**
% Change 3 months after intervention starts	+23.9	-58.5	-24.4	+26.3	-59.6	-25.7
% Change 6 months after intervention starts	+43.5	-67.4	-16.2	+47.2	-68.5	-18.1
% Change 12 months after intervention starts	+88.9	-78.5	-1.6	+96.1	-79.6	-5.0
% Change 18 months after intervention starts	+144.5	85.1	+10.9	+157.4	-86.1	+6.2

$Model includes an adjustment for autocorrelation, *percentage changes not significantly different from zero, ^adjusted for bimodal rainy seasons.

Table S6.5: Changes in level and trend of overall visits at three health centres, results from a segmented linear regression model, unadjusted and adjusted results.

	Overall visits unadjusted			Overall visits adjusted^		
	Kikongi Health Centre II	Kikarara Health Centre II	Bwambara Health Centre III[$]	Kikongi Health Centre II	Kikarara Health Centre II	Bwambara Health Centre III
Constant (β_0)	73.4***	0.52	219.4***	72.7***	-0.5	218.5***
	(11.1)	(20.5)	(30.5)	(10.4)	(20.6)	(30.4)
Secular trend (β_1)	9.2***	18.0***	5.6	8.2***	17.2***	4.4
	(1.5)	(2.8)	(4.1)	(1.5)	(2.9)	(4.2)
Change in level after intervention starts (β_2)	-132.4***	-142.4***	-156.0***	-125.1***	-137.9***	-148.1***
	(13.0)	(24.6)	(34.6)	(12.7)	(25.2)	(35.3)
Change in slope after intervention starts (β_3)	-7.6***	-19.8***	-4.0	-6.8***	-19.1***	-3.0
	(1.7)	(3.1)	(4.6)	(1.6)	(3.1)	(4.7)
Rainy season (β_4)				14.9*	12.0	18.5
				(7.0)	(12.8)	(17.0)

Standard errors in parenthesis; ***p<0.001, **p<0.01, *p<0.05; [$]model includes an adjustment for autocorrelation, ^adjusted for bimodal rainy seasons.

Table S6.6: Percentage change at each health centre for overall visits over time unadjusted and adjusted results.

	Overall visits decrease unadjusted			Overall visits decrease adjusted^		
	Kikongi Health Centre II$	**Kikarara Health Centre II***	**Bwambara Health Centre III$***	**Kikongi Health Centre II**	**Kikarara Health Centre II***	**Bwambara Health Centre III*$**
% Change 3 months after intervention starts	-73.5	-76.9	-55.6	-69.7	-77.9	-67.8
% Change 6 months after intervention starts	-74.5	-82.1	-56.4	-71.0	-83.1	-67.8
% Change 12 months after intervention starts	-75.8	-88.9	-57.7	-73.0	-89.8	-67.8
% Change 18 months after intervention starts	-76.8	-92.9	-58.9	-74.4	-94.0	-67.8

*Percentage changes not significantly different from zero in these health centres, $model includes an adjustment for autocorrelation, ^adjusted for bimodal rainy seasons

Supplementary analysis

Background

In addition to assessing the impact of introducing a CHW trial on the under-5 utilisation of health centres in Uganda, an additional analysis was conducted to examine whether coverage of malaria diagnosis and treatment with mRDTs and ACTs increased amongst CHWs when compared to diagnosis and treatment for malaria from health centres. A descriptive observational study was used to compare the incidence of malaria visits at CHWs with the incidence of malaria visits at health centres. Due to the closer proximity of treatment services from CHWs compared with health centres we hypothesised an increase in malaria incidence from CHWs compared to health centres.

Methods

The number of malaria visits from CHWs during the intervention-period was captured from treatment recording forms which recorded patient name, age, gender and treatment on the basis of malaria diagnosis by mRDT or by signs and symptoms. We estimated the expected number of malaria visits at health centres during the intervention-period by projecting the number of visits during the pre-intervention period using a linear regression model. This provided the counterfactual to compare rates expected at health centres in the absence of the CHW trial. The population of children under-5 in Rukungiri District was obtained from the most recently available census in 2002 (Rukungiri District Local Government, 2009). These data were then used to calculate incidence rates of malaria visits from CHWs and health centres and calculate incidence rate ratio (IRR) comparing the CHW rate with the health centre rate. The standard error of the log rate ratio was used to derive 95% confidence intervals (95% CI) and a Wald test was used to test the null hypothesis of no difference between the CHW and health centre rates.

Results

During the intervention-period (May-2010 and April-2011) 12,483 child visits were diagnosed with malaria at CHWs compared with 1,162 at health facilities (Table S6.7). Based on the population of children under-5 the incidence rate of malaria was 2.53 per 100 children at health centres and 27.21 per 100 children at CHWs (Table S6.7). The rate varied substantially at CHW during the intervention-period, there was a sharp increase in malaria incidence at CHWs which gradually declined during the period of observation (Figure S7.0). However, for the majority of the intervention-period these rates remained greater than the expected incidence rates from health centres. The overall incidence rate ratio indicated malaria visits at CHWs were more than 10 fold greater (IRR 10.74, 95% CI 5.91 – 19.54, p<0.001) than health centres (Table S6.7).

	Health centres (intervention-period)	**CHWs (intervention-period)**	**Incidence rate ratio (95% CI)**	**p-value**
Total malaria visits	1162	12483		
Total under-5 population	45881	45881		
Overall rates (per 100 child under-5)	2.53	27.21	10.74 (5.91-19.54)	<0.001

Table S6.7: Rates and incidence rate ratio comparing malaria visits at CHWs with rates at health centres during the intervention-period.

Discussion

The analysis found the rate of malaria diagnosis and treatment was 11-fold greater among CHWs compared with health centres during the intervention-period (Table S6.7). The increase at CHWs compared to health centres began immediately after the trial started and was sustained for the majority of the months during the intervention period (Figure S7.0). This analysis may suggest a shift in caregiver's treatment seeking from health centres to CHWs as well increase in coverage of malaria diagnosis and treatment when CHWs were trained and supplied with mRDTs and ACTs.

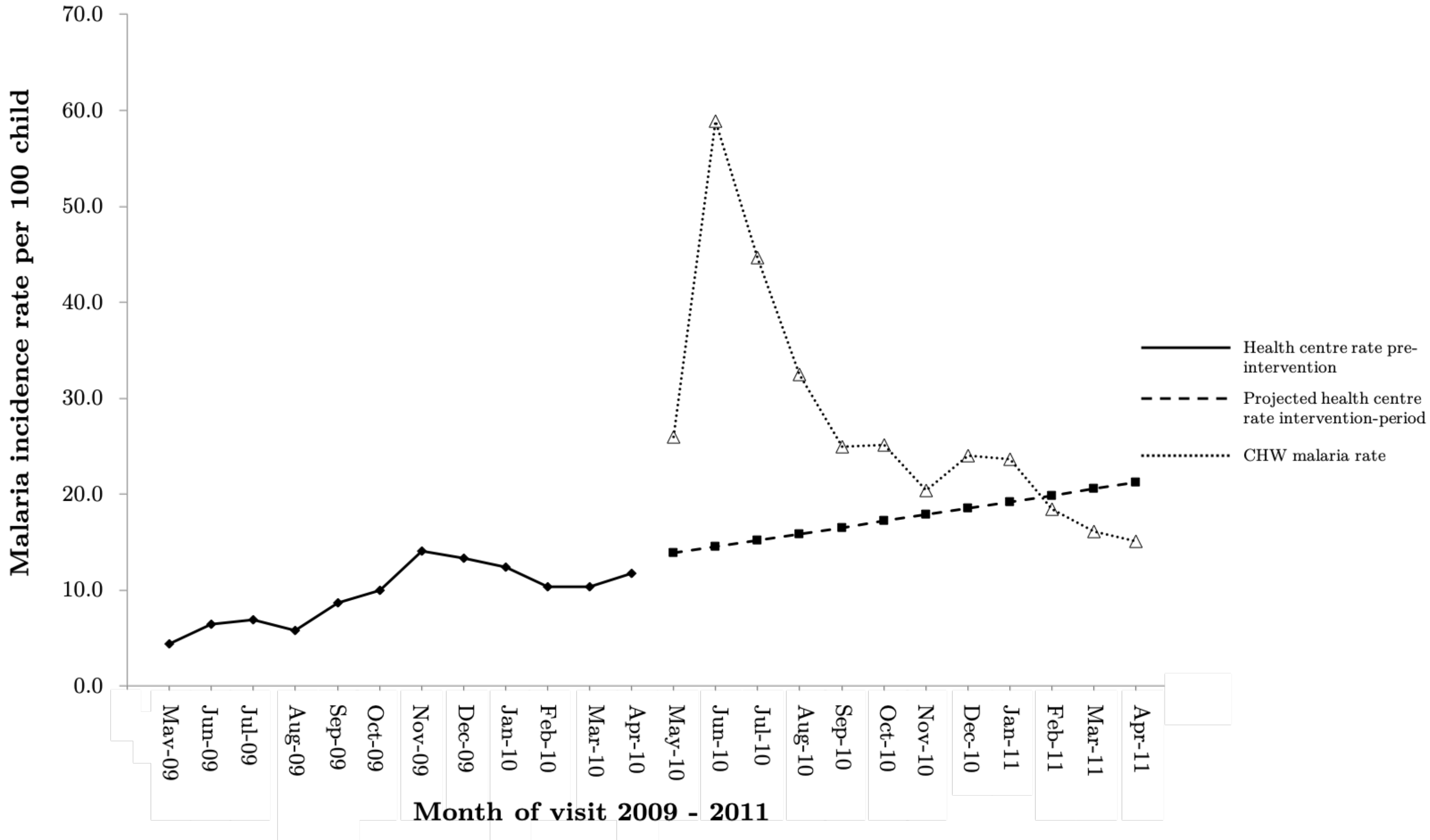

Figure S7.0: Malaria incidence rate observed at health centres during the pre-intervention period (solid line), projected malaria incidence rate at health centres during the intervention period (dashed line) and incidence rate observed at community health workers (dotted line).

Counter factual calculation in chapter 6

In chapter 6 we compared the estimated intervention-period visits at health centres with a predicted counterfactual which was the absence of the CHW-intervention. The counterfactual was derived from baseline level of visits (β_0) and trend (β_1) and specified in equation 2.

$$Y_{without\ CHW-intervention} = \beta_0 + \beta_1 \qquad (2)$$

This counterfactual was then compared with the predicted number of visits seen at health centres with the CHW-intervention, specified in equation 3.

$$Y_{with\ CHW-intervention} = \beta_0 + \beta_1 + \beta_2 + \beta_3 \qquad (3)$$

The difference between equations 2 and 3 is the estimate of the absolute effect of the CHW-intervention and the relative change associated with the intervention was expressed as a percentage change in equation 4 and used for the percentage changes in Table 6.3.

$$\frac{Y_{with\ CHW-intervention} - Y_{without\ CHW-intervention}}{Y_{without\ CHW-intervention}} \text{ x } 100 \qquad (4)$$

The estimated effect of the intervention on malaria visits 1 month after the intervention began has been illustrated below using the counterfactual in equation 2 and projected values in equation 3.

$$\hat{Y}_{without\ CHW-intervention} = \beta_0 + \beta_1 \times 1$$

$$\hat{Y}_{with\ CHW-intervention} = \beta_0 + \beta_1 \times 14 + \beta_2 + \beta_3 \times 1$$

Using the results in Table 6.2, we estimated that in month 14 (1 month after the CHW-intervention began) health centres saw on average 204.4 malaria visits per month. In the absence of the CHW intervention (the counter factual) the average number of visits would have been 226.9 per month. Thus, the average number of malaria visits decreased by 22.5 per month or by 9.9% 1 month after the CHW-intervention started compared with the trend in visits without the intervention.

Chapter 7: Discussion

Summary of key findings

The broader objective of this thesis was to assess a referral system in the context of a community-based trial where CHWs were trained to use mRDTs and provide ACTs based on test results to communities at risk of malaria. The existing evidence on CHW intervention research has typically evaluated the effectiveness of CHWs to follow case management guidelines often in rural areas with poor access to health facilities (Lehmann and Sanders, 2007; Lewin *et al.*, 2010). Whilst the existing evidence is essential for understanding the performance of CHW programmes and the conditions under which this has been achieved, it is insufficient to understand the effectiveness of the referral system and the continuum of care from communities to health facilities for community-based programmes (Ruizendaal *et al.*, 2014; Black *et al.*, 2016; Sunguya *et al.*, 2017; Ludwick *et al.*, 2018). Since an effective referral process is a key component of primary health care, the findings presented in this thesis seek to contribute to the growing but limited evidence on referral processes. The findings show that the community-based referral system operated sub-optimally to ensure continuum of care for children under-5. Children with severe signs and symptoms were not always referred and many of the caregivers of referred children failed to comply with CHW's advice. These findings are consistent with evidence on referral between primary level health facilities in LMIC countries. Two studies from Tanzania, found <1% of children presenting at first level health facilities were referred to second level health facilities and only 25% of severely ill children were referred to hospitals for further management (Font *et al.*, 2002; Walter *et al.*, 2009). Failure to provide referral advice leaves gaps in the service provision of community-based programmes and potentially undermines their effectiveness to improve health.

The thesis also sought to bring an understanding of the barriers to referral encountered at each stage of the referral system using Obrist and colleagues health access framework (Figure 1.1.). Whilst this thesis was not a comprehensive evaluation of the referral system it strived to present a broad understanding of the matters that arise from the implementation of a CHW initiated referral process within a primary health care setting. This was explored in chapters 3-6 that evaluated each stage in the processes of a referral system (Figure 7.0). This final chapter summarises the key findings that emerged from this analysis as well as its limitations. It also identifies research gaps and recommendations for future research for community-based programmes Finally, it seeks to provide recommendations to policy makers and health delivery organisations in charge of implementing CHW programmes and funding bodies that finance and monitor the effectiveness of programmes. It also highlights limitations that need to be considered when interpreting these findings and also some reflections and suggestions for future research on CHWs in primary health care settings.

The first chapter outlined the CHW literature and context of the proposed research, the current trends in malaria morbidity and mortality, as well as the international health community policies and strategies that accelerated the declines in malaria. It described the roles and responsibilities of CHWs in primary health care, malaria case management programmes and the changes in the implementation of CHW programmes since the beginning of primary health care. Throughout the history of CHWs described in this thesis, the case management evidence for malaria was detailed, and described their evolving responsibilities from the management of a single disease to the diagnosis and treatment of multiple conditions with point of care testing for malaria. This chapter also highlighted the evidence gaps that persist with regards to community referral systems, such as CHWs adherence to referral guidelines and caregiver's compliance to referral advice. The final component of this chapter also framed the proposed research on the community referral systems in a series of objectives that followed decision making process and actions taken by CHWs and caregivers when a child is referred.

With respect to the first step of the referral process, chapter 3 explored the availability dimension of access framework (Figure 1.1) and described the CHW's ability to follow referral guidelines. Previous operational research studies in Ghana had found CHWs adhered poorly to referral guidelines (Chinbuah *et al.*, 2006, 2013). Chapter 3 reinforces the previous reports where it was observed in this thesis that nearly 60% of children with a high fever were eligible for referral were not referred. Perhaps a more concerning observation was the failure of CHWs to give pre-referral rectal artesunate to children with a high fever that had mRDT confirmed malaria. This chapter also expands the evidence base by exploring some of the factors associated with CHW non-adherence to referral guidelines, and showing that factors such as ACT prescription, wet season CHW visits and distance to health facilties, lowered the odds of CHWs making a referral decision. These quantitative analyses of treatment records indicate that the decision to refer is the start of a complex process involving both CHWs and caregivers, and CHWs decision may be influenced by whether the caregiver will comply. CHWs may not have referred knowing that caregivers were unlikely to attend, if access to facility would be difficult or other constraints not captured in this chapter, such as any occupational obligations at home or at work or the additional treatment seeking costs that may be incurred with being referred. To fully assess what influences CHW's decision making, further qualitative research is needed with CHWs, in the form of focus group discussions. These could identify the common themes CHWs encounter from caregivers when they attempt referral and better understand the appropriateness of the referral guidelines for community settings.

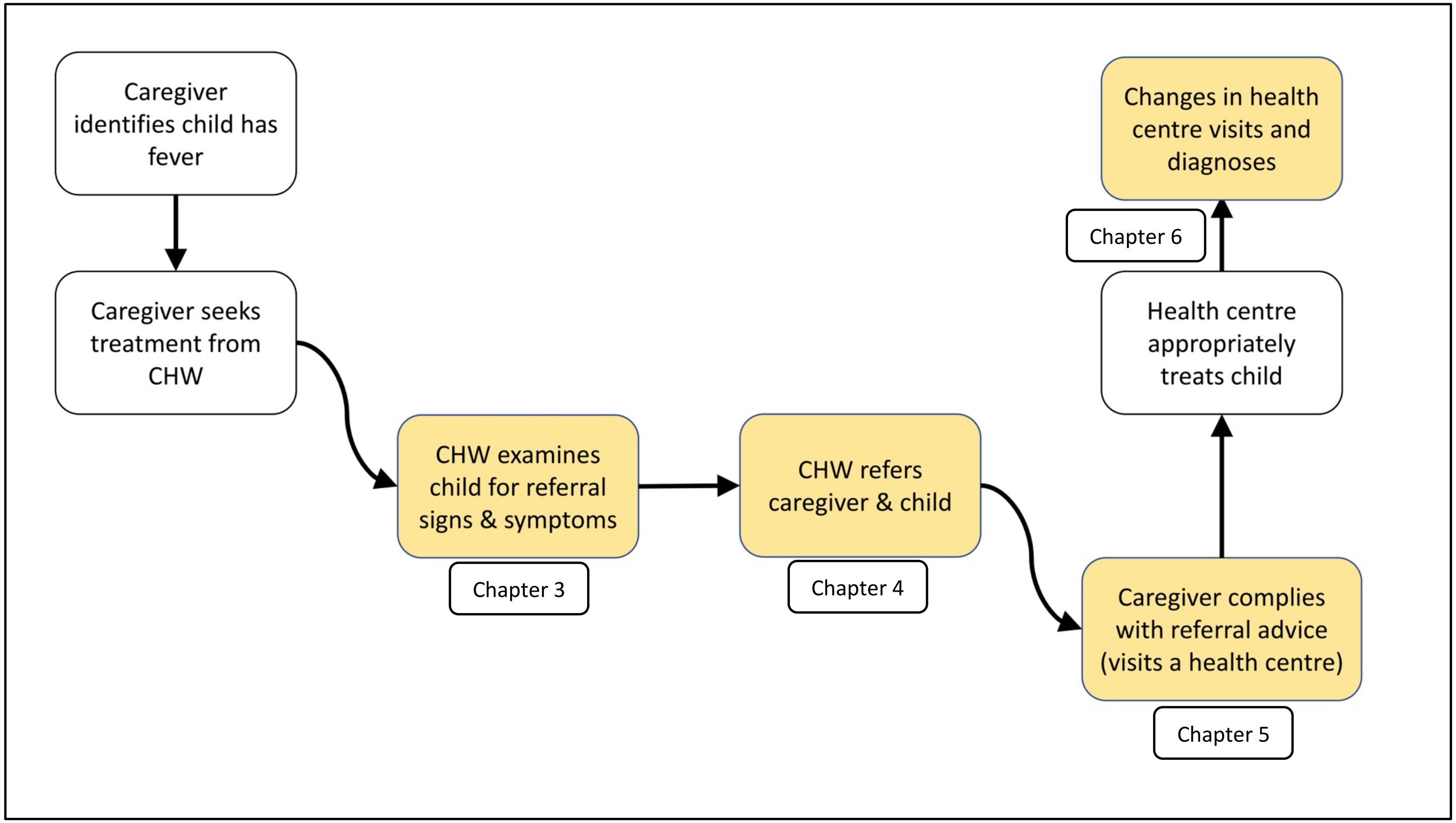

Figure 7.0 Components of a community-based referral process and impact on health centres.
Yellow filled components indicate topics explored in this thesis

The second step of referral process explored in chapter 4 described the impact of training CHWs to use mRDTs on referral when compared CHWs using a signs and symptoms approach for malaria diagnosis. At the time of the study conceptualisation and data collection two studies in Sierra Leone and Tanzania examined the role of mRDT results and their impact on referral compliance. The findings in fourth chapter of this thesis reinforces some of the findings observed in previous studies, that referral occurs more often with mRDTs compared with a sign and symptoms diagnosis, and mRDT negative children are more frequently referred compared to positive children (Mubi *et al.*, 2011; Thomson *et al.*, 2011). Chapter 4 also contributes additional evidence on the factors associated with referral for children under-5. Providing ACTs also affected whether or not a referral was made, such that when caregivers received an ACT they were often not referred and conversely, when an ACT was not given caregivers were often referred. Whilst it was encouraging to see a high referral rate amongst mRDT negative children (>60%) which could indicate to CHWs the presence of other diseases that need management, the relatively few referrals amongst mRDT positive children (<3%) may suggest co-infections in addition to malaria could remain untreated by CHWs when they follow positive mRDT results and give an ACT. There was also a small but important proportion of children who were prescribed pre-referral rectal artesunate but were not referred. This is also concerning because it is likely that children had severe signs and symptoms requiring referral and further management at the nearest health facilties. However, it is plausible that the CHW's decision to not refer caregivers who received an ACT or rectal artesunate, may have been appropriate due to the condition of children improving. Although this study could not investigate whether non-referral was an appropriate decision by CHWs, nor could the study determine the health outcomes of these children. As iCCM becomes a key strategy to prevent child deaths, CHW training programmes should reinforce the importance of examining children for all referral signs and symptoms regardless of confirmed diagnostic test results, such as elevated respiratory rate from respiratory rate timers and positive malaria results from mRDTs.

Referral advice is only effective when caregivers comply with the referral advice and take their child to a health facility for further care (Newbrander *et al.*, 2012). Earlier studies in Sierra Leone and Zambia also found poor compliance to referral but did not investigate the barriers to referral compliance, more contemporary iCCM studies only found a few access barriers associated with referral, such as increased household costs , distance and poor quality of care at health facilities (Nanyonjo, Bagorogoza, *et al.*, 2015; English *et al.*, 2016). Chapter 5 examined the accessibility domain of the framework (Figure 1,1) and whether caregivers complied with referral and explored additional barriers that can hinder caregiver's compliance with referral. Compliance and access of health facilities was poor with up to 90% of referrals failing to visit a health facility after being referred. As described in chapter 2 and 3, CHW adherence to referral guidelines was poor (chapter 2) and a lower frequency of referrals by CHWs when an ACT was prescribed (chapter 3). Similarly, in this study caregivers were unlikely to comply with referral if an ACT or rectal artesunate was prescribed. This is particularly concerning because pre-referral treatment with a single dose of rectal artesunate is used to reduce the risk of death or permanent disability, until a full therapeutic course of treatment can be administered by skilled health professionals at health facilities. Failure to comply with referral when pre-referral treatment is given increases the risk of medical complications and deaths amongst these children. With respect to the accessibility domain, the findings from this chapter suggested that geographical access to health facilities for referral manangement may have prohibited caregivers to comply with referral advice. Similarly, access in terms of the availability of the health services not fully staffed or open on the weekend may have deterred caregivers from complying. Further research should examine the CHW advice provided to caregivers about the importance of seeking further treatment, as well as caregivers' care seeking attitudes and barriers for children with severe signs and symptoms that require referral.

The final chapter (chapter 6) assess the availability domain of the access framework and describes the visit utilisation changes health centres experienced when a CHW diagnosis and treatment intervention was introduced into the catchment area of the centres. The study used routinely available outpatient health register data to fit segmented regression models to estimate changes in utilisation before and after the introduction of the CHW intervention. Overall utilisation of health centres declined shortly after the introduction of the intervention and continued to remain lower than pre-intervention levels during the intervention, concomitantly there were increases in the utilisation of CHWs when compared to health centres. These findings suggested there was a shift in the volume treatment seeking by caregivers from health centres to CHWs, suggesting CHWs were available to provide diagnosis and treatment. However, there was no evidence to suggest changes in the average visits of non-malaria between the two periods. Since CHW were only trained to treatment malaria it was hypothesised that non-malaria visits would increase due to referrals from CHW. This is consistent with the findings from chapter 4 which suggested referral was low amongst CHWs diagnosing presumptively and many caregivers failed to comply with referral advice and visit a health centre (chapter 5). Thus, both the low referral rate and poor referral compliance were unlikely to affect the average number of non-malaria visits at health centres. The findings from chapter 6 are also supported by the findings from previous studies, that reported similar declines in utilisation, between 46% to 83% (Sievers *et al.*, 2008; Tiono *et al.*, 2008; Lemma *et al.*, 2010). The findings from this chapter also showed the reduction was shortly after the start of the intervention and in contrast to the previous studies, the declines were sustained throughout the intervention period. It also documented that were there was limited change in non-malaria visits at health centres. Future research should investigate whether utilisation changes at health centres are seen when iCCM programmes are introduced. In summary, the substantial declines in utilisation suggest there may be more health service human resources available, that could be redistributed within the health system to ensure an efficient allocation between CHW programmes and health centres. This could allow health workers to spend more time manging more complex cases or supervising CHWs.

Limitations

The context of this research on referral was set within an on-going randomised trial designed to evaluate the effectiveness of training CHWs using mRDTs on appropriate treatment of malaria. Whilst this provided the opportunity to investigate referral it may have been difficult to provide in-depth and comprehensive analysis of the referral system. The general limitations of methods are discussed below whilst the limitations with respect to each research question are explored in-depth the discussion section of each of the results chapters.

The primary outcome and focus of the trials were to assess the validity of CHWs using mRDTs for the diagnosis and treatment of malaria and the referral research component was a secondary set of activities embedded within the broader trial. This was an advantageous opportunity to explore some of the issues related to referral in community-based setting, however the lack of specific focus on referral also presented a number of limitations in conducting research around referral. A referral study that focused on evaluating CHWs adherence to referral guidelines may have used alternative methods. Previous studies in the literature have used objective structured clinical examinations with CHWs in hospital based settings to assess health worker adherence to clinical guidelines and whilst these are often subject to the Hawthorne effort in this study the results from using this method could have supplemented data collected from routine registers (Kelly *et al.*, 2001).

An additional limitation related to embedding the referral study within larger trials was the collection of data from a single perspective, CHW's routine treatment registers. In contrast, there was limited data collected from caregivers and their children. Follow-up surveys or in-depth follow-up interviews with caregivers could have supplemented data collected by CHWs to better understand caregiver's compliance to CHW's referral advice. This data could have included referral outcome status as well as the final health status of the child. Additional data caregiver socio-demographic information could have been collected such as household size, education, occupation, socio-economic status, treatment seeking behaviours and knowledge and attitudes towards CHWs and referral. This could help ensure complete referral outcome data was available irrespective of whether the caregiver accepted a routine referral form or whether a CHW completed a referral form. These data were also lacking from CHWs and may have provided further explanations as to why CHWs failed to refer. General socio-economic, demographic data from CHWs and caregivers may have also helped generalise the findings from this referral study to studies conducted in other community-based settings. In future studies that examine referral within community-based settings a greater emphasis should be placed on utilising methods appropriate for referral, which should also be supplemented with the data collection tools specifically relevant for referral.

Another general methodological limitation is the focus on the quantitative approaches used throughout this thesis. The emphasis on quantitative methods had some strengths particularly in the standardised collection of routinely reported data from CHWs that enabled differences and similarities to emerge as part of the research process. These methods also allowed assessments of the strengths of relationships between explanatory variables and outcomes. This is apparent in chapter 4, where the relationship of CHWs use of mRDTs and referral was shown and in chapter 6, which demonstrated the use of quantitative methods to estimate the effect of introducing a community-based programme on the utilisation of health centres. However, in chapter 3 and chapter 5 the use of qualitative methods could have been combined with the quantitative methods in a mixed-methods study to triangulate the reasons CHWs adherence to referral guidelines. It may have also provided insights on caregivers' underlying values, beliefs and around treatment seeking and their understanding of the importance of complying with referral advice.

An important methodological limitation to acknowledge is the use of routine records completed by CHWs and health centres workers used to address each of the objectives in this thesis. The data collection process involved health workers hand writing all the clinical, demographic and child history data on to paper forms. These paper-based methods may have resulted in incorrect reporting of data and or missing data which may have resulted in inconsistencies appearing in datasets. There were also significant challenges in merging different forms of the same child due to ineligible handwriting, poor record keeping and poor storage conditions making unique identifiers unreadable. To address these challenges an electronic data capture (EDC) system could have been used to collect data. This offers some advantages; validation checks can be built-in to electronic forms to ensure data is captured within appropriate ranges and in a standardised format with must enter data fields. This reduces missing data and the data entry time as well reducing any inaccuracies at the point of data capture. EDCs can also ensure linkage of data across multiple forms thereby ensuring completion of different records for each study participant. However, there are some disadvantages that need to be considered, for example a higher financial expense may be incurred compared to a paper-based method to develop EDC systems and it may also require additional training and supportive supervision to ensure their correct operation when compared with a paper-based system.

The use of paper forms specifically affected the results and findings of chapter 5. Forms were used to determine caregiver's compliance to referral advice and missing forms may have underestimated compliance. In the referral making process CHWs recorded referrals on treatment recording forms (Appendix I) which served as the referred population. A separate referral form was then completed which captured data on the severity of referral and the referral signs and symptoms, 3 copies of these were made by using a triplicate referral book (Appendix I). Upon completion of the referral form one copy of the form was given to the caregiver to take with them to the health centre, another copy was collected from the CHW by the research team and the last copy remained with the CHW in their referral book. Caregiver's referral compliance was defined by completion of a referral form completed by a health worker at the health centre. In contrast, non-compliance to referral advice was defined as the absence of a referral form completed by the health worker. The completed health centre referral forms were then linked by a unique identifier to treatment recording forms. However, in some circumstances CHWs reported making a referral on the treatment recording form but did not complete the referral form for the caregiver. It was unclear what the exact cause of this was but, in many cases, caregivers often refused referral advice and either the CHWs did not complete the referral form or the caregivers refused a completed referral form. In both these circumstances a referral would have been recorded via the treatment recording form and non-compliance to referral due to the absence of a completed referral form from a health centre. The use of CHW's treatment recording form to define referral may have overestimated caregivers who were referred with a referral form, which could alternatively be defined as instances where the CHWs completed a referral form. Considering the caregivers who had referral forms completed, the percentage of referral compliance would likely to be much higher. In the moderate-to-high transmission setting caregiver compliance amongst those with a CHW completed referral form was 57% compared with 9% when referral was indicated on the CHW's treatment recording form. Similarly, in the low-transmission setting referral completion was 81% according to completed referral forms compared with 10% from completed treatment record forms. An additional analysis was undertaken to examine whether there were any important differences between characteristics (age, sex, net use, duration of fever) of the referred caregivers who had a completed referral form and the referred caregivers that did not (Table S5.4, Table S5.5). The characteristics were generally similar amongst those who had a form and those that did not; except that in the moderate-to-high transmission setting, the proportion of caregiver referrals made during the dry season or with non-severe referral signs was higher amongst those with a referral form compared to those without a referral form (Table S5.4). In the low-transmission setting, caregivers with referral forms more often had non-severe referral signs, were tested with an mRDT, and seen on weekday, compared with those without referral forms (Table S5.5). In both settings, age, sex, net use, duration of fever was similar between those with and without referral forms (Table S5.4, Table S5.5). The trends in referral form completion by CHWs were also compared over time (Figure S5.1 and Figure S5.2) and by cluster in each trial setting (Figure S5.3 and Figure S5.4). In both settings, forms were not completed for more than 70% referred caregivers between January 2010 and July 2011, in the moderate-to-high transmission setting only there was also a rise in non-completion of more than 90% in September 2010 (Figure S5.1 and Figure S5.2). There was also substantial variation between clusters in each trial setting, the proportion of caregivers not receiving referral forms ranged from 0% to 39% and 0% to 100% in the moderate-to-high and low-transmission setting respectively (Figure S5.3 and Figure S5.4). In both settings, the tendency to complete referral forms for non-severe severe referral signs may indicate CHWs were willing to refer for signs they were unable to manage or treat with an ACT or rectal artesunate. The differences between referral form completion and non-completion according to whether the caregiver was referred during the dry season (moderate-to-high transmission setting) or the weekday (low-transmission setting), may be due to CHWs knowing in advance that caregiver would likely to accept referral and comply with the advice, if the referral health centre was geographically accessible during the dry season and open during the weekday. These findings are also consistent with those of chapter 3, where CHW's adherence to referral criteria was also associated with seasonality and the weekday. Taking into consideration the additional analyses of caregiver referral compliance from completed referral forms, together with the evidence from chapter 3, it becomes more suggestive that the dialogue about referral between CHWs and caregivers may have affected the CHWs decision to refer and adhere to the referral guideline and complete a referral form for the referred caregiver. This is evidenced by CHW's poor adherence to the referral criteria and CHW's failing to complete a referral form for all children who were recorded as referred on the treatment recording form.

Chapter 6 examined the impact of introducing the CHW trial on the visits seen at public health facilities in the moderate-to-high transmission area. In this analysis, we expected to observe a change in visits to health centres during the same month the trial was implemented. This is because immediately before the trial began extensive community sensitisation and mobilisation was undertaken to inform caregivers of the forthcoming malaria treatment services that would be available in the community. Additionally, 127 CHWs had been trained in 64 villages for the first time since the end of the home based management of fever programme. The large number of CHWs delivering a new malaria case management service close to caregiver's homes would likely increase visits at CHWs compared to the further away health facilities. It was therefore hypothesised that in the same month of the trial starting we would expect to see a decline in visits at health centres. The ITS regression model therefore specified β_2 as the change in visits at health facilities seen when the trial began.

A final limitation is the generalisability of the findings from this single malaria case management study to iCCM programmes that manage multiple childhood diseases. The broader research trial was conceived in 2009 when there was limited evidence on the use of mRDT and ACTs in community-based settings and continued until 2012. During this time the Ugandan Ministry of Health officially adopted iCCM as part of its national health care strategy in 2010 which meant the findings from these trials upon completion may not have been fully generalizable to the national healthcare strategy at the time (Morgan and Wambua, 2015). It is plausible that a different set of findings for each of the objectives considered here could have emerged had iCCM trials been conducted. CHWs that are a part of iCCM programmes that treat pneumonia, diarrhoea and malaria, are likely to refer children according to a different set of signs and symptoms and caregivers compliance may also differ according to these referral signs and symptoms (Friedman and Wolfeim, 2013). The changes in health centre utilisation might have changed because malaria, pneumonia and diarrhoea are managed in the community and the utilisation of health facilities might be lower compared to a CHWs managing only malaria. The case-mix, the types of cases diagnosed at health centres might be different when CHWs manage three conditions compared to when they managed a single condition in the community. Another case where the guidelines were different applies to chapter 5. There was a difference between the trial's training guidelines which predated the iCCM policy on referral, which may affect generalisation of the findings reported in this chapter to the iCCM referral compliance literature. The treatment algorithm used in the trial indicated the provision of a full course of ACT for children who are referred for non-severe signs, including children with a fever lasting 7 days or more (Appendix I). However current iCCM guidelines recommend the first dose of an ACT as a pre-referral treatment rather than giving the full ACT course to these children (WHO, 2011a; English *et al.*, 2016). This has potential positive and negative consequences for caregiver's compliance to referral; first, caregivers may be more likely to comply with referral advice and obtain a complete course of ACT from health centre if they do not receive a full course of ACT from CHWs. Second, a potential negative outcome may occur under iCCM guidelines. There could be circumstances where caregivers fail to comply with referral advice after receiving the first dose, this is perhaps due to a child's temporary resolution of symptoms and they may increase the risk of the illness progressing to severe disease with further complications. The trial's guidelines to provide ACTs may have been a cautious approach because it ensured a full course of ACT for those with non-severe signs of referral who were mRDT positive. This approach may have been mitigated the progression to severe disease, in contrast had only the first dose of ACT been given as per iCCM guidelines and the caregiver failed to comply with referral advice, then a more negative outcome may have occurred. Despite these limitations some of the barriers to accessing health centres are likely to be similar as are the challenges to ensuring CHWs adherence to appropriate case management guidelines as part of iCCM programmes.

Future directions

During this doctoral study, community-based programmes for the management of childhood infections have expanded across many low and middle-income countries. Influential global health actors, such as WHO, UNICEF and the Global Fund, have advocated that countries implement integrated disease programmes with routine monitoring and evaluation of activities within existing health systems (WHO/UNICEF, 2012). It is envisaged that integration of separate disease specific programmes into shared health delivery platforms, such as iCCM, will improve the effectiveness of programmes and their sustainability, through efficient allocation of health resources (Kim, Farmer and Porter, 2013). Whilst this might be feasible for health workers in health centres, there are a different set of challenges in adopting a similar approach with CHWs in communities at the periphery of health centres. To address the challenges, recommendations for improving the practice of CHW programmes emerged as part of this thesis.

Since the development of community programmes in the 1980s, the role of CHWs has gradually expanded to encompass the management of more than one childhood illness, and in some countries CHWs are following increasingly complex guidelines for the treatment of; diarrhoea, malaria, pneumonia and neonatal infections. In the past, there have been concerns as to whether volunteer CHWs with limited medical training and experience can still be expected to deliver high quality primary health care to populations with a high burden of childhood conditions, and others have questioned the ethics of using unpaid volunteer labour in poor communities (Charlwood, 2004; D'Alessandro, Talisuna and Boelaert, 2005; Maes, Kohrt and Closser, 2010; Aubouy, 2011; de Sousa *et al.*, 2012). It is plausible that as the complexity of the role increases with the management of additional conditions under iCCM, CHWs quality of care may decline. In order to improve the evidence base and performance of iCCM programmes a global monitoring and evaluation indicator framework has been developed by the iCCM Task Force (an association of multilateral and civil society organisations promoting iCCM). This is broad framework and covers many areas of monitoring iCCM programmes (MCHIP, 2013). The framework's indicator for correct referral has been defined as the proportion of children with danger signs that are referred through direct observation of CHWs practice, and it is recommended that monitoring should be undertaken periodically as part of special studies conducted on an ad-hoc basis and data are not expected to be available on a continuous basis (MCHIP, 2013). This limited indicator does not fully capture all elements of the referral process described here and the monitoring framework excludes the extent to which caregivers comply with CHWs referral advice. In addition, direct observation of CHWs may be costly to undertake and may not provide accurate assessment of their performance. The findings from this thesis suggest that data reported by CHWs as part of routine practice could be used regularly to assess CHWs performance of managing children with danger signs. As such, recommendations for practice include developing quality of care indicators that include adherence to referral guidelines using routinely reported data by CHWs, especially for programmes where CHWs are treating multiple conditions, as well as the caregivers adherence to referral advice. These indicators and guidelines should complement existing referral indicators and serve to strengthen the monitoring of programmes and quality of care.

The current monitoring and evaluation framework attempts to determine the performance of iCCM programmes during initiation, implementation and scale-up (MCHIP, 2013). The majority of these are typically focused at CHW programmes and include indicators such as CHW density in a catchment area, supply chain of essential diagnostic tests, medicines, caseload, and supervision of CHWs (MCHIP, 2013). These are important indicators for understanding the 5 domains of access (availability, adequacy, affordability, accessibility, acceptability) as part of the theoretical framework, that are likely to inform caregivers access of CHWs (Figure 1.1). However, a similar set of indicators at the health centre level are absent but are also likely to influence the performance of CHWs and the domains of access that are likely to influence care seeking by caregivers. For instance, in this thesis we found CHW were unlikely to refer children eligible for referral during the weekend when health facilities were closed. In addition, other care seeking studies have reported caregivers are reluctant to seek care from health facilities when there are stock-outs of essential medicines (Mikkelsen-Lopez *et al.*, 2013). Therefore, an additional recommendation for practice includes expanding the current monitoring and evaluation framework to include monitoring and evaluation indicators related to the service delivery at health centres. Information from these indicators could be synthesised with indicators from CHW programmes to identify barriers that are affecting access to care from both CHWs and health facilities.

The learnings derived from quantitative monitoring and evaluation indicators could also be considered alongside qualitative data that explores the quality of care from CHWs and health facilities. The use of information obtained from ethnographic approaches such as FGDs with caregivers, CHWs and health centre health workers could be triangulated with quantitative indicators to provide detailed insights on how the access barriers shape choices of care-seeking from CHWs and health facilities as well as their overall performance. The use of qualitative data would be recommended as part of a monitoring and evaluation framework of CHW programme. The information from a more comprehensive quantitative and qualitative monitoring and evaluation framework will assist in addressing the gaps of primary health care delivery and the access barriers caregivers may encounter. It will also assist in sustainable planning of CHW programmes integrated with health facilities and the broader health system with short- and long-term perspectives.

The referral access barriers highlighted in this thesis, such as poor geographical access to health services, may be synonymous with other health programmes such as maternal and new-born health and learnings from these interventions may be adapted to iCCM referral systems. Some iCCM studies have found the average out of pocket expenditure for a completed referral ranged from USD 7.35 to USD 11.00, which is approximately 2 or 3 times greater than the average daily income for rural Ugandan households (Peterson *et al.*, 2004; UBOS, 2014; Nanyonjo, Bagorogoza, *et al.*, 2015). There was limited assessment of the affordability domain of access (Figure 1.1) in thesis and whether households could afford the out-pocket-costs associated with referral. Conditional cash transfers (CCTs) are financial mechanisms in the form of vouchers or cash incentives that can be exchanged for subsidised goods or services and have been used to alleviate some of the household financial barriers associated with seeking care at health centres for pregnant women. Studies in Honduras and Mexico found intervention areas that used CCTs were between 12%-20% more likely to use prenatal care from health centres compared to areas without CCTs (Morris *et al.*, 2004; Barber and Gertler, 2009). In addition a large study in India found improvements in health outcomes, with reductions in perinatal and neonatal deaths (Sidney *et al.*, 2016). Future research with iCCM referral systems could explore the development and adaptation of existing CCT mechanisms to financially assist caregivers with the household costs to comply with CHWs referral advice and visit health centres.

Since the Alma Ata declaration, referral has been considered as a core component of primary health care and advocated by many influential actors such as The World Bank as part of the district health system which advocates for allocative efficiency of scarce specialist medical care particularly in low and middle income countries (WHO, 1987; The World Bank, 1993). However, much of published literature on referral systems in rural areas of SSAs countries as well as the evidence presented in this thesis suggest referral systems have operated less than effectively, with caregivers either rarely referred or failing to comply with referral advice (Bossyns *et al.*, 2006; Nanyonjo, Ssekitooleko, *et al.*, 2015; English *et al.*, 2016). There is also evidence that despite the national implementation of iCCM in many SSA countries, care seeking from CHWs remains low (Geldsetzer *et al.*, 2014). Rather caregivers prefer primarily to seek care from pharmacies, drug shop vendors and traditional healers for malaria and pneumonia (Geldsetzer *et al.*, 2014). Consequently, there is a growing need for the development of interventions that are sensitive to the realities of health care seeking in SSA. Particularly to the acceptability domain of health care access from a plurality of providers. Traditional and unqualified practitioners could be acknowledged as important sources of primary care and supported and strengthen to delivery high quality primary health care which could then be integrated with existing health systems (Kane *et al.*, 2010). Future research should focus on developing community health system interventions that broaden the health care providers used for referral and create a supportive and inclusive environment of health structures that allow caregivers to seek care from their preferred provider. This could be explored as part of the acceptability domain of health care access, which was not fully explored in this thesis (Figure 1.1). These interventions could then address some of the challenges around referral found in this thesis, CHWs would be confident to appropriately refer caregivers, knowing in advance that there are available health providers who would be able to provide further care. Similarly, caregivers may be confident to comply with CHWs referral advice knowing that there are preferred and trusted providers available to provide health care. Interventions would include developing a network of dialogues between different providers that exchange information about referred patients as well sharing medical knowledge and skills to build capacity amongst health providers that ensures the sustainability of heath care in a community. Any such interventions could draw on the WHO's health system's building blocks approach to ensure the relationship between CHWs, communities and health workers are clearly mapped and understood to develop appropriate interventions along each strep of the referral process that ensures the continuum of care during referral.

Despite the growing evidence that caregivers prefer to choose private or traditional providers, limited studies have explored the capacity of private providers to provide a high quality of care. In Uganda, evaluations of drug shop vendor interventions found they were able to follow treatment algorithms with mRDTs and ACTs and improve the quality of care caregivers receive when compared with usual practices without mRDTs (Mbonye *et al.*, 2013). In addition, caregiver treatment seeking has also shown to increase from drug shops when sellers are trained to follow iCCM guidelines (Awor *et al.*, 2014). Typically drug shop sellers often come from a clinical background and have more training and experience than CHWs and whilst these evaluations have focused on common childhood illness, further research could explore the possibility of strengthening private providers to provide referral care. (Mbonye *et al.*, 2015).

The findings from this thesis confirms some of the existing evidence on referral and given the consistently poor performance of referral systems in rural settings where access to healthcare is limited it would be useful to discuss the utility of referral in these settings. In this context referral can be considered as a process by which one health care provider at a lower level of the health system transfers responsibility of an individual's care from one health care provider to another provider, who has more skills and experience to manage a specific clinical condition (Al-Mazrou, Al-Shehri and Rao, 1990). The aim of this process is there to ensure continued management of the individual. Referral as a modern Western biomedical concept emerged in 19th Century Europe when medical specialities and sub-specialities of medicine were being formally established during the Age of Enlightenment (Spray, 2012). However, under this definition, referral does not consider the health of the community that may be negatively affected by a community member's referral nor does it consider the role of a community to manage their condition. In many African communities the health of individuals is a shared responsibility amongst all members of a community this is often expressed in the Nguni Bantu humanist philosophy of thought Ubuntu, which emphasises an interdependence of individuals with others, through communities (Gade, 2011). Thus, the Western biomedical concept of referral that focuses on sick individuals with one or more health providers separates individuals from their community. This separation and isolation of sick individuals from their community may not be culturally acceptable for individuals in countries with strong community bonds and where communities share health responsibilities. The current evidence from CHW programmes managing the health of children under-5 , indicates many caregivers reluctance to accept CHW referral advice, this may partly be explained by the cultural acceptability of the biomedical concept of referral in countries where individual health is a communal responsibility (Strachan *et al.*, 2014).

This thesis examined the referral process from the perspective of multiple actors including; CHWs, caregivers and to a lesser extent from health centre workers, and it highlighted the successes and challenges as the process intersected each of these actors. This is particularly important as CHWs are uniquely placed to interact with formal health providers and members within their local communities in complex and context specific relationships. However, there is limited research on how CHWs can engage with and create trust within communities to deliver primary health care (Singh, Cumming and Negin, 2015). Therefore, a community health systems perspective that involves all health providers within a community could be taken to develop interventions that strengthen referral processes within CHWs programmes and also deliver curative and preventative primary health care healthcare services.

Community-based participatory research (CBPR) frameworks offer the opportunity to develop interventions which involves community stakeholders from the beginning and throughout the research process (Minkler and Wallerstein, 2008). This format can help develop community centred interventions that are culturally sensitive, which in turn can improve the implementation and sustainability of interventions in real-world contexts (Tandon *et al.*, 2007). Future research could explore using these CBPR frameworks to address the 5 domains of access from both CHWs and health facilities, or possibly other higher-level providers. Whilst there is limited evidence of this approach to support the strengthening of referral with community-based programmes, lesson can be learned from similar community programmes.

A key feature of CBPR frameworks are establishment of community platforms which ensures the inclusion of views from a variety of stakeholders in a community, these could be private for-profit providers, CHWs, traditional medicine practitioners, influential community groups and the formal health system. These platforms are able to address the needs of the community and provide a means by which decisions can made on the allocation of health care delivery as well as financing. Examples of interventions using CBPR approaches include the integrated rural health projects in the 1970s in Saradidi, Kenya and Narangwal, India (Kaseje and Spencer, 1987; Taylor and Parker, 1987). Both these interventions were developed and led by communities that were able to conduct their own health needs assessment. They also identified health providers that required strengthening which determined when to seek government or international financial and technical support. The interventions in Kenya and India involved sustained support supervision of CHWs by formal health centre personnel, development of resilient and flexible networks of health centres, training CHWs, private providers and traditional medical practitioners. Members of the community gradually became responsible for planning, implementing, monitoring and evaluating health related activities. These community directed initiatives led to high coverage of health programmes with substantial community participation and leadership, however, there were no improvements in under-5 child mortality in Saradidi predominantly due to chloroquine resistance to malaria (Spencer *et al.*, 1987). In Narangwal reductions in under-5 child mortality rates in Narangwal and improved referral compliance (Taylor and Parker, 1987).

In the allied field of maternal and neonatal health, participatory learning and action (PLA) methods with women's groups have led to substantial declines in neonatal and maternal mortalities in LMIC (Prost *et al.*, 2013). PLA methods often involve 4 key phases to develop interventions, in the first phase groups of women identify common problems related maternal and newborn health within their community. The second phase involves exploring potential solutions and selecting the priority ones. In the third phase groups implemented their solutions and in the last, fourth phase, they reviewed their progress, detailing the lessons learned and planned future solutions (Seward *et al.*, 2017). The success of these interventions in reducing mortality in SSA and Asia has led to UNICEF and The WHO to recommend PLA women's as community strategies to improve maternal and newborn health. In these intervention the researchers often used formative participatory methods together with the community members to inform the development of the intervention (Morrison *et al.*, 2008). It is plausible that this method could be utilised to inform the development of CHW intervention that address the 5 domains of access barriers and could also support a functioning referral network. Future research with PLA groups with communities should also be explored to assess their feasibility to address the 5 domains access in under-5 CHW programmes and poor performance of referral networks between providers.

An important recent example of strengthening community health systems involved the removal of user fees at health centres in peri-urban Mali, active case detection by CHWs, community mobilisation, a community awareness network and micro-financing initiatives. The network included community mobilisers, religious leaders, education centres and households who were trained to identify sick children in the community and encourage their caregivers to seek care from CHWs. These combined activities resulted in more than a halving of under-5 mortality rates (Johnson *et al.*, 2013). It is plausible in future research, that the same network could be mobilised to support referral of very sick children to appropriate providers of care.

In another CBPR initiative in Uganda, researchers developed an intervention to which involved communities scoring the quality of care of their providers. The aim of this scorecard approach was to strengthen the accountability of health providers by identifying areas for improvement (Björkman and Svensson, 2009). In nine districts the researchers collaborated with community organisations to facilitate village level meetings to inform communities about the condition of health care delivery in the community and in neighbouring areas. The community members were encouraged to rate existing health services, identify areas of improvement and develop action plans to improve services (Björkman and Svensson, 2009). Overall the intervention sought to create a community led process of monitoring health care. The findings of an evaluation one year after implementation found compared to control communities without the intervention, community-based monitoring improved the quality of care, increased coverage of childhood immunisations and reduced the number of under-5 deaths (Björkman and Svensson, 2009). In addition improving health outcomes, a more recent systematic review of studies from Peru, Zimbabwe and Kenya found community platforms can increase coverage of essential health services and improve communities satisfaction of health services (McCoy, Hall and Ridge, 2012).

Despite the emerging evidence that programmes using CBPR methods have benefits for communities, the quality of evidence is weak, mainly drawn from a few non-randomised or before and after studies (Iwami and Petchey, 2002; Loewenson, Rusike and Zulu, 2004). Another challenge that emerged from these community-based interventions is the difficulty to obtain reliable data on the burden of disease in local communities. Solely relying on communities and local health providers to give information on health needs resulted in gaps in the provision of more chronic care. Health providers also had reservations about sharing quality of care information with some failing to provide information, whilst others were reluctant to give over decision making powers to communities (Björkman Nyqvist and Svensson, 2014). Lastly there are also concerns whether governments may devolve themselves from health care responsibilities and pass them on to communities. It still also remains to be known whether these interventions are cost-effective and sustainable at scale. Further work could explore mechanisms to improve the reporting of local epidemiological data from multiple sources both governmental and non-governmental using mHealth technological solutions. These could be low cost and help ensure the process of sharing data between different providers in a structured format on a regular basis for referred cases. These areas of further research could also explore how community participation interventions can be successful in facilitating referral and caregivers complying with referral.

During the course of this thesis the international development agenda, as advocated by the United Nations transitioned from the MDGs to the Sustainable Development Goals that were adopted in 2016 (UN, 2015). The SDGs, in contrast to the MDGs place people and communities at the centre of the development agenda, it emphasises the need to support and strengthen the participation of communities and in improving health care and health care decision making (Tangcharoensathien, Mills and Palu, 2015). Future guidelines and health policies should prioritise decentralised and intersectoral interventions that take an inclusive approach of involving a range health actors.

Conclusion

There has been considerable international donor and political support to scale-up national CHWs programmes to deliver evidence-based interventions for the treatment of uncomplicated childhood conditions. However, this thesis found sub-optimal performance of the referral component that intended to ensure the effective management of severe and non-severe illnesses. CHWs failed to refer children and caregivers failed to comply with referral advice, when referred. However, the referral guidelines may be too broad in terms of which signs get referred and a greater understanding of the appropriateness and the purpose of referral is needed in different contexts. There is also a need for strengthening community health systems through the involvement of multiple primary health care providers to establish a referral pathway. This would create the conditions for CHWs to refer and for caregivers to comply referral and seek further health care. Community health strengthening requires a greater emphasis to be placed on empowering communities to determine their health needs and the delivery of primary health care. This in turn could help ensure the continuum of care for referred children.

SDG 3 seeks to ensure healthy lives and well-being for all ages and seeks to end the preventable deaths of children under-5 by 2030. Developing management guidelines that are sensitive to community's health needs, that are monitored, reviewed and include novel diagnostics and data are key to ensuring these global health targets are met. More importantly it would ensure universal access to primary health care not only for caregivers living beyond the reach of professional health services but also for caregivers referred as part of a community programmes. Countries and communities will then be better placed to achieve health for all as envisaged by the Alma-Ata declaration.

Chapter 8: References

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Appendix I: Data collection forms

Treatment recording form – Intervention (mRDT) arm

White form – RDT villages

COMMUNITY MEDICINE DISTRIBUTOR'S REGISTER

TREATMENT RECORDING FORM

Record no:		**Month:**	**Year:**
Subcounty (LCIII):		**Parish (LCII):**	**Village (LCI):**
CMD ID:		**Name of CMD:**	**Date of consultation:**

Patient ID:	**Name of child:**	**Sex:**	**Age:**

Child's Village of Residence:	**Child's head of household:**

Does child come from the same village as CMD?	Yes – resident	
	No – non-resident	
Did child sleep under a mosquito net last night? (*circle*)	Yes / No	

Record of treatment:

When did the fever start?	Today (same day)		**Body temperature:**		
	Yesterday (day before)				
	2 days ago				
	More than 2 days ago				
Quick Malaria Test done?	Yes		**Blood slide taken?**	Yes	
	No			No	
	Refused			Refused	
RDT result?	Positive				
	Negative				
Treatment given:	Co-Artem Yellow				
	Co-Artem Blue				
	Malaria Suppository				
	No treatment given				

Referred?	Yes		*If yes,* **Reason for referral:**	Danger Signs	
	No			Other Signs for Referral	

Additional Comments:

Treatment recording form – Control (signs and symptoms) arm

White form - Presumptive (control) villages

COMMUNITY MEDICINE DISTRIBUTOR'S REGISTER

TREATMENT RECORDING FORM

Record no:		**Month:**	**Year:**	
Subcounty (LCIII):		**Parish (LCII):**	**Village (LCI):**	
CMD ID:		**Name of CMD:**	**Date of consultation:**	
Patient ID:		**Name of child:**	**Sex:**	**Age:**
Child's Village of Residence:		**Child's head of household:**		
Does child come from the same village as CMD?			Yes – resident	
			No – non-resident	
Did child sleep under a mosquito net last night? (*circle*)			Yes / No	
Record of treatment:				
When did the fever start?	Today (same day)		**Body temperature:**	
	Yesterday (day before)			
	2 days ago			
	More than 2 days ago			
Blood slide taken?	Yes			
	No			
	Refused			
Treatment given:	Co-Artem Yellow			
	Co-Artem Blue			
	Malaria Suppository			
	No treatment given			
Referred? Yes		*If yes,* **Reason for referral:**	Danger Signs	
No			Other Signs for Referral	
Additional Comments:				

Severe referral form

Red form: Presumptive (control) villages

CMD Emergency Referral Form

Patient Registration no:	
Patient name:	
Name of Head of household:	
Village name:	
Parish:	
Name of CMD:	
Date of referral:	Time of referral:
Age of child:	Temp:
Pre-referral treatment given by CMD or parents (Circle)?	
NO	Yes – Coartem Yes – Rectal Artesunate Yes – Other (*specify)*

Reasons For Emergency Referral:	✓
Illness in child below 2 months of age	
Convulsions or fits now or within the past 2 days	
Coma / Loss of consciousness	
Patient is confused or very sleepy - cannot be woken	
Extreme weakness – unable to stand or sit without support	
Very Hot – with temperature of 38.5 or more	
Very Cold – with temperature of 35.0 or less	
Vomiting everything - cannot keep down food or drink	
Not able to drink or breastfeed	
Severe anaemia – very pale palms, fingernails, eyelids	
Yellow eyes	
Difficulty in breathing	
Severe dehydration	
Any other symptoms? Describe:	

REFERRAL DETAILS - TO BE COMPLETED AT HEALTH FACILITY		
Name of Health Facility:	Sub-county:	Date seen: Time seen:
Name of attendant:	Position of attendant:	
Signs and Symptoms recorded:	Diagnostic tests done: YES NO *If no, specify why:*	
Management of patient		
Diagnosis:	Patient Admitted: YES NO	Treatment given:
Final Outcome	Date:	
Referred: YES NO		*If referred, referred to:*
Discharged: YES NO		
Died: YES NO		

Non-severe referral form

Blue form: Presumptive (control) villages

CMD Referral Form

Patient Registration no:	
Patient name:	
Name of Head of household:	
Village name:	
Parish:	
Name of CMD:	
Date of referral:	Time of referral:
Age of child:	Temp:
Pre-referral treatment given by CMD or parents (Circle)?	
NO	Yes – Coartem Yes – Rectal Artesunate Yes – Other (*specify)*

Reasons For Referral:	✓
Fever that has lasted more than 7 days	
Vomiting and diarrhoea	
Blood in faeces or urine	
Pain when passing urine, or frequent urination	
Wound or Burns	
Skin abscess	
Painful swellings or lumps in the skin	
Ear infection (runny ear or child pulling at ear)	
Sticky or red eyes	
Fever in babies less than 4 months old	

REFERRAL DETAILS - TO BE COMPLETED AT HEALTH FACILITY

Name of Health Facility:	Sub-county:	Date seen: Time seen:
Name of attendant:	Position of attendant:	
Signs and Symptoms recorded:	Diagnostic tests done: YES NO *If no, specify why:*	
Management of patient		
Diagnosis:	Patient Admitted: YES NO	Treatment given:
Final Outcome	Date:	
Referred: YES NO		*If referred, referred to:*
Discharged: YES NO		
Died: YES NO		

Appendix II: Research paper cover sheets

Research paper cover sheet – Chapter 3

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RESEARCH PAPER COVER SHEET

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

SECTION A – Student Details

Student	Sham Lal
Principal Supervisor	Sian Clarke
Thesis Title	Community case management and referral of children with fever within the primary health care system in Uganda.

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

SECTION B – Paper already published

Where was the work published?	Malaria Journal		
When was the work published?	24 November 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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

SECTION C – Prepared for publication, but not yet published

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

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the idea for this work, conducted the analysis and wrote the first draft of the paper.

Student Signature: [redacted] **Date:** 08/04/2018

Supervisor Signature: [redacted] **Date:** 6 April 2018

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RESEARCH PAPER COVER SHEET

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

SECTION A – Student Details

Student	Sham Lal
Principal Supervisor	Sian Clarke
Thesis Title	Community case management and referral of children with fever within the primary health care system in Uganda.

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

SECTION B – Paper already published

Where was the work published?	The American Journal of Tropical Medicine and Hygiene		
When was the work published?	31st Ocotber 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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

SECTION C – Prepared for publication, but not yet published

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

SECTION D – Multi-authored work

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

Student Signature: [redacted] **Date:** 6/04/2018

Supervisor Signature: [redacted] **Date:** 6 April 2018

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Research paper cover sheet – Chapter 5

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RESEARCH PAPER COVER SHEET

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

SECTION A – Student Details

Student	Sham Lal
Principal Supervisor	Sian Clarke
Thesis Title	Community case management and referral of children with fever within the primary health care system in Uganda.

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

SECTION B – Paper already published

Where was the work published?	BMC Health Services Research		
When was the work published?	April 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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

SECTION C – Prepared for publication, but not yet published

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

SECTION D – Multi-authored work

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

Student Signature: [redacted] **Date:** 12/04/2018

Supervisor Signature: [redacted] **Date:** 12 April 2018

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RESEARCH PAPER COVER SHEET

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

SECTION A – Student Details

Student	Sham Lal
Principal Supervisor	Sian Clarke
Thesis Title	Community case management and referral of children with fever within the primary health care system in Uganda.

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

SECTION B – Paper already published

Where was the work published?	PLOS ONE		
When was the work published?	10 September 2015		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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

SECTION C – Prepared for publication, but not yet published

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

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived, designed and performed the experiments, analysed the data and wrote the first draft of the research paper.

Student Signature: [redacted] **Date:** 06/04/2018

Supervisor Signature: [redacted] **Date:** 6 April 2018

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