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Beyond "test and treat"

Malaria diagnosis for improved pediatric fever management in sub-Saharan Africa

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Abstract

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This thesis examined malaria test use, adherence and integration into clinical practice for improved pediatric fever management in sub-Saharan African countries and explored *Access, Facility Readiness* and *Clinical Practice* bottlenecks to achieve this program goal.

Study I examined diagnostic testing rates and its determinants for pediatric fevers across 13 countries in 2009-2012 including *Access* bottlenecks. *Study II* evaluated the effect of testing on treatment decisions at the population level in 12 countries in 2010-2012 and explored reasons for varying country results across *Access, Facility Readiness* and *Clinical Practice* bottlenecks. *Study III* explored *Facility Readiness* and *Clinical Practice* bottlenecks for using malaria diagnosis for improved pediatric fever management in Mbarara District Uganda. *Study IV* examined integrated pediatric fever management using RDT and IMCI in Malawi health facilities in 2013-2014 including *Facility Readiness* and *Clinical Practice* bottlenecks.

Malaria testing of pediatric fevers was low (17%) and inequitable at the outset of new guidelines with febrile children in least poor household more often tested than in poorest (OR: 1.63, 95% CI: 1.39-1.91) (Study I). Significant variability was found in the effect of testing on ACT use across countries (e.g. Uganda OR: 0.84, 95% CI: 0.66-1.06; Mozambique OR: 3.54, 95% CI: 2.33-5.39). Four main themes explained varying results: available diagnostics and medicines; quality of care; care-seeking behavior; and malaria epidemiology (Study II). In Mbarara District Uganda malaria over-treatment for RDT-negative results reportedly occurred and was driven by RDT perceptions, system constraints and provider-client interactions (Study III). In Malawi health facilities, there was common compliance to malaria treatment guidelines in sick child consultations. 72% were tested or referred for malaria diagnosis and 85% with RDT-confirmed malaria were prescribed first-line anti-malarials. Yet integrated pediatric fever management was sub-optimal in terms of other assessments completed and antibiotic targeting. 28% with IMCI-pneumonia were not prescribed any antibiotic and 59% 'without antibiotic need' were prescribed any antibiotic. Few eligible clients had respiratory rates counted to identify antibiotic need for IMCI-pneumonia (18%). RDT-negative children had 16.8 (95% CI: 8.6-32.7) times higher antibiotic over-treatment odds compared to positive cases and this effect was conditioned by cough or difficult breathing complaints (Study IV).

Thesis findings highlight *Access*, *Facility Readiness* and *Clinical Practice* bottlenecks that need to be addressed to use malaria diagnosis for improved pediatric fever management. Programs must move beyond malaria-focused *'test and treat'* strategies towards *'IMCI with testing'* in order to conceptualize RDT as one part of the established algorithm for managing sick children in an integrated manner. RDT should also be viewed as an important entry point for contributing to ongoing health system strengthening efforts.

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”Bill and I still believe very strongly in the power of science. What we had to learn was that the second wheel is delivery.”

Statement by Melinda Gates
Global Partners Forum, May 2015

List of Papers

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

I Johansson, E., Gething, P., Hildenwall, H., Mappin B., Petzold, M., Peterson, S., Selling K. (2014) Diagnostic testing of pediatric fevers: meta-analysis of 13 national surveys assessing influences of malaria endemicity and source of care on test uptake for febrile children under five years. *PLoS One*, 9(4): e95483.

II Johansson, E., Gething, P., Hildenwall, H., Mappin B., Petzold, M., Peterson, S., Selling K. (2015) Effect of diagnostic testing on medicines used by febrile children less than five years in 12 malaria-endemic African countries: a mixed-methods study. *Malaria Journal*, 14(194): e95483.

III Johansson, E., Kitutu, F., Mayora, C., Awor P., Peterson, S., Wamani, H., Hildenwall H. (2016) *'It could be viral but you don't know, you have not diagnosed it.'* Health worker challenges in managing non-malaria pediatric fevers in the low transmission setting of Mbarara District, Uganda. *Submitted.*

IV Johansson, E., Selling, K., Nsona, H., Mappin B., Gething, P., Petzold, M., Peterson, S., Hildenwall, H. (2016) Integrated pediatric fever management and antibiotic over-treatment in Malawi health facilities: data mining a national facility census. *Submitted.*

Contents

Abbreviations

ACT	Artemisinin-based Combination Therapy
CDB	Cough or Difficult Breathing
CHAM	Christian Health Association of Malawi
CHW	Community Health Worker
DHS	Demographic and Health Survey
FGD	Focus Group Discussion
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
HC	Health Center
HRP2	Histidine-Rich Protein II
iCCM	Integrated Community Case Management
IMCI	Integrated Management of Childhood Illness
IRB	Institutional Review Board
ITN	Insecticide-Treated Net
M&E	Monitoring and Evaluation
MIS	Malaria Indicator Survey
MDG	Millennium Development Goal
NMCP	National Malaria Control Program
$Pf PR_{2-10}$	Plasmodium Falciparum Prevalence Rate in 2-10 year olds
pLDH	Plasmodium Lactate Dehydrogenase
PSU	Primary Sampling Unit
RDT	Rapid Diagnostic Test for Malaria
SDG	Sustainable Development Goal
SP	Sulfadoxine-Pyrimethamine
SPA	Service Provision Assessment
UNICEF	United Nations Children's Fund
USAID	US Agency for International Development
USD	US Dollars
WHO	World Health Organization

Introduction

Child health and survival

In September 2015, world leaders agreed to a new global development agenda underpinned by the Sustainable Development Goals (SDG). The SDGs include 17 goals and 169 targets that aim to end extreme poverty while protecting the planet and its people for generations to come [1]. The SDG target for child survival specifically calls for a reduction in under-five mortality to at least as low as 25 per 1,000 live births by 2030.

Indeed, the SDG target builds on the enormous progress made in child survival over the past two decades as countries worked toward achieving the Millennium Development Goals (MDG). Between 1990 and 2015, the global under-five mortality rate declined by more than half from 90 to 43 deaths per 1,000 live births [2].

Despite this progress, the global rate of decline was too slow to achieve MDG4 that called for a two-thirds reduction during this time period. Moreover, this global average obscured uneven progress experienced across regions and countries [3], notably Eastern Asia with the fastest progress and sub-Saharan African with the slowest. Sub-Saharan Africa continues to have the world's highest child mortality rates despite reducing child mortality from 179 deaths per 1,000 live births in 1990 to 86 in 2015.

This uneven global progress has led to the increasing concentration of child deaths in the world's poorest regions. Today, approximately half of global child deaths – or three million in total – occur in sub-Saharan Africa alone. Even within countries, child deaths are largely concentrated among the poorest and most marginalized groups [4]. Moreover, these deaths are largely caused by preventable and treatable infectious causes or complications during the neonatal period [5]. Leading infectious causes include pneumonia (16%), diarrhea (9%), neonatal sepsis (7%) and malaria (5%). Leading neonatal complications include preterm birth (16%) or intra-partum related (11%) issues.

Taken together, there is general consensus that achieving further under-five mortality reductions to achieve the SDG target will require delivering interventions with the greatest potential for reducing these leading causes of death to the most vulnerable children at highest risk of dying [6]. This includes many well-known, proven and available interventions that if delivered at national scale could avert approximately two-thirds of global child

deaths [7]. Effective and timely treatment of leading infectious causes of death has consistently been identified as a critical life-saving intervention, notably treatment for childhood pneumonia, malaria and diarrhea. This thesis focuses on the potential of malaria diagnostic testing to improve treatment targeting and quality care for sick children in order to reduce child deaths.

Integrated Management of Childhood Illness

Early and appropriate treatment of the leading infectious causes of child deaths is critical for reducing mortality. Yet in most low-income settings there remains limited or non-existent diagnostic tools at first-level health facilities to identify underlying etiologies of sickness in children. In these settings, health providers must primarily rely on symptom presentation and simple clinical assessments to determine a treatment course for their patients.

For many years, health staff treated these conditions based on disease-specific guidance that did not address co-morbidities in sick children or symptom overlap across diseases requiring further differentiation [8]. Given this experience, there became a growing recognition that integrated protocols were needed to optimally manage the sick child [9].

Since the 1990s, the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) have promoted the Integrated Management of Childhood Illness (IMCI) strategy to improve management of the most common causes of child morbidity and mortality in an integrated manner [10]. The IMCI strategy aims to improve the quality of preventive and curative sick child care provided at health facilities using an integrated syndrome-based approach. It also aims to improve care provided by communities and families since sick children in these settings often seek care outside the formal health sector or not at all [8].

Specifically, the three main pillars of the IMCI strategy include: (1) improving case management skills of health providers (2) improving overall health systems (3) improving family and community practices [8]. At health facilities, IMCI focuses on improving assessment and treatment of common childhood illnesses, counselling of caregivers and referral of severe cases. In communities, IMCI focuses on improving recognition of danger signs, appropriate and timely care-seeking, nutrition and feeding practices, prevention measures (e.g. immunizations) and adherence to prescribed treatment regimens. Specific IMCI algorithms are described in the next section.

A multi-country evaluation was undertaken during the decade after IMCI initiation to evaluate the effectiveness of the strategy in various settings [11-15]. Overall, this evaluation concluded that IMCI improved health worker performance and quality of care for sick children at first-level health facilities [11]. The cost-effectiveness of the IMCI strategy was also demonstrated compared to previous disease-specific guidance [12]. Yet despite the poten-

tial of IMCI to improve quality sick child care, numerous studies conducted in different low-income settings have documented its poor implementation in routine practice and lack of uptake at the national level that greatly limits its potential to improve quality care and overall health outcomes [16-17]. Reasons for poor adherence to IMCI guidelines are diverse but are often attributed to low motivation, work overload, lack of effective supervision, inadequate drugs and supplies, client demands, perceived low utility of guidelines compared to simple 'rules of thumbs' for managing cases, among other issues [14,18-21].

Integrated community case management

The multi-country evaluation also found that the community component had not been well implemented and that additional attention was needed to improve family and community health behaviors [16]. In recent years, there has been renewed attention to community-based services and the need to bring treatment of leading infectious causes of child deaths closer to families [22]. To this end, the IMCI algorithm has been adapted and simplified for use by community health workers (CHW) in order to classify and treat malaria, pneumonia and diarrhea along with malnutrition and other conditions [23-24]. This community strategy is known as integrated community case management (iCCM) and has been successfully implemented in various settings by both community health workers [25], and in some cases private drug sellers [26]. Evidence indicates that CHWs can classify and treat these leading causes of death according to iCCM guidelines and some studies suggest improved child survival outcomes using this approach [25,27-28]. Nevertheless, community-based programs have varied greatly across countries, including different CHW roles and responsibilities, education requirements, training, supervision and salaries, which has led to different program outcomes [29]. Program performance may also be hindered by issues plaguing formal health systems, such as inadequate supplies or supervision, which need to be overcome to achieve expected child survival gains [23,25,30].

IMCI algorithms

IMCI uses a simple algorithm based on symptom presentation and clinical assessments in order to help health workers classify and treat the most common causes of morbidity and mortality in sick children. These algorithms were designed to have high sensitivity with reasonable or even low specificity compared to gold-standard diagnoses (e.g. x-ray, parasite blood count) in order to ensure that potentially dangerous underlying conditions are classified and immediately treated using this algorithm [10]. This design typically results in substantial over-treatment of targeted conditions.

Specifically, IMCI algorithms are available to help classify and treat the following potential conditions in sick children: malaria, pneumonia, diarrhea, dehydration, measles, malnutrition, anemia, mastoiditis, ear infections,

mouth conditions and HIV infection. IMCI algorithms also help health workers identify danger signs of severe disease for immediate referral. The next section summarizes IMCI algorithms relevant to this thesis:

IMCI fever algorithm: If a child presents with reported fever, history of fever or high temperature (>37.5C), the health worker should first ask how long the fever has occurred in order to classify persistent fever (over seven days). Persistent fever could be a sign of measles, resistant malaria or other condition and requires further diagnostic testing to identify the cause. The health worker should also ask if the child had measles within the last three months and look for current signs of measles (e.g. generalized rash and either cough, runny nose or red eyes as well as mouth ulcers, pus draining from eye or clouding of the cornea). Neck stiffness should also be checked as a sign of meningitis or severe febrile disease for immediate referral. For many years, the IMCI fever algorithm also promoted presumptive malaria treatment for sick children in malaria-endemic African settings. This recommendation was due to high malaria mortality rates in young children coupled with the critical need for early and appropriate treatment to avoid severe outcomes. In addition, there is also a lack of other defining features to adequately differentiate malaria from other fever causes using clinical algorithms [9]. An evaluation of the IMCI algorithm for uncomplicated malaria found that the sensitivity of fever was close to 100 per cent compared to confirmed malaria diagnosis using microscopic examination [31]

IMCI CDB algorithm: If a child presents with reported cough or difficult breathing (CDB), the health provider should count the child's breathing rate for one minute. A respiratory rate of 50 breaths or more per minute (2 up to 12 months) or 40 breaths or more per minute (12 months up to 5 years) is used to classify IMCI pneumonia in sick children. Sick children meeting this classification threshold who do not have wheeze should receive oral amoxicillin. Severe pneumonia disease is based on the child having IMCI pneumonia and any general danger sign that requires referral to higher level care and injectable antibiotic therapy. An evaluation of the IMCI algorithm for uncomplicated pneumonia found that the sensitivity of cough or rapid breathing was 79 per cent compared to x-ray confirmed pneumonia [32]. More recent studies also found that only half of IMCI pneumonia cases had x-ray confirmed pneumonia [33] and an even lower percentage was found in another setting [34].

IMCI diarrhea algorithm: If a child presents with diarrhea, the health worker should ask how long the diarrhea has occurred to identify persistent diarrhea (over 14 days). Persistent diarrhea can cause nutritional issues and contribute to mortality and severe cases with some dehydration should be referred immediately. Diarrhea cases should also be checked for blood in the

stool to classify dysentery for ciprofloxacin treatment. The health worker should also check for signs of dehydration based on lethargy or unconsciousness, inability to drink or breastfeed, irritability, sunken eyes and by pinching the abdominal skin. The child is then classified as having diarrhea with or without moderate or severe dehydration.

IMCI and fever symptoms

Fever is a common symptom of many childhood illnesses in sub-Saharan Africa, including most conditions included in IMCI algorithms, notably malaria, pneumonia, diarrhea, measles, acute ear infections, among others. However, the historical presumption of all fevers as 'malaria' has often impeded probing for these other underlying conditions that could cause fever illness [9,35-36].

Malaria and pneumonia, in particular, are among the leading infectious causes of child mortality in sub-Saharan Africa and were estimated to cause over one million child deaths in this region in 2015 alone [3]. These two conditions also have substantial symptom overlap such that childhood pneumonia cases commonly present with fever while childhood malaria cases may also exhibit respiratory distress [9]. Studies indicate that between 37 per cent and 80 per cent of sick children under five years with reported fever (or IMCI malaria) also met the IMCI pneumonia classification depending on the context [9,37-38]. Moreover, nearly all sick children under five years with IMCI pneumonia also had reported fever symptoms, or IMCI malaria. While sick children meeting both classifications should receive dual treatment, studies indicate common mistreatment of IMCI pneumonia with anti-malarial medicines in both health facility and community settings [35-36,38], which delays appropriate care for IMCI pneumonia with potentially fatal consequences [39].

Childhood fever etiologies

The causes of childhood fever illness are often difficult to distinguish clinically and the limited diagnostics available in resource-poor settings restricts the ability to identify underlying etiologies in routine conditions. Nevertheless, there have been various etiology studies conducted over the years to identify the most common underlying causes of childhood febrile illness across sub-Saharan African settings.

While malaria is often perceived as a primary cause of childhood fevers, the malaria-attributable fraction of fevers is highly variable across age groups, seasons and locations [40]. Studies from the early- to mid-2000s indicated that malaria caused fever illness in between 40-97% of febrile cases in rural areas [41] compared to 0-12% in urban settings [42]. Moreover, the malaria-attributable fraction of fevers has declined significantly in most endemic areas in recent years due to expanded control efforts notably mass insecticide-treated net distribution [43-44].

Beyond malaria, other main causes of childhood fevers often targeted by control measures (e.g. vaccines or other prevention measures) include invasive bacterial diseases, such as *Haemophilus influenzae* and *Streptococcus pneumoniae* [45-47]. In settings with high and equitable vaccine uptake, the contribution of these causes to childhood fever etiologies will become substantially reduced [48], which will lead to the increasing importance of viral causes along with other conditions [33-34,49].

More recent etiology studies of childhood fevers from various settings have indeed borne this out. These studies found that viral disease is a far more common cause of fever illness in children compared to bacterial or parasitic infections [33-34,50-51]. D'Acremont et al (2013) in particular identified viral causes in 71% of febrile children compared to 22% with bacterial disease and 11% with parasitic disease [34]. Acute respiratory infection was found in 62% of children, and 5% of these cases had xray-confirmed pneumonia. Other causes included nasopharyngeal viral infection (12%), malaria (11%), gastroenteritis (10%), urinary tract infection (6%), typhoid fever (4%), skin infection (2%) and meningitis (0.2%).

Malaria *'test and treat'* guidelines

For many years, the IMCI strategy promoted presumptive anti-malarial treatment for all febrile children in malaria-endemic African countries given the lack of equipment and trained technicians to diagnose malaria at first-level health facilities. This resulted in widespread malaria over-diagnosis [35-36], non-rational use of anti-malarial drugs [52], and poor quality treatment of other fever causes [37-38], particularly pneumonia given its substantial symptom overlap with malaria [9,37-38].

In 2010, however, the World Health Organization revised malaria treatment guidelines to recommend parasitological diagnosis of all suspected malaria cases prior to initiating treatment [53]. This recommendation was based on the development and refinement of rapid diagnostic tests (RDT) over the past two decades that allows for malaria diagnosis in remote and resource-poor settings [54].

A number of other reasons also underpinned the policy shift toward universal malaria diagnosis [55]. First, diagnosis of suspected malaria cases in communities and at first-level health facilities has great potential to improve early and more accurate treatment of malaria and other febrile conditions to improve patient health outcomes as previously described.

Second, parasite resistance to anti-malarial drugs has long been a problem for effective malaria treatment in sub-Saharan Africa and other regions [56]. Growing resistance to chloroquine and later sulfadoxine-pyrimethamine (SP/Fansidar) reduced malaria treatment efficacy in many sub-Saharan African settings over the past decade [57-58]. The problem of drug resistance is

exacerbated by inappropriate prescriptions and poor adherence to treatment regimens that drives the need for better targeting to confirmed malaria cases.

Third, by the mid-2000s, most malaria-endemic African countries adopted artemisinin-based combination therapies (ACT) as first-line treatment for uncomplicated malaria given growing parasite resistance to other antimalarial drugs [59]. These modern medicines, however, are more expensive than previous drugs and improved precision in ACT treatment is needed to reduce health care costs to governments and international donors [56,60]. ACT costs approximately USD2 per treatment course compared to a few cents for chloroquine treatment.

Fourth, in recent years, there have been rapid and significant reductions in malaria transmission in many sub-Saharan African settings, particularly in the southern region and along coastal areas [43-44,61]. This is largely due to strengthened prevention efforts including mass distribution of insecticide-treated nets (ITN) to prevent infection [44]. In these settings, there is a lower fraction of malaria-attributable fevers such that malaria diagnosis would result in even greater treatment reductions if targeted to confirmed cases.

Fifth, malaria surveillance in sub-Saharan African countries has long been hampered by imprecise malaria case definitions that have historically been based on reported fever cases attending first-level health facilities. Malaria diagnosis could lead to more accurate case definitions that could in turn improve malaria surveillance, burden estimation and health system management for planning and financing malaria control activities [55]. Moreover, in settings moving towards malaria elimination, malaria diagnosis is a cornerstone of enhanced surveillance efforts in order to actively detect malaria cases in communities or to identify clusters or high-risk groups for targeted control efforts [62].

Malaria diagnosis methods

Malaria diagnosis has historically been conducted using microscopic examination of the patient's blood. Newer methods have also been developed to improve availability and quality of malaria diagnosis in remote and resource-poor settings [54]. These methods include antigen detection tests, known as malaria rapid diagnostic tests (RDT), as well as newer molecular techniques such as polymerase chain reaction (PCR) although the latter is not routinely used in control programs and is not discussed in this thesis.

Microscopic examination

For malaria diagnosis using microscopic examination, a drop of the patient's blood is smeared over a microscope slide, known as a blood smear [63]. This blood smear is stained to help the microscopist distinguish parasites from other blood particles. This method, using both thick and thin smears, allows for the detection of parasites in the blood to confirm malaria infection

(by thick smears), and the identification of parasite species and parasite load, or the percentage of red blood cells infected with malaria parasites (by thin smears). Parasites could potentially be detected at levels as low as five parasites per microliter of blood depending on the quality of the examination.

However, laboratory equipment, trained microscopists and infrastructure to support microscopy are rarely available at first-level health facilities, and community-level diagnosis using this method is not possible. The utility of malaria microscopy as a central means for achieving universal diagnosis goals is therefore quite limited. In addition, the quality of malaria case detection by microscopy, particularly at low parasitemias, greatly depends on the training and experience of the microscopist. Studies from various settings over the past decade have consistently shown poor quality microscopy for malaria diagnosis in routine practice [64-69].

Rapid diagnostic tests

Malaria rapid diagnostic tests are antigen detection tests that commonly use a lateral-flow immuno-chromatographic method to screen for proteins produced by malaria parasites present in the infected patient's blood [70]. If the targeted antigen is present, the test strip displays a visible colored line within approximately 20 minutes. Compared to microscopic examination, malaria RDTs can typically detect parasite levels as low as 100 parasites per microliter of blood but are not able to determine parasite load or disease progression.

Malaria RDTs are designed to detect either single or multiple antigens in order to screen for the presence of one or more parasite species [71]. Malaria caused by *P falciparum* is typically at least one of the species detected using rapid tests since it is the most common and severe form of malaria in endemic African areas. Four other parasite species also infect humans including: *P vivax, P. ovale, P malariae* and *P knowlesi.* Malaria RDTs are commonly available to detect histidine-rich protein 2 (HRP2) produced by *P falciparum* parasites or to detect *Plasmodium* lactate dehydrogenase (pLDH) enzyme secreted by multiple parasite species.

Malaria RDTs are well-suited for use at first-level health facilities as well as in communities across low-income countries, which makes universal diagnosis goals potentially achievable with this method. Malaria RDTs largely meet the ASSURED criteria for evaluating point-of-care diagnostic tests, including **A**ffordable (low-cost), **S**ensitive (few false-negatives), **S**pecific (few false-positives), **U**ser-friendly (simple to perform with minimal training), **R**apid (rapid results for timely treatment), **R**obust (easy storage and transport), **E**quipment-free (does not require additional supplies or equipment) and **D**elivered to those in need (or where most cases present) [72].

Malaria RDTs cost approximately USD1 per test, provide results in approximately 20 minutes, require limited training and allows for diagnosis at first-level health facilities or in community settings where pediatric fevers

are commonly managed [71]. RDT performance can vary depending on test type and parasite/antigen load. A systematic review evaluated the accuracy of RDTs compared to microscopy or PCR for detecting *P falciparum* malaria parasites [73]. This review found that RDTs can be as accurate as these other diagnostic methods, and performance differences between RDT types (HRP2- or pLDH-based methods) was not substantial. HRP2-based RDTs were more sensitive but less specific than pLDH-based RDTs. Specifically, HRP2-based RDTs had a mean sensitivity and specificity of 95 per cent across studies while pLDH-based RDTs had 93 per cent and 99 per cent sensitivity and specificity, respectively, across reviewed studies.

There are also some technical limitations that affect malaria RDT performance in certain conditions. Some issues relevant to this thesis include: First, RDTs are less sensitive to low parasite/antigen loads compared to other methods for detecting malaria infection [70]. WHO product endorsement requires a panel detection score of 75 per cent at parasite loads of 200 per microliter of blood, which limits RDT detection for nascent infections or asymptomatic carriers [71]. Nevertheless, evidence indicates that RDTs are sufficient to clinically manage suspected cases in low transmission settings with equal or better performance to routine microscopy [74], particularly given documented low-quality performance of routine microscopy as previously described. Second, histidine-rich protein 2 (HRP2) from *P falciparum* may persist in an infected patient's blood for two weeks or more after parasite clearance, which may lead to a false positive result if a malaria RDT is performed on a recovering patient within this timeframe [70]. Note that WHO product endorsement requires a false positive rate of less than 10 per cent [71]. Other potential issues include RDT inability to quantify parasite load, susceptibility to extreme heat or humidity, and potentially subjective interpretation of RDT test lines [70].

Current evidence: from guidelines to practice

The shift from presumptive treatment of febrile children to test-based case management has great potential to improve malaria surveillance, rational drug use and appropriate management of other febrile conditions. National malaria control programs (NMCP) are heavily investing in wide-scale provision of malaria RDTs in order to achieve these desired program objectives.

By 2010, 37 African countries had a malaria diagnosis for all age groups with plans for wide-scale RDT deployment to achieve universal diagnosis goals [75]. Global RDT sales rose from less than 50 million tests in 2008 to over 300 million in 2014 according to manufacturer reports [76]. Globally, NMCPs distributed less than 30 million RDTs to public sector facilities in 2008 compared to 163 million in 2014 [76]. Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) in particular has provided substantial

financial support to wide-scale malaria RDT deployment. Between 2005 and 2010, GFATM supported 81 countries to invest in malaria diagnosis leading to 115 million RDTs procured during this time period. As a result, 123,132 health facilities became equipped with malaria RDT and 137,140 health personnel were trained in RDT performance across these 81 countries [77].

Despite this investment, evidence to date shows mixed program success [78-96]. While most studies indicate a reduction in anti-malarial treatment after RDT introduction into health facilities [e.g.79,83,86,95], several also indicate frequent anti-malarial prescriptions despite a negative RDT result [e.g.81,87,89,96]. In studies where first-line malaria treatment (ACT) was largely restricted to positive cases [e.g.82,85,91-92], some research that reported secondary treatment outcomes showed widespread prescriptions of other anti-malarial [e.g.90,92] or antibiotic [e.g.79,85,91] drugs to RDT-negative patients and not according to established clinical guidelines [10]. Qualitative interviews with health workers largely conducted in areas with intense malaria transmission have generally indicated RDT mistrust and reliance on clinical judgment as main reasons for continued malaria over-diagnosis [97-106]. Nevertheless, some recent research shows improved test-based case management practices over time [83,95]. In addition, clinical trials of advanced support measures, such as daily SMS messages or interactive training sessions, have also led to improved RDT adherence practices among health workers [107-108]. These methods hold promise of improving future program performance if more widely implemented. Finally, community-based studies of RDT practices have generally indicated appropriate RDT use and adherence among community health workers [109-111] and in private drug shops [26,112-113], which could further improve access to and equity in use of malaria RDTs.

Evidence gaps and research agenda

Yet evidence has largely been derived from small-scale adherence studies conducted in limited facility settings within a limited number of countries, notably Kenya, Malawi, Tanzania, Uganda and Zambia [78]. Evidence remains limited for most other countries despite, in many cases, comparable RDT investments [114]. While a few countries have conducted national facility studies to examine case management practices across different sub-national contexts [96,115-116], there remains limited understanding of how these practices may differ across key sub-national groups, such as by malaria risk [83,86,89]. In addition, few facility-based studies have explicitly investigated how RDT is integrated into the IMCI framework in order to improve overall pediatric fever management, and there is no evidence from mainland sub-Saharan Africa [80,117]. Moreover, facility studies by their nature do not provide evidence from community settings where pediatric fevers are

commonly managed in low-income countries. There has also been increased RDT deployment to communities in recent years, including to community health workers and private drug shops, which would not be captured by most facility-based studies. There is also limited evidence from routine conditions compared to controlled study trial contexts, and how broader program contexts could influence test-based treatment practices, notably care-seeking behaviors.

Rationale for thesis

The rationale for this thesis originated from the identification of these critical evidence gaps. At the same time, routine national survey programs described in the next section had improved their malaria diagnosis data collection and those results were becoming increasingly available for secondary analyses. There seemed great potential to use these public high-quality datasets to answer some of these important research questions including examining the extent and determinants of testing rates for pediatric fevers at the population level across multiple countries (Study I); analyzing the effect of testing on pediatric fever treatment at the population level across multiple countries (Study II) and assessing the quality of integrated pediatric fever management and determinants of poor treatment decisions (e.g. antibiotic over-treatment) in Malawi health facilities (Study IV). Mixed-methods approaches had also been under-utilized in this research area at the initiation of this doctoral project, and there seemed similar potential to complement these analyses with qualitative methods to better understand reasons for observed findings.

Harnessing national surveys

Routine national cross-sectional population- and facility-based surveys are available to answer some of these important research questions, but have primarily been used for program monitoring with less focus on in-depth analysis for research purposes. USAID-supported Demographic and Health Surveys (DHS), Malaria Indicator Surveys (MIS) and Service Provision Assessments (SPA) are routinely implemented in low- and middle-income countries to monitor a variety of health and demographic issues using comparable methods across countries and over time [118]. These survey programs are further described in later sections (see Methods), and were recently modified to improve their malaria diagnosis data collection.

There are advantages and limitations to using these survey datasets for research purposes. Limitations are discussed in later sections (see Methodological Considerations). Some important advantages include: First, surveys are routinely implemented about every three to five years (for DHS) in most low- and middle-income countries to provide comparable information over time or across countries to compare results. This allows researchers to an-

swer ‘space or time’ research questions using these datasets that are not generally answerable through small-scale research studies. Second, these surveys are professionally-supervised and implemented by experienced personnel to provide high-quality information (see Methods). Third, datasets are standardized, cleaned and provided free to researchers in useful formats for secondary analysis purposes. This avoids time and cost associated with primary data collection and makes important use of readily available data.

Finally, and importantly, surveys include large sample sizes and broad data collection scopes that typically allow researchers to detect differences in outcomes, identify explanatory predictors and adjust for a wide range of potential confounding variables. This allows for important exploratory or hypothesis-generating analyses that could help inform future research to better understand any observed differences identified in these large datasets. Furthermore, it is often possible to combine different country datasets for research purposes using meta-analysis techniques, which further increases sample size to conduct important sub-group analyses or to detect rare outcomes that may not be possible using one country dataset alone. For example, there is often limited malaria risk diversity within a single country and analysis of multiple country datasets allows for detection of outcome differences across these different transmission zones. Similarly, the broad data collection scope in SPA allowed for an expanded analysis of RDT integration into the IMCI framework that would not have been possible with malaria-focused facility-based studies implemented to date.

Mixed-methods approaches

Mixed-methods approaches using both quantitative and qualitative methods are increasingly used in health services research in order to answer complex questions that may not be adequately addressed using one method alone [119]. Such approaches have potential to provide a broader understanding of complex phenomena in order to inform policy decisions or future research agendas. One form of this approach is nesting a qualitative component into a quantitative analysis in order to answer the ‘why’ or ‘how’ questions arising from observed findings. This could be done by reviewing program records, examining implementation processes or interviewing key stakeholders to explore plausible reasons for quantitative results. In this thesis, the mixed-methods approach included quantitative analysis of population- and facility-based surveys to examine malaria diagnostic test use, adherence and integration into clinical practice in multiple countries along with qualitative methods to better understand reasons for observed differences identified in quantitative studies.

Conceptual framework

The conceptual framework chosen for this thesis modified the standard monitoring and evaluation (M&E) logical framework for health system performance by incorporating a bottleneck analysis that explores implementation challenges in intermediate stages of health service delivery. A common monitoring and evaluation framework has been promoted and used by numerous governments and organizations to monitor health system performance [120]. This framework documents how inputs to the system (e.g. resources, infrastructure) are reflected in outputs (e.g. services delivered) and then outcomes and impact in the target population. Yet there are also numerous underlying factors that could hinder performance at each stage that may be best understood using bottleneck analyses. In 1978, Tanahashi developed a bottleneck analysis to comprehensively evaluate health service coverage [121] through five important steps: service availability, accessibility, acceptability, contact and effectiveness. This model has been modified over the past few decades [122-123]. One recent adaptation, known as the Implementation Pathway model, includes three intermediate stages [124]:

- **Access** may include financial, geographic or cultural bottlenecks
- **Facility readiness** may include available guidelines, staff, training, supplies, supervision, referral systems or other facility or health system bottlenecks
- **Clinical practice** may include provider knowledge, perceptions, client demands, motivation or other bottlenecks during the clinical encounter that could impede the delivery of the intervention as intended by guidelines or with sufficient quality for effective care.

Figure 1 depicts how doctoral studies in this thesis relate to this conceptual framework. **Study I** reported the outcome of testing rates among the target population of febrile children under five years across multiple countries, and examined *Access Bottlenecks* in test uptake. **Study II** evaluated the effect of diagnostic testing on treatment decisions among this target population, and used case studies to better understand reasons for varying country results across a range of potential bottlenecks (*Access, Facility Readiness, Clinical Practice*). **Studies III-IV** used both quantitative and qualitative methods to further examine *Facility Readiness* and *Clinical Practice* bottlenecks that could potentially hinder effective use of malaria diagnosis to improve pediatric fever management in Uganda and Malawi.

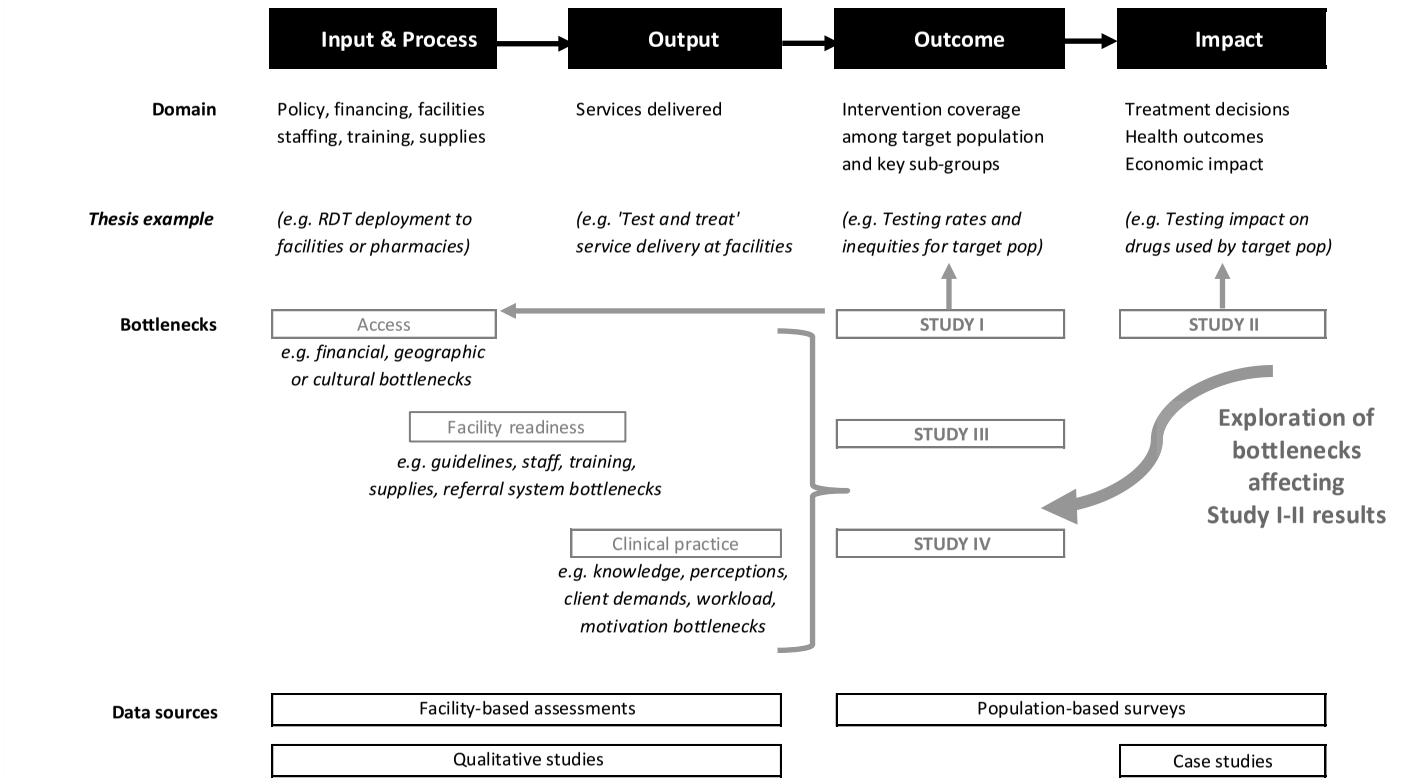

Figure 1. Conceptual framework for doctoral thesis

Aim

The aim of the doctoral project was to assess malaria diagnostic test use, adherence and integration into clinical practice for improved pediatric fever management in multiple sub-Saharan African countries as outlined in the conceptual framework.

The specific objective of each doctoral paper was:

- To assess malaria diagnostic testing rates for pediatric fevers and its determinants at the population level across multiple sub-Saharan African countries (Study I)

- To evaluate the effect of malaria diagnostic testing on pediatric fever treatment at the population level across multiple sub-Saharan African countries and to explain varying country results (Study II)

- To explore health worker and caregiver readiness to use malaria diagnostic tests for improved pediatric fever management in the low transmission setting of Mbarara District, Uganda (Study III)

- To analyze the quality of integrated pediatric fever management in outpatient consultations in Malawi health facilities including the effect of RDT results on antibiotic over-treatment (Study IV)

Methods

This doctoral project employed a mixed-methods approach. Quantitative methods examined malaria diagnostic test use, adherence and integration into clinical practice for pediatric fever management using population- and facility-based surveys in multiple sub-Saharan African countries (Studies I, II, IV). Qualitative methods were employed to better understand reasons for observed findings from quantitative studies (Studies II-III). Table 1 summarizes methods used in doctoral papers and the sections below explain the choice of methodology and their advantages for these analyses.

Mixed-effects models

Studies I-II used mixed-effects models in order to account for correlated data derived from the two-stage cluster sampling strategy in DHS and MIS. Mixed-effects models include both fixed and random effects that essentially provide two sets of parameters to summarize the average treatment effect and the variation in this effect across different levels or groupings [125]. Fixed effects are variables with specified levels and the research interest is to make inferences across only those levels and to potentially generalize results to other studies analyzing those same levels. Random effects, in contrast, are variables with specified levels that are considered a random sample of all possible levels of that variable, which allows for variation to be taken into account around those levels. The research interest is to understand the effect of *other* variables across these levels. In Studies I-II, all variables were included as fixed effects in order to make inferences about their effect on the outcome (e.g. maternal education, household wealth). Primary sampling units (PSU) were included as random effects given the two-stage cluster sample design that resulted in clustering of observations within PSUs, and such correlated data needs to be taken into account in the regression model. Indeed, PSUs were randomly selected in the DHS/MIS sampling strategy from the set of all possible PSUs in the country. Moreover, fixed versus random effects applies to single variables but the relationship between variables also needs to be considered in regression models, which is known as nested or crossed effects. Nested means observations at one level occur only inside a given unit of another variable, which was the case in Studies I-II. Observations for all variables were nested within PSUs, and for the meta-analysis of country datasets, PSUs were nested within countries.

Table 1. *Methods overview*

Study	Design	Data source	Sample size	Outcomes and predictors	Methods
I	Meta-analysis of national cross-sectional population-based surveys	DHS and MIS in 13 countries in 2009-2012	27,916 febrile children under five years in 13 countries (2009-2012)	*Outcome(s):* Malaria diagnostic test uptake *Main predictor(s):* Malaria risk and source of care	Meta-analysis with mixed-effects logistic regression models
II	Mixed-methods: (quantitative) national cross-sectional population-based surveys; (qualitative) multiple case studies	DHS in 12 countries in 2010-2012; 6 country case studies with expert consultations and document reviews	16,323 febrile children under five years and taken to care in 12 countries (2010-2012); 6 country case studies	*Outcome(s):* ACT use, any anti-malarial use and any antibiotic use *Main predictor(s):* Malaria diagnostic test uptake	Mixed-effects logistic regression models; Multiple case study design leading to a cross-case synthesis
III	Qualitative	In-depth interviews and FGDs in Mbarara District, Uganda	20 health worker interviews; 7 caregiver focus group discussions		Content analysis
IV	Data mining using classification tree analysis of a national facility census	Malawi SPA 2013-2014	977 audited facilities; 2,950 sick child client observations	*Outcome(s):* Antibiotic over-treatment *Main predictor(s):* RDT results and RDT conducted	Classification trees using model-based recursive partitioning

Meta-analysis

Meta-analysis is a statistical technique for combining the effect of individual studies compiled through a systematic review of all relevant research [126]. A primary advantage of meta-analyses is the increased sample size derived from combining studies in order to improve power to detect rare outcomes or conduct important sub-groups analyses. Meta-analyses employ mixed-effects models described above in order to estimate a combined effect size and its variation across individual studies. Study I could be considered a meta-analysis of 13 individual country datasets from DHS and MIS, although meta-analysis is traditionally associated with combined results from individual research studies. These datasets were combined in a meta-analytical approach using mixed-effects models with country identifiers included as random effects. This technique greatly increased the sample size in Study I, and importantly, allowed for detection of outcome differences across malaria transmission areas, which would not have been possible using one country dataset given limited malaria risk diversity within countries.

Classification trees

Data mining includes a series of tasks to discover relationships and patterns in large datasets and to use this information to build predictive models [127]. These tasks generally include summarization, classification, clustering, association and trend analysis, which may be used together or separately in order to understand complex relationships among variables in relation to an outcome when these associations are not well-understood in advance.

Classification and regression trees (CART) is a common method used in data mining in order to generate decision rules for predicting an outcome using a set of 'if-then' algorithms [128]. Study IV employed classification trees to analyze the binary outcome of antibiotic over-treatment. There are several advantages to using classification trees over traditional logistic regression methods. First, the latter assumes that the influence of a predictor on an outcome is uniform unless interactions are included in the model, which is unrealistic in real-life contexts and complicates results interpretation. Classification trees in contrast automatically detect statistical interactions involving multiple variables and use decision rules to determine the relative importance among different variables on an outcome and their interrelationships. This also helps overcome the issue of incorporating many predictor variables in the same model. Second, classification trees are non-parametric models that fit outcomes that are not normally distributed and variable transformations are not required for inclusion in the algorithm. Third, classification trees and their resulting decision rules are more easily interpreted by policymakers and may better reflect the complex nature of decision-making that occurs, for example, in clinical encounters.

Classification trees, however, have been found to be unstable and may be affected by small changes in the dataset. Newer techniques, or ensemble methods, have been developed to generate multiple trees by repeatedly sampling parts of the dataset and assessing the combined performance of individual trees to improve predictive accuracy of the final algorithm [129]. In recent years, there has also been growing interest in incorporating parametric models into tree-based algorithms particularly because trees often become large and difficult to interpret using other methods even after the pruning stage [130]. Model-based recursive partitioning, as used in Study IV, embeds recursive partitioning into statistical model estimation and variable selection in order to produce segmented parametric models associated with each terminal node [131]. The basic steps of the algorithm include fitting a parametric model to the full dataset, assessing parameter instability over the set of partitioning variables, computing split points starting with partitioning variables causing greatest instability and repeating the procedure for each terminal node. Some advantages of this method include the ability to model non-linear relationships, automatic detection of interactions among variables, clear results visualization, and straightforward interpretation of well-known parametric models and their associated coefficients.

Case studies

Case studies is a common qualitative research method that seeks to specifically describe or explain a 'case' [132]. This method generally answers 'why' or 'how' research questions by gaining an in-depth understanding of a certain event, person or process. Case studies use a flexible methodology that includes specifying research questions, determining analytic strategies, identifying data needs, conducting literature reviews and/or interviews and collecting any other information needed to inform the case study. Data collection and analysis occur simultaneously in order to continually review data and identify new information needs to further develop the case study. In Study II, a multiple case study design was used to understand non-intuitive varying country results from quantitative analyses and to compare results to develop a cross-case synthesis. This approach drew on published literature, program documents and expert consultations to inform case studies.

Content analysis

Study III used a content analysis approach to analyze interview and FGD transcripts. Content analysis is one qualitative method for analyzing textual information such as transcripts, media materials or other documents [133]. This approach focuses on language characteristics, textual content and its broader meanings. Hsieh and Shannon (2005) define content analysis as a research method for the subjective interpretation of the content of text data through the systematic classification process of coding and identifying themes or patterns [134]. To this end, content analysis starts with immersion

in the textual materials to understand the full dataset. This is followed by condensing textual content or phrases into meaning units that reflect key ideas or concepts based on a line-by-line reading of the full dataset. These meaning units inform initial coding schemes that are sorted and linked into categories and subsequently into clusters or themes to describe response patterns. It is often an iterative process to develop final codes and themes.

Study settings

This thesis included analyses of datasets from multiple countries (I-II) along with qualitative and quantitative studies in Uganda (III) and Malawi (IV). Table 2 and Figure 2 highlight the countries included in Studies I-II:

Table 2. *(Studies I-II) List of countries*

Study	Country	Survey Type	Year	N febrile under-fives
I	Angola	MIS	2011	7,782
	Burkina Faso	DHS	2010-2011	14,001
	Burundi	DHS	2010-2011	7,418
	Lesotho	DHS	2009-2010	3,348
	Liberia	MIS	2011	2,876
	Madagascar	MIS	2011	6,377
	Malawi	DHS	2010	18,013
	Nigeria	MIS	2010	5,519
	Rwanda	DHS	2010-2011	8,605
	Senegal	DHS	2010-2011	10,893
	Tanzania	AIS/MIS	2011-2012	8,216
	Uganda	DHS	2011	7,535
	Zimbabwe	DHS	2010-2011	5,208
II	Benin *	DHS	2011-2012	12,497
	Burkina Faso	DHS	2010-2011	14,001
	Burundi *	DHS	2010-2011	7,418
	Cote d'Ivoire	DHS	2011-2012	6,862
	Gabon	DHS	2012	4,848
	Guinea	DHS	2012	6,448
	Malawi *	DHS	2010	18,013
	Mozambique *	DHS	2011	10,835
	Rwanda *	DHS	2010-2011	8,605
	Senegal	DHS	2010-2011	10.893
	Uganda *	DHS	2011	7,535
	Zimbabwe	DHS	2010-2011	5,208

** Countries selected for case studies to better understand quantitative results*

Figure 2. (Studies I-II) Map of countries

Uganda (Mbarara District)

Uganda is a low-income country located in East Africa that borders Kenya, Democratic Republic of the Congo, Sudan, Rwanda and Tanzania (Figure 2). It has a total population of approximately 35 million people with about half under the age of 15 years old in 2014 [135]. Uganda has experienced considerable progress in key child health indicators over the past two decades. The under-five mortality rate declined from 187 to 55 deaths per 1,000 live births between 1990 and 2015 [136]. The leading causes of child deaths outside the neonatal period were pneumonia (16%), diarrhea (8%), malaria (7%), injuries (7%), HIV/AIDS (6%), other (23%), and nearly half are attributed to under-nutrition. More than one-third (35%) of child deaths occur during the neonatal period, and important causes of neonatal deaths are preterm birth (10% of all under-five deaths), asphyxia (10%) and sepsis (7%).

Study III was conducted in Mbarara District, which is located 270 kilometers southwest of Kampala (Figure 3). The district is home to nearly 500,000 people with half the population less than 18 years old. Mbarara has grown rapidly in recent years given its central location in the region and its importance as a transportation hub connecting to Rwanda, Burundi, Tanza-

nia and the Democratic Republic of Congo. Nevertheless, the district remains a largely rural farming area based mainly on subsistence agriculture.

The District has 58 health facilities that include 49 and 9 government- or private-run facilities at different levels with one large hospital in Mbarara town [135]. The first level of the Ugandan health system (Health Center I, or HC-I) includes community-based services delivered by village health teams. The next level includes Health Center (HC)-II facilities that provide outpatient services, and are generally led by an enrolled or registered nurse trained to manage common diseases and to provide family planning and antenatal care services. HC-III facilities are generally led by a clinical officer, and are equipped with an outpatient clinic, maternity ward and may have functional laboratory services for malaria diagnosis. HC-IV provide more advanced services such as surgery and blood transfusions in addition to other essential services. Private drug shops are also an important means to obtain medicines for community members and are often the first source of care visited for common childhood illnesses in rural areas [137].

Malaria is endemic in most of the country with unstable or epidemic-prone transmission areas in the south and west highlands, or along the eastern border with Kenya or northeastern border with South Sudan. In Mbarara District, transmission peaks in March-May and September-December. Recent research shows substantial declines in malaria transmission in this district [138], and a recent survey found low malaria prevalence (4%) in young children in the Southwestern region that includes Mbarara District [139].

IMCI guidelines were last updated in 2012 but there has been no recent IMCI training in the district according to the District Health Educator. At the same time, nationwide RDT deployment was initiated in December 2012 and was accompanied by basic RDT training and integrated malaria management that targeted all health workers including the private sector. WHO-recommended Astel™ or CareStart™ for the detection of histidine-rich protein 2 (HRP2) from *Plasmodium falciparum* are the malaria RDTs mainly used in Uganda [54].

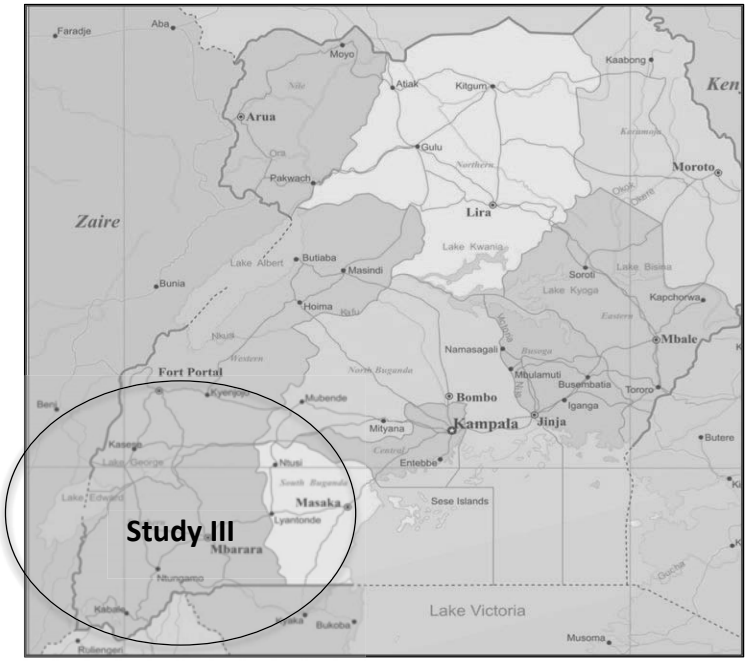

Figure 3. (Study III) Map of Uganda

Malawi

Malawi is a low-income country located in South Central Africa that borders Tanzania, Zambia and Mozambique (Figure 4). The total population was estimated at nearly 17 million people with about half under the age of 15 years old in 2014 [140]. Approximately 85% of people live in rural areas with incomes from subsistence farming. Malaria is highly endemic in most of the country with higher transmission in lowland areas of the lower Shire Valley and near Lake Malawi [141]. The recent Malawi Malaria Indicator Survey in 2014 found 33% malaria prevalence among children 6 months to five years, which represents a decline from 43% prevalence found in 2010 [142].

Malawi's health system is primarily comprised of government-run facilities and publicly supported facilities run by the Christian Health Association of Malawi (CHAM) [143]. Unlike Uganda, there is a limited role of private drug sellers in the treatment of common childhood illnesses even in rural areas. The Malawi health system contains three main tiers: regional hospitals, district hospitals and health centers. The primary tier is the health center, which provides essential services including family planning, antenatal care and other outpatient care. The secondary tier is the district hospital, which are referral facilities that also provide in-patient care, laboratory diag-

nostics and maternity care. The tertiary level is the central or regional hospital, which are teaching and research centers that provide specialized medical care.

IMCI guidelines were last updated in 2013 to include test-based malaria case management in the IMCI fever algorithm. Nationwide RDT deployment was initiated in July 2011 and was accompanied by training in RDT safety and use along with basic information on managing RDT-negative cases [144]. This training targeted all service providers in government and CHAM facilities. Malawi mainly uses SD Bioline AG *Pf*™ or Paracheck Ag *Pf*™ for the detection of histidine-rich protein 2 (HRP2) from *Plasmodium falciparum*.

Figure 4. (Study IV) Map of Malawi

Data sources

Demographic and Health Surveys

Demographic and Health Surveys (DHS) are cross-sectional cluster surveys based on a nationally representative sample of households that are comparably implemented every three to five years in low- and middle-income countries in order to routinely monitor key demographic and health issues relevant to these countries [118]. This survey program is primarily funded by USAID with technical support from The DHS Program. Since its inception in 1984, about 300 surveys have been conducted in over 90 countries.

DHS collects a wide range of information on health and demographic issues, including key indicators to measure fertility rates, child mortality, maternal and child health status, among others. The target population is therefore defined as women of reproductive age (15-49 years) and their young children (0-5 years) living in residential households in a country. In 2010, this survey program was modified to include additional questions on malaria diagnostic test uptake for children less than five years with reported fever in the two weeks prior to the interview.

DHS is based on a probability sample that aims to cover the full target population [145]. The sample is designed to be representative at the national level and among survey domains that generally include first administrative units (e.g. provinces or regions) and urban/rural residence. The survey design is therefore based on a two-stage cluster sample that typically includes explicit stratification at the first sampling stage by urban/rural residence within each region. In the first stage, a stratified sample of enumeration areas is selected with probability proportional to size using a pre-existing sampling frame based on a recent population census. The second stage randomly selects households within each enumeration area based on a complete household listing. In each household, every woman aged 15-49 years is identified and interviewed. Each woman responds to a questionnaire about all of her children under five years old. The total sample size depends on the desired precision at the domain level and number of domains. This generally translates into at least 800 or 1,000 completed interviews among women living in high or low fertility countries, respectively, in order to generate key indicators (e.g. total fertility or child mortality rates) at the national level and among survey domains.

Surveys are implemented by National Statistical Offices and The DHS Program. Data collection is carried out by experienced personnel including team supervisors, data editors and interviewers who are typically trained over a one-month period. This training includes interview techniques, field procedures and coordination, questionnaire reviews, and data quality controls. Questionnaires are pre-tested in a few clusters over a one-week period using all local languages to ensure translation is understood by respondents.

Malaria Indicator Surveys

Malaria Indicator Surveys (MIS) were developed in 2006 by the Roll Back Malaria Monitoring and Evaluation Reference Group (MERG) and is primarily funded by USAID with technical support from The DHS Program for those surveys publicly available for secondary analyses purposes [146]. Since this time, approximately 30 MIS have been implemented in various sub-Saharan African countries and mostly by The DHS Program.

MIS is designed to measure Roll Back Malaria (RBM) core population-based malaria indicators measured through DHS, and additionally includes data collection on malaria knowledge or indoor residual spraying (in addition to standard DHS/MIS questions on malaria diagnostic test use, bed nets, intermittent preventive treatment or childhood curative treatment). MIS is conducted during the peak malaria transmission season as opposed to DHS conducted in the dry season.

The target population is defined similarly to DHS but is limited to populations living in areas with malaria risk (either endemic or epidemic-prone areas). This target population often includes entire sub-Saharan Africa countries. In those sub-Saharan African countries that contain areas without malaria transmission, these regions could either be excluded from the sampling frame or considered a survey domain. MIS is designed to be similar to DHS in terms of employing a stratified two-stage cluster sampling design. The sample size similarly depends on the desired precision for key indicators at the domain level and the number of domains. However, MIS generally has a smaller sample size than DHS because it typically does not collect certain indicators that require larger samples, such as maternal or child mortality.

Service Provision Assessments

Service Provision Assessments (SPA) are cross-sectional cluster surveys based on a nationally representative sample of health facilities in a country, including both public and private sector sources [147]. SPA is primarily funded by USAID with technical support from The DHS Program. Since its inception in 2000, approximately 20 surveys have been conducted worldwide. The survey measures health service readiness to deliver quality care to patients and is a comprehensive assessment of a wide range of facility-based services that includes facility audits, health worker interviews, observed consultations and patient exit interviews.

The Malawi SPA 2013-2014 was conducted in June 2013-February 2014 and was designed as a census of all formal health facilities in the country, including both public and private sources [148]. At each facility, clients were systematically selected for observation based on the expected patient load for outpatient sick child curative services on the interview date in order to yield no more than 15 observations per facility and 5 observations per provider. Clients were eligible to participate if they were less than five years

old and presented with an illness complaint rather than an exclusive injury or non-disease condition. Client observations aim to assess clinical practices according to Malawi IMCI guidelines [149].

For health worker interviews, the aim was to interview an average of eight providers in each facility that provided services measured in the assessment. In facilities with fewer than eight providers, all providers present on the interview date were interviewed. In facilities with more than eight providers, efforts were made to include all providers whose consultations were observed. If additional interviews were needed, remaining providers were randomly selected until eight interviews in total were obtained.

In 2012, SPA was updated to improve its malaria diagnosis data collection. This includes questions on RDT availability through laboratory and service site audits; training in malaria diagnosis through health worker interviews; and RDT use and adherence through observed sick child consultations. This new data collection was added to established questions on availability of IMCI charts and supportive tools (e.g. timers with second hands) through service site audits; training in IMCI through health worker interviews; and IMCI assessments during sick child consultations. In addition, the Malawi SPA included a re-examination component for the IMCI pneumonia algorithm to assess adherence to that specific IMCI protocol.

However, it is not possible to analyze overall IMCI adherence using this dataset since clinical findings from the observed consultation are not recorded; the observation does not record all IMCI assessments conducted; nor is there a 'gold standard' IMCI re-examination to assess overall correct management. Nevertheless, it is possible to understand whether certain 'tracer' IMCI assessments were conducted for sick children (e.g. checked for neck stiffness, counted breathing rates, checked skin turgor for dehydration). Malawi SPA also contains a limited re-examination protocol specifically for the IMCI pneumonia algorithm, and health workers report RDT results if the test result was available by the initial consultation time. This allows for an assessment of (in)correct treatment of RDT-confirmed malaria, IMCI-classified pneumonia and clinical diarrhea during observed consultations.

Malawi SPA data collection was carried out by 86 health providers from the Ministry of Health (nurses, nurse midwives and clinicians). Training took place over a three-week period that included questionnaire reviews, interview techniques, field practice and procedures, tablet data entry, and mock interviews. Additional training was provided in the protocol for observed consultations. Pre-testing of interview tools took place over a three-week period in Lilongwe to test the flow of questions and computer programs for data entry [148].

Study designs

Study I

Study I was a meta-analysis of 13 DHS and MIS to examine extent and determinants of malaria diagnostic test use for pediatric fevers. The main outcome was malaria diagnostic test use for children less than five years old with reported fever in the previous two weeks. Table 3 defines the main predictors (source of care and malaria endemicity) and other variables.

Table 3. *Study I variables*

Variable	Description and categories
Source of care	hospital, non-hospital formal medical, pharmacy, CHW, other
Malaria risk	Malaria Atlas Project estimates of malaria-free, unstable, low (P*f*PR<5%), moderate (5-40% PfPR), high (>40% PfPR) stable endemic transmission.
Child's age	0-5, 6-11, 12-23, 24-35, 36-47, 48-59 months
Child's sex	male, female
Maternal age	15-24, 25-29, 30-34, 35-39, 40-49 years
Maternal education	none, primary or at least secondary education attendance
Household wealth	poorest, second, middle, fourth, least poor household quintile
Household size	1-4, 5-8, 9-12, 13 or more household members
Residence	urban, rural

Mixed-effects logistic regression models were used to quantify the influence of all variables on the binary outcome of malaria diagnostic test uptake in pooled and individual country datasets. PSUs were nested within country identifiers and normal distribution of random effects was assumed. All variables were included as categorical fixed effects nested within PSUs. The level of statistical significance was set to 0.05. National point estimates were tabulated using sample weights to account for unequal probabilities of selection. Standard error estimates accounted for data clustering. Stata 12 (STATA Corp, College Station, TX) was used for analyses.

Study II

Study II used a mixed-methods approach to analyze the effect of diagnostic testing on pediatric fever treatment at the population level across 12 DHS countries and among key sub-national groups including by malaria risk, illness symptoms, transmission season, source of care and child's age. Qualitative methods were used to plausibly explain varying results across countries and sub-national groups. The main binary outcomes were any antimalarial use, ACT use and any antibiotic use. Table 4 defines the main predictor (malaria diagnostic test use) and other variables in the analysis.

Table 4. *Study II variables*

Variable	Description and categories
Malaria test use	yes, no
Child's age	0-5, 6-11, 12-23, 24-35, 36-47, 48-59 months
Child's sex	male, female
Child's symptoms	fever only, fever with cough, fever with cough & rapid breaths. Proxy for illness severity and multiple symptoms were assumed to reflect more severe cases.
Maternal age	15-24, 25-29, 30-34, 35-39, 40-49 years
Maternal education	None, primary or at least secondary education attendance
Household wealth	poorest, second, middle, fourth or richest.
Household size	1-4, 5-8, 9-12, 13 or more household members
Residence	urban, rural
Source of care	hospital, non-hospital formal medical, pharmacy, CHW, other
Source of care	public, private
Access to care – money as problem	Proxy for attendance at facility stocked with drugs and diagnostics. Money is a problem or not for seeking care for self.
Access to care – distance as problem	Proxy for attendance at facility stocked with both drugs and tests. Distance is a problem or not for seeking care for self
Health card	child health care possession or not. Proxy for attendance at facility stocked with both drugs and diagnostic tests.
Malaria risk	Malaria-free, unstable, low (P*f*PR<5%), moderate (5-40% PfPR), high (>40% PfPR) stable endemic transmission.
Transmission season	peak or off-peak categories were classified by comparing each observation's PSU location and interview date with historical seasonality maps for malaria transmission produced by the Mapping Malaria Risk in Africa (MARA) project.

Mixed-effects logistic regression models separately quantified the influence of diagnostic testing on the binary outcomes: (1) ACT use (2) any antimalarial use (3) any antibiotic use. All variables were included as categorical fixed effects nested within PSUs, and normal distribution of the random effects was assumed. The level of statistical significance was set to 0.05. National point estimates were tabulated using sample weights to account for unequal probabilities of selection. Standard error estimates accounted for data clustering. Stata 12 (STATA Corp, College Station, TX) was used for all analyses.

A multiple case study design was employed to help understand results in Benin, Burundi, Malawi, Mozambique, Rwanda and Uganda that drew on published studies [82,89,94,96,150-151], program records [152] and expert consultations. For expert consultations, seven respondents were purposively selected based on their country program experience and advanced research training to include university researchers, epidemiologists and pediatricians.

Interviews were based on a semi-structured topic guide that focused on the plausibility of results, program explanations and perceived value of findings as additional program evidence. The lead author [EWJ] conducted seven interviews in English via Skype during July-September 2014 (one for each country; two for Benin). Extensive written notes were taken during interviews and transcribed after discussions. Explanation building leading to a cross-case synthesis was the overall analytic strategy [153]. Thematic analysis identified dominant themes within each case [154]. All transcripts were read multiple times to establish preliminary codes in order to generate within-case themes, and to subsequently compare and revise themes across countries. This led to a typology of plausible explanations for quantitative results for the six countries.

Study III

Study III was conducted in Mbarara District Uganda and included 20 in-depth interviews with health workers and 7 focus group discussions with caregivers of children under five years as determined by topical saturation [155]. Data collection was carried out during a three-week period in July 2014. For health workers, in-depth interviews were conducted with one provider from each purposively selected facility (largely government-run HC-II or HC-III facilities). Interviews were conducted in English in a private office using two interview teams each comprised of two people. For caregivers, FGDs were conducted in catchment areas of facilities. Each FGD included 6-12 purposively selected caregivers with children under five years, and were led by an experienced social scientist and accompanied by a note taker.

Interviews were based on a semi-structured topic guide that focused on RDT perceptions and experiences, influences on treatment decisions, and strategies to differentiate fevers. FGDs asked about alternative fever causes, treatment preferences for RDT-negative children and acceptability of withholding anti-malarial medicines. All discussions were audio recorded, transcribed and translated, as well as cleaned or checked for accuracy.

All transcripts were carefully read multiple times by the lead authors [EWJ, FEK] and were separately coded using a content analysis approach [133]. Data were extracted into meaning units that informed an initial coding scheme. Preliminary codes were refined by the lead author [EWJ] and applied back to transcripts. These codes were discussed and reviewed by the lead authors [EWJ, FEK] and grouped into mutually agreed themes to describe response patterns. These themes were further refined into a set of final categories that reflected the study objectives and notable ‘clusters of influence’ according to the Diffusion of Innovations theory (see Discussion). Open Code 4.01 (University of Umeå, Sweden) was used for analyses [156].

Study IV

Study IV assessed integrated pediatric fever management using RDT and IMCI during outpatient consultations in Malawi health facilities in 2013-2104 including other presenting complaints, completed assessments, diagnoses/classifications and (in)correct treatment for RDT-confirmed malaria, IMCI-classified pneumonia and clinical diarrhea. Model-based recursive partitioning was used to analyze the effect of RDT results and its interrelationship with other variables on antibiotic over-treatment. Children aged 2 months to 5 years with a fever complaint were included if it was a first time visit for the illness and consent was obtained for participation in both the observation and exit interview. Table 5(a)-(d) defines key variables.

Table 5(a). *(Study IV) Main complaints*

Variable	Description and categories
Fever Cough or difficult breathing (CDB) Watery or frequent stools Danger signs: Lethargy or excessive sleepiness Vomits everything Convulsions Inability to drink, eat or breastfeed	During the exit interview, the caregiver is separately asked about each of the main symptoms or danger signs listed here.
Ear problem Eye problem Skin problem Other issue	During the exit interview, the caregiver is subsequently asked about other reasons for bringing the child to this facility today and the response categories are listed here.

Table 5(b). *(Study IV) Completed assessments*

Variable	Description and categories
Asked about or mentioned [insert complaint] Took the child's temperature or felt body for hotness Counter respiration (breaths) for 60 seconds Checked skin turgor for dehydration Checked pallor by looking at palms Looked into the child's mouth Checked for neck stiffness Undressed the child (up to shoulders/down to ankles)	During the consultation, the interviewer silently records the performance of physical examinations. Those listed here are general assessments for presenting complaints of fever, cough or difficult breathing or diarrhea.

Table 5(c). *(Study IV) Classifications or diagnoses*

Variable	Description and categories
RDT-confirmed malaria	After the consultation, the provider is asked if a malaria RDT was conducted anywhere in the facility prior to coming into the consultation room that day and if so, the provider is asked to report the test result if seen.
IMCI-classified pneumonia	During the exit interview, there is a limited re-examination that includes a 60-second respiratory rate count if cough or difficult breathing is present. IMCI-pneumonia classification is defined as reported cough or difficult breathing and a respiratory rate of 50 breaths or more per minute (2 up to 12 months) or 40 breaths or more per minute (12 months up to 5 years).

Table 5(d). *(Study IV) Treatment prescriptions*

Variable	Description and categories
Anti-malarial prescriptions	After the consultation, the provider is asked to report treatments prescribed to the client and a hierarchical coding was used to assign the more appropriate prescription to the observation. First-line anti-malarial prescription is defined as artemether/artesunate (oral, injection or suppository) or ACT/AL (oral). Second-line is quinine (oral or injection), amodiaquine (oral), fansidar (oral) or other anti-malarial (oral or injection). Anti-malarial over-treatment is any anti-malarial prescription for an RDT-negative result.
Antibiotic prescriptions	After the consultation, the provider is asked to report treatments prescribed to the client and a hierarchical coding was used to assign the more appropriate prescription to the observation. First-line antibiotic prescription is defined as benzyl penicillin injection or amoxicillin (capsule or syrup). Second-line is cotrimoxazole (syrup or tablet) or other antibiotic (injection, syrup or capsule). Antibiotic over-treatment is the main outcome and is defined in the next section.

The main outcome is antibiotic over-treatment or any antibiotic prescription 'without antibiotic need', which is defined in this paper as IMCI-pneumonia negative classification based on re-examination in addition to excluding the following self-reported diagnoses recorded in the consultation: sepsis, acute ear infection, mastoiditis, dysentery, abscess or severe malnutrition. Table 6 defines the main predictor and 38 input variables at facility-, provider, and patient-levels included in the model-based recursive partitioning analysis.

Table 6. *(Study IV) Input variables*

Input	Description	Source
MAIN		
RDT done	RDT done prior to consultation (yes or no)	Provider interview
RDT result	RDT result (positive or negative)	Provider interview
PATIENT		
Caregiver sex	Gender (male or female)	Exit interview
Child sex	Gender (male or female)	Observation
Caregiver age	Age (numeric: 11 to 74 years)	Exit interview
Diarrhea	Diarrhea complaint (yes or no)	Exit interview
CDB	Cough or difficult breathing (yes or no)	Exit interview
Danger sign	Any danger sign complaint (yes or no)	Exit interview
Temperature	Temperature (numeric: 35 to 40.8 degrees)	Re-examination
Illness duration	Illness duration (numeric: 0 to 60 days)	Exit interview
Nearest facility	Nearest facility to home (yes or no)	Exit interview
Clinical examination	Counted breaths for 60 second (yes or no)	Observation
Consultation length	Derived from consultation start and end times (numeric: 0 to 307 minutes)	Observation
Consultation start hour	Derived from consultation start time (numeric: 7:00 to 17:00)	Observation
Wait time	Reported wait from arrival to consultation (numeric: 0 to 600 minutes)	Exit interview
PROVIDER		
Provider sex	Gender (male or female)	Observation
Job qualification	Doctor/clinical officer/technician or medical assistant or nurse/midwife/HSA	Observation
Supervisor status	Supervisor or in-charge (yes or no)	Provider interview
Experience	Year received current job qualification (numeric: 1950 to 2014)	Provider interview
Work hours	Average work hours per week (numeric: 1 to 90 hours per week)	Provider interview
Training	RDT training (ever received or not)	Provider interview
Training	IMCI training (ever received or not)	Provider interview
Supervision	Provider supervision (ever received or not)	Provider interview
Supervision quality	Discussed work issues during most recent supervisory visit (yes or no)	Provider interview
FACILITY		
Malaria risk	P*f*PR in 2-10 year olds (numeric: 0.0 to 0.4)	MAP
Transmission season	Transmission season (peak or off-peak)	MARA
Location	Residence (urban or rural)	Facility audit
Region	Region (central or north or south)	Facility audit
Facility type	Hospital (central, district, rural, other) or other	Facility audit

	facility (center, post, dispensary, clinic)	
Managing authority	Government or CHAM/other	Facility audit
Management	Routine management meetings (yes or no)	Facility audit
Staffing	Total staff doctors (numeric: 0 to 119)	Facility audit
External supervision	External supervisory visit to facility (ever received or not)	Facility audit
User fees	Routine general user fees (yes or no)	Facility audit
Medicine stocks	Antibiotic (any type available or not)	Facility audit
Medicine stocks	Anti-malarial (any type available or not)	Facility audit
Supply stocks	RDT (observed valid or not in either service area or laboratory)	Facility audit
Supply stocks	Facility or staff timer (available or not)	Facility audit
Guidelines	RDT job aid or guidelines (available or not)	Facility audit
Guidelines	IMCI guidelines (available or not)	Facility audit

Frequencies and cross-tabulations were calculated using sample weights to account for the unequal probabilities of selection due to differing client volumes at facilities. Standard error estimation accounted for clustering of client observations within facilities. The level of statistical significance was set to 0.05. Stata 13.1 (Stata Corp., College Station TX) was used for analyses.

A model-based recursive partitioning approach [131] was used to initially fit a mixed-effects logistic regression model to estimate the relationship between the RDT result (or RDT conducted) and the binary outcome of antibiotic over-treatment with observations nested within facility identifiers. The influence of other input variables was learned through recursive partitioning that allowed for detection of sub-group interactions and estimation of random effects parameters [157]. Parameter instability over the set of 38 partitioning variables was repeatedly assessed using a Bonferroni-corrected significance level of 0.05. The minimal node size was set to 20 observations. This approach yields a tree fitted to models associated with each terminal node along with estimated odds ratios for significant classifiers conditional on including the main predictor in the model. R version 3.2.2 was used for this analysis [158] including the R "partykit" package [159].

Ethical considerations

Studies I, II, IV were based on secondary analysis of public datasets. Ethical approval for collection of these data was obtained by The DHS Program from the Department of Health and Human Service Institutional Review Board (IRB) and the host country IRB. IRB approval includes authorization to distribute all unrestricted survey data files for legitimate research purposes on the condition of receiving a full research project description. A research project description was submitted for each thesis study using these datasets. These applications were approved by The DHS Program and datasets were subsequently released for use in these analyses.

Study III ethical approval was obtained from the WHO Ethical Review Committee, the Makerere University School of Public Health IRB [IRB00011353] and the Uganda National Council for Science and Technology [HS 1385]. Informed consent to participate in the studies was obtained from all respondents. Main ethical considerations in this thesis relate to qualitative components that include respondent discomfort and confidentiality issues as described below.

Respondent discomfort

In Study III there was concern about health worker discomfort in discussing potential non-adherence to clinical guidelines. Prior to involvement, participants were verbally informed about the research purpose, protocols, study team, and confidentiality arrangements. Interviews were conducted in a private office within facilities and interviewers reiterated their status as researchers unaffiliated with the government or international donors. Importantly, topic guides were not designed to explicitly ask about non-compliance practices although the aim was to gain insights into reasons for such practices. To this end, health workers were asked: "If there were certain situations where a negative RDT result could be wrong?" or "If there were any downsides to giving malaria treatment to a RDT negative result?" or "If they experienced any challenges in managing a RDT negative patient?". Many respondents chose to discuss their own non-compliance practices although questions were not specifically designed to elicit such a response.

In Study II, there were similar concerns about the discomfort of experts consulted to discuss potentially poor performance of programs with which they were professionally involved. Prior to involvement, respondents were informed both verbally and through the initial email contact about the re-

search purpose and their role in helping to understand country programs in order to explain non-intuitive quantitative findings. Interviews were not audio recorded but extensive written notes were taken, which seemed more appropriate given the professional nature of the interview and the overall research interest in simply understanding general country themes (e.g. status of RDT deployment, health system structure) rather than to document specific language used by the respondent. Importantly, topic guides were designed to ask factual questions about the country situation rather than to elicit program opinions. Respondents were asked to describe RDT deployment status, stock outs, malaria epidemiology, health system structure or general perceptions of case management practices. In addition, respondents were invited to review country case studies and the full manuscript if desired. They were also explicitly asked to approve any non-attributed quotes in the manuscript.

Confidentiality

Another ethical consideration is breach of confidentiality. All participants in each study were verbally informed about confidentiality arrangements and how any audio recordings would be handled. All personal information identifying participants was omitted from transcripts and non-attributed quotes used in the manuscripts identified respondents vaguely as 'health worker' or "FGD participant" or "case study respondent" to further maintain their confidentiality. In Study III, FGD participants were specifically asked not to disclose group discussions or report other participant responses that would breach confidentiality. In Study II, confidentiality issues further arose due to snowballing sampling techniques. An initial respondent identified and introduced researchers to two additional country experts. This sampling technique introduces ethical concerns regarding 'gatekeeper' knowledge about the identities of other respondents and potential confidentiality breaches. We explicitly contacted the initial respondent by email and asked him/her to maintain the confidentiality of all other known respondents.

Results

Studies I-II analyzed extent, determinants and changing treatment patterns associated with malaria diagnostic testing of pediatric fevers at the population. These findings provided a bridge to further examine potential implementation pathway bottlenecks primarily in Studies III-IV but also other studies as well. The first part of this section highlights results from Study I (extent and determinants) and Study II (changing treatment patterns) followed by findings reported according to *Access, Facility Readiness* and *Clinical Practice bottlenecks* found across each paper in this doctoral thesis.

Malaria diagnostic testing of pediatric fevers

Study I examined the outcome of malaria diagnostic testing rates among the target population of febrile children less than five years old in 13 malaria-endemic countries in 2009-2012. Study II evaluated the effect of malaria testing on medicines used by febrile children under five years taken to any care at the population level in 12 malaria-endemic countries.

Extent and determinants

Study I examined extent and determinants of malaria diagnostic test uptake for pediatric fevers, which is summarized in this section. Study I included 105,791 children under five years across 13 countries. 27,916 (26.5%) had reported fever in the two weeks prior to the survey interview, and 4,990 (16.9%) were tested for malaria. Testing rates ranged from the lowest in Burkina Faso (5.3%) in 2010-2011 and Nigeria in 2010 (5.4%) to a highest of 33.3% in Liberia in 2011 followed by Burundi (27.0%) in 2010-2011 and Uganda (25.9%) in 2011 (Table 7).

Table 7. *(Study I) Malaria diagnostic testing rates for pediatric fevers in 13 studied countries in 2009-2012*

Country	Survey	Year	N febrile under-fives	Percent febrile under-fives tested (95% CI)	
Angola	MIS	2011	2,652	25.9	(23.0-28.9)
Burkina Faso	DHS	2010-2011	2,886	5.3	(4.3-6.3)
Burundi	DHS	2010-2011	2,236	27.0	(24.4-29.6)
Lesotho	DHS	2009	577	10.0	(6.7-13.2)
Liberia	MIS	2011	1,610	23.4	(20.1-26.8)
Madagascar	MIS	2011	938	6.2	(4.0-8.5)
Malawi	DHS	2010	6,214	17.4	(15.8-19.1)
Nigeria	MIS	2010	1,956	5.4	(4.1-6.8)
Rwanda	DHS	2010-2011	1,355	21.0	(18.5-23.5)
Senegal	DHS	2010-2011	2,463	9.7	(7.8-11.6)
Tanzania	AIS/MIS	2011-2012	1,675	24.9	(21.2-28.7)
Uganda	DHS	2011	3,042	25.9	(23.2-28.6)
Zimbabwe	DHS	2010-2011	506	7.4	(4.9-9.8)

Table 8 presents the associations between source of care, malaria endemicity on malaria test uptake for pediatric fevers across 13 countries. Study I results indicate that febrile children in high-risk areas were less often tested than those in low-risk areas. Compared to low-risk areas, the odds of testing declined by 49% for febrile children in high-risk areas (OR: 0.51, 95% CI: 0.42-0.62), and by 54% (OR: 0.46, 95% CI: 0.34-0.63) in malaria-free areas. There was a non-significant difference in the odds of testing febrile children in moderate stable transmission areas when compared to low-risk areas (OR: 1.04, 95% CI: 0.86-1.25).

Source of care was consistently and significantly associated with malaria test uptake after controlling for other variables. Compared to hospitals, the odds of testing febrile children decreased by 38% if attending non-hospital sources (OR: 0.62, 95% CI: 0.56-0.69), and by 69% (OR: 0.31, 95% CI: 0.23-0.43) if visiting CHWs. 2). Results also indicate an important socioeconomic dimension to malaria testing with lower odds of uptake among rural children, those living in poorest households, and those born to less educated mothers.

Table 8. *(Study I) Effect of source of care, malaria endemicity and socioeconomic covariates on test uptake*

		AOR	(95% CI)	p-value
Source of care	Hospital	1.00		
	Non-hospital formal medical	0.62	(0.56 – 0.69)	<0.001
	Community health worker	0.31	(0.23 – 0.43)	<0.001
	Pharmacy	0.06	(0.05 – 0.09)	<0.001
	Other	0.10	(0.08 – 0.13)	<0.001
	No care sought	0.05	(0.04 – 0.06)	<0.001
Malaria endemicity	No transmission	0.46	(0.34 – 0.63)	<0.001
	Unstable	1.32	(0.11 – 15.50)	0.823
	Low stable	1.00		
	Moderate stable	1.04	(0.86 – 1.25)	0.697
	High stable	0.51	(0.42 – 0.62)	<0.001
Child's age (in months)	0 - 5	0.72	(0.59 – 0.87)	0.001
	6 - 11	1.00		
	12 - 23	1.24	(1.09 – 1.41)	0.001
	24 - 35	1.27	(1.11 – 1.45)	<0.001
	36 - 47	1.10	(0.95 – 1.26)	0.203
	48 - 59	1.18	(1.02 – 1.37)	0.030
Child's sex	Male	1.00		
	Female	0.98	(0.91 – 1.06)	0.676
Maternal age (in years)	15 - 24	1.00		
	25 - 29	1.01	(0.91 – 1.12)	0.891
	30 - 34	1.06	(0.94 – 1.20)	0.336
	35 - 39	1.06	(0.92 – 1.21)	0.425
	40 - 49	0.99	(0.83 – 1.17)	0.890
Maternal education	No attendance	1.00		
	Primary	1.32	(1.19 – 1.46)	<0.001
	Secondary or higher	1.33	(1.16 – 1.54)	<0.001
Household wealth	Poorest	1.00		
	Second	0.99	(0.87 – 1.13)	0.850
	Middle	1.03	(0.90 – 1.18)	0.670
	Fourth	1.21	(1.06 – 1.40)	0.006
	Least poor	1.63	(1.39 – 1.91)	<0.001
Household members	0 - 4 members	1.00		
	5 - 8 members	0.95	(0.86 – 1.05)	0.307
	9 - 12 members	0.87	(0.76 – 0.99)	0.036
	13 or more members	0.66	(0.54 – 0.80)	<0.001
Residence	Urban	1.00		
	Rural	0.71	(0.62 – 0.82)	<0.001

Changing treatment patterns

Study II examined changing treatment patterns associated with malaria diagnostic testing in 12 countries in 2010-2012, and these results are summarized in this section. 16,323 children under five years had fever in the previous 2 weeks and were taken to any care across 12 countries. In Study II, 5,729 (35.1%) of these children received any anti-malarial drug; 2,873 (17.6%) received ACT; 6,382 (39.1%) received any antibiotic drug; and 3,607 (22.1%) received a diagnostic test according to caregiver reports.

Table 9 presents the association between the main predictor and the three outcomes (ACT use, any anti-malarial use and any antibiotic use) in each of the 12 countries. Study II results indicate significant variability in the effect of diagnostic testing on pediatric fever treatment across countries, and no country reduced ACT use associated with testing as hypothesized.

ACT use

In six countries, tested pediatric fevers had significantly higher ACT use odds compared to untested cases according to caregiver reports (Burundi, Cote d'Ivoire, Gabon, Mozambique, Senegal, Zimbabwe), although Zimbabwe and Cote d'Ivoire results should be interpreted with caution due to few observations and positive outcomes. Burundi and Mozambique were among the countries with highest ACT use odds for tested pediatric fevers compared to untested ones (Burundi OR: 2.78, 95% CI: 1.81-4.27; Mozambique OR: 3.54, 95% CI: 2.33-5.39). In contrast, Rwanda and Uganda had relatively lower odds of ACT use associated with testing (Rwanda OR: 0.88, 95% CI: 0.51-1.51; Uganda OR: 0.84, 95% CI: 0.66-1.06).

Any anti-malarial use

Six countries demonstrated significantly higher anti-malarial use odds associated with reported testing (Burundi, Cote d'Ivoire, Gabon, Malawi, Mozambique, Senegal). There was also variability in results across countries as exemplified by Burundi (OR: 3.71, 95% CI: 2.63-5.25) and Mozambique (OR: 2.79, 95% CI: 1.92-4.05) compared to Rwanda (OR: 0.83, 95% CI: 0.48-1.44) and Uganda (1.24, 95% CI: 0.96-1.61).

Any antibiotic use

Only Rwanda and Uganda had significantly higher antibiotic use odds associated with diagnostic testing (Rwanda OR: 2.95, 95% CI: 1.82-4.79; Uganda OR: 1.37, 95% CI: 1.09-1.72) while Burundi had significantly lower antibiotic use odds for tested pediatric fevers compared to untested cases (OR: 0.53, 95% CI: 0.40-0.72).

Table 9. *(Study II) Effect of diagnostic testing on pediatric fever treatment in 12 studied countries in 2010-2012*

Country	N	Any anti-malarial use			N	ACT use			N	Any antibiotic use		
		COR (95% CI)	**AOR (95% CI)**	**pvalue**		**COR (95% CI)**	**AOR (95% CI)**	**pvalue**		**COR (95% CI)**	**AOR (95% CI)**	**pvalue**
Benin	298	2.61 (1.51-4.51)	1.65 (0.92-2.98)	0.096	109	2.37 (1.20-4.70)	1.96 (0.91-4.19)	0.084	177	1.83 (1.06-3.17)	1.15 (0.64-2.08)	0.636
Burkina Faso	875	2.08 (1.39-3.11)	1.32 (0.84-2.05)	0.225	228	1.64 (0.99-2.71)	1.45 (0.84-2.52)	0.18	803	1.22 (0.82-1.81)	0.89 (0.57-1.40)	0.616
Burundi	371	3.62 (2.64-4.96)	3.71 (2.63-5.25)	<0.001	258	2.62 (1.79-3.83)	2.78 (1.81-4.27)	<0.001	782	0.62 (0.47-0.81)	0.53 (0.40-0.72)	<0.001
Cote d'Ivoire	220	3.29 (2.05-5.25)	1.89 (1.14-3.13)	0.013	32	7.09 (2.45-20.54)	16.83 (1.03-276.13)	0.048	334	1.99 (1.31-3.01)	1.08 (0.68-1.74)	0.737
Gabon	194	2.25 (1.40-3.61)	2.00 (1.16-3.44)	0.013	78	2.74 (1.45-5.16)	2.45 (1.13-5.33)	0.024	436	0.88 (0.58-1.35)	0.84 (0.52-1.35)	0.467
Guinea	412	1.70 (1.08-2.67)	1.28 (0.78-2.11)	0.33	20	4.29 (1.25-14.68)	2.42 (0.43-13.68)	0.319	378	1.76 (1.11-2.78)	1.05 (0.63-1.75)	0.862
Malawi	2384	1.65 (1.40-1.94)	1.34 (1.11-1.61)	0.002	2019	1.26 (1.07-1.48)	1.12 (0.94-1.34)	0.206	1285	1.12 (0.94-1.33)	1.00 (0.82-1.22)	1.000
Mozambique	371	2.85 (2.02-4.02)	2.79 (1.92-4.05)	<0.001	225	3.65 (2.45-5.42)	3.54 (2.33-5.39)	<0.001	107	1.04 (0.67-1.61)	1.01 (0.64-1.59)	0.966
Rwanda	134	0.93 (0.57-1.52)	0.83 (0.48-1.44)	0.506	129	0.96 (0.59-1.56)	0.88 (0.51-1.51)	0.633	322	3.70 (2.38-5.74)	2.95 (1.82-4.79)	<0.001
Senegal	180	1.75 (1.11-2.75)	1.69 (1.04-2.76)	0.036	70	2.54 (1.24-5.19)	2.99 (1.32-6.79)	0.009	547	1.90 (1.27-2.85)	1.50 (0.97-2.31)	0.07
Uganda	1704	1.50 (1.19-1.89)	1.24 (0.96-1.61)	0.097	1158	1.13 (0.92-1.39)	0.84 (0.66-1.06)	0.133	860	1.45 (1.18-1.78)	1.37 (1.09-1.72)	0.007
Zimbabwe	11	13.23 (1.56-112.52)	170.9 (0.30-98480.04)	0.113	6	12.18 (1.94-76.45)	25.55 (1.69-385.68)	0.019	84	0.62 (0.24-1.60)	0.55 (0.20-1.51)	0.244

Implementation pathway bottlenecks

Study I-II results led to new research questions about the mechanisms that could have contributed to quantitative findings at the population level. Main thesis results from all papers are reported below according to *Access, Facility Readiness* and *Clinical Practice* bottlenecks in the conceptual framework.

Access

Access bottlenecks include geographic, financial or cultural issues that may hinder accessing malaria diagnostic services. A major *Access* bottleneck identified in this thesis was care-seeking behavior. As previously described, Study I found that seeking care from lower-level facilities or informal sources greatly reduced the likelihood of testing at the outset of new guidelines. This *Access* bottleneck was crudely quantified in Study I by estimating the total number of pediatric fevers attending and tested at different sources of care in 2010 across 13 studied countries (Figure 5).

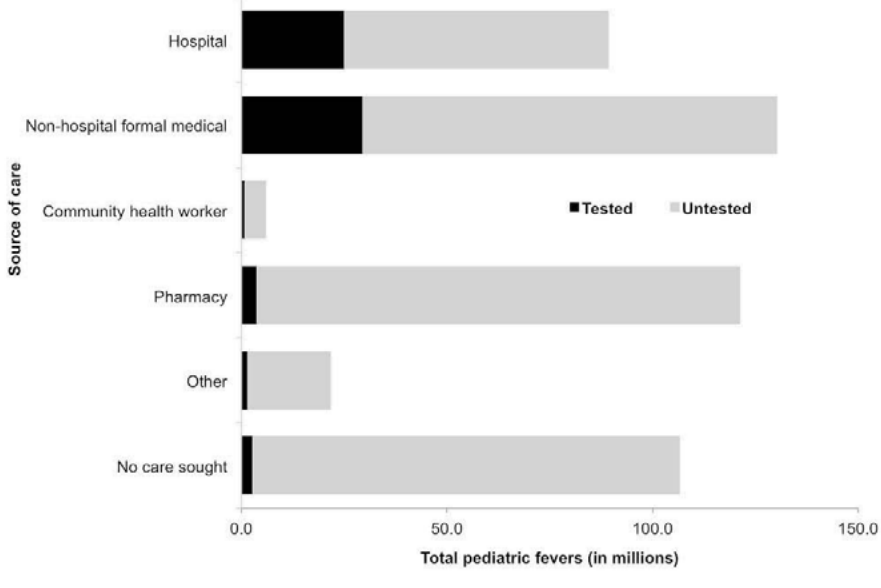

Figure 5. (Study I) Estimated pediatric fevers attending and tested at different sources of care in 13 countries in 2010

Table 10. *(Study II) Descriptive typology of plausible explanations for quantitative results in six countries*

		Rwanda	Uganda	Malawi	Benin	Mozambique	Burundi
		DHS 2010-11	**DHS 2011**	**DHS 2010**	**DHS 2011-12**	**DHS 2011**	**DHS 2010-11**
Outcomes (see Table 9) *	AOR - Any anti-malarial use	0.83 (0.48-1.44)	1.24 (0.96-1.61)	1.34 (1.11-1.61)	1.65 (0.92-2.98)	2.79 (1.92-4.05)	3.71 (2.63-5.25)
	AOR - ACT use	0.88 (0.51-1.51)	0.84 (0.66-1.06)	1.12 (0.94-1.34)	1.96 (0.91-4.19)	3.54 (2.33-5.39)	2.78 (1.81-4.27)
	AOR - Any antibiotic use	2.95 (1.82-4.79)	1.37 (1.09-1.72)	1.00 (0.82-1.22)	1.15 (0.64-2.08)	1.01 (0.64-1.59)	0.53 (0.40-0.72)
Available diagnostics and medicines	National ACT scale-up initiated	Yes	Yes	Yes	Yes	Yes	Yes
	National RDT scale-up initiated	Yes	No	No	Yes	Yes	No
	Reported inconsistent RDT supplies	No	N/A	N/A	Mixed reports	Yes	N/A
	Reported inconsistent ACT supplies	No	Yes	No	Yes	Yes	Yes
	Diagnostics at community-level	Yes	No	No	No	No	No
Quality of care	Diagnostics at peripheral facilities (% test-negatives prescribed ACT)	Yes	Yes	No	Yes	Yes	No
Care-seeking	Extensive informal private sector use	No	Yes	No	Yes	No	No
Malaria risk	Malaria endemicity in 2010	Malaria-free to moderate-risk	Malaria-free to moderate-risk	Moderate to high-risk	Moderate to high-risk	Moderate to high-risk	Malaria-free to high-risk

In Study II, *care-seeking behavior* was also a main theme that explained varying effects of testing on pediatric fever treatment across countries (Table 10). As case studies highlighted, this *Access* bottleneck is particularly important in countries where drug shops are commonly used to treat sick children or where there is simply difficult access to formal care. In these countries, caregivers may self-treat sick children at home or in communities either before or after visiting a facility where diagnostic testing occurs. This could result in over-treatment associated with diagnostic testing at the population level that is unrelated to quality of care at facilities. This practice may also delay visiting formal providers such that children are more severely ill once they reach facilities with diagnostics, which was further hypothesized to explain Study II results.

Facility readiness

Facility Readiness bottlenecks may include available guidelines, staff, training, supplies, referral systems or other facility or system constraints that hinder the use of malaria diagnosis to improve pediatric fever management. In Study III, one health worker clearly expressed these interconnected constraints to managing RDT-negative cases as follows:

> You can see the result is negative. The child is seriously sick. When you talk of referral, the mother is there complaining. Then you are there, and you say: "Now what? What can I do?" But if we could be equipped well with other things. You can do a test and it proves the cause of the sickness or if you have other cadres of human resources, they can do it. There is no doctor. You are there. You are alone. So at least if you are a nurse and you fail on something, you can consult a doctor or a nursing officer. There is nobody. (Study III: Health worker 8)

Supplies

In Study II, a central theme across all country case studies was *available diagnostics and medicines* to explain varying country results. Among the six case study countries, Mozambique and Burundi were the countries with the highest anti-malarial treatment odds associated with testing. In these countries, diagnostic services were concentrated at hospitals at the time of survey fieldwork given lack of RDT scale-up (e.g. Burundi) or widespread RDT stock-outs (e.g. Mozambique). At the same time, both of these countries experienced ACT shortages at peripheral clinics such that febrile children attending locations with diagnostic tests probably had better access to medicines. In contrast, Uganda and Rwanda had the lowest anti-malarial treatment odds associated with testing, and in both countries diagnostic services were more widely available with microscopy at Ugandan health centers and RDT at community level in Rwanda. In Uganda, however, ACT stock-outs at health centers with microscopy services could also have impacted results.

> Children getting tested are probably at locations that also have medicines, and those not tested likely have worse access to ACT. That's a key issue. (Study II: Benin case study)

Human resources

Human resources in this thesis refers to having adequately trained staff to use malaria diagnosis to improve pediatric fever management. In Mbarara District, several respondents mentioned inadequate skills for differential diagnosis and this issue seemed compounded by working alone without opportunity to confer on difficult cases, notably RDT-negative patients.

> Sometimes we have been asking ourselves what happens to the RDTs. What brings that? As I have told you that I am a nursing assistant. So I start asking myself what can I do. Maybe I think about if I am with a clinical officer but on my own, according to how I can manage, if I can't manage I refer. (Study III: Health worker 13)

Referral systems

In Study III, referral was a commonly mentioned challenge in Mbarara District and many HC-II nurses expressed a desire to refer RDT-negative cases for microscopy confirmation or doctor's care since they felt unable to manage these cases themselves. Yet referral challenges limited this option.

> Yes, it is a challenge! Now what do you think we can do with those patients that test negative? What do you think we can do? And they don't have any other causes of fever. We do what, we refer. Yes, you refer. It is difficult because you tell them refer by the mother has no transport. It's a problem. (Study III: Health worker 18)

In contrast, Malawi results (Study IV) indicated relatively good facility readiness in terms of staff, training, supplies and supervision, although direct comparisons are not possible given different methodologies. Specifically, among 1,981 clients with fever complaints, 236 (11.9%) were seen by a doctor, 1,481 (74.8%) by a medical assistant and 264 (13.3%) by a nurse/midwife; 1,593 (80.4%) were attended by a provider that had ever received supervision; 1,291 (65.2%) were attended by a provider that had ever received RDT training and 939 (47.4%) of these providers had ever received IMCI training. Nearly all facilities were stocked with RDT, ACT and amoxicillin. Nevertheless, there was sub-optimal clinical practices for pediatric fever management in terms of general fever assessments completed and poor antibiotic targeting, as described in next sections.

Clinical practice

Clinical Practice bottlenecks in this thesis included perceptions, client demands and motivations that influenced the use of malaria diagnosis for im-

proved pediatric fever management. In this section, *Clinical Practice* bottlenecks are first reported for Malawi based on quantitative results (Study IV) and then for Mbarara District based on qualitative findings (Study III).

Main complaints

In Study IV, a total of 1,981 eligible clients had a fever complaint in observed outpatient consultations (Figure 6). Among these cases, 1,436 (72%) also reported cough or difficult breathing complaint; 569 (29%) had diarrhea complaint; 359 (18%) reported other complaints including skin problems, eye problems, ear problems, stomach problems, injuries or other issues; 1,021 (52%) reported any danger sign; 117 (6%) reported fever alone with no other complaint or danger sign.

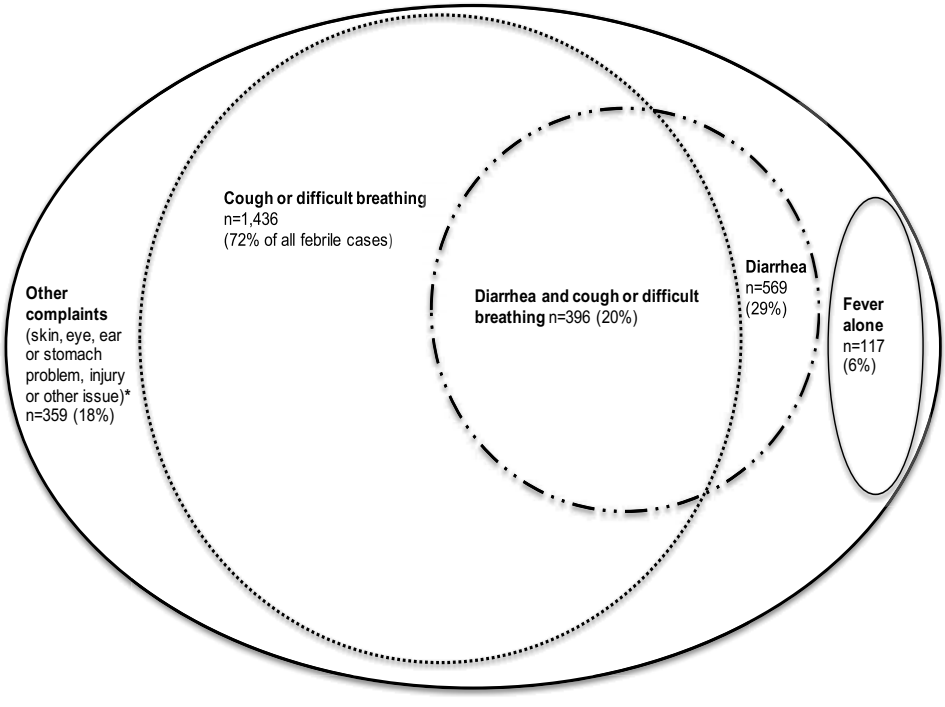

Figure 6. (Study IV) Other complaints among clients with fever complaints, Malawi health facilities, 2013-2014

Clinical assessments

In Study IV, among the 1,981 clients with fever complaints, 1,426 (72.0%) had a malaria RDT done prior to the consultation or was referred for malaria diagnosis. Yet only 44 (2.2%) had their neck checked for stiffness; 524 (26.5%) had their palm pallor checked; 185 (9.3%) had the inside of their mouth's checked; and 563 (28.4%) were undressed for examination (up to shoulders/down to ankles). Among the subset of 1,436 clients with *both*

fever and cough or difficult breathing complaints, 256 (17.8%) had their respiratory rate counted for 60 seconds. Among the subset of 569 clients with fever and diarrhea complaints, 98 (17.3%) had skin turgor checked for dehydration (Table 11).

Table 11. *(Study IV) Completed assessments of clients with fever complaints, Malawi health facilities, 2013-2014*

	N	% Assessed (95% CI)
Fever complaint	**1,981**	
Fever mentioned or asked about by provider	1,684	85.0 (82.8-87.2)
Temperature taken or body felt for hotness	1,386	70.0 (65.5-74.1)
RDT done prior to consultation or referral for malaria diagnosis	1,426	72.0 (69.0-74.7)
Checked neck for stiffness	44	2.2 (1.4-3.5)
Checked for pallor by looking at palms	524	26.5 (23.5-29.6)
Looked into child's mouth	185	9.3 (7.4-11.6)
Undressed child to examine (up to shoulders/down to ankles)	563	28.4 (25.2-31.9)
Fever and CDB complaint	**1,436**	
Both symptoms mentioned or asked about by provider	1,010	70.3 (66.7-73.7)
Counted breaths for 60 seconds	256	17.8 (14.8-21.2)
Fever and diarrhea complaint	**569**	
Both symptoms mentioned or asked about by provider	307	53.9 (48.3-59.4)
Checked skin turgor for dehydration	98	17.3 (13.3-22.1)

Anti-malarial prescriptions

Table 12 shows anti-malarial prescriptions according to provider reported RDT results in Study IV. Among 1,981 observations, 746 (37.7%) had malaria RDT done prior to the consultation with a reported result. Among 312 reported positive cases, 265 (85.1%) received first-line anti-malarial prescription; 22 (7.0%) received second-line anti-malarial prescription; and 25 (7.9%) received no anti-malarial prescription (anti-malarial under-treatment). Among 434 reported negative cases, 44 (10.2%) received any anti-malarial prescription (anti-malarial over-treatment).

Table 12. (*Study IV) Anti-malarial prescriptions for clients with fever complaints, Malawi health facilities, 2013-2014*

	N	% with prescription (95% CI)
Fever complaint	**1,981**	
RDT done prior to consultation or malaria diagnosis referral	**1,426**	
RDT done prior to consultation with result reported	**746**	
RDT-positive result	**312**	
First-line anti-malarial prescription	265	85.1 (77.5-90.4)
Second-line anti-malarial prescription	22	7.0 (4.4-10.8)
No anti-malarial prescription	25	7.9 (3.6-16.7)
RDT-negative result	**434**	
Any anti-malarial prescription (over-treatment)	44	10.2 (6.8-14.9)

Antibiotic prescriptions

Table 13 reports antibiotic prescriptions according to IMCI pneumonia classifications based on re-examination in Study IV. Among 1,981 observations, 1,367 (70.3%) were assessed for IMCI pneumonia and their classification result was reported. 376 (27.5%) had a positive IMCI pneumonia classification, and 148 (39.4%) of these cases received a first-line antibiotic prescription; 123 (32.7%) received a second-line antibiotic prescription; and 105 (27.9%) received no antibiotic prescription (antibiotic under-treatment). There were 917 IMCI-pneumonia negative cases and a total of 1,411 were further categorized as 'without antibiotic need' based on their IMCI-pneumonia negative classification and by additionally excluding observations with the following diagnoses recorded during the consultation: sepsis, dysentery, mastoiditis, acute ear infection, abscess or severe malnutrition. Among 1,411 clients 'without antibiotic need', 830 (58.8%) received any antibiotic prescription (antibiotic over-treatment).

Table 13. *(Study IV) Antibiotic prescriptions for clients with fever complaints, Malawi health facilities, 2013-2014*

	N	% with prescription (95% CI)
Fever complaint	**1,981**	
IMCI pneumonia assessment with result reported	**1,367**	
IMCI-pneumonia positive classification	**376**	
First-line antibiotic prescription	148	39.4 (32.3-46.9)
Second-line antibiotic prescription	123	32.7 (26.3-39.8)
No antibiotic prescription	105	27.9 (20.7-36.5)
'Without antibiotic need'	**1,411**	
Any antibiotic prescription (over-treatment)	830	58.8 (55.1-62.4)

Antibiotic over-treatment

Figure 7 further depicts the relationship between the RDT result and other input variables on antibiotic over-treatment. RDT-negative clients had 16.8

(95% CI: 8.6-32.7) times higher antibiotic over-treatment odds compared to RDT-positive clients in the crude mixed-effects logistic regression model. The remaining input variable that was a statistically significant classifier of antibiotic over-treatment conditional on RDT result in the model was cough or difficult breathing complaint. The split is largely driven by the change in intercepts while the slope, or effect size, is similar across nodes. Clients without cough or difficult breathing complaint and a positive RDT result had very low risk of antibiotic over-treatment, and this risk increased with the negative RDT result (Node 2, OR: 8.9). In contrast, clients with cough or difficult breathing complaint already had relatively high underlying risk of antibiotic over-treatment irrespective of the RDT result, and the association between RDT results and the outcome was slightly weaker in this group (Node 3, OR: 5.6). Furthermore, even if their result was positive, clients with cough or difficult breathing had similar risk of antibiotic over-treatment as clients without this complaint and a negative RDT result (Nodes 2 and 3).

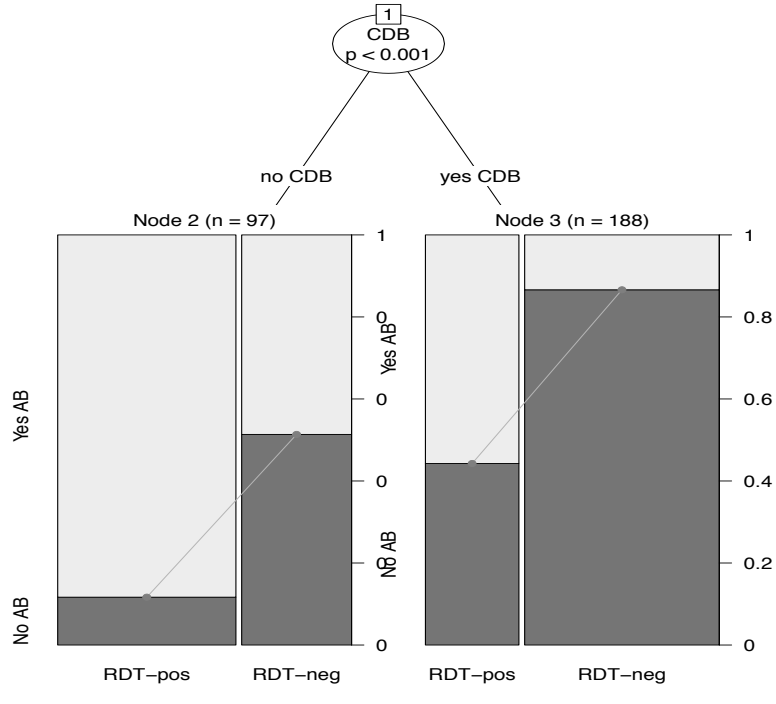

Figure 7. (Study IV) Inter-relationship between RDT results and other input variables on antibiotic over-treatment among clients with fever complaints, Malawi health facilities, 2013-2014

Study III also described important *Clinical Practice* bottlenecks in Mbarara District Uganda, notably RDT perceptions, client demands and motivations. These qualitative findings are described in the following sections.

RDT perceptions

In Study III, many health workers interviewed expressed general RDT mistrust that seemed in large part driven by expectations of false negative results in certain situations, including low parasite/antigen loads, previous anti-malarial dose or test detection of only one species. Taken together, these RDT perceptions underpinned *Clinical Practice* bottlenecks for using (or not) malaria diagnosis to improve integrated pediatric fever management.

Low parasite/antigen loads: Many health workers explained that an RDT positive result was difficult to obtain during initial illness stages since RDTs may be insensitive to low parasite/antigen loads. In these cases, malaria treatment for an RDT negative result was generally seen as appropriate in order to treat the malaria infection the RDT could not yet detect. Some health workers reported this period could last about three days from the start of the fever episode.

> I think that these RDTs to become positive that malaria might have persisted or it might have taken like three days. But the malaria of one day cannot be positive on an RDT. It can't. (Study III: Health worker 18)

Previous anti-malarial dose: Many health workers mentioned prescribing malaria treatment for an RDT negative result if the child had recently taken an anti-malarial dose. There were two distinct reasons for this practice. Some respondents suggested a need to complete the treatment course even if the patient had no detectable malaria infection. A few health workers also stated that a positive result could be difficult to obtain if an anti-malarial drug was already present in the child's system. One caregiver related this experience during the focus group discussion.

> Some of us go to clinics first and we are given medicine without testing. So the malaria parasites hide. But somehow when they go to test elsewhere the malaria is not detected but the doctor kind of understands this and goes ahead and treats malaria. (Study III: FGD 1 participant)

Test detection of only one species: A few health workers mentioned that the RDT detects only one parasite species and malaria infection may not be detected if caused by another species.

Provider-client interactions

In Study III, client demands seemed to influence clinical practices, particularly demands for certain drugs or desires to know the 'exact' disease cause.

Many health workers complained that caregivers demanded malaria treatment and felt health workers *must* treat the sick child. Similarly, most caregivers said they wanted treatment to cure the child's sickness. Some would demand malaria treatment if they strongly felt that was the fever cause, although others talked about accepting the result and following the clinical decision. In general, caregivers wanted to know the 'exact' disease cause if not malaria.

> My thinking would be that if they don't detect malaria then they should be able to detect any other diseases. If they don't say anything else I would go to another hospital with testing machines and get to know what the child is suffering from. (Study III: FGD 2 participant)

Motivations

In Study III, health workers also described various dilemmas or feelings that could motivate malaria over-treatment practices. Many health workers expressed uncertainty about how to manage non-malaria fevers; feared doing wrong, loss to follow-up or patient death; worried caregivers would lose trust; or felt unsatisfied without a clear diagnosis.

Some health workers seemed unsure about how to manage non-malaria fevers, and many expressed a desire to consult with doctors given this uncertainty. Some health workers also feared doing wrong, patient loss to follow-up or patient death, which was clearly expressed as follows:

> We know malaria is a killer. It actually kills more people than accidents. So if you left this child and the child went back home, especially those young ones below five years, you are not sure whether the parents are going to continue to both assess and monitor the status of this child. So in case you miss out, we fear maybe this child is going to die before they come back. So you would rather give treatment than leave this child to go home because some of them come from very far. Others do not even have money maybe to rush to the nearest clinic in case things happen when it is late. So you know, you put all those things into consideration. (Study III: Health worker 10)

Several health workers worried that caregivers would lose trust in their services, and caregivers did express less trust in peripheral clinics to manage non-malaria pediatric fevers underscoring such concerns.

> These hospitals to me they are good because they have skilled professionals, sometimes when you go to a nurse they may not detect the disease. (Study III: FGD 1 participant)

A few health workers also felt unsatisfied without a clear diagnosis, desired to do a better job, and expressed dissatisfaction to *'just blindly treat to see what will come out' (Study III: Health worker 15).*

> Sometimes when somebody has fever and the RDT is negative, and they don't have pneumonia and they just have fever, it is quite challenging because we don't know the cause of the fever. You could think it could be viral but you don't know, you have not diagnosed it. So we just give antipyretics. But inside you, you are not satisfied. You feel you would have done better but you can't. You don't have anyway how to do it. (Study III: Health worker 5)

Many caregivers shared this desire to know the *exact* cause of the illness:

> You want to make sure you know the exact disease cause. It is like the reason why you take the child to hospital is to know the exact disease. Because one may as well go to the drug shop to buy drugs. (Study III: FGD 5 participant)

Discussion

Overall, the doctoral thesis documented low and inequitable malaria diagnostic testing rates for pediatric fevers across multiple sub-Saharan African countries at the outset of new guidelines, and there were significant country differences in the effect of testing on treatment decisions at the population level. Thesis results also identified important *Access, Facility Readiness* and *Clinical Practice* bottlenecks that need to be addressed going forward for malaria diagnosis to improve pediatric fever management in these settings.

Access

Study I found malaria diagnostic testing rates lowest at locations where pediatric fevers are more often managed, particularly for the poorest children. Seeking care from lower levels or less formal sources greatly reduced the likelihood of testing, as occurs with other facility-based interventions [160]. This is most plausibly explained by lower test availability at these locations including their near absence among CHWs and pharmacies [55]. Crude estimates of total pediatric fevers attending and tested at different sources of care in 2010 further illustrated that diagnostic testing had not reached sources of care bearing the disproportionate burden of fever cases (Study I).

This is a particular challenge to improve equitable access to diagnostic testing since these are same sources where poor families often seek care [161]. Indeed, our study also demonstrated an important socioeconomic dimension to malaria testing plausibly also due to lower test availability where marginalized families seek care. While initial RDT implementation largely targeted formal health system sources, pediatric fever cases in these settings are commonly managed at home or in community settings where these tests are not available [161]. This is consistent with research from Zambia that shows that the greatest contributor to reduced systems effectiveness for malaria case management is where care was sought [162].

A major shift in RDT deployment is therefore needed to improve access to and equity in malaria diagnostic use for pediatric fevers. Indeed, universal diagnosis goals will *never* be achieved without extending the reach of malaria diagnostic services into community settings. Yet RDT deployment to community-based sources outside the formal health sector is not straightforward, and there are legitimate concerns about quality of care that could be

provided by lay personnel or by those potentially with a business interest that promotes over-treatment [163]. Nevertheless, integrated community case management (iCCM) is a promising approach to improve equitable access to testing and care [23]. Studies have shown that CHWs can appropriately use rapid diagnostic tests to manage pediatric fevers [25,27]. The iCCM approach has also been extended to drug shops with similarly promising results in terms of RDT use and adherence [26].

Facility readiness

Studies in this thesis identified various *Facility Readiness* bottlenecks that reduced the effective use of malaria diagnosis to improve pediatric fever management, including inadequate human resources, training, supplies, and referral systems.

Study II identified *available medicines and supplies* as a central theme to explain the varying effect of testing on pediatric fever treatment found across countries. In many studied countries, malaria diagnostic tests remained concentrated at higher level facilities that generally had better medicine stocks and more severely ill patients given our early assessment at the outset of new treatment guidelines. This again underscores the need to expand access to testing and care into lower level facilities and communities.

Beyond potential supply shortages, other important facility or system bottlenecks were identified in Studies III-IV including inadequate training in integrated pediatric fever management despite recent RDT training. Quantitative results for Malawi (Study IV) indicated that while malaria-specific assessments and RDT-guided malaria treatment seemed common, integrated pediatric fever management was sub-optimal in terms of other fever assessments completed and poor antibiotic targeting. This lack of training in integrated fever management protocols was also found in Mbarara District Uganda (Study III). Few health workers in this district specifically mentioned using IMCI guidelines to differentiate among fever causes, which suggests a lack of awareness of the primary tool available to classify non-malaria fevers. Some health workers referred to aspects of this tool but none described employing it consistently or even correctly in their practice. These findings are consistent with other research showing poor IMCI implementation in Malawi, Uganda and various other settings [16-21].

It is critical that lower level health workers feel empowered to manage non-severe non-malaria pediatric fever cases without referral. There is general consensus about the need to deploy RDT as part of integrated fever management protocols, notably IMCI for sick children [10]. IMCI has been shown to improve quality care for common causes of child morbidity and mortality (e.g. malaria, pneumonia, diarrhea, measles, malnutrition and ear infections), which often include fever as a presenting complaint. There are

also ongoing initiatives to strengthen the IMCI algorithm based on recent etiology studies [33-34] and in recognition of its poor implementation to date. Our results from Malawi highlight the critical need to review these guidelines to clarify when antibiotics are (or are not) indicated, which is confusing and unclear in the recent IMCI adaption for test-based malaria case management [164].

Inadequate guidelines, training and skills for integrated pediatric fever management using IMCI and RDT together was also compounded in Mbarara District by other facility or system readiness constraints including poor referral systems and working alone without opportunity to confer of difficult cases (Study III). These are well-known issues in Uganda and other low-income countries with weak health systems [135,137,141,143]. Future implementation research needs to try to address these entrenched health system barriers in order to improve the use malaria diagnosis for integrated pediatric fever management, such as through innovative methods informed by the Diffusion of Innovations theory (see Future Research section). Nevertheless, in settings with weak health systems, our findings suggest that some over-treatment of dangerous illnesses will *and arguably should* remain the norm if providers fear the child may not return if symptoms worsen and are unable to refer them for further testing and medical care.

Clinical practice

Studies in this thesis identified various *Clinical Practice* bottlenecks including perceptions, client demands and motivations, feelings or dilemmas that hinder the use of malaria diagnosis to improve pediatric fever management.

Study IV findings from Malawi health facilities suggested good compliance with new malaria treatment guidelines, which contrasts previous studies that showed poor adherence to negative blood smear readings prior to nationwide RDT deployment [94]. Indeed, most sick child clients with fever attending Malawi health facilities either received a malaria test or were referred for diagnosis, and RDT-guided malaria treatment seemed common according to provider reports. However, general fever assessments were less commonly conducted despite being essential for differential diagnosis. There was also poor antibiotic targeting with *both* under- and over-treatment that was in part due to poorly assessing clients to identify antibiotic need. A strong predictor of antibiotic over-treatment was the RDT negative result conditioned by cough or difficult breathing complaints.

These results underscore concerns about growing irrational antibiotic prescription practices in the era of test-based malaria case management [165]. Our results draw particular attention to the need to implement IMCI and RDT *together* to strengthen quality pediatric fever care that could in turn improve rational use of both anti-malarial and antibiotic medicines. This

should be considered for inclusion in national action plans to combat antibiotic resistance that need to be developed in the coming years in line with the new World Health Assembly resolution [166]. Moreover, such concerns about worsening antibiotic use as a side effect of test-based malaria case management will inevitably grow as countries move towards malaria elimination making integrated assessments of patients even more critical [62].

In Mbarara District Uganda (Study III), in contrast, malaria over-treatment of RDT negative results seemed common according to provider interviews particularly if an alternative fever cause could not be identified. RDT perceptions was a central issue shaping clinical decisions, notably RDT mistrust that has been described in other settings as well [97-105]. In this setting, RDT mistrust developed in part from perceptions that a positive result was difficult to obtain for certain reasons: low parasite/antigen loads, previous anti-malarial treatment and test detection of only one species. These findings showed a proven awareness about potential problems with RDT malaria detection such as for low parasitemias or to detect certain parasite species [70], and legitimate concerns regarding anti-malarial drug resistance [56]. Yet this awareness has been misconstrued to inappropriately justify RDT non-compliance, and to support a general preference to diagnose malaria using routine microscopy or to confirm RDT negative results with blood smears. This preference is reinforced by Uganda national guidelines that promote microscopy as the 'gold standard' for malaria diagnosis in Uganda [167]. It may have also reflected an underlying desire to continue presumptive treatment practices – a long-standing policy that is generally easier for health workers to implement.

In Study III, client demands also emerged as a *Clinical Practice* bottleneck, which has been highlighted elsewhere [97-105]. Many health workers in Mbarara District perceived clients as lacking knowledge and demanding certain medicines. Yet these perceptions were not necessarily supported by FGDs with caregivers. While some caregivers mistrusted RDTs and might demand anti-malarial medicines, many also seemed willing to accept a negative test result but desired an alternative diagnosis to understand their child's sickness. Many caregivers preferred visiting doctors or higher level facilities seen as better equipped to identify the *exact* disease cause (Study III).

The inability of health workers to identify the *exact* disease cause combined with client demands to know their child's underlying condition led to various feelings or dilemmas that also seemed to shape clinical practice. Many health workers expressed uncertainty about how to manage non-malaria fevers, feared doing wrong, loss to follow-up and patient death, worried caregivers would lose trust, or felt unsatisfied without a clear diagnosis. These motivations, dilemmas or feelings also seemed to result in malaria over-treatment decisions, and health workers commonly justified these decisions by noting that RDT-negative patients improved on malaria treatment.

Future research

The constraints identified in the qualitative study from Mbarara District (Study III) in particular could shape a future implementation research agenda derived from this thesis in order to reduce critical *implementation pathway* bottlenecks. Specifically, the constraints identified – RDT perceptions, provider-client interactions and system constraints – reflect long-established clusters of influence on the spread of new innovations or practices according to the Diffusion of Innovations theory [168-171], which was recently adapted to the RDT experience in sub-Saharan Africa [99].

Diffusion of Innovations

RDT perceptions

According to the Diffusion of Innovations theory, innovation perceptions may explain a large part of the variance in adoption of new practices, which makes building trust in RDT negative results a top intervention priority for Mbarara District and other settings. Five innovation perceptions are most influential for successful uptake: benefit, compatibility, simplicity, trialability and observability.

First, users need to see a relative *benefit* to the status quo if RDTs are adopted, which includes reducing any perceived risks in employing the new innovation or practice. While most health workers understood the advantages of malaria diagnosis and caregivers seemed eager for testing, most respondents perceived inherent 'risks' in the new practice of managing RDT-negative patients – notably missing a malaria diagnosis – that may greatly reduce any perceived benefits. This perception of missing a malaria diagnosis as 'risky' is consistent with other research [98]. These perceived risks could be addressed through messaging that focuses on the reliability of RDT-negative results [53-55], the demonstrated safety of withholding antimalarial treatment [172], and the deliberate over-treatment built into the IMCI algorithm for other fatal febrile illnesses (e.g. bacterial pneumonias, measles, diarrheal diseases) in order to specifically avoid severe consequences in patients [10]. This could help build trust in negative results, and reduce perceived risks in managing non-malaria pediatric fevers if RDT and IMCI are correctly implemented together.

Second, RDT implementation needs to be *compatible* with current clinical practice. In our study, however, most health workers did not find their current training or available tools compatible with the new practice of managing RDT-negative patients. Third, *simple* technologies are often more readily adopted than complex ones. While RDTs are simple to use, RDT-negative patients were generally perceived as complicated to manage. Finally, *trialability* (having a trial or testing period) and *observability* (watching others use the innovation or employ the new practice) also aids adoption. Trialability and observability, in particular, are especially important for adopting 'risky' practices to give users space to experiment with the new practice and to understand how others have incorporated it into their own work. This provides critical, early opportunities to share experiences, answer questions, give feedback, address concerns, adapt the new practice to routine work, and build confidence that others are working in a similar manner [173].

Provider-client interactions

The Diffusion of Innovation theory also highlights user characteristics as another sphere of influence on innovation adoption, which in this context includes both providers and clients. According to the literature, some authors categorize users as 'innovators', 'early adopters', 'early majority', 'late majority' and 'laggards', and these categorizations may also pertain to adopters in service organizations [168]. 'Early adopters' in particular are characterized as opinion leaders, professionally respected and resourceful, and evidence points to the critical role of opinion leaders in promoting innovation adoption by shaping peer opinion [168,173]. In Study III, some clinical officers could naturally fit that role but greater investments would be needed to build up this network, and to subsequently connect 'opinion leaders' with other health workers in the district. Clinical officers seemed more knowledgeable than lower health worker cadres regarding pediatric fever causes and their management, which was a perception shared by most caregivers too. In fact, both nurses and caregivers interviewed expressed a clear desire to consult with doctors in order to manage non-malaria pediatric fevers.

Moreover, evidence suggests that organizations that foster informal exchanges among users may experience faster rates of practice adoption [168,170,173], and some research has also demonstrated improved health outcomes by facilitating such interactions [174]. Along these lines, recent studies have shown improved RDT compliance using interactive training programs or daily SMS reminders that essentially form a basis for improved communication networks and connectedness among adopters [107-108]. Other researchers have also recommended establishing communities of practice, Balint groups or peer-learning networks to increase problem-solving and mentorship opportunities to improve RDT compliance [99]. One additional intervention could include providing airtime to nurses at lower level

clinics to facilitate real-time consultations with 'opinion leaders' on difficult cases, such as RDT-negative patients.

Clients are also 'users' in this context and play a role in determining care seeking strategies and shaping the clinical encounter. Community 'opinion leaders' are therefore needed to raise awareness about new clinical practices and build community trust in negative results. To date, community sensitization to new clinical practices in Mbarara District has largely relied on health worker counseling of patients despite their limited time. While there is a need to strengthen health worker counseling skills, our findings also suggest that health workers may not be suitable 'opinion leaders' within communities given some negative perceptions expressed by caregivers.

System constraints

Contextual factors or system constraints in this thesis included poor referral systems, working alone without opportunity to confer on difficult cases, and lacking skills and/or tools for differential diagnosis. These are well-known issues in low-income settings with weak health systems [143]. Nevertheless, even within weak health systems, it is critical that lower level health workers feel empowered to manage non-severe non-malaria pediatric fevers without referral.

Again the Diffusion of Innovations theory and other researchers emphasizes developing communities of practice and fostering exchanges among health workers that could not only improve RDT practices but also strengthen health systems that could help alleviate some of these entrenched constraints. For example, developing interactive, professional communities as previously discussed could potentially reduce feelings of working alone without support, reduce the desire to refer non-severe cases, build trust in nurses' ability to handle non-malaria fevers, and satisfy caregiver desire to attend bigger hospitals by better linking doctors to peripheral clinics. Such interventions could not only improve RDT compliance, rational drug use and quality fever care, but could also potentially strengthen overall health systems with RDT as the entry point.

Methodological considerations

There are a number of methodological issues to consider in the interpretation of results from this thesis. These issues mainly pertain to preforming secondary analyses of previously collected data as well as specific data limitations in both quantitative and qualitative studies.

Secondary analyses

There are numerous advantages to performing secondary analyses of routinely implemented surveys that were previously described (see Introduction). Yet there are also a number of methodological considerations: First, the primary purpose of these survey programs are to measure key health and demographic indicators (DHS, MIS) or facility readiness to provide quality care (SPA). Therefore, only standard questions that are not in-depth on any one topic are included in these surveys, including for malaria diagnosis. This results in missing information to help results interpretation or to measure important confounding variables (See Confounding and Measurement).

Second, country datasets were included if inclusion criteria were met, but country selection could have been more strategic for this thesis if data were available. Uganda, for example, was the qualitative study setting (Study III) and was also included in Studies I-II. A facility-based study from Uganda would have been more appropriate but only Malawi SPA was available.

Third, there is a time lag in using datasets from these survey programs. Datasets may only become publicly available to researchers about one or two years after data collection. It then takes time for data analysis and publication which could potentially lead to a time lag of two or even three years from data collection to published results. A particular problem in this thesis was that population-based data (Studies I-II) was largely collected around 2010 at the outset of new treatment guidelines with countries at different stages of implementation while results were published in 2014-2015.

Fourth, meta-analysis methods used in secondary analysis of published studies or datasets have important advantages (see Introduction) but also limitations that notably occurs when there is heterogeneity across individual studies or if small studies contribute undue influence to the pooled result. In Study I, countries were heterogeneous in terms of RDT implementation stage that may have impacted meta-analysis results, although countries mainly showed odds ratios for determinants of test uptake in similar direc-

tions as the pooled result. Individual country results were published in a paper supplement for this important reason.

Confounding

Confounding occurs when an extraneous variable is independently associated with both the exposure of interest and outcome variable [175]. In this situation, the exposure-outcome relationship may be incorrectly estimated in regression analyses if the extraneous variable is not taken into account such as through adjustment, stratification and/or matching procedures. Residual confounding is the effect of confounding that remains after such adjustment procedures, which is a concern in most observational studies including Studies I-II. Residual confounding may occur because these extraneous variables were not considered and there was no attempt to adjust for them using the above methods. It is also possible that these extraneous variables were not measured or inappropriately measured during data collection so that adjustment was not possible. There could also be misclassification or imprecise classification (e.g. "young" versus "old" rather than age groupings) of the extraneous variable such that the confounding effect remains even after adjustment procedures.

In Study II, for example, important confounding variables were not measured through surveys, such as illness severity or RDT/ACT stocks, that confound the relationship between diagnostic testing and medicine use for pediatric fevers. We attempted to address this issue by including proxy variables in the regression analysis that could potentially substitute for these unmeasured confounders. However, the exposure-outcome relationship likely remained confounded (residual confounding) as highlighted in case studies. It could be argued that these confounders represent basic omitted variables given their central importance in understanding the relationship between testing and treatment, which again was one reason for the use of case studies to explore quantitative results.

Information bias

In Studies I-II, information to construct outcome variables was derived from asking caregivers of children under five years with reported fever in the previous two weeks if those children were tested for malaria and the treatments received. Caregivers may not correctly recall this information when asked in survey interviews. This could bias results if there are systematic differences in caregiver recall of key variables across examined groups. A recent validation study found that caregiver recall of a child's diagnostic test receipt was not highly sensitive (61.9%) but had reasonable specificity (90.0%) when compared to direct facility observation [176]. The authors of that paper found no significant differences in recall across examined caregiver characteristics. A few studies have also investigated caregiver recall of medicines given to sick children showing mixed results [176-177]. Other studies show

worse recall for previous health events among poor, rural or less educated mothers [178]. Study I-II findings could overestimate effect differences across these groups. Another issue in Study IV is that providers may perform better during observations than in routine work conditions, known as the Hawthorne effect, which could bias results toward better practices including RDT compliance [179].

Data collection and measurement

For Studies I-II, surveys only measure whether blood was taken for testing but do not probe further about the type of test used (RDT or microscopy) that is critical for results interpretation. Similarly, surveys do not record the child's test result and analysis of (in)appropriate test-based treatment is not possible using these data, which makes Study II results difficult to interpret.

For Study IV, there were a number of data collection issues that affected analyses and results interpretation. First, assessments recorded during sick child observations aim to observe IMCI practice but do not record all IMCI assessments completed such as whether the provider asked about fever duration or measles history. Study IV instead used tracer interventions to assess assessments completed for relevant IMCI algorithms. Similarly, there is no recording of assessment quality or clinical findings from the examination that limits the ability to analyze correct case management using this dataset. There is also no gold-standard re-examination for the full IMCI assessment but only a limited re-examination component for IMCI pneumonia.

Second, RDT results are only reported for clients with the result available by the consultation, and do not include blood smear or other RDT results. Facilities conducting RDT prior to the consultation may be systematically different from other facilities in ways that influence compliance, such as larger facilities with better quality care. RDT results are also based on provider reports without supporting documentation. It is possible that some providers may misreport a negative result as positive if anti-malarial drugs were prescribed. Third, the main outcome is antibiotic over-treatment, or prescribing any antibiotic drug to clients 'without antibiotic need', which is notoriously difficult to measure in settings without diagnostics to differentiate bacterial from other pathogenic causes. Study IV defines 'need' according to antibiotic indications based on IMCI pneumonia classification and provider self-reported diagnoses requiring antibiotics: sepsis, dysentery, mastoiditis, acute ear infections, abscess or severe malnutrition. Urinary tract infection is not a diagnostic category and is therefore not included in this definition. Clients assigned these diagnoses may not necessarily have the underlying condition and may not in fact need antibiotics. Our 'without antibiotic need' definition therefore underestimates true lack of need.

Qualitative considerations

There are also specific methodological limitations associated with the qualitative components of this thesis. First, respondents may 'want to seem to do correctly' and may not have been fully forthcoming about certain practices. Second, respondents may 'want to please the interviewer' by giving responses they believe are desired. If respondents viewed interviewers as associated with government of international donors, they may have been less likely discuss non-adherence practices. Nevertheless, triangulation of data with FGDs and across interview teams suggested broad consistency in responses. Similarly, experts consulted for case studies may not have wanted to negatively report on programs with which they were professionally involved. Their responses were triangulated with other sources to confirm information reported during consultations.

Conclusions and recommendations

- **Study I** found low and inequitable testing of pediatric fevers across 13 countries at the outset of new guidelines in 2009-2012. Lower testing rates were found in high-risk settings and among the youngest children meriting further investigation. There was also lower uptake among children living in the poorest households and among those with least educated mothers indicating an important socioeconomic dimension to malaria testing.

- **Study II** showed significant variation across 12 countries in the effect of testing on pediatric fever treatment at the population level in 2010-2012, and qualitative results suggested the impact of diagnostic scale-up on treatment practices may depend on contextual factors in the local setting, such as access to care or supply stock outs.

- **Study III** indicated that malaria over-treatment of RDT-negative patients reportedly occurs in Mbarara District Uganda if no alternative fever cause can be found. RDT non-compliance seemed further driven by a combination of RDT perceptions, system constraints and provider-client interactions that need to be addressed in order to use malaria diagnosis for improved pediatric fever management in this district.

- **Study IV** documented sub-optimal integrated pediatric fever management practices in Malawi health facilities in terms of poor assessments and antibiotic targeting despite common compliance to malaria treatment guidelines. The RDT negative result was strongly associated with antibiotic over-treatment conditioned by cough or difficult breathing complaints.

Thesis findings highlight important *Access*, *Facility Readiness* and *Clinical Practice* bottlenecks that need to be addressed going forward in order to use malaria diagnosis to improve pediatric fever management and rational use of *both* anti-malarial and antibiotic medicines. This is best accomplished by integrating RDT into established systems and practices while also strengthening them at the same time. Indeed, RDT should be viewed not only as a

tool for malaria diagnosis, but more broadly as a unique entry point to help strengthen weak health systems and improve sub-optimal clinical practices that have plagued health sectors in sub-Saharan African countries for years. Taken together, this thesis points to moving beyond malaria-focused *'test and treat'* strategies toward *'IMCI with testing'* in order to conceptualize RDT as one element for managing sick children in an integrated manner within a strengthened health system context that supports adherence to established clinical guidelines, including malaria diagnostic test results.

Access

- Deploy RDT to communities where pediatric fevers are commonly managed to achieve universal diagnosis goals (Study I).

- Expand integrated community case management in order to extend access to testing and care in an equitable manner (Study I).

Facility readiness

- Review IMCI guidelines based on recent etiology studies and to clarify when antibiotics are (or are not) indicated for sick children, particularly in relation to RDT-negative cases (Study IV).

- Integrate RDT and IMCI with combined guidelines, deployment, training and support in order to improve quality fever care and rational use of *both* anti-malarial and antibiotic drugs. This should be considered for inclusion in national action plans to combat antibiotic resistance in endemic African countries (Studies III-IV).

Clinical practice

- Empower health workers at first-level facilities to manage non-severe non-malaria pediatric fevers without referral. This includes, at a minimum, building health worker and community trust in RDT negative results; reinforcing skills in integrated care; and fostering Communities of Practice, or using other innovative means, informed by the Diffusion of Innovations theory to help improve clinical practices (Study III).

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