Imperial College London

Barriers to effectiveness: Artemisinin Combination Therapies (ACTs) and the Health System

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Bhargavi Rao
IMPERIAL COLLEGE LONDON: Department of Infectious Disease Epidemiology; Faculty of Public Health

ABSTRACT

As international funding for malaria programmes plateaus, it is critical to better understand how to implement interventions such as first-line Artemisinin Combination Therapies (ACTs) most effectively through an existing health system.

This thesis presents an expansion of a mathematical model of malaria transmission to provide insight to the role of health systems factors as barriers to the effectiveness of ACTs, and interventions to overcome them; considering dimensions of access to care, different sectors through which care is delivered, and the quality of care provided. Data from the IMPACT 2 study in Tanzania was used to parameterise this approach.

Primary-care based interventions had most impact on transmission. In low-prevalence scenarios some single interventions, e.g. ensuring 100% care-seeking, eliminated parasite prevalence. Diagnostic-led therapy with adequate stocks of ACTs was as effective in all settings as a policy of presumptive treatment, reducing parasite prevalence in under-fives in moderate transmission settings by up to 86% depending on the sector of implementation.

Modelling combinations of hospital-based interventions shifted the pattern of severe malaria away from a peak at early ages (greater than 70% relative reduction in 0-5 year olds in medium transmission settings) towards a more sustained lower incidence across 0-20 years of age as seen in low prevalence settings. This was not immune-mediated and demonstrates the role of health systems interventions preventing the development of severe malaria in those at risk, and reducing mortality.

Weak health systems and a poorly controlled diversity of antimalarial sources act as barriers to deploying ACTs effectively both as a control measure and first-line treatment. Addressing these constraints needs consideration of existing healthcare provision and local priorities, e.g. reducing ACT wastage, but through specific planning may improve progress towards targets set by Roll Back Malaria to decrease clinical disease and mortality, and in low transmission settings, to approach elimination.

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STATEMENT OF OWN WORK

Declaration of Originality

I declare that this thesis is my own work, completed under the supervision of Professor Azra Ghani and Professor David Schellenberg. I acknowledge the following assistance and collaboration in specific parts of the thesis: Dr JT Griffin assisted by sharing with me the differential equations from the original malaria transmission model and further alterations to the model (Chapter 3) which are referenced in the thesis (Griffin et al., 2014, Griffin et al., 2014 , Griffin et al., 2010). The IMPACT 2 study shared data collected in Tanzania through household, outlet and health facility studies (Chapter 5). Dr Lucy Okell shared with me her thesis (2009) and publications on modelling the impact of Artemisinin Combination Therapies and alternative antimalarials on transmission intensity of *Plasmodium falciparum* malaria, which formed a pre-cursor to some of the work in this thesis (Okell et al., 2008a, Okell et al., 2008b). Dr Michael White assisted with the production of figure 38. The work in Chapter 2 and most of the work in Chapter 4 has been published (Rao et al., 2013a, Rao et al., 2013b). I have acknowledged all results and quotations from the published and unpublished work of other people or agencies.

Copyright Declaration

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Firstly and above all I would like to thank my two supervisors, Azra Ghani and David Schellenberg, for their unflagging support, for their kindness and availability in times of need, and especially their efficiency and generosity with time as deadlines (invariably) approached. I have gratefully appreciated their wealth of experience and endlessly positive encouragement throughout my research time.

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LIST OF ABBREVIATIONS

An. : Anopheles
ACTs: Artemisinin Combination Therapies
ADDO: Accredited Drug Dispensing Outlet
AL: artemether-lumefantrine
AMFm: Affordable Medicines Facility-malaria
AS: artesunate
AS-AQ: artesunate-amodiaquine
CCM: Community case management of malaria
CI: Confidence Interval
CHW: Community Healthcare Worker
CQ: Chloroquine
DDT: Dichloro-diphenyl-trichloroethane
DHS: Demographic and Health Survey
DLDB: *Duka la Dawa baridi* (Swahili)
EIR: Entomological Innoculation Rate
FOI: Force of infection (lambda)
HCW: Healthcare worker
ibbppy: infectious bites per person per year
IM: intramuscular
IMCI: Integrated Management of Childhood Illness
IPT: intermittent preventative treatment
IRS: Indoor Residual Spraying
ITN: insecticide treated nets
IV: intravenous
LLINs: Long lasting insecticide treated nets
MDA: Mass Drug Administration
MIS: Malaria Indicator Survey
MQ: mefloquine
MSAT: Mass Screening and Treatment
NMFI: Non-malarial febrile illness
OR: Odds Ratio
P. : Plasmodium
PCR: Polymerase Chain reaction
*Pf*PR: P. falciparum parasite rate i.e. prevalence
POP: Part One Pharmacies
QAACT: Quality Assured ACT
R_0: basic reproductive number
RBM: Roll Back Malaria
RDTs: rapid diagnostic tests
SMS: Short Message Service
SP: sulphadoxine-pyrimethamine
THMIS: Tanzania HIV/AIDS and Malaria Indicator Survey
U5: under-fives
UI: Uncertainty Interval
UN: United Nations
WHO: World Health Organisation

1 INTRODUCTION

Man ploughs the sea like a leviathan, he soars through the air like an eagle; his voice circles the world in a moment, his eyes pierce the heavens; he moves mountains, he makes the desert bloom; he has planted his flag at the north pole and the south; yet millions of men each year are destroyed because they fail to outwit a mosquito.

- Paul F. Russell (1931)

Despite being both treatable and preventable, malaria remains one of the most persistent and pressing public health problems of our time, with complex upstream social, political, economic and environmental determinants. It is a parasitic infection, caused by one of the five species of the protozoan parasite known to infect humans, *Plasmodium*: namely *P. falciparum, P. vivax, P. malariae, P. ovale* and the zoonotic species *P. knowlesi,* all transmitted by female Anopheles mosquitoes prevalent throughout Africa, Latin America, and Asia (Greenwood et al., 2008). Of these, *P. falciparum* is the most virulent and thus will be the focus of this thesis, causing the majority of the estimated 207 million cases and 627,000 malaria-related deaths between 2011-2012 (WHO, 2013), as well as the major morbidities of cerebral malaria and severe anaemia which may have long-term sequelae. This burden falls most heavily on children and pregnant women in sub-Saharan Africa, often with the most limited access to health care services (Kiszewski and Teklehaimanot, 2004). Malaria is associated with poor levels of development, but in addition the economic consequences of malaria are widespread and devastating, with significant direct and indirect costs (estimated at over $12 billion annually in Africa alone), and have been shown to further hinder development (ESPD: Poverty and Social Policy Team, 2005, McKinsey, 2008).

In recognition of this, since 2000 there has been renewed interest in seeking to control the transmission of malaria, even to the point of elimination in some contexts, using widespread targeting of the Anopheline vector through deployment of long-lasting insecticide treated nets (LLINs) (Lengeler, 2004) and promoting treatment with artemisinin combination therapies (ACTs) as a first-line agent (Sinclair et al., 2009). In addition, recent reports demonstrate significant progress towards the development of vaccine candidates against clinical forms of malaria in children (Birkett et al., 2013, Moorthy et al., 2013a, Moorthy et al., 2013b, Targett et al., 2013, Abdulla et al., 2013).

1.1 EPIDEMIOLOGY OF PLASMODIUM FALCIPARUM MALARIA

An important component of recent malaria control initiatives has been a focus on determining the distribution of transmission, morbidity and attributable-mortality in order to evaluate the success of interventions. Quantifying malaria transmission is complex (Anderson RM, 1991). The Entomological Inoculation Rate (EIR) is defined as the mean number of infectious mosquito bites per person per year (ibppy). This is calculated from the number of mosquitoes that take a blood meal on a human adult over the course of 24 hours and the proportion of these that show evidence of infective forms of the malaria parasite (sporozoites; described in section 1.2) in the salivary glands. However not all infectious bites actually result in a malaria human infection; this is given by the force of infection (FOI or lambda Λ) i.e. the number of infectious bites that progress to establish an infection in the host (Anderson RM, 1991). Also commonly used to assess malaria control is the proportion of a population infected with malaria i.e. the parasite prevalence or parasite rate (*Pf*PR for *P. falciparum*) – defined to be the proportion of a cross-sectional cohort testing positive for parasites. The estimates for parasite prevalence are more accurately calculated using PCR techniques rather than slide microscopy (Okell et al., 2009b).

Malaria levels may also be assessed by calculating the clinical burden (Mendis et al., 2009). Malaria infection may present as sub-patent (asymptomatic with no detectable parasitaemia), asymptomatic (with no detectable clinical symptoms but parasitaemia may be detectable), or symptomatic disease, which is defined as fever plus parasite density above a given threshold (Gething et al., 2011). Clinical incidence is defined as the average number of episodes of clinical malaria per person per year. The morbidity and mortality associated with malaria may be estimated as the proportion of clinical episodes that progress to severe malaria, which in practice is calculated through cases that present and are admitted to hospital or tertiary level facilities (Reyburn et al., 2004). The broad spectrum of manifestations of severe malaria are described in section 1.4, and may account for variations in estimates of severe disease incidence (WHO, 2010a).

However in many malaria-endemic countries, collection of the relevant epidemiological data is handicapped by poor health information systems, lack of robust death registries, and health care delivery by a variety of providers, who are often informal (Greenwood et al., 2008). Thus disease burden is often estimated through demographic surveillance system and sentinel health facility and community surveys including verbal autopsies, as well as clinical data and laboratory reports where available (Lozano et al., 2012, Greenwood, 2008, Greenwood et al., 2008).

In 2012, 3.4 billion individuals were deemed at risk of malaria, of which 1.2 billion were classified at high risk (namely greater than 1 case per 1000 population per year). Approximately half of those at high risk (47%) reside in Sub-Saharan Africa and 37% in South-East Asia (WHO, 2013). The 2013 World Malaria Report estimates that between 2000 and 2012 malaria mortality rates fell by 45% across all ages and by 51% in

children under-five (U5s). Of the 103 countries identified to have ongoing malaria transmission, 59 document falling infection incidence but 41 were unable to sufficiently assess trends in disease due to inadequate data (WHO, 2013).

Figure 1 depicts the distribution of *P.falciparum* prevalence in 2 to 10 year olds globally, as estimated by the Malaria Atlas Project (MAP), indicating high levels of transmission across sub-Saharan Africa, with particular hot spots in Nigeria, Democratic Republic of Congo and Tanzania (Gething et al., 2011).

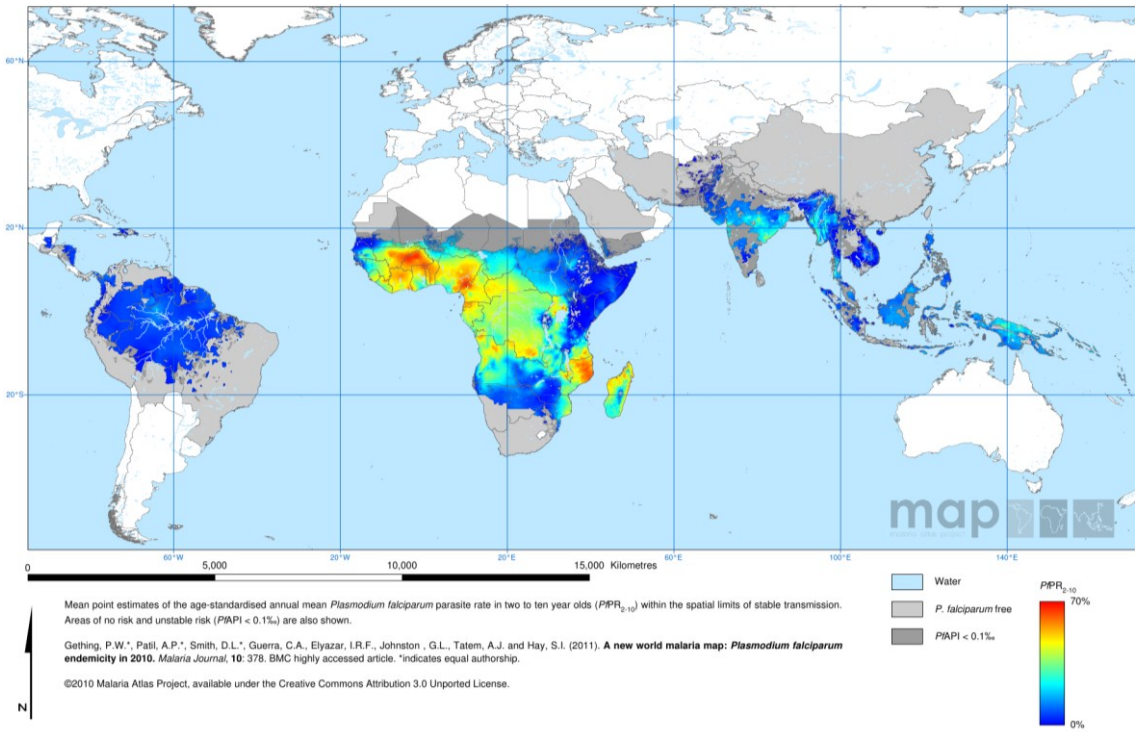


Figure 1: The spatial distribution of Plasmodium falciparum endemicity in 2010

(Gething et al., 2011)

According to the World Malaria Report 2013, 90% of the estimated 627,000 malaria-attributable deaths in 2012 occurred in Sub-Saharan Africa; three quarters of which were in U5s. Furthermore 80% of the global burden is estimated to occur in just 18 countries; Nigeria and the Democratic Republic of Congo account for 40% between themselves. Greater than 80% of malaria deaths occur within 17 countries (WHO, 2013). This geographic distribution is depicted in Figure 2, based on figures from Roll Back Malaria (RBM) and the WHO report of 2012 (WHO, 2012c).

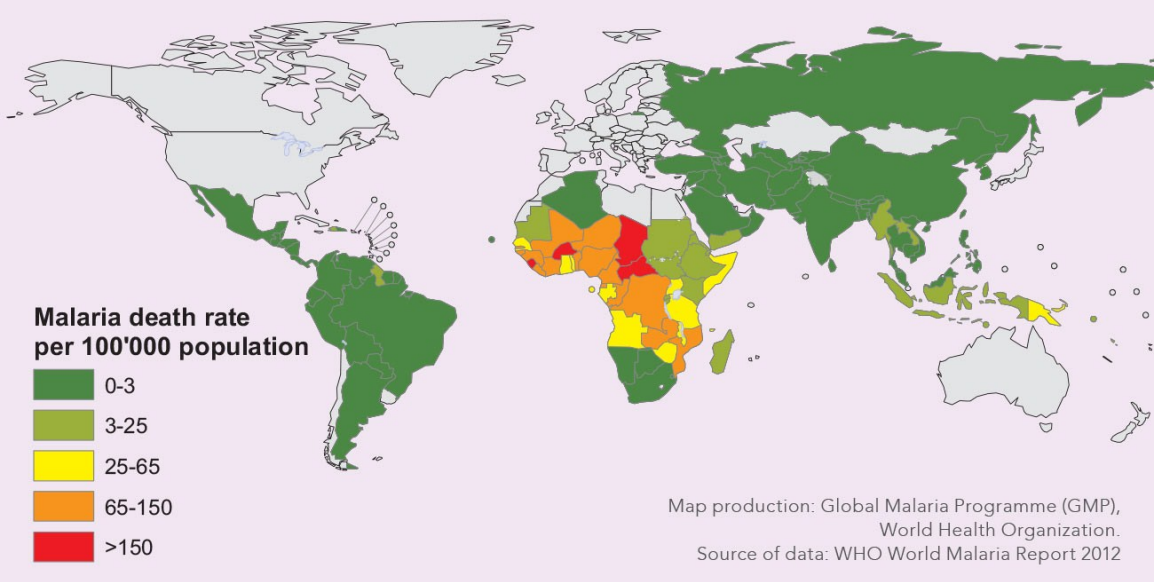


Figure 2: Global distribution of malaria deaths per 100,000 population

(WHO, 2012c)

1.2 LIFECYCLE OF THE PLASMODIUM FALCIPARUM PARASITE

The lifecycle of a *P.falciparum* infection begins as an infected female Anopheline mosquito bites and blood-feeds upon humans, injecting *Plasmodium* sporozoites into the bloodstream (Figure 3; Stage 1). The sporozoites migrate to the liver and invade hepatocytes (Stage 2). Here they multiply and differentiate into merozoites, via a process of schizogonic development that takes approximately 6.5 days.

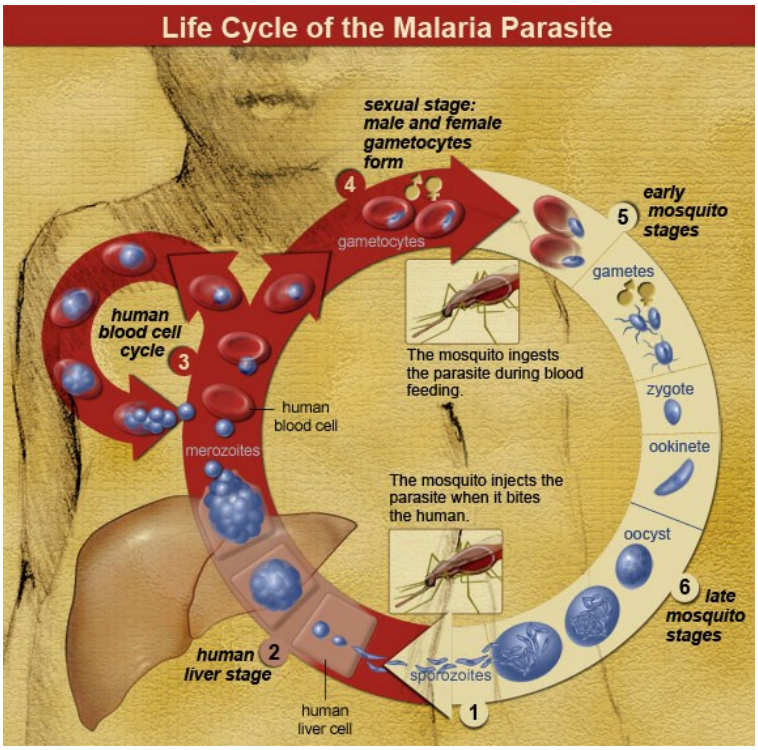


Figure 3: The malaria parasite lifecycle

(Source The National Institute for Allergy and Infectious Diseases, USA (NIAID)

***http://www.niaid.nih.gov/topics/malaria/pages/lifecycle.aspx*: accessed 4th February 2014)**

These forms in turn re-enter the blood stream and commence a cycle of red cell invasion and asexual replication leading to the rupture and release of more merozoites, known as the erythrocytic phase (Stage 3). This multiplication process results in thousands of parasite-infected cells in the host bloodstream, leading to a detectable parasitaemia. The invasion-rupture sequence occurs typically over a period of two days, hence resulting in a periodic fever ("tertiary fever") every 48 hours. *Plasmodium falciparum* is distinguished from other species by its ability to sequester in organs such as the brain causing recognised clinical features such as splenomegaly and cerebral malaria. A subset of merozoites develops within red cells into the sexual

forms of the parasite, male and female gametocyte (haploid) forms that circulate within the blood stream, and may be ingested by a feeding mosquito (Stage 4).

Once inside the midgut of a mosquito the gametocytes mature to gametes (Stage 5). If both male and female gametes are present, they can fuse to form diploid zygotes, which subsequently develop into ookinetes. These motile forms can invade the gut wall of the mosquito and form oocysts (Stage 6); here they undergo multiplication (the sporogonic cycle) from which sporozoites are eventually released into the body cavity of the mosquito. The sporozoites go on to invade the mosquito salivary glands, where they render the mosquito infectious for its next blood meal on humans, completing the lifecycle.

1.3 MALARIA: CLINICAL FEATURES, TRANSMISSION AND IMMUNITY

Clinical uncomplicated malaria typically presents with a febrile illness and systemic non-specific symptoms such as vomiting and headaches; a picture not dissimilar to other childhood diseases. The symptoms are primarily due to schizont rupture with release of metabolic products of parasite growth and destruction of erythrocytes. Physical signs include fever, tachycardia, jaundice, and even hepato- and spleno-megaly following repeated infections (Eddleston et al., 2008).

Severe malaria may occur gradually or follow a more fulminant and rapidly progressive course. Greenwood *et al.* estimate the mean duration between of onset of symptoms and the development of severe features to be 1.8 days if untreated (Greenwood et al., 1991). In adults, severe malaria may be complicated by multi-organ damage including renal failure. Children are more likely to present with respiratory distress, severe anaemia and especially cerebral malaria (Eddleston et al., 2008).

It is not clearly understood why some individuals progress to severe malaria whilst others may regress to asymptomatic infections. The age of the patient and the local intensity of transmission may determine susceptibility to develop more serious complications (Reyburn et al., 2005, Okiro et al., 2009, Roca-Feltrer et al., 2010), but may also be influenced by genetics (Kwiatkowski, 2005).

Local transmission is thought to underlie the pattern of protective immunity seen in both children and adults. The acquisition of malaria immunity is not fully understood, but is assumed to be both age (Baird, 1995) and exposure (Snow et al., 1997) dependent, and to develop in a sequential manner. Immunity to severe malaria is attained early in malaria-endemic regions; hence adult severe malaria is not common. With time, immunity to symptomatic episodes of malaria may develop and eventually increase to give immune tolerance to blood-stage parasites (Langhorne et al., 2008a). Maternal immunity can be passed placentally, and protects infants for a short period post-partum. The presence of foetal haemoglobin also impairs parasite development. This protective effect wanes over the first few months as passively-acquired maternal immunity declines and foetal haemoglobin is replaced with adult forms. This renders children under the age of five particularly susceptible to infection and progression to severe states (Riley et al., 2001). Figure 4 depicts the patterns of severe disease and malaria mortality in three transmission intensity settings, taking into consideration the effect of seasonality.

The process by which immunity to severe malaria is acquired is believed to be step-wise, and may be rapid (Gupta et al., 1999a). However the rate by which this immunity is acquired is thought to be different for different manifestations of severe malaria, e.g. respiratory or cerebral malaria, and also varies with age (Roca-Feltrer et al., 2010, Reyburn et al., 2005). In all transmission settings, levels of severe disease decrease

with age, but especially so at medium-high prevalence with a peak in incidence below the age of five (Carneiro et al., 2010, Griffin et al., 2014).

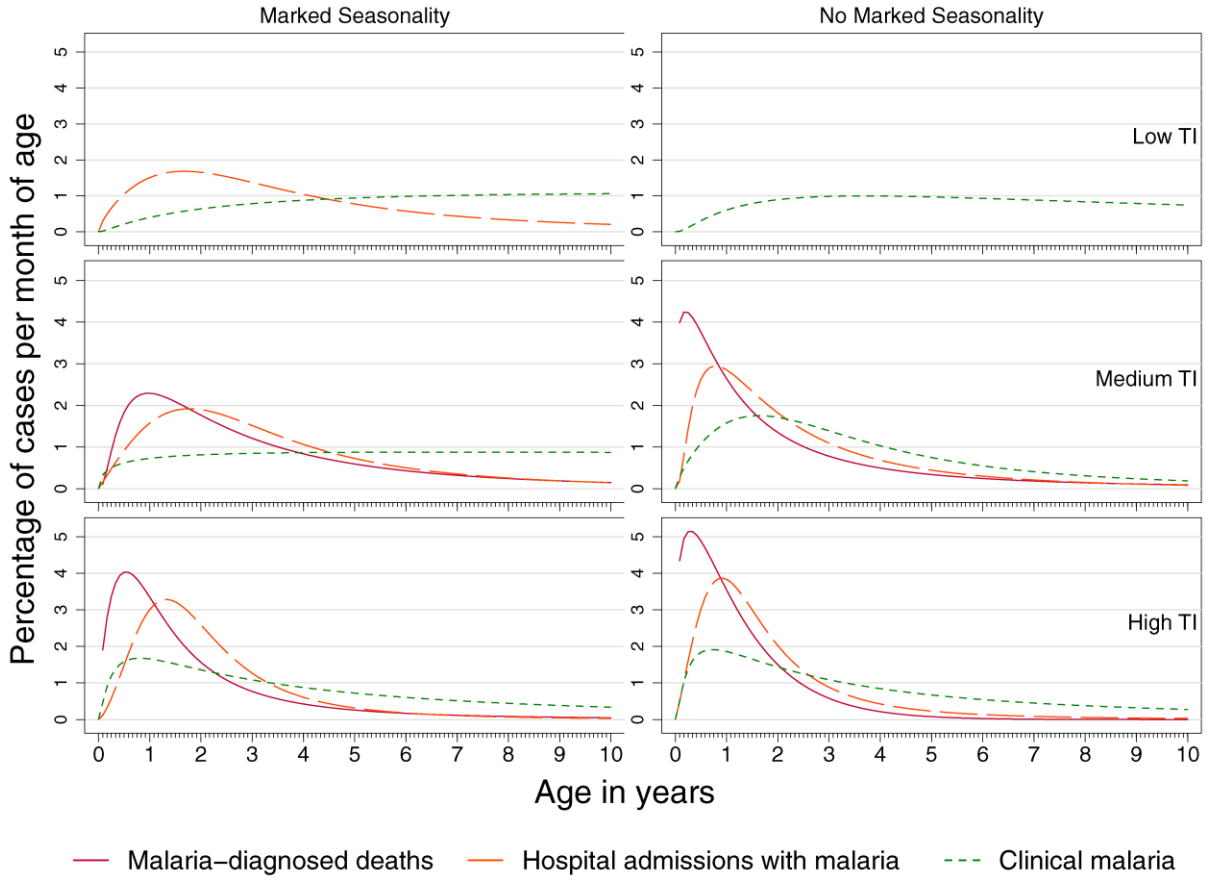


Figure 4: Age-patterns of *P. falciparum* malaria in Sub-Saharan Africa

Percentage of uncomplicated clinical malaria, hospital admissions with malaria and malaria-diagnosed deaths per month of age in children under ten years of age, by transmission intensity (TI) and seasonality of malaria transmission (Carneiro et al., 2010)

Development of immunity to symptomatic clinical malaria occurs at a slower rate than immunity to severe malaria. As indicated in Figure 4, the pattern of disease varies with transmission intensity, with a peak in children between 1 – 10 years of age (Reyburn et al., 2005, Carneiro et al., 2010). Age patterns of parasite prevalence are determined by multiple complex immune responses that influence the demography and proportion of the population that is symptomatically infected and asymptomatic.

The blood-stage immune response that develops over time results in a reduction in parasite densities and hence can lead to a lower proportion of detectable infection in older children and adults compared to young children. Parasite prevalence could also be influenced by a pre-erythrocytic immune response that reduces the rate of re-infection (Bretscher et al., 2011, Collins and Jeffery, 1999, Griffin et al., 2014). Whilst the magnitude of the acquired pre-erythrocytic response is poorly characterised (White et al., 2013), it may

account in part for the age patterns seen; namely prevalence is highest typically in children and decreases with age (Drakeley et al., 2005, Griffin et al., 2014).

The transmission intensity of malaria, calculated by the factors described in Section 1.2 - namely the EIR and the force of infection - is also dependent on vector-related quantities (Hay et al., 2010, Guerra et al., 2008) including the biting rate of the mosquito and the human blood index, which measures the proportion of mosquito blood meals that are taken from humans (Anderson RM, 1991). As a result malaria transmission is also impacted by changes in mosquito densities resulting in temporal variation and seasonality dependent on rainfall (Carneiro et al., 2010, Drakeley et al., 2005). Malaria transmission may also vary at a community level due to local drainage and standing water forming larval breeding site (Smith et al., 2004a) or even due to housing with eaves allowing vector entry (Lindsay and Snow, 1988). Even within households, there may be heterogeneous transmission due to heterogeneity in mosquito biting due to use of LLINs and sleeping times, skin exposure or other personal characteristics such as smell (Knols et al., 1995, Burkot, 1988).

1.4 ERADICATION, ELIMINATION AND CONTROL

Malaria has haunted mankind for centuries. Descriptions of the symptoms and signs of malaria date back to the origins of recorded history, and recognition of the association with the presence of stagnant water led the Romans to initiate drainage programmes and swamp clearance to reduce levels of disease (Feachem et al., 2010). From an epidemiological perspective, the aims of strategies to reduce levels of malaria transmission are demonstrated in Figure 5, and may be defined as (Mendis et al., 2009, Moonen et al., 2010):

1) Control: a reduction of the disease burden to a level at which it no longer represents a public health problem
2) Elimination: the interruption of local mosquito-borne transmission and a deliberate reduction of infection incidence to zero in a delineated geographical area; interventions are actively required to prevent re-establishment including activities to identify and manage small foci of both clinical and asymptomatic infections that may perpetuate transmission.
3) Eradication: the permanent global reduction of infection incidence to zero through deliberate efforts; interventions are thus no longer required.

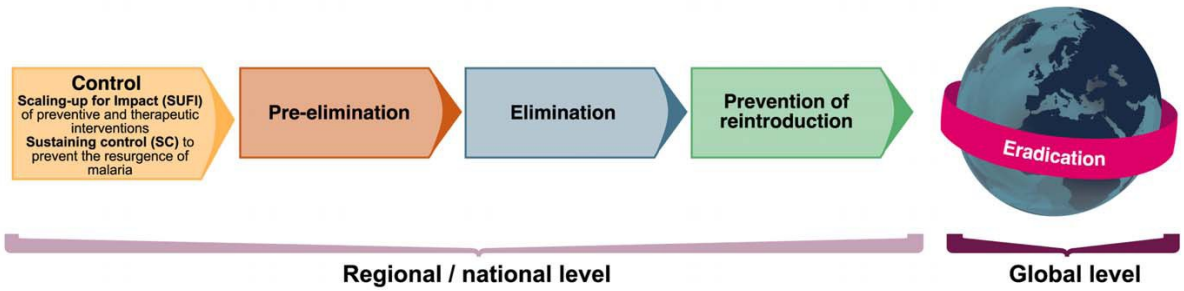


Figure 5: Epidemiological milestones of reducing malaria transmission

(Alonso et al., 2011b)

Initial eradication programmes during the late 1950s collapsed within 20 years, and many of the early gains in countries which had not eliminated malaria were quickly reversed. In the 1990s international focus returned to disease control through the Millennium Development Goals, and the Roll Back Malaria initiative with some significant success (Feachem et al., 2010).

In October 2007, the Bill and Melinda Gates Foundation altered the paradigm of current efforts by calling for a shift of strategy from malaria control to a new goal of global eradication, since echoed by the WHO and other major donors (Mendis et al., 2009). The feasibility of eradication is still contentious, given the multiplicity of vector species with diverse feeding and breeding habits, and complex epidemiological, economic, social and political contexts (Alonso et al., 2011b). It is however believed that local elimination

may be possible in many parts of the world (Greenwood, 2009, Feachem et al., 2010). Guerra *et al*. estimated that 1 billion people are at risk of unstable malaria transmission, and that in these areas elimination is epidemiologically feasible (Guerra et al., 2008).

Epidemiological planning for the success of malaria control depends in part on the basic reproductive number for malaria, R_0. Smith *et al*. (Smith et al., 2008) estimated R_0 for 121 African populations, ranging from around one to more than 3,000. Their results support the conclusion that malaria elimination presents varied challenges across the transmission spectrum. In populations where R_0 is highest, elimination will require multiple, integrated methods, including a focus on those bitten most and who drive transmission.

At present, of 97 countries in 2013 with ongoing malaria transmission, 12 are classified as in the pre-elimination phase of malaria control, and 7 in the elimination phase, with a further 7 in the prevention of re-introduction (WHO, 2013).

1.5 MALARIA CONTROL INTERVENTIONS

Existing malaria control interventions may be aimed at either treatment or prevention of infections targeting both the malaria parasite and the mosquito vector. Treatment of clinical episodes of malaria may reduce symptoms and seeks to clear parasitaemia through elimination of blood-stage parasites. Recommended treatment has evolved over the past two decades due to drug resistance, however the current first-line drug as per the WHO guidelines is artemisinin combination therapy (ACT); further discussed in Section 1.6 (WHO, 2010a). Antimalarial drugs may also be used to prevent malaria infections, especially in those groups at high risk of infection or vulnerable to morbidity, e.g. pregnant women, as listed in Figure 6. More recently, interest has grown in using drugs across entire populations to clear asymptomatic or sub-patent infections in order to reduce onward transmission.

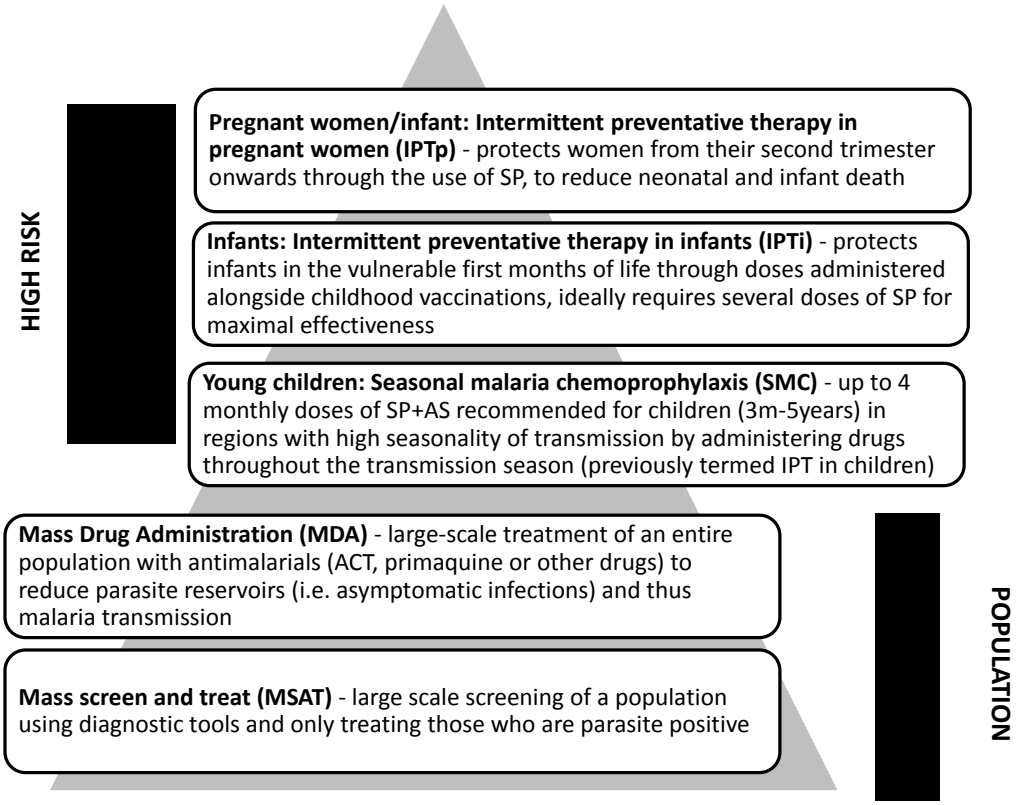


Figure 6: Schematic depicting the use of antimalarial drugs as prophylactic malaria control interventions.

Interventions taregtting in high risk groups (pregnant women (Gross et al., 2011, Gosling et al., 2011), infants (Aponte et al., 2009, Schellenberg et al., 2011) and young children (Greenwood, 2006, Gosling et al., 2011)) and as population–level measures (Gosling et al., 2011, Okell et al., 2011, Shekalaghe et al., 2011)

Currently recommended interventions that target the vector are aimed at preventing malaria infection occurring through two mechanisms a) by killing the mosquito or any of its life-stages or b) by providing barrier-contact between mosquitoes and human. Figure 7 depicts the most commonly used vector control interventions.

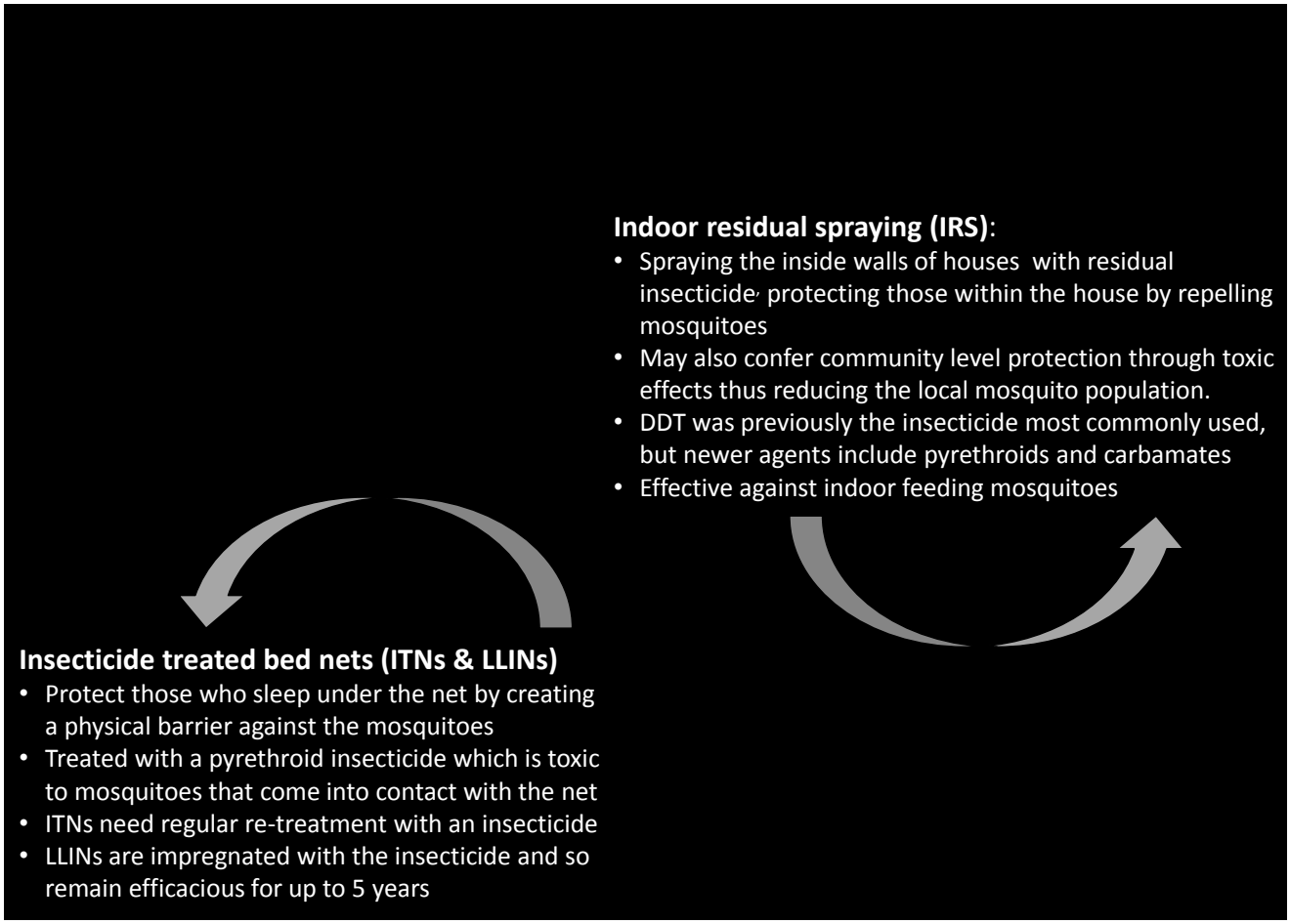


Figure 7: Schematic depicting vector control interventions.

Interventions targeting house walls with residual insecticide(Pluess et al., 2010) (Indoor Residual Spraying) and insecticide-treated nets(Lengeler, 2004) inside the house including long-lasting insecticide treated nets (LLINs)(Kilian et al., 2011)

1.6 THE ROLE OF ACT IN REDUCING TRANSMISSION

The *Artemesia annua* plant has long been used as a herbal remedy in China but only recently recognised as an effective anti-malarial by policy makers, especially against *P. falciparum* and even more so when in combination with other anti-malarials (White, 1997). Artemisinins were first used in South-East Asia where high levels of resistance were noted in response to other anti-malarials, but use has grown since 2001 and Artemisinin Combination Therapies (ACT) are now the first line treatment for uncomplicated and severe malaria recommended in WHO guidelines (WHO, 2010a). Several different partner-drug combinations of ACTs exist with varying dosage schedules, but the most commonly used ACT in Africa is artemether-lumefantrine (AL) followed by artesunate-amodiaquine (AS-AQ) (Littrell et al., 2011a).

1.6.1 ACT as treatment

ACTs are recognised to produce the most rapid clearance of parasites and decline in the symptoms of malaria associated with parasitaemia of all anti-malarial therapies in current use (White, 1997, Sinclair et al., 2009). Despite a relatively short half-life compared with other treatments (Stepniewska et al., 2008), ACTs are active against all stages of malarial parasite, except late stage gametocytes (Stages 4 and 5 in Figure 3), and thus are highly effective at clearing infection provided the full dosage is taken (Sinclair et al., 2009). However as a result of the relatively short half-life of artemisinin re-infections may be common and thus the partner drug in the combination is important in clearing any residual parasites (Adjuik et al., 2004, White, 1997, Sinclair et al., 2009).

1.6.2 ACT effects on gametocytaemia and onward infectiousness (transmission)

The aim of antimalarial treatment is to achieve clearance of the asexual stages of the parasite since these are mainly responsible for the symptoms of malaria. However, effective clearance of asexual parasites should also mean clearance of the gametocytes they produce, thereby reducing the individual's infectiousness to any mosquito taking a blood meal and thus onward transmission (Okell et al., 2008b, Warrell, 2002).

The duration of time for clearance of *P. falciparum* gametocytes from the circulation of a treated patient is longer than the time taken for clearance of asexual stages (White, 1997). The rate at which the gametocytes are reduced varies by the nature of treatment administered, and although most anti-malarials exert some anti-gametocyte action (Nosten and White, 2007), some studies show that there are circumstances in which the release of gametocytes is promoted by treatment (Sowunmi et al., 2007), thereby increasing an individual's onward infectivity (Dunyo et al., 2006). The only licensed anti-malarial with a full-spectrum action against gametocytes is primaquine, one of the family of 8-aminoquinolines (Price et al., 1996). This

drug is used for treatment of *Plasmodium vivax* as it additionally kills the hypnozoite stage of that infection. However, it cannot be used in infants or individuals with G6PD deficiency (WHO, 2010a). Despite this, low dose primaquine has been recommended by the WHO, to be used alongside ACTs in areas of low prevalence in order to block onward transmission when moving towards elimination (White, 2013, White et al., 2012).

Artemisinin derivatives are also known to have specific anti-gametocyte properties (Sinclair et al., 2009, Price et al., 1996, Sowunmi et al., 2007), reducing the duration of gametocyte carriage *in vivo* faster than non-ACT antimalarials (Bousema et al., 2010) and reducing onward infectiousness compared to previous first line treatments (Sawa et al., 2013, Okell et al., 2008b, Ezzet et al., 2000, White, 2008). ACTs are thought to also be able to reduce malaria transmission through their post-treatment prophylactic effect, which is contributed mainly through the partner-drug of the ACT rather than the artemisinin derivative (Sinclair et al., 2009). The studies estimating the durations of these effects are discussed further in section 3.3.2.2, but ACTs are believed to have a potential role through "treatment-as-prevention" in malaria control and elimination efforts (White, 2008).

1.6.3 The use of ACT for transmission control

Previous campaigns to use curative doses of anti-malarials for transmission control through Mass Drug Administration (MDA) have been unsuccessful due to the development of parasite resistance, difficulties scaling up to required levels of coverage, drug contraindications (e.g. pregnancy) and individual reluctance amongst a wealth of other reasons (Greenwood, 2010). A recent Cochrane review of MDA programmes over the past 50 years concluded that the strategy reduced the initial risk of malaria parasitaemia substantially. However, this impact was rarely sustained beyond 6 months, and those that did were conducted on small islands or in highland settings (Poirot et al., 2013).

However, the use of ACT in order to reduce population transmission intensity as a result of its gametocytocidal action has garnered much interest recently. Unlike primaquine, ACTs are suitable for general first-line treatment of malaria, thus potentially could have a role in reducing overall population-level transmission if appropriately rolled out at scale. Evidence for the impact of ACT on transmission is derived mainly from areas where ACT has been deployed as first-line therapy, where subsequent reductions in prevalence or clinical disease have been noted.

Barnes *et al* (Barnes et al., 2009) published a review of the impact of a large scale deployment of ACTs in South Africa, Zambia and Ethiopia. They note that Zambia, one of the first countries to adopt ACT as first-line therapy alongside scaling up of vector control, has experienced decreases of 61% in-patient severe cases and

66% deaths since their introduction, as well as a 91-93% reduction in severe malaria cases at health facilities (Zurovac et al., 2007) (Figure 8A below).

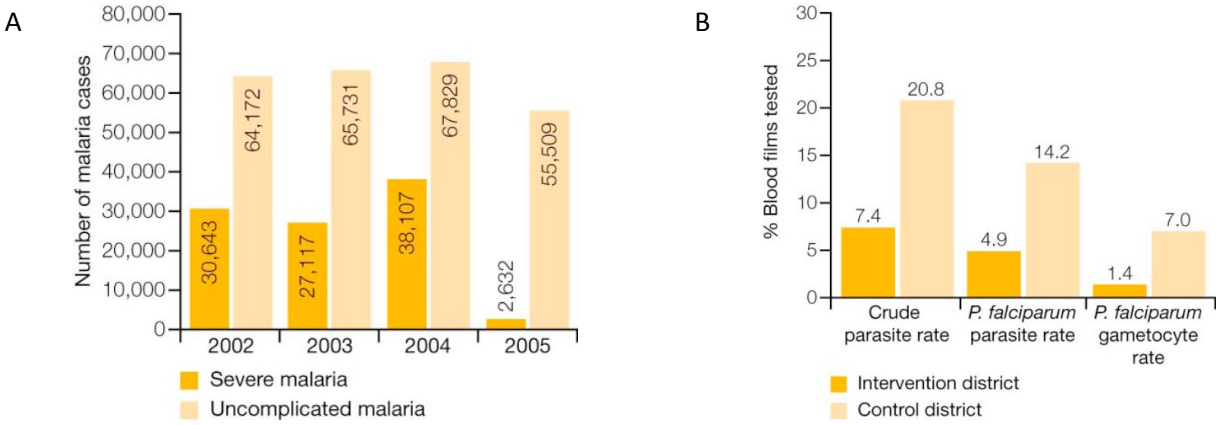


Figure 8: Large scale use of ACTs in Zambia and Ethiopia.

A) Number of cases of severe and uncomplicated malaria in Zambia by year (from 18 cost-effectiveness study sites). B) Malaria parasite reservoir in the control and intervention districts of the Tigray study region. Malaria parasite reservoir was three-fold lower in the intervention district during 2005 high-transmission season. (Barnes et al., 2009)

Similarly, in Kwa-Zulu Natal (Barnes et al., 2009, Barnes et al., 2005) treatment with AL was used as first-line therapy, in combination with strengthening of vector control. This provincial use caused the number of malaria-related outpatient cases and hospital admissions to each fall by 99% from 2001 to 2003, and malaria-related deaths decreased by 97% over the same period, with this sustained for seven years since the original deployment. A prospective study with 42 days follow up also showed that AL had a cure rate of 99% and prevented gametocyte development in all patients(Barnes et al., 2009).

In Ethiopia, AL was introduced as first-line anti-malarial treatment in 2004 in the Tigray region in a community-based programme (Lemma et al., 2010, Barnes et al., 2009). Over the two-year study period, they found that this method of deployment of AL significantly lowered the risk of malaria-specific mortality by 37%. A study comparing the malaria parasite reservoir was three-fold lower in the intervention district than in the control district during the 2005 high-transmission season (Lemma et al., 2010), which is depicted in Figure 8B above.

Other reports of the use of ACT reducing transmission include Bhattarai *et al.* who documented that following deployment of ACTs (AS-AQ and AL) in the public sector in Zanzibar 2003 (Bhattarai et al., 2007), although malaria-associated morbidity and mortality did not show any change initially, within 2 years diagnoses and deaths declined significantly. *P. falciparum* prevalence in children decreased in this time period (2003 – 2006) and LLINs (long-lasting Insecticide-treated nets) were not introduced until 3 years after deployment of ACTs.

Nosten *et al* (Nosten et al., 2000) published some of the first reports of the impact of large-scale use of ACT on the Thai-Cambodian border, an area known for high levels of drug resistance (White, 2004, Pongtavornpinyo et al., 2008). The mean monthly incidence of symptomatic malaria was 3.7% in the two years prior to the introduction of ACT. Although incidence and transmission had been decreasing slowly in the region at that time, following widespread ACT (AS-MQ) use the incidence of malaria fell to a mean of 1.58% per month. This was further substantiated by a further study (Carrara et al., 2006), in a region of the border distinct from that studied by Nosten, where a decrease in *P. falciparum* incidence of 40-50% was seen within a year of introducing AS-MQ as first line treatment.

The results of these studies indicate a trend of the widespread use of ACT as first line treatment for *P. falciparum* malaria being associated with a reduction in malaria transmission, although there are a number of confounding factors and it is not clear whether these effects would occur at different transmission intensities.

Okell *et al* developed a mathematical model to predict the potential impact on transmission outcomes of introducing ACT as first-line treatment for uncomplicated malaria, under conditions of varying intensity in Tanzania (Okell et al., 2008a, Okell et al., 2008b). They predicted that the relative reductions in prevalence of infection and incidence of clinical episodes achieved by ACT would be highest in the areas with low baseline transmission. In real terms however, Okell *et al* noted that in high transmission areas 54 clinical episodes per 100 persons were averted as compared with 5 per 100 persons in low transmission settings assuming that coverage of treatment was high (100%)(Okell et al., 2008b). Okell *et al* also estimated variations in the impact that could be achieved by antimalarials with different efficacy, prophylactic time, and gametocytocidal effects. An efficacious antimalarial regimen without any specific gametocytocidal properties but which produces a long duration of inhibitory anti-malaria effect, i.e. long prophylactic time, was predicted to be more effective at reducing transmission than a short-acting ACT in the highest-transmission setting.

Shekalaghe *et al* conducted the first study of MDA in mainland Africa using ACTs; a cluster-randomized trial in four villages in Tanzania, to test the use of artesunate (with primaquine and SP) given over 3 days in an area of very low and seasonal malaria transmission. Parasite prevalence decreased from 2.2-2.7% at baseline to undetectable following the intervention in both control and intervention clusters. As a reduction in transmission intensity in this region had occurred prior to the intervention, whether due to ITN use or presumptive treatment with ACTs, the impact of MDA was difficult to assess in this setting (Shekalaghe et al., 2011).

In contrast to MDA, MSAT involves treating only parasitaemic individuals identified through either field tests or more formal laboratory PCR in order to treat asymptomatic carriers and reduce the pool of parasites thereby also transmission (Greenwood, 2010). Tiono *et al* conducted a cluster randomised-controlled trial of community-wide screening and treatment in 18 malaria-endemic villages in Burkina Faso, using rapid diagnostic tests (RDTs) and ACTs. At 12-month follow-up, the incidence of symptomatic malaria episodes in under-fives (U5s) did not differ between control or intervention areas. The authors concluded greater levels of parasite clearance may be needed to impact malaria transmission sustainably in such settings (Tiono et al., 2013). Similarly a randomised controlled trial in 101 schools in Kenya using MSAT (with RDTs and ACTs) found that over a 2 year follow-up period there were no significant improvements in parasitaemia or anaemia. In addition, there appeared to be no school-wide improvement in the consequences of ill-health such as educational indices (Halliday et al., 2014).

Mathematical modelling of mass treatment by Okell *et al* predicted MDA could provide sustainable reduction in transmission in low transmission settings (for at least 2 years), but this was likely to last less than 1 year in high prevalence scenarios (Okell et al., 2011). Adding vector control measures potentiated the impact of recurrent courses of MDA due to a reduction in infectious bites (due to the diminished infectious reservoir), indicating that MDA or MSAT strategies need to be in combination with other control interventions and repeated for sustainable impact.

1.7 MATHEMATICAL MODELS OF MALARIA TRANSMISSION

Simple models of malaria transmission were amongst the earliest attempts to understand the biological processes underlying transmission in a mathematical form, or through *'a priori'* modelling (Ross, 1911). Ross (Ross, 1911) was first to apply mathematical models to infectious disease and is considered the forefather of malaria modelling. Later Macdonald used simple mathematics to capture the critical steps of the transmission cycle, involving both human and mosquito (Macdonald, 1957).

The schematic given in Figure 9 (McKenzie and Samba, 2004) indicates the basic structure of the Ross and Macdonald models. In a steady state population, individuals can be allocated to distinct compartments, namely susceptible, infected (i.e. a latent period during which the individual is infected but not able to transmit the infection) and infectious. Infection is assumed to occur as a result of random mixing between humans and mosquitoes in the relevant infectious or susceptible states leading to infection spread. This is dependent on relative mosquito population size, human-blood meal rate, the prevalence of infection in both human and mosquitoes, and the probability of transmission from human to mosquito and vice versa. The model assumes that mosquitoes die before they recover but that humans can recover from infection.

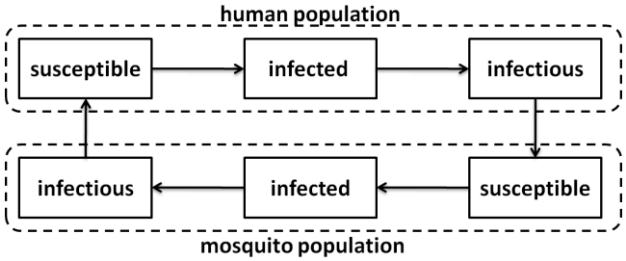


Figure 9: Schematic diagram of the Ross-Macdonald model

(McKenzie and Samba, 2004)

The Ross-Macdonald model can be used to derive the relationship between variables such as the proportion of infectious (sporozoite-positive) mosquitoes, parasite prevalence (PfPR), the EIR (number of infectious bites each individual receives annually) and the basic reproductive number (R_0: the average number of secondary infections arising from a typical primary case in a fully susceptible population). In malaria, this consists of the product of reproductive numbers (R_0) concerning both mosquito-to-human infections and human-to-mosquito infections (Anderson RM, 1991). Insights from Ross-Macdonald type models, such as the sensitivity of transmission to the ability of adult mosquitoes to survive the latent (infected) period, were used to inform policies during the eradication efforts of the 1950s, such as the deployment of indoor residual spraying (IRS) as a vectorcidal measure (Anderson RM, 1991, Benenson, 1997).

In the 1970s, a large-scale malaria elimination programme influenced by Ross-Macdonald modelling, was undertaken in an area of northern Nigeria with known high transmission. This landmark programme became

known as the Garki Project (Molineaux and Gramiccia, 1980). Using the data collected as part of the Garki Project, Dietz and Molineaux developed a more sophisticated age-structured transmission model, and incorporated both the phenomenon of super-infection, i.e. infection with different parasite clones which may extend duration of infection (Anderson RM, 1991) and explicit considerations of human immunity, including the loss of infectivity, loss of detectability and increased recovery rate (Dietz et al., 1974, Molineaux et al., 1978). The aim of this model was to generate comparative forecasts for specific interventions, conditional upon given entomological inputs (Molineaux and Gramiccia, 1980, Molineaux et al., 1978).

Since then, mathematical models of malaria have evolved to reflect our progressive understanding of malaria immunology, seasonality and climate dependence, and vector biology, and of the development of novel interventions such as transmission blocking treatments such as ACTs and candidate malaria vaccines (Smith et al., 2008, Griffin et al., 2010, McKenzie et al., 2002, Griffin et al., 2014). With the recent policy swing towards elimination and eradication, intervention-focussed modelling has been particularly emphasised including LLINs (Smith et al., 2009a), increased access and coverage of ACTs (Okell et al., 2008a, Griffin et al., 2010), mass treatment with ACTs (Okell et al., 2011), ACT resistance (Yeung et al., 2004, Pongtavornpinyo et al., 2008) malaria vaccines (Tediosi et al., 2009, Penny et al., 2008) as well as packages of available tools (Smith et al., 2008, Griffin et al., 2010, Griffin et al., 2014).

A particular difficulty when modelling malaria transmission is the incorporation of immunity. *Plasmodium falciparum* infections induce an increase in clinical immunity with exposure to the parasite, and this acquisition is dependent on an interaction of parasite, vector, host and environmental factors (Miller et al., 2002). However this immunity is only partial, and aside from altering risk age-groups for infections, can also affect the probability of developing clinical symptoms despite being infectious (Snow et al., 1997, Smith et al., 2004b). Thus, despite imperfect understanding of this phenomenon, there has been emphasis on exploring and modelling this relationship of immunity with clinical incidence and parasite rates across a range of transmission settings (Snow and Marsh, 2002, Filipe et al., 2007) as well as fitted to and validated against data collected in the field (Ghani et al., 2009, Smith et al., 2005, Smith et al., 2008, Griffin et al., 2010, Griffin et al., 2014, Griffin et al., 2014).

As the feasibility of control and elimination strategies are still being debated, malaria models form a vital tool with which to explore the expected impact of interventions against malaria, both individually and in combination.

1.7.1 Transmission modelling and health systems

A health system is, according to the WHO definition, "the sum of all organizations, institutions and resources whose primary purpose is to improve health" (WHO, 2007). Whilst policymakers often use decision analytical and cost-efficiency modelling to guide decisions (Ringel et al., 2010, Weinstein et al., 2001) as well as business cases of economic impact (McKinsey, 2008), the implications of health systems issues are not frequently explored explicitly in transmission models.

Tediosi *et al* used a decision-tree modelling approach to predict incidence and mortality, and integrated this into a malaria transmission model to predict the cost-effectiveness of treatment in different prevalence and coverage scenarios (Tediosi et al., 2006). Their model predicted high treatment rates exerted a proportionately greater epidemiologic impact at low transmission levels, most likely due to increased clinical presentation. Cost-effectiveness analysis has been used to evaluate the use of RDTs to reduce childhood mortality in different transmission settings (Rafael et al., 2006, Lubell et al., 2008). However previous studies modelling health systems effects on malaria transmission were not identified.

The impact of health systems and case management on transmission has been explored for other infectious diseases. White *et al* considered the need for prompt treatment of sexually transmitted infections, and the ability of genitourinary medicine services to provide appropriate and timely care in the face of increasing demand (White et al., 2005). This exploration of the relationship between capacity and demand for care demonstrated that at high levels of incidence, inadequate treatment capacity leads to high levels of untreated infections which in turn fuel further incidence and demand rendering health care provision even more inadequate. His results suggest that a substantial increase in capacity is essential to interrupt the "vicious" cycle in the dynamics of infection and provision of healthcare, to ensure a more "virtuous" cycle in which adequate levels of treatment lead to lower levels of infection, demand, improved health and cost savings.

1.8 MALARIA AND HEALTH SYSTEMS

The risk of malaria and its sequelae is influenced not only by immunity, social and behavioural factors but also by the prevailing political and economic environment. Kaplan highlighted in his analysis of the role of epidemiology in poverty reduction that global patterns of malaria are not random nor due to any particular biological vulnerability, but instead correspond to global patterns of poverty and resource allocation (Kaplan, 1998). Indeed poverty is recognised as the most potent risk factor for malaria (Lucas and McMichael, 2005), with the poorest strata of the global population suffering over two-third of all infections (Guerin et al., 2002). In addition, the linkages between poverty and worse outcomes are well documented (Farmer, 2005, Sen A, 1998) as seen in Figure 10 highlighting the countries from sub-Saharan Africa.

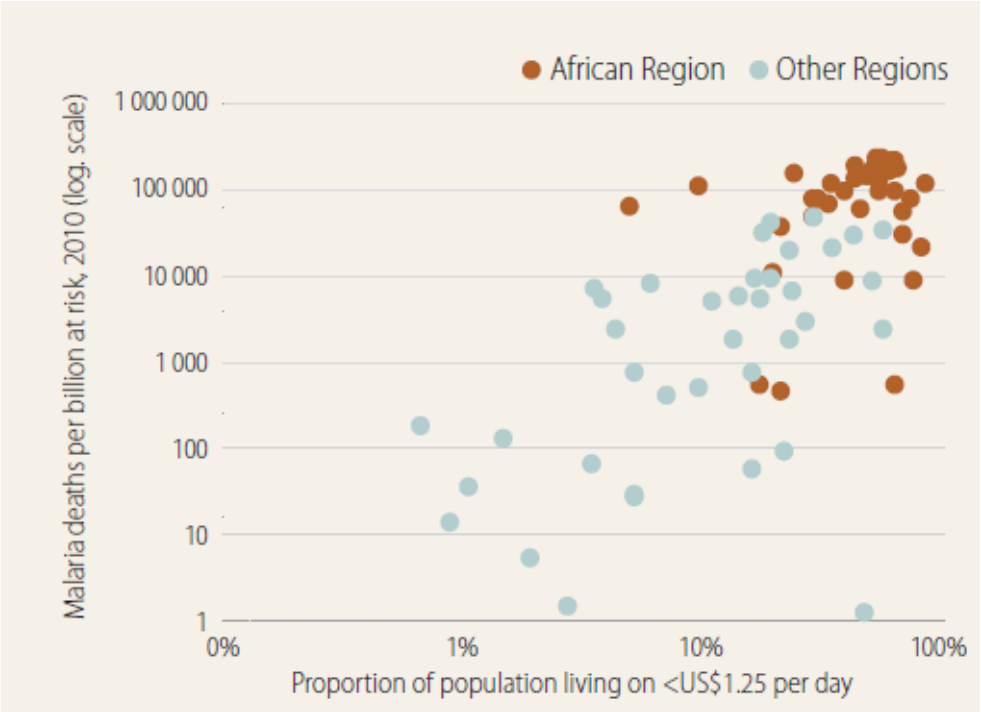


Figure 10: Relationship between proportion of country's population living in poverty and malaria mortality rates.

Source Human Development Report 2011

Despite promises made at Alma Ata in 1979, reforms due to rising national debts brought widespread cuts in public spending on health and education in the late 1970s and 80s (Peabody, 1996), which were followed by rising infant mortality rates and a decrease in other measures of population health (Manfredi, 1999). Manfredi suggested in his analysis of the resurgence of malaria in the latter half of the 20th century that these debt reforms may have laid the terrain for this at both micro and macro levels (Manfredi, 1999). The impoverishment of the public health sector and resulting reduction in government provision of healthcare can lead to a greater need for out-of-pocket spending for healthcare. At the same time rising health care

costs may also delay treatment seeking for serious cases of malaria. Economic deprivation leads to environmental degradation and also at a policy level can divert the resources necessary to address environmental risk factors for malaria. Finally, worsening women's health, resulting from the uneven allocation of household resources in scarce times, can cause less investment at a household level in child and infant health. Peabody suggests that reductions in investment in publicly provided healthcare led to reduced staffing levels and impoverished infrastructure (Peabody, 1996). Packard notes in his history of malaria that conditionalities on loans by agencies such as the World Bank such as limits to wages in Zambia, led many trained healthcare workers to leave the this sector or take better-paying jobs abroad (Packard, 2007, WHO, 2006), leaving local African health systems underfunded, understaffed and incapable of delivering of antimalarials and other essential healthcare to these areas further ravaged by HIV/AIDS, fuelling a spiral of disease and poverty.

Treatment for malaria has also suffered from neglect in the past due to weak health systems globally. Factors believed to limit effective large-scale use of ACTs in sub-Saharan Africa include: availability of ACTs and high risk of stock-outs in the public sector; the high cost of ACTs and the rise in the availability of counterfeit drugs and continued presence of artemisinin-derived monotherapies through the informal sector; a lack of knowledge and public awareness about combination therapies (Newton et al., 2006, Kaur et al., 2008, Mutabingwa, 2005, Yeung et al., 2004), and the erosion of primary health care systems throughout Africa (Alilio et al., 2004). This is further discussed in Chapter 2. The WHO estimates that a package of essential health care services needed to deliver the health-related goals set by the Millennium Development Goals (MDG) which include targets for malaria treatment and prevention as well as equitable access to quality essential service, requires approximately US$44 per capita per annum in low income countries. In 2009, none of the 29 least-developed nations reached this level (Taskforce for Innovative Financing for Health Systems, 2009).

1.9 THESIS AIMS

Health systems can impact on the outcomes of preventative and curative interventions against malaria. The aim of this thesis is to use mathematical models to provide insight to the effect of health systems factors acting as barriers to the effectiveness of ACTs considering dimensions of access to care, the different sectors through which care is delivered and the quality of care provided, and to estimate the effect of overcoming these barriers.

- **Chapter 2:** I review the literature and consider interventions to overcome the health systems barriers to successful malaria treatment
- **Chapter 3:** I develop through an iterative process malaria transmission models incorporating health systems variables including the treatment of non-malarial febrile illness, private sector outlets and tertiary level management of severe disease.
- **Chapter 4:** I develop a decision-tree approach to estimating quality of care and explore the impact of improving appropriate treatment for fever on malaria and non-malarial febrile illness (NMFI) case management
- **Chapter 5:** I use the models developed in Chapters 3 and 4 to explore the impact of health systems interventions on transmission and clinical outcomes in a mainland Tanzania case study
- **Chapter 6:** I discuss the implications of the model findings with respect to health systems interventions in malaria control programmes regionally and nationally

Throughout this thesis I aim to demonstrate that mathematical models provide an ideal framework to examine the complexities of health systems strengthening, enabling the synthesis of data and practices from across different disciplines and regions, and having a role in guiding malaria control policy.

2 OVERCOMING HEALTH SYSTEMS BARRIERS TO SUCCESSFUL MALARIA TREATMENT

2.1 INTRODUCTION: THE CONUNDRUM OF HEALTH SYSTEMS

Over the past ten years, rapid scale-up of preventative interventions against malaria have resulted in substantial declines in the burden of disease (WHO, 2011a). Whilst such trends are encouraging, the risks of malaria morbidity and mortality remain influenced by the performance of prevailing health systems (Stratton et al., 2008, de Savigny D, 2009). The success of national malaria control programmes is increasingly recognised to be handicapped not only by resource constraints but also by the absorptive and technical capacities of the health systems to deliver interventions at the required levels of coverage and quality (WHO, 2011a, de Savigny D, 2009). Given that international funding for such programmes is expected to plateau, it is critical to better understand how to implement a proven intervention most effectively through an existing system, and where the barriers are to an intervention achieving its predicted potential (WHO, 2011a, Alonso et al., 2011a).

The failure of previous 'vertical' attempts to eradicate malaria (1955 – 1969) illustrates that sustained disease control requires integration into a functioning and efficient health system (Stratton et al., 2008, de Savigny D, 2009, Alonso et al., 2011a). Although substantial progress has been made in understanding the strengthening of health systems, much of the evidence is context-specific, descriptive or qualitative. High quality evidence on the effectiveness of strengthening interventions into health systems and their resulting impact on health outcomes remain limited.

There have been few approaches to address the delivery of case management. The 'systems effectiveness framework' (Tanner M 1993) outlined by Tanner *et al*. describes how interventions decay in efficacy and are rendered less effective in practice through a cascade of interacting system barriers. This may be applied in the context of anti-malarial delivery (Figure 11): first-line treatment for malaria, Artemisinin Combination Therapies (ACTs), are highly efficacious, but issues such as the proximity of healthcare or availability of diagnostics may exert a sequential and cumulative impact leading to low ACT effectiveness i.e. less than 50% of febrile children being cured (WHO, 2011a).

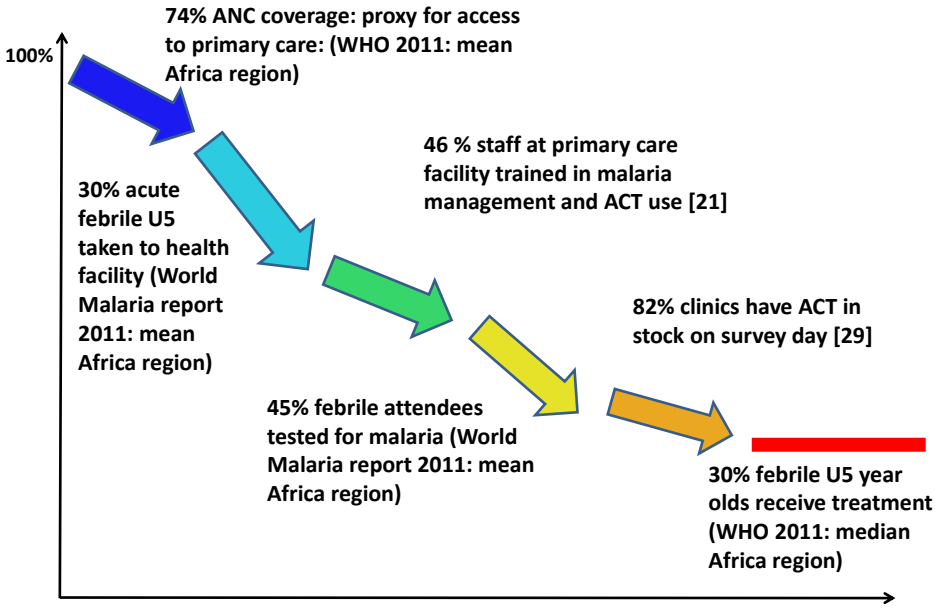


Figure 11: Illustration of the systems barriers to effectiveness for treatment of children under five with fever

Using this framework of barriers to effectiveness, I summarise potential systems constraints into two main categories:

(i) timely access to healthcare

(ii) quality of care at the source of treatment (including human resources, drug stocks and the use of diagnostics),

and review their impact on the implementation of ACT programmes considering both public and private sectors. Additionally, I present a systematic summary of the effectiveness of interventions deployed to target the identified barriers in both the private and public sectors.

2.2 METHODS

2.2.1 Search strategy and selection criteria

From September – November 2011, I searched PubMed, Embase and Ovid Journals databases to identify peer-reviewed articles. I used the following search terms and their variations (i.e. Artemisinin Combination therapy and ACT) in combination: “Africa”, “malaria”, “falciparum”, “health systems”, “delay”, “distance”, “healthcare worker”, “ACT/Artemisinin Combination Therapy”, “antimalarial”, “treatment”, “health facility”, “community health worker”, “home management”, “service delivery”, “travel”, “testing”, “microscopy”, “RDT/Rapid Diagnostic Test”, “private”, “diagnostics”, “drug seller”, “drug shop”, “subsidy”, “AMF-m”, “underdiagnosis”, “overtreatment”, “delivery”, “supply chain”, “stockout”, “staffing”, “shortage”, “training”, quality”, counterfeit” and “pharmacy”. Searches were limited to English-language articles published between January 1981 and November 2011. Additional publications not found in the electronic searches were selected from bibliographies of relevant articles and literature reviews. A formal review protocol was not utilised.

2.2.2 Data extraction and analysis

The abstracts of the identified articles were screened for inclusion: I included randomised controlled trials, quasi-experimental trials, observational and qualitative studies as well as reports from health agencies, e.g. WHO World Malaria Report. I excluded conference abstracts, editorials, letters to the editor, and other grey literature. I also excluded studies on pregnant women, or intermittent malaria treatment programmes. Although “Asia” was not included in the search terms, studies based outside Africa were not excluded. Selected papers were then stratified as either a) summarising barriers to effectiveness or b) reporting on an intervention to improve effectiveness, particularly focussing on studies including the recent WHO diagnostics guidance. For each paper I extracted the following items: study year, country and district/setting, age group, type of study population.

Under the reports of impact of barriers to effectiveness I extracted data under the following headings: distance to healthcare setting with respect to treatment seeking, delays in care and treatment outcomes, staffing levels and training, drug stockouts and quality of care (namely diagnosis and use of ACTs) in the public sector and private (informal) sector. The impact of user fees and cost of accessing care was not considered. For impact of interventions I extracted data under the following headings: drug stockouts and supply chain management, rational case management, training of healthcare workers, community health workers, informal sector training and drug subsidies.

Given the variety of ways in which the data were reported it was not possible to undertake any formal meta-analysis of the results.

2.3 RESULTS

In total, 135 articles were identified through the primary search of the databases and additional searching of reference lists (Figure 12).

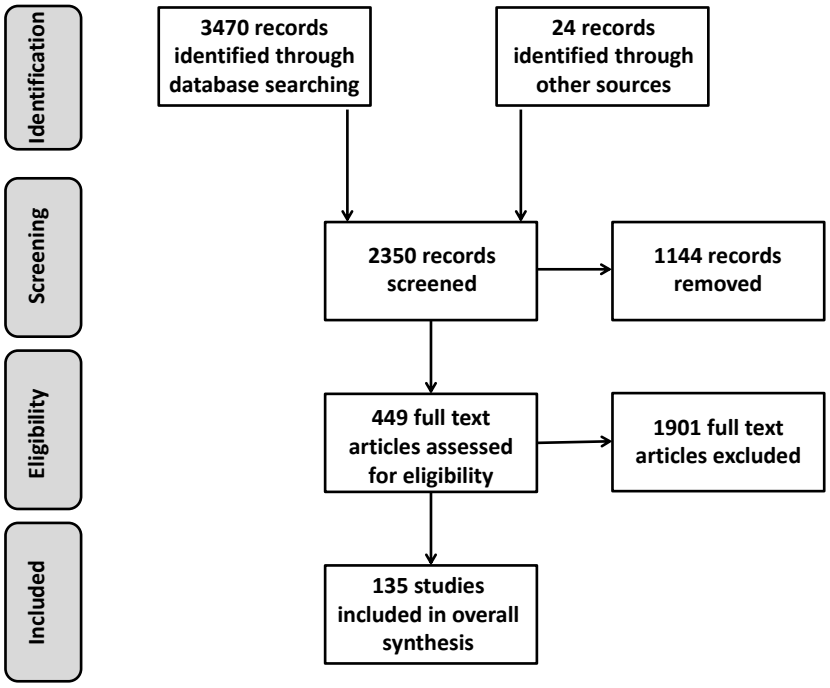


Figure 12: PRISMA diagram: literature search results

2.3.1 Barriers to effectiveness

2.3.1.1 Impact of geographical access, treatment seeking and delays

The geographical distance travelled to access care varies widely across different national and regional settings, e.g. a median of eight kilometres in Ethiopia (Okwaraji et al., 2012) to two kilometres in Kenya (Feikin et al., 2009). This is also dependent on transport infrastructure; for example, in parts of rural Ethiopia over 90% of children live more than 1.5 hours walk from a health centre (Okwaraji et al., 2012). Timely access (less than 24-48 hours after symptom onset) to treatment, especially for the lowest two economic quintiles, is a Roll Back Malaria and Abuja declaration target (RBM, 2005).

The impact of distance on seeking treatment for fever differs by country and context. Most studies reviewed show a clear reduction in accessing treatment with increasing distance to a health facility, e.g. 13.9% per kilometre (Stock, 1983) to 34% per kilometre (Feikin et al., 2009) with access declining to low levels (<10%)

once the health facility is more than five kilometres from the home (Feikin et al., 2009). In addition, families that live further from primary care facilities wait longer to seek care for their febrile child than those living nearby, with a twofold increase in the odds of delay if the distance to healthcare was greater than approximately three kilometres (Getahun et al., 2010).

The impact of distance as a barrier to treating malaria becomes apparent given the narrow time limits for malaria infections to develop more serious complications (Greenwood et al., 1987). Delays in seeking treatment can lead to disease progression requiring inpatient care. Individuals living in close proximity to primary health care services have reduced odds of malaria advancing from mild to severe disease (Feikin et al., 2009, O'Meara et al., 2009, Al-Taiar et al., 2008). O'Meara *et al*. found that the incidence of severe malaria more than doubled as travel time to the nearest primary care facility increased from ten minutes to two hours in Kenya (O'Meara et al., 2009). In 2002, a Malaria Indicator Survey of Papua New Guinea (Mueller et al., 2005) indicated that prevalence of infection was significantly lower in communities living within closer reach of a health facility (22.4% versus 35.6%)(Mueller et al., 2005). Similarly in Côte D'Ivoire the presence of a healthcare facility was associated with protection against malaria infections (Raso et al., 2005).

2.3.1.2 Quality of care

2.3.1.2.1 Staffing and Training

Staff shortages are frequently highlighted as a concern. In Kenya, ten of thirty-four public facilities had to close on the day surveyed due to staff absence (Chuma et al., 2010). A further Kenyan study of 36 government facilities in 2008 (Wasunna et al., 2008) identified inadequate staffing as a barrier to adherence to ACT prescription guidelines, due to additional time required for counselling, direct observation of the first dose, record keeping, and confirming the diagnosis, as well as poor supervision and inadequate quality of training. None of the healthcare workers (HCWs) had been exposed to full training in the use of first-line ACTs, and only half had experience of the minimum intervention training package in one Kenyan study (Wasunna et al., 2010). Similar findings were reported in Uganda, Kenya, Angola and Zambia (Hamer et al., 2007, Zurovac et al., 2008d, Zurovac et al., 2008c, Rowe et al., 2009a, Njogu et al., 2008). Rural and poor areas where the malaria burden is disproportionately high suffer the most critical gaps in trained HCWs (WHO, 2011a, Stratton et al., 2008, WHO, 2007).

2.3.1.2.2 Stockouts

Effective and sustained expansion of a treatment programme requires reliable and uninterrupted stocks. However, poor supply chain management is a common problem (WHO, 2007). In Africa, availability of essential medicines in the public sector is 29.4% compared to 54% in the private sector, albeit with diversity by country (Cameron et al., 2009).

Initially the proportion of public facilities stocking at least one form of ACT, by weight or dosing schedule, on survey day ranged from 51% (2004) (Zurovac et al., 2007) to over 95% (Rowe et al., 2009a, Njogu et al., 2008), with 20% of health centres having no ACT stock (Kangwana et al., 2009). Up to 75% of facilities reported stockouts over the preceding 6 months with a median of 49 to 138 days with no stock (Njogu et al., 2008, Zurovac et al., 2008d, Zurovac et al., 2008c, Zurovac et al., 2007). More recent studies show some improvement (Nyandigisi et al., 2011, O'Connell KA, 2011, Rowe et al., 2009a, Uzochukwu et al.), although in others the issue remains refractory (Noor et al., 2009, Kangwana et al., 2009, O'Connell KA, 2011). Bottlenecks leading to stockouts at the point-of-service include delays to delivery at a facility (8 – 105 days since ordering) (Lufesi et al., 2007, Zurovac et al., 2008c), poor forecasting at district and national levels, resource allocation, limited information systems, and lack of governance in national procurement (Windisch et al., 2011, Hensen et al., 2011).

In a systematic review of six studies comparing facilities with ACT stock to those without, ACT prescriptions increased, and non-recommended prescriptions decreased in the presence of stock, however existence of stock did not ensure recommended treatment practice (Hensen et al., 2011). In a Ugandan study only 60% of those needing an ACT were prescribed it despite adequate stock (Zurovac et al., 2008d). Interviews with Kenyan rural HCWs revealed that nearly all rationed ACTs because of uncertainty in supply; with some admitting giving it to patients they felt were most 'deserving' of treatment (Wasunna et al., 2008). In both Uganda and Kenya, despite ACT stock difficulties, there was usually an excess of non-recommended antimalarials such as chloroquine or amodiaquine (Wasunna et al., 2008, Zurovac et al., 2008d).

2.3.1.2.3 Underdiagnosis and Overtreatment

Until recently presumptive treatment and syndromic management was advocated in WHO guidelines and national policies. This approach resulted both in overtreatment, ranging from 47% - 95% of patients with non-malarial febrile illness (NMFI) being treated with antimalarials (Hamer et al., 2007, Reyburn et al., 2004, Zurovac et al., 2008b, Rowe et al., 2009a, Nicastri et al., 2009, Nankabirwa et al., 2009, Okebe et al., 2010, Nyandigisi et al., 2011, Bastiaens et al., 2011), and in some cases under-diagnosis of malaria of up to 30-40% (Nankabirwa et al., 2009, Nicastri et al., 2009, Bastiaens et al., 2011). Overtreatment is often with non-recommended antimalarials (Zurovac et al., 2008b, Noor et al., 2009), but may also involve ACTs, with between 5.7% and 63.7% of those untested or with negative test results receiving first-line treatment (Okebe et al., 2010, Rowe et al., 2009a, Hamer et al., 2007, Nyandigisi et al., 2011, Zurovac et al., 2008b). Non-adherence to test results can be detrimental to those patients who are not parasitaemic. A Tanzanian study found the case fatality rate in test negative patients to be significantly higher (12.1%) than for test positive (6.9%), and over 60% of NMFI were not treated appropriately with antibiotics (Reyburn et al., 2004).

Diagnostic capacity has increased over time; in Zambia 17% of public facilities surveyed in 2004 had access to diagnostic facilities for malaria, rising to 73% by 2006, mainly due to the introduction of RDTs (Zurovac et al., 2008d, Hamer et al., 2007). In other countries diagnostic capacity ranged from 25% to 100% of facilities surveyed (Nankabirwa et al., 2009, Zurovac et al., 2008c, Rowe et al., 2009a, Noor et al., 2009). However, testing of febrile patients before treatment has been limited (Rowe et al., 2009a, Zurovac et al., 2008b, Nankabirwa et al., 2009, Okebe et al., 2010, Noor et al., 2009, Bastiaens et al., 2011) and varies widely between and within countries (e.g., 11% in one district of Tanzania to 99% in other districts)(Bastiaens et al., 2011). Nankabirwa *et al*. showed low utilisation of diagnostic tools and reliance on clinical symptoms in high transmission areas of Uganda led to almost 40% of children under five years (U5s) not being diagnosed or treated despite being parasitaemic (Nankabirwa et al., 2009).

The under-treatment of confirmed cases is recognised at low levels (0.7-3.8%) (Zurovac et al., 2008d, Nyandigisi et al., 2011, Zurovac et al., 2008b, Rowe et al., 2009a, Nicastri et al., 2009, Bastiaens et al., 2011), but one Tanzanian study showed up to 18.8% (Nicastri et al., 2009) of patients with a positive diagnostic test were not treated with any antimalarial medication.

2.3.1.2.4 Informal sources of treatment

Informal sources for antimalarials, ranging from drug shops and pharmacies to general village stores and itinerant peddlers, are often geographically closer to home (Alba et al., 2010a, Abuya et al., 2007), less expensive to the individual (Kangwana et al., 2011, Chuma et al., 2010, Amin et al., 2003), more likely to have drugs in stock (Alba et al., 2010b), and can be perceived as being of better quality than public facilities (Patouillard et al., 2010, Goodman et al., 2007a, Rowa et al., 2010). The legal status of private retail outlets differs by country but most are not formally licensed to dispense malaria treatment (Goodman et al., 2007b, Goodman et al., 2007a). Generally drug retailers are unskilled workers with limited knowledge of the drugs, dosages and how to store them appropriately (O'Connell KA, 2011, Abuya et al., 2007, Patouillard et al., 2010, Goodman et al., 2007a), although in some cases government HCWs may work in drug shops (Patouillard et al., 2010, Goodman et al., 2007a). As a result antimalarials are often incorrectly prescribed or overprescribed presumptively for NMFI (Kangwana et al., 2011, Noor et al., 2009, Uzochukwu et al., Ringsted et al., 2011, Alba et al., 2010a, Littrell et al., 2011b, Littrell et al., 2011a). Sumba *et al*. found the likelihood of full recovery following a febrile illness was significantly less for those who attended private outlets (37%) compared to public facilities (85%) (Sumba et al., 2008).

Private outlets are run as businesses and hence have perverse incentives (Ringsted et al., 2011). The patient is a client wanting an affordable product, even if potentially less effective. The seller wants a satisfied customer, but also needs to sell a product regardless of actual need. If appropriate diagnostics are deployed to confirm the diagnosis, sellers lose their profit margin from dispensing antimalarials (Rowa et al., 2010,

Abuya et al., 2010). Two related qualitative Ugandan studies found that although community acceptability of RDT use was high regarding improving access to effective treatment of malaria, there were fears that drug shops would compensate by overpricing RDTs and not adhere to the results (Chandler et al., 2011, Mbonye et al., 2010).

There is good evidence of extensive distribution through the informal sector of antipyretics, substandard or counterfeit antimalarials, and artemisinin monotherapy or chloroquine as first-line treatments, although with substantial variation regionally (O'Connell KA, 2011, Kaur et al., 2008, Littrell et al., 2011a, Bate et al., 2008, Newton et al., 2006, AMFm Independent Evaluation Team, 2012, Littrell et al., 2011b). A recent survey by ACT Watch (including DRC, Uganda and Zambia) confirmed that availability of ACTs is particularly low in the private sector, while less effective drugs and artemisinin monotherapy are often readily available (Littrell et al., 2011b, Littrell et al., 2011a, O'Connell KA, 2011). Quality assured ACTs (QAACTs) represented less than 20% of the antimalarial market (Kangwana et al., 2011, O'Connell KA, 2011, AMFm Independent Evaluation Team, 2012, Ringsted et al., 2011). ACTs are also priced higher in the private sector compared to other antimalarials, despite this being the most common point of access. Recent studies report that older treatments such as chloroquine remain very cheap (under one US dollar), whilst ACTs were 4 – 22 times more expensive than the most commonly dispensed antimalarial in the private sector (a non-artemisinin based treatment in all countries surveyed) (O'Connell KA, 2011, AMFm Independent Evaluation Team, 2012).

2.3.2 Interventions to improve quality of care

2.3.2.1 Reducing stockouts

Evidence of interventions at scale that lead to improved stock at the facility level is scarce (Table 1). A study in 24 Zambian districts demonstrated the use of a commodity planner within the district logistics team coupled with direct central monthly ordering and pre-packed drugs tailor-made for each facility increased the availability of paediatric ACTs to 88% compared with 51% in districts with no intervention. Similar improvements were seen for other essential medicines. Stockouts were almost eliminated in some cases, with scale-up of this supply chain model estimated to reduce child malaria deaths by 37% (WorldBank, 2010).

More recently, mobile phone technology has been applied to supply chain management, albeit limited to small studies. In Uganda, a short message service (SMS) reporting system deployed by the government resulted in over 85% of the facilities reporting weekly, although ACT stockouts remained at 54% (Asiimwe et al., 2011). Promisingly, a Tanzanian study using mobile phones to improve stock-counts showed a substantial reduction in the proportion of facilities without any antimalarials from 78% at baseline to 26% at follow-up, with stockouts eliminated by week eight in one district (Barrington et al., 2010). Furthermore, a Kenyan

study evaluating the use of SMS reporting for stocks of ACTs and RDTs found a reduction in the stockout of one or more ACT packs by 38% at the end of the 26 week period, and a decline in RDT stockouts by 24%. Importantly, district managers also responded to address to 44% of ACT and 73% of RDT stockout signals (Githinji S, 2013).

Indirect interventions may also improve supply. The introduction of subsidised ACTs in the private sector was associated with decreased public-sector stockouts in Kenya, Madagascar, Niger, Nigeria, Tanzania, Uganda and Zanzibar, with ACT stock present more than 80% of the time in all except Nigeria and Niger (Alba et al., 2010b, Alba et al., 2010a, Tougher et al., 2012). Improved stock levels in Tanzania were accompanied with a near fivefold increase in treatment seeking amongst adults (Alba et al., 2010a, Alba et al., 2010b).

Table 1: Interventions: improving quality of care in public health facilities

Reference	Country	Setting	Intervention	Outcome	Impact
Improved stock management: reducing stockouts					
(WorldBank, 2010)	Zambia	24 districts: 8 to each intervention and 8 control (3 arms)	• Both models: logistics commodity planner at district level • Model A: health facilities place orders to districts that transfer the order to the central level. Procured drug kits disaggregated at central level and distributed to the district store for assembly and delivery to facilities • Model B: direct ordering monthly to central level and the drugs are packed at the central level in sealed packages tailor-made for each individual facility. District only delivers to facilities.	• Model A resulted in some improvement of drug availability in the health facilities • Model B intervention dramatically improved the availability of essential medicines: e.g. availability of paediatric ACT was up to 88%, compared with 51% in control areas • Similar improvements were seen for other essential medicines, such as antibiotics	• Authors estimated that by 2015 scaling up this supply chain model could reduce child malaria deaths by 37% • Scaling up: estimated to treat an additional 110 000 children/ year and avert 5400 child deaths/year • Considering improvements also in availability of other drugs – impact may be greater
(Asiimwe et al., 2011)	Uganda	2 districts: Gulu, Kabale – 147 facilities Ministry of Health led	• SMS-based malaria monitoring platform • Training at facility and district level • Set-up cost of $100 USD/health facility, local technician support of $400 USD per month, and a cost of $0.53 USD/week/clinic	• ACT stockouts: 54% Kabale and 54% Gulu • RDT stockouts: 48% Kabale and 71% Gulu • > 85% health facilities reported weekly and without monetary incentives or additional supervision	• Potential to improve timeliness in reporting of specific, time-sensitive metrics at modest cost and to manage stock data at district level
(Alba et al., 2010a)	Tanzania	Kilombero and Ulanga districts and	• Subsidy for ACTs: free for U5s and pregnant women and	• After subsidised ACT introduced in 2007 – stocks	• Treatment seeking amongst adults increased by 27%

		Ifakara town – 10 facilities	subsidised price of TSH 300 (USD $0.25) to others	were high for >80% months observed (90/108 in 2007; 88/108 in 2008)	(unadjusted) • Treatment seeking adjusted for socioeconomic status: nearly five-fold increase (OR=4.6 p=0.001)
(Barrington et al., 2010)	Tanzania	3 rural districts: Lindi, Kagama, Ulanga – 129 facilities (Novartis led)	• SMS management tool and a web-based reporting tool • Training at national, district and facility levels • 21 week pilot study • Involved 2 weight specific ACT packs and injectable quinine	• 95% mean facility response rate to SMS requests for stock data • 94% accuracy of stock reports • Decrease in facilities with stockout of one or more ACTs: 78% (baseline) to 26% (week 21) • In one rural districts: stockouts virtually eliminated by week 8 • Overall: ACT stocks increased by 64% and quinine stock increased 36%	• Use of simple SMS technology, via a public-private partnership model may be effective
(Githinji S, 2013)	Kenya	5 rural districts: Machakos, Msambweni, Ijara, Manga, Vihiga – 87 public health facilities	• SMS management tool and a web-based reporting tool • 26 week study • Training at facility and district levels • Involved 4 weight specific ACT packs and RDTs	• 97% mean facility response rate • 79% accuracy of stock reports but 93% accuracy of stockout reports • 38% decrease from baseline to 26 weeks in stockouts of one or more ACT packs • Total stockouts reduced by 5% • RDT stockouts reduced by 24% • District managers responded to 44% of ACT stockout and 73% of RDT stockout signals	• Incentives were used to encourage reporting: may introduce reporting bias • Web-based platform was regularly accessed by national and district level teams: possibility of better integration between levels and surveillance-response • Important impact on RDT stocks also
Impact of rational (diagnosis-led) case management					

Reference	Country	Setting	Intervention	Outcome	Impact
1) Testing of over 5 year olds whilst presumptive treatment of under five year olds					
(Zurovac et al., 2008c)	Kenya	3 districts: Bondo, Siaya, Kericho - 60 health facilities, 1540 patients (as below)	• Modelling implications of rational case management • Primary data from Skarbinski 2009 (below) • Policy: RDT use in all over 5 year olds and treatment with first-line ACTs	• High transmission: 61% less overtreatment and 21% lower costs but potential for 8% increase undertreatment • Low transmission: reduction in undertreatment errors (36% less – but low numbers) but increase in costs by 41%	• High transmission: majority patients would not be correctly treated with ACTs despite RDT use • High & low transmission: adherence to guidelines has potential to decrease treatment errors with acceptable costs
(Skarbinski et al., 2009)	Kenya	3 districts: Bondo, Siaya, Kericho - 60 health facilities, 1540 patients	• Cluster RCT: RDTs plus training, guidance and supervision (TGS) or TGS alone • Policy: RDT use in all over 5 year olds and treatment with first-line ACTs • 100% RDT availability in intervention facilities	• 9% RDT negatives given ACT • Overtreatment low in both arms and not significantly reduced by RDT provision: 12% ($p = 0.3$) • Presumptive treatment reduced: 36% ($p = 0.03$) • 88% RDT positive treated with ACTs (vs. 51% of smear-positive treated with ACTs)	• RDTs could improve case management but more effective implementation strategies for guidelines required
(Masanja et al., 2012b)	Tanzania	Ifakara district (14 facilities) pre-RDT implementation and Rufiji district (16 health facilities) post-RDT implementation	• Policy change: over 5 year olds to be treated after use of RDT if possible to guide decision making	• 12.6% increase in febrile patients tested ($p=0.05$) • 7% all test-negatives treated with antimalarials (7.8% RDT negative): 7.6% reduction from pre-baseline (significant only for RDT) • Overtreatment reduced: 39.1% to 24.7% ($p=0.01$) • 83.2% RDT-positives treated with ACT vs. 41.7% microscopy-	• High adherence to test result in rural settings possible • Impact of RDTs limited by overall low levels of appropriate testing • Greater impact during high transmission season

				positives	
(Juma and Zurovac, 2011)	Kenya	National cross sectional cluster survey: 88 facilities with diagnostics (1096 patients) and 71 facilities no diagnostics (880 patients)	• Kenyan national guidelines change promoting ACTs and parasitological diagnosis in over-5 year olds • Presumptive treatment remained policy in U5s • Only results in over-5 age group given	• At facilities with diagnostics: 53.7% tested (CI: 45.4-61.9) • 32.8% with negative test received ACTs (50.4% of negative test received some antimalarial treatment) • 58% untested received ACTs • 86.5% test-positives received ACTs • 1.2% RDT positives did not receive any antimalarial treatment	• ACT use prevailed in all age groups • Overtreatment remained despite test provision • Use of diagnostics remained limited
(Ishengoma et al., 2011)	Tanzania	2 districts: Korogwe and Muheza. Longitudinal passive detection in 6 villages in Korogwe and cross sectional survey in 6 villages in both districts	• Supply of RDTs: – comparing performance of RDT use to microscopy with respect to treatment	• Sensitivity and specificity of RDTs in longitudinal study: 88.6 (87.5-89.7) and 88.2 (87.7 – 88.7) • Sensitivity and specificity of RDTs in cross sectional surveys: 63.4 (59.8 – 67.1) and 94.3 (93.6 – 95) • Using RDTs reduced antimalarial dispensing in over-5 year olds from 98.9% to 32.1% • Post RDT: 3.4% negative RDTs in over 5-year olds were treated • Pre-RDT period: 1.4% (79) cases not treated with antimalarials including 0.3% (19 – including 11 U5s) that were slide positive	• Variation in sensitivity and specificity of RDTs depending on fever and parasite density • RDTs reduced overtreatment significantly.

				Post RDTs: 0.8% (108) over-5 year olds not treated with ACTs	
(Zurovac et al., 2008a)	Kenya	3 districts: Bondo, Siaya, Kericho - 60 health facilities, 1540 patients (as below)	• Modelling implications of rational case management • Primary data from Skarbinski 2009 (below) Policy: RDT use in all over 5 year olds and treatment with first-line ACTs	• High transmission: 61% less overtreatment and 21% lower costs but potential for 8% increase undertreatment • Low transmission: reduction in undertreatment errors (36% less – but low numbers) but increase in costs by 41%	• High transmission: majority patients would not be correctly treated with ACTs despite RDT use • High & low transmission: adherence to guidelines has potential to decrease treatment errors with acceptable costs
2) Universal testing and treatment: all ages					
(Njama-Meya et al., 2007)	Uganda	601 children between 1-10 years recruited from census population & followed in study clinic	• Standard microscopy performed if fever – and treated only if smear positive	• 6 of 1608 smears falsely identified as negative – of which 4 went onto develop uncomplicated malaria and 2 cleared parasites without treatment • 13/1602 negative smears developed malaria within 7 days (0.8%) – all uncomplicated	• 32% febrile episodes were malaria • Withholding treatment on the basis of negative smear was safe • Saved >1600 treatments in 601 children over 18 months
(Msellem et al., 2009)	Zanzibar	4 health facilities: 1187 patients	• Crossover validation trial Comparing clinical diagnosis with RDT-aided treatment	• RDT use associated with lower ACT prescription than clinical diagnosis: OR – 0.04 (CI: 0.03 – 0.05, p<0.001) • Prescription of antibiotics higher after RDT use: OR – 1.8 (CI 1.5 – 2.2, p<0.001) • Re-attendance due to perceived unsuccessful cure: lower after RDT consultation than clinical diagnosis: OR– 0.5 (CI 0.3 – 0.9, p=0.005)	• Total average cost per patient was similar: USD 2.47 in RDT consultation vs. 2.37 for clinical diagnosis • Some risk of undertreatment if RDT false-negative

				• 28/552 smear-positive not treated (of which 26 due to false-negative RDTs)	
(Mosha et al., 2010)	Tanzania	2 districts: Same and Korogwe Methods included – routine health information data, health facility cross sectional RDT survey (8 facilities) and passive surveillance of cohort childhood morbidity	• Modelling cost implications of improving diagnosis in children • Primary data: RCT of different antimalarials for intermittent preventative treatment of malaria in infants (IPTi: Gosling et al Lancet 2009) • Comparison of routine care vs. RDT aided care	• Overdiagnosis of malaria with routine care compared with RDTs: highest in U5 in low transmission sites (RR 17.9; CI 5.8 – 55.3) and then over 5s in low transmission site (RR 14.0; CI 8.2 – 24.2) • Less overdiagnosis risk in moderate transmission comparing routine vs. RDT (RR 2.2 in U5 and 4.2 in over 5s) • Higher proportion diagnosed with respiratory infections in under 2 year old RDT cohort vs. routine care (42% vs. 26%, p<0.001)	• In low transmission: proportion of morbidity attributed to malaria was lower in under 2 year olds RDT cohort compared to routine care: 0.08% vs. 28.2% (p<0.001) • Use of RDT reduced overall drug and diagnostic costs: 10% in moderate transmission and 15% in low transmission compared with routine care
(d'Acremont et al., 2010)	Tanzania	Urban (Dar es Salam) and rural (Kilombero) - Prospective 2 arm study: 2 facilities – 1000 children (603 negative RDT)	• No antimalarials if RDT was negative • Main outcome: occurrence of complications in untreated children	• 97% children symptom-free by day 7 • 600 /603 children were RDT negative when repeated after 7 days • 3/603 children with negative RDT later developed positive test within 7 days: no complication • 4 children with negative RDT admitted to hospital (NMFI)	• Not treating RDT negative children with antimalarials is safe even in U5s
Impact: training of healthcare workers					
Reference	Country	Setting	Intervention	Outcome	Impact

(Ngasala et al., 2008)	Tanzania	2 districts: Kibaha and Bagamoyo: 16 health facilities – 3131 children	• RCT: staff training in clinical diagnosis & microscopy vs. clinical training alone vs. no training	• Antimalarial prescriptions did not significantly reduce in training alone arm (95.3% vs. 99.5% untrained) • No difference in antibiotics prescriptions • No statistical significant difference in recovery rates or outcomes	• Additional training and supervision did not result in any significant impact on improving malaria case management compared with untrained workers
(Skarbinski et al., 2009)	Kenya	3 districts: Bondo, Siaya, Kericho - 60 health facilities, 1540 patients	• Cluster RCT: Training, guidance and supervision (TGS) alone vs. TGS and provision of RDTs • Baseline survey in both groups and follow up • Results presented here for impact of TGS only in control group	• Increased ACT treatment of patients with uncomplicated malaria: 41% (p=0.05) (compared with reduction of 22% in group with RDTs) • Reduction in treatment with non-recommended drugs: 46% (p=0.003) • No significant Increase in over treatment with ACT • Significant increase in use of RDTs: 11% (p<0.001) but no overall increase in diagnostic testing (any tool): 16% (p=0.07)	• Overall no significant impact of Training, guidance and supervision (TGS) alone on prescription of ACTs according to diagnostic result or by clinical diagnosis
(Rowe et al., 2009a)	Benin	South eastern Benin: 1244 consultations – survey in 1999 then	• IMCI training plus additional study supports including supervision/ non-financial incentives vs. control group with only “usual” IMCI supports (job aids/limited supervision) • Baseline survey in 1999 and follow up in 2001 - 2004	• Performance increased in intervention and control groups: no significant overall difference (but diluted by persistence of untrained IMCI workers) • Per-protocol analyses: IMCI training plus study support provided better care than those with “usual” supports	• IMCI training is useful but insufficient for high levels of adherence • Additional supports can lead to additional improvements and are low cost

				(27.3% improved; p<0.05) • Both groups outperformed untrained workers • Only 29% of supervision visits occurred	
(Wasunna et al., 2010)	Kenya	Bondo district: 22 public health facilities, 48 HCW, 386 febrile children	• Enhanced in service training programme of HCW and provision of job aids re: new malaria management guidelines No follow up training or supervision	• 67% staff received the enhanced in service training (none received full package) Trained HCWs: no significant improvement in reported case management tasks	May need to consider inclusion of supervision and post-training follow-up

Abbreviations: ACTs: Artemisinin Combination Therapies; CI: confidence interval; HCW: healthcare worker; IMCI: integrated management of childhood illness; NMFI: non-malarial febrile illness; OR: Odds Ratio; PCR: Polymerase Chain reaction; RCT: randomised controlled trial; RDT: rapid diagnostic test; RR: Relative Risk; SMS; short message service; U5s: under 5 year olds.

2.3.2.2 Universal rational case management

The 2010 WHO guidelines on the treatment of malaria state that whenever possible 'prompt parasitological confirmation by microscopy or alternatively by RDTs is recommended in all patients suspected of malaria before treatment is started'. This policy change towards universal 'test and treat' acknowledged the widespread overtreatment of malaria and the risk of spreading drug resistance or tolerance, the need for improved disease surveillance and better quality of care, including for NMFI (WHO, 2010a).

As outlined above, implementing rational (diagnostic-led) case-management has proven difficult, especially at scale beyond trials under controlled conditions. Guidelines limiting treatment for children over five years to diagnosis-confirmed cases did not reduce unnecessary antimalarial use (Table 1), although ACT prescription for diagnostic-positive cases did improve (88-98.6%) (Juma and Zurovac, 2011, Skarbinski et al., 2009, Ishengoma et al., 2011, Masanja et al., 2012b). However, recent studies have found increased emphasis on universal RDT use to be associated with reductions in unnecessary antimalarial treatments (up to 68% in several studies), albeit varying by transmission setting (D'Acremont et al., 2011, Bastiaens et al., 2011, Nyandigisi et al., 2011, Msellem et al., 2009, Sserwanga et al., 2011, Ansah et al., 2010, Kyabayinze et al., 2010). Undertreatment of test-positive cases at low levels was documented in a few studies (Msellem et al., 2009, Bastiaens et al., 2011, Ansah et al., 2010).

Several studies demonstrated that withholding antimalarials in test-negative cases does not result in increased malaria-related deaths or severe morbidity, even in U5s (d'Acremont et al., 2010, Mtove et al., 2011b, Njama-Meya et al., 2007). Management of test-negative patients has also been shown to improve, with substantial decreases in antimalarial prescription and concomitant increases in prescription of antibiotics (odds ratio: OR = 1.45-1.8) (Msellem et al., 2009, Bastiaens et al., 2011, D'Acremont et al., 2011). However, it is unclear if the latter reflects correct antibiotic treatment.

The cost implication of adding RDTs has been of concern although several studies show little difference compared to clinical diagnosis (Msellem et al., 2009, Mosha et al., 2010, Zurovac et al., 2008a, Batwala et al., 2011).

2.3.2.3 Training

Delivering quality care depends on the capabilities and performance of HCWs. A 2009 review of 23 studies to improve HCW management of malaria confirmed very little is known about which interventions work (Smith et al., 2009b). Aside from two studies of Integrated Management of Childhood Illness (IMCI) which showed significantly improved appropriate treatment (Smith et al., 2009b), one public sector study demonstrated training, mainly of limited duration and in didactic or workshop format, was significantly associated with

recommended treatment of malaria when supplemented by additional inputs such as job aides or regular supervision.

Recent trials show the link between levels of staff training and clinical performance is not straightforward (Table 1). In Uganda, patients were significantly less likely to receive malaria treatment if seen by formally qualified HCWs (Zurovac et al., 2008d). In some studies, diagnosis-based management of malaria with ACTs did not improve with in-service training, increased access to national guidelines, or provision of malaria wall charts (Zurovac et al., 2008d, Nyandigisi et al., 2011, Ngasala et al., 2008), however, in others pre-service and in-service training increased the likelihood of ACT prescription (Hamer et al., 2007). In Kenya (Zurovac et al., 2008c) and Uganda (Zurovac et al., 2008d) supervision of HCWs was associated with improved adherence to guidelines. Multiple surveys (Wasunna et al., 2010, Rowe et al., 2009b, Skarbinski et al., 2009) have found that uptake of training programmes is patchy and alone do not result in any significant improvements in case management, except a 46% reduction in the use of non-recommended drugs in one Kenyan study (Skarbinski et al., 2009).

Outside malaria, a recent IMCI evaluation suggests frequent supervision and other non-financial incentivisation (framed certificates and acknowledgement in local media) may improve care (Rowe et al., 2009b).

2.3.3 Interventions to increase access

2.3.3.1 Community case management and community health workers

A number of countries are addressing the challenge of limited access to facilities in rural and poor areas by training local individuals to act as community health workers (CHWs), enabling integrated community case management of malaria (iCCMm) often with pre-packaged drugs (Christopher et al., 2011). Implementation of CCM programmes across Malawi, Mali and Zambia is estimated to improve effective access (i.e. access to a trained provider and to appropriate medicine) from 14% (9-17%) to 30-57% (Guenther et al., 2012).

Two systematic reviews evaluating presumptive treatment of febrile children by CHWs have been published. Hopkins *et al.* (Hopkins et al., 2007) identified six studies, concluding CHW schemes could improve treatment delivery and adherence, especially for groups located far from formal facilities. A second review considered evaluations of CHW programmes delivering multiple paediatric treatments and included several studies showing reduction in all-cause paediatric mortality up to nine years after programme initiation (Christopher et al., 2011). Studies published since concur that CHWs in Africa can successfully provide presumptive ACT

treatment along with packages of preventive services in both rural and urban settings (Akweongo et al., 2011, Staedke et al., 2009, Chinbuah et al., 2012, Kalyango et al., 2012, Rutebemberwa et al., 2012).

More recent studies (Table 2) evaluating the performance of CHWs in delivering diagnostic-led management describe increased treatment-seeking (Yeboah-Antwi et al., 2010, Seidenberg et al., 2012, Elmardi et al., 2009, Mukanga et al., 2012a) and no increased progression to severe disease (Lemma et al., 2010, Mukanga et al., 2012b). In addition, they document reduced overtreatment with ACTs (upto 96.8% adherence to RDT results seen in Tanzania (Mubi et al., 2011)), and improved management of NMFI, including increased referral and appropriate treatment for pneumonia (Yeboah-Antwi et al., 2010, Mukanga et al., 2012b). Two studies showed a reduction in malaria incidence and parasite prevalence in areas covered by CHW interventions, although it is not clear the extent to which this was causal (Lemma et al., 2010, Tine et al., 2011).

Predictions of the cost effectiveness of CHW programmes using presumptive treatment vary. Only one study considered community level utilisation of RDTs, and found in Zambia the cost per case diagnosed and correctly treated was less by iCCM rather than facility-level management (Chanda et al., 2011a).

Table 2: Interventions: improving access through community case management of malaria (CCMm)

Reference	Country	Setting	Intervention	Outcome	Impact
(Elmardi et al., 2009)	Sudan	South Kordofan state: 20 villages	• Community volunteers trained in CCMm (RDT use plus ACT treatment) with supply from rural HC	• 30% CHW volunteers did not rely on negative RDT • Improved accessibility to ACTs: 25% to 64.7% • Improved treatment seeking behaviour: 83.3% to 100%	• Issue of overtreatment i.e. test negative patients treated • Community acceptance of programme
(Yeboah-Antwi et al., 2010)	Zambia	Catchment area of Chikankata hospital: Siavonga and Mazubuka districts: 3215 children with fever	• Cluster RCT: CHWs with access to RDTs, ACTs and antibiotics (18) vs. CHWs relying on clinical diagnosis (19 - control) with access to ACTs only in the management of matched febrile U5 year olds	• 27.5% children in RDT arm received ACTs vs. 99.1% in control arm (RR 0.23; 95% CI: 0.14-0·38) • Non severe pneumonia: 68.2% children in RDT arm received early and appropriate treatment vs. 13.3% in control (RR 5.32; 95% CI: 2.19 – 8.94) • 2 deaths in intervention arm vs. 1 in control	• Promising result for reduction in overuse of ACTs and increase early and appropriate treatment for pneumonia and other NMFI
(Lemma et al., 2010)	Ethiopia	Tigray region: 2 districts	• 2 year pilot study: ACT at clinic and CHW level – 50% access to RDTs in Year 2 vs. control : ACTs and RDTs at clinic only	• Crude parasite prevalence at peak of transmission: 7.4% (CI: 6.1-8.9%) in intervention district vs. 20.8% (CI: 18.7-23) in control • No difference in all-cause mortality (Incidence RR 1.03) • Risk of malaria specific mortality lower in intervention district (Incidence RR 0.6; 95% CI: 0.4-0.9; p=0.013)	• Community based deployment of ACTs: reduced malaria transmission, lowered case burden for facilities and reduced malaria mortality and morbidity in study period
(Chanda et al., 2011b)	Zambia	2 districts: Chongwe (9 CHWs for 16079 populations) & Kalomo (7 CHWs for 18279	• CHW as delivery points for ACT and RDTs for CCMm (adult and paediatric)	• 23 – 35.1% attended at CHW • 99.2-100% uncomplicated malaria treated with ACTs • All severe malaria cases and non-malaria fevers referred appropriately	• Good community reception • High levels adherence to test result • CCMm more efficient than health facility level management

		population)		• Negative RDT cases not prescribed ACT: 99.4-100% • No progression to severe malaria or deaths • Cost per case correctly diagnosed: USD 4.22 for CCMm vs. USD 6.12 for facility level • Utilisation of diagnostics and adherence to results & guidelines higher with CHW than facility	
(Mubi et al., 2011)	Tanzania	Kibaha District: 5 villages, 22 CHWs, 2930 patients	• Alternating cluster RCT: CHWs trained in RDT use and clinical diagnosis – randomly assigned to one method on alternating weeks	• ACTs provided to 53.2% patients in RDT weeks vs. 96.5% patients in clinical weeks (OR 0·039; 95% CI: 0.029 – 0.053) • CHWs adhered to RDT results: 96·8% patients (CI: 95.8 – 97.6) • Referral: 10% in RDT weeks vs. 1·6% clinical weeks • Perceived non-recovery more common after RDT diagnosis • No severe or fatal malaria in RDT negative patients (not treated with ACTs) • 4 deaths: 2 test positive and treated with ACT, 2 RDT negative)	• Opportunity for improved access, timely treatment and improved NMFI treatment
(Tine et al., 2011)	Senegal	Bocconto health post: 8 villages, 12 CHWs, 1000 children	• RCT : CHW trained in CCMm (oral for uncomplicated and pre-referral rectal for severe malaria) compared to this plus some CHWs able to administer monthly intermittent preventative therapy to children (IPTc)	• Incidence of malaria episodes: 7.1/100 child months at risk (95% CI: 3.7-13.7) in IPTc plus CCMm communities vs. 35.6/100 child months at risk (95% CI: 26.7-47.4) – OR 0.2; 95% CI: 0.09 – 0.41; p=0.04 • Parasitaemia prevalence lower in communities with IPTc plus CCMm (2.05% vs. 4.6%; p=0.03)	• CHWs are able to deliver both CCMm and IPTc • Combining these interventions can provide significant additional benefits

				• Adjusted OR shows protective effect of IPTc plus CCMm against anaemia (OR=0.59; 95%CI: 0.42-0.82; p=0.02)	
(Mukanga et al., 2012a)	Uganda	Iganga district: 423 households from 7 villages with U5s	• Semi-structured questionnaire for caregivers • Acceptability survey following one year use of RDTs by CHWs in CCM programme	• 86% households lived within 1km of CHW home vs. 25% within 1km of health facility • Households further than 1km from facility were more likely to use a CHW (OR: 1.72; 95% CI: 1.11-2.68) • 89% acceptability of CHWs using RDTs	• CHW programmes increase access and were the first choice for more than 50% of caregivers sampled
(Mukanga et al., 2012b)	Burkina Faso, Uganda, Ghana	Multicentre: 12 villages in Burkina Faso, 16 villages in Ghana and 14 in Uganda 4216 febrile children	• Open cluster RCT: two-arm • Comparing CHWs programmes with diagnostic tests, ACTs and antibiotics vs. presumptive diagnosis and ACTs (plus antibiotics in Ghana)	• High compliance with RDT results • 4.9% RDT negative children given ACTs • Antibiotic overuse was common in Burkina Faso and Ghana for children who were RDT negative but also no increased respiratory rate	• RDT use by CHWs limits overuse of ACTs • Unclear re: impact of diagnostic tools by CHW (respiratory rate) on antibiotic use • No increased fever persistence due to use of diagnostic tools
(Seidenberg et al., 2012)	Zambia	Catchment area: Chikankata Mission Hospital: 440 women from 62 villages	• Cluster RCT: CHWs with A) diagnostic tests and ACTs vs. B) presumptive diagnosis and ACTs • Household surveys of caregivers of U5s	• In both arms increase in care seeking from CHWs (Relative risk 1.39 in CHW A and 1.55 in B) • Decrease in care seeking at health facility and traditional healers • For severe symptoms (e.g. difficult breathing): increase in CHW utilisation only seen in CHW with diagnostics areas (A)	• CHW programmes can reduce burden on health facilities • Availability of diagnostics increases treatment-seeking at CHWs for severe symptoms

Abbreviations: ACTs: Artemisinin Combination Therapies; CCMm: community case management of malaria; CHW: community health worker; CI: confidence interval; IMCI: integrated management of childhood illness; IPTc: intermittent preventative therapy for children; NMFI: non-malarial febrile illness; OR: Odds Ratio; PCR: Polymerase chain reaction; RCT: randomised controlled trial; RDT: rapid diagnostic test; RR: relative risk; SMS; short message service; U5s: under 5 year olds.

2.3.3.2 Targeting the private sector

Training programmes targeting the performance of private sector drug outlets are included in two systematic reviews undertaken prior to RDT introduction (Goodman et al., 2007a, Smith et al., 2009b). In both, visual aids and on-site supervision aimed at informal providers were shown to improve performance. However, both reviews emphasise the difficulty in incorporating actors operating outside traditional regulatory frameworks into treatment programmes, and sustaining behaviour change. Since then, studies have further shown training can improve the performance of private retailers; in Kenya trained retailers were more likely to sell the correct dose of antimalarial (OR 9.4 in one region and OR 53.5 in another) (Abuya et al., 2010), and formally accredited training can reduce the numbers of unregulated drug shops, as shown by the Accredited Drug Outlet (ADDO) scheme in Tanzania (Alba et al., 2010a, Alba et al., 2010b) (Table 3).

The price and quality of ACTs has been a barrier to effectively expanding their use in the private sector. In 2009, the subsidy programme Affordable Medicines Facility for malaria (AMFm) was launched, seeking to reduce price through a co-payment facility, thereby increasing access to quality-assured ACTs (QAACTs) and driving out ineffective drugs (AMFm Independent Evaluation Team, 2012) (Table 3). The original AMFm pilot study in Tanzania showed significant increases in ACT market share (from 1% to 44.2% sales) (Sabot et al., 2009), and a randomised controlled trial of subsidised ACTs in Kenya found an increased proportion of children receiving ACTs within 48 hours of fever (14.6% to 40.2%), with significant reduction in the use of antimalarial monotherapy (Kangwana et al., 2011). In both studies, the drug subsidy was passed to the end users. However, spatial analysis of the pilot showed subsidised ACTs were more likely to be stocked in shops closer to towns, major roads and with richer clientele, indicating that price reduction alone may not address inequities in access (Cohen et al., 2010). One early evaluation from Kenya showed the subsidy was passed to customers, but only 11% of drug shops surveyed stocked the subsidised brand (Smith et al.). Two recent independent evaluations of AMFm (Phase One) concluded that dramatic increases in QAACT availability (26.3-71.3% increase), market share (30-58.7% increase) and affordability had been seen in almost all pilot sites (except Niger and Madagascar) with reductions in availability of artemisinin monotherapy, although diagnostics stock remained low (AMFm Independent Evaluation Team, 2012, Tougher et al., 2012).

The Consortium for ACT private sector subsidy (CAPSS) study in Uganda also piloted an AMFm subsidy approach to investigate whether access to QAACTs in the private sector could be improved. Evaluation at 2 years found increased market share with ACTs accounting for 69% of antimalarial purchases in pilot areas. The odds of purchasing an ACT within 24 hours of symptoms onset in an intervention region compared with control areas was 6.11 (95% confidence intervals: 4.32-8.62; $p<0.0001$)(Talisuna et al., 2012).

Table 3: Interventions: improving access and quality of care in the informal private sector

Reference	Country	Setting	Intervention	Outcome	Impact
Training of private sector providers					
(Abuya et al., 2010)	Kenya	2 districts: Kwale and Kisii	• 2 training initiatives for private sector retailers (PMRs): i) Kwale: 2 day Ministry of Health training, per diems, no follow up plus community education ii) Kisii: 3 day NGO training, per diems and follow up visits but no community education	• Kwale: 18.8% trained PMRs sold correct dose vs. 2.3% untrained (OR 9.4; 95% CI: 1.1-83.7) • Kisii: 60.5% trained PMRs sold correct doses vs. 2.8% untrained (OR 53.5; 95%CI: 6.7-428.3) • Kwale: programme coverage 25.3% outlets • Kisii: programme coverage 69·7% outlets	• Kwale: potential utilisation of 48,000 U5s Kisii: potential utilisation of 30,000 U5s

(Alba et al., 2010b)	Tanzania	Kilombero and Ulanga DSS and Ifakara town	• National scheme: training accredited drug dispensing outlets (ADDOs)
			• Subsidised ACTs available at ADDO level
				• Increased proportion of cases treated with an antimalarial: 31% (47/154) in 2004 to 43% (54/127) in 2008 (Odds ratio OR: 1.68; p=0.038)
				  ○ Confounded by SES (adjusted Odds ratio = 1.18; p=0.632) and decreased in poorest quintile
				  ○ Increase was in patients over age 5 (38% in 2004 to 52% in 2008) and not U5 (25% - 28%)
				• ACTs supply: 2% in 2006 (unsubsidised) to 29% in 2008
				• ACT stock in urban area than rural: 38.1% in Ifakara vs. 20-25.9% in rural drug shops
				• Reduction in market share of SP: 64% (2005) to 51% (2008): ACT 17% in 2008
					• Availability of ACTs is needed for subsidy scheme to take effect

				• Reduction in Artemisinin monotherapies found: urban - 20% outlets (2007) to 12% (2008)	
AMFm and ACT subsidies					
(Sabot et al., 2009)	Tanzania	2 districts: Maswa and Kongwa plus Shinyanga district as control	• AMFm subsidy pilot: ACTs at 90% subsidy through private supply chain reviewed Aug 2007 upto Aug 2008	• Increased stocking of ACTs: 0% - 72% (p<0.001) • % customers purchasing ACTs rose from 1% baseline to 44.2% at 1 year (p<0.001) • Increase in ACT purchase for U5s significantly higher than for adults (p=0.005) • No change in control districts • Consumers paid mean USD 0.58 for ACT (similar to SP price) • Highly populated areas more likely to stock ACTs than remote (p<0.001)	• Subsidy passed to consumers successfully • Price similar to other alternative antimalarials
(Cohen et al., 2010)	Tanzania	2 districts: Maswa and Kongwa	• AMFm subsidy pilot: reviewed at Nov 2007 upto Nov 2008	• Total ACT stocks rose: 55.8% -72.9% (SP unchanged) • % sales ACT: 31.5% - 39.3% (although total sales increased) • Geographic variation in stocking & sales: In shops closer to district town (p<0.01), major roads (p<0.01) and in those with higher SE clientele (p<0.01)	• Overall increase in ACT availability • Similar geographic disparity patterns to other antimalarials need to be addressed
(Kangwana et al., 2011)	Kenya	3 districts – Busia, Butere-Mumias, Teso	• RCT comparing subsidised ACTs through private sector retailers with training and community awareness. No interventions in control arm	• 95.3% of those in intervention who bought ACTs purchased it at subsidy price (USD 0.25) • % children receiving ACT within 48 hours of fever increased by 14.6% in control group vs. 40.2% in intervention (25% difference in means: 95% CI 14.1-35.9; p=0.0001)	• Cost subsidy can increase ACT coverage • No significant difference in adequacy of dosing obtained or provided despite training in intervention arm

				• Significant difference between groups in % children receiving antimalarial monotherapy (reduction -10.4%; 95% CI-3.9 to -16.9; p=0.0074)	
(Smith et al., 2011)	Kenya	Webuye DSS area: 97 shops and 13 mission facilities	• National AMFm subsidy scheme: review at 5 months	• ACT stocked by 44% retailers; • Quinine most stocked (61% shops),SP: 57% • 47% retailers regularly report stockouts of all antimalarials • 11% retailers stocked the subsidised brand ACT • Subsidised brands of ACT - mean cost USD 1.60: 40% less than non AMFm brands of ACT (mean cost USD 2.86) • Artemisinin monotherapies cost more than twice as much as subsidy brands (USD 5.40) • SP cost USD 0.50 compared to mean cost ACT (USD 2.7)	• Cost subsidy is apparent for AMFm brands of ACT • Large difference still between effective and ineffective therapies
(AMFm Independent Evaluation Team, 2012)	Kenya, Niger, Ghana, Tanzania, Nigeria, Uganda, Madagascar, Zanzibar	Evaluation of AMFm pilots in 8 countries	• National AMFm subsidy scheme; Phase 1 evaluation	• Of the 8 pilots, success benchmarks met in 5 pilots for availability & QAACT price relative to most popular non-QAACT antimalarial and 4 pilots for QAACT market share • Large increases in QAACT availability, decreases in QAACT prices, and increases in QAACT market share (except Niger and Madagascar) • Response similar in rural and urban areas • The price of co-paid QAACTs: variable across pilots, ranging from USD 0.51 in Madagascar to USD 1.96 in Uganda	• Subsidy schemes can result in increases in QAACT availability and affordability (seen in almost all pilot sites (except Niger and Madagascar) with reductions in availability of artemisinin monotherapy • However diagnostics stock and use in the private sector remained low • Impact was limited in Madagascar and Niger: possibly due to lack of full-scale mass media campaigns and the structure of the

				• In Nigeria and Zanzibar where artemisinin monotherapy was previously common, large and significant falls were observed with AMFm	private for-profit antimalarial sector (higher proportion of general stores, and in Niger itinerant vendors) •
(Talisuna et al., 2012)	Uganda (CAPSS study)	4 pilot districts: Kamuli, Kaliro, Pallisa, Budaka (104 public health facilities and >750 private outlets) and 1 control district: Soroti.	• As per AMFm approach i.e. subsidised ACTs with supporting interventions including provider training and demand generation.	• QAACT accounted for 69% of market share in intervention districts • Purchase of ACT within 24 hours of symptom onset for U5s increased from 0.8% at baseline to 26.2% (95% CI: 23.2-29.2%) • Odds of purchasing ACT within 24h in intervention vs control district: 6.11 (95% CI: 4.32-8.62; p<0.0001)	• 6-fold increase in all people (10-fold in U5) purchasing effective malaria treatment within 24 hours of symptom onset • 70% caregivers who purchased ACT complied with treatment schedule • Affordable treatment drives availability and uptake
(Tougher et al., 2012)	Ghana, Kenya, Madagascar, Niger, Nigeria, Uganda, Tanzania & Zanzibar	Evaluation of AMFm pilots in 8 countries	• National AMFm subsidy scheme: 6-15 months after rollout	• In all pilots except Niger and Madagascar: large increases in QAACT availability (26.3-71.3%) and in market share (15.6-58.7%) in the private sector • Fall in median price for QAACTs per adult dose in private sector from USD 1.28 – 4.82 (in 6/8 pilots) • Decreased market share of oral artemisinin monotherapies in Nigeria and Zanzibar (where previously >5%) • Also found increases in QAACT availability in public sector facilities especially Niger, Nigeria and Madagascar	• Limited effect in Madagascar and Niger at this stage • Impact mainly observed in the private sector although some improvement in public sector stocks • Small scale pilots can be replicated at scale

Abbreviations: ACTs: Artemisinin Combination Therapies; ADDOs: accredited drug dispensing outlets (ADDOs); AMFm: Affordable medicines facility (Malaria); CCMm: community case management of malaria; CHW: community health worker; CI: confidence interval; IMCI: integrated management of childhood illness; IPTc: intermittent preventative therapy for children; NMFI: non-malarial febrile illness; PMR: Private medical retailer; QAACT: quality assured ACT; RCT: randomised controlled trial; RDT: rapid diagnostic test; SES: socioeconomic status; SP: Sulfadoxine-pyrimethamine; SMS; short message service; U5s: under 5 year olds.

2.4 DISCUSSION

The relationship between improving treatment delivery through health systems and resulting impact on health outcomes of infectious diseases is not straightforward (de Savigny D, 2009). Ethiopia, South Africa, Zambia and Zanzibar (Barnes et al., 2009, Bhattarai et al., 2007) provide examples of how large-scale distribution of long-lasting insecticide treated nets (LLINs) and ACTs through formal health channels may be associated with reductions in malaria prevalence, admissions and deaths.

From a public health perspective, the key to reducing malaria mortality is to ensure diagnosis-led, first-line treatment in a timely fashion, before infections progress to severe disease. The INDEPTH-Network Effectiveness and Safety Studies (INESS) group studied the decay in efficacy of ACTs in Ghana, and estimated the systems effectiveness of ACTs to be 13.5% (i.e. 865 of 1000 patients were not treated effectively), with the steepest decline due to lack of access to treatment within 24 hours (Binka et al., 2012).

In this review, I have outlined the barriers posed by health systems factors limiting the potential success of malaria treatment programmes, and presented a review of interventions targeting these barriers. The population effects of improving individual dimensions of care are unknown and very difficult to predict or quantify in isolation, however, a few insights into potential strategies to alleviate delivery bottlenecks emerge (Figure 13).

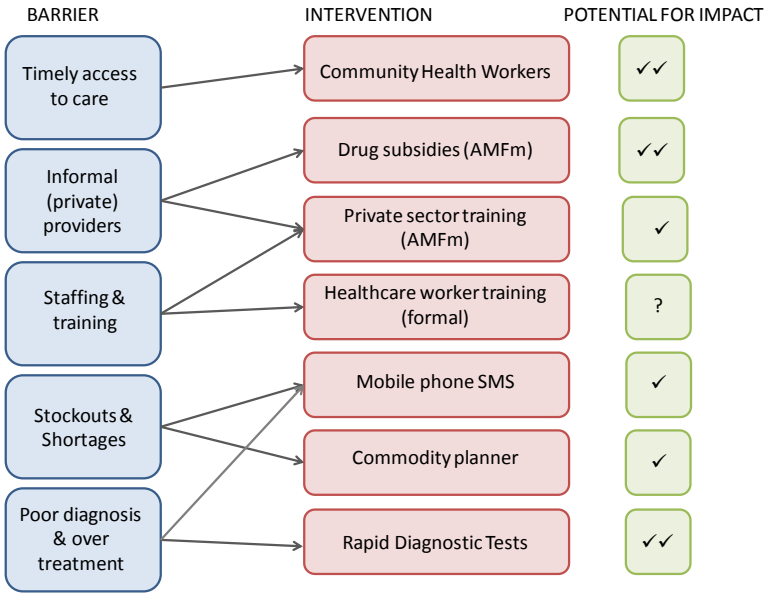


Figure13: Summary of health systems barriers to implementation and potential strategies to alleviate delivery bottlenecks

CHWs have been successfully deployed in several settings to reduce delays in accessing care, increase treatment-seeking, and provide diagnostic-led care of high quality including administration of pre-referral rectal artesunate to decrease the risk of severe malaria (Gomes et al., 2009). Although the cost-effectiveness

of a community-based strategy may vary with transmission intensity and local infrastructure, CHW schemes are especially valuable for communities that are traditionally hard to reach.

Interventions to improve the quality of care provided within the public sector present a mixed picture and are likely interdependent. The impact of stockouts on treatment delivery is evident and the threat of stockouts appears to alter both provider and patient behaviour with reports of stock-withholding, prescription of non-recommended drugs and reluctance of patients to seek care at venues where they cannot be guaranteed treatment. Unfortunately there is a paucity of published research on interventions to improve supply-chains, although mobile phone technologies appear to offer hope with implications for other essential drugs. By contrast, there have been many evaluations of training in the public sector but few have shown sustained improvement in performance, further underscoring the importance of robust supply-chains as without drugs, training has little impact. Supervision may increase adherence to treatment guidelines and mobile phone technologies may also be used to improve performance (Zurovac et al., 2012).

The impact of increasing use of diagnostics is also complicated. There are individual benefits of ensuring that NMFI are correctly treated, but also community benefits of limiting potential emergence of ACT resistance. Conversely overtreatment may potentially be associated with reduced risk of malaria transmission due to the prophylactic effect of ACTs (Okell et al., 2008a), and so a universal test-and treat policy may in theory lead to increased transmission and altered demographics of infection.

The private informal sector may be seen as a barrier to national malaria strategies, or instead acknowledged as an important source of care and included in the spectrum of malaria control efforts. Schemes such as AMFm provide an innovative attempt to harness the private sector; however, challenges to success include ensuring a reliable supply chain and passing the subsidy to the patient. Lower prices encourage use of first-line drugs. Training interventions aimed at private outlets have been partially successful in Kenya and Tanzania, although long-term sustainability is unclear, and none of these studies address introducing diagnosis-led treatment.

The Research Agenda for Malaria Eradication (MalERA) collaboratively identified key knowledge gaps and strategies for health systems in reducing malaria transmission. They concluded that the overarching systems issue was the ability to assess bottlenecks to effective coverage of interventions, and the integration of interventions into health systems. In addition the group defined specific research priorities; at facility level identifying HCW performance, at district level highlighting greater applications of existing strengthening tools, surveillance, and the importance of linking surveillance to actions i.e. surveillance-response, and at national level using disease specific programmes to strengthen health-systems (Alonso et al., 2011a).

The barriers to successful malaria treatment identified in this review are consistent with the MalERA approach and equally applicable to other parasitic and infectious diseases managed at a primary care level. The review of interventions to address these barriers show that improving access and quality of care is a complex, interdependent process, often with unpredictable outcomes. Traditional strategies such as training appear to have less impact than hoped, whilst use of technologies to ease stockouts, task-shifting to CHWs, and incorporation of informal points of care into planning appear more promising. As malaria control improves, such interventions may need to be tailored for surveillance as well as delivery, for example using the SMS data on stockouts to improve disease surveillance and linking this with appropriate control responses (surveillance-response). These interventions require further research extending beyond controlled small-scale trials, but may be critical to the sustained success of malaria control strategies.

3 DEVELOPMENT OF TRANSMISSION MODELS INCORPORATING HEALTH SYSTEMS

3.1 INTRODUCTION

Transmission of malaria depends on the presence of gametocytes in the blood of human hosts, which eventually progress to sexual reproduction following ingestion by mosquitoes. Mosquitoes become infectious to humans once sporozoites appear in the salivary glands(Warrell, 2002). ACTs are known to clear malarial parasites in man and also improve clinical symptoms of malaria more rapidly than alternative antimalarials (Sinclair et al., 2009). Artemisinin derivatives are also known to have specific anti-gametocyte properties (Sinclair et al., 2009, Price et al., 1996, Sowunmi et al., 2007), reducing the duration of gametocyte carriage in vivo (Bousema et al., 2010) and reducing onward infectiousness compared to previous first line treatments (Okell et al., 2008b)(Sawa et al., 2013). The mean duration of gametocyte carriage varies between different ACTs (Sawa et al., 2013). ACTs may additionally be able to reduce malaria transmission through their post-treatment prophylactic effect, which is contributed mainly through the partner-drug of the ACT rather than the artemisinin derivative (Sinclair et al., 2009). Therefore ACTs potentially also have a "treatment-as-prevention" role in malaria control and elimination (White, 2008) if they can be delivered at the required levels of coverage and quality.

Large-scale ACT programmes, implemented alongside LLIN distribution and IRS schemes, have resulted in reductions in clinical disease, hospitalisations and mortality in multiple settings (Barnes et al., 2009, Barnes et al., 2005, Lemma et al., 2010) (Bhattarai et al., 2007, Nosten et al., 2000). However the impact of widespread ACT delivery on malaria transmission has been less tangibly demonstrated. The malaria parasite reservoir was three-fold lower in districts with ACT programmes compared with control districts in Ethiopia (Lemma et al., 2010), and in Zanzibar *P. falciparum* prevalence in children decreased following ACT deployments (and before introduction of LLINs (Bhattarai et al., 2007)). However there are a number of confounding factors and it is not clear what the differential impact of ACTs would be at different transmission intensities.

Mathematical modelling (Okell et al., 2008a) predicts that the relative reduction in prevalence of infection and in the incidence of clinical episodes achieved by ACTs as first-line treatment would be highest in the areas with low baseline transmission, assuming high levels of treatment coverage. However, in contrast, the public health impact is predicted to be greatest in high transmission settings. Okell *et al* also considered the impact of reducing presumptive treatment of malaria, which appeared to reduce the number of treatment courses required, at the expense of a loss of impact on transmission (Okell et al., 2008a). Thus earlier modelling, as described in Section 1.6.3, suggests that with high rates of coverage and adherence, ACTs do

potentially have a public health impact in reducing transmission. However there have been no modelling studies to date that consider the most efficient way to increase coverage by improving access to and quality of care.

Here I describe the extension of a previously developed model for the transmission of *P. falciparum* malaria (Griffin et al., 2010) to investigate the potential role of health systems and ACT delivery in reducing malaria morbidity, mortality and transmission. The impact of health systems barriers on delivery of efficacious treatment interventions was described in Chapter 2. The literature review also included the potential impact of overcoming barriers such as access to treatment and the quality of care received (Rao et al., 2013a). Using the results from this review, I focus on:

- Treatment seeking and access to healthcare
- Different sectors through which individuals access treatment
- The quality of care received by symptomatic cases of malaria (here the probability of receiving the correct antimalarial)
- Inappropriate prescription of antimalarials to non-malarial febrile illnesses and the potential role of diagnostics
- The role of community and tertiary level care for cases of severe malaria

I extend the original model iteratively to incorporate the systems barriers above to understand the bottlenecks to achieving predicted levels of ACT coverage and impact, and effect of interventions to overcome these critical junctures.

3.2 BASELINE TRANSMISSION MODEL

The model extensions are based on the compartmental version of the malaria transmission model published by Griffin *et al.* (Griffin et al., 2010). This model incorporates the transmission cycle in both the vector and humans and has been fitted to a large dataset on the relationship between EIR and parasite prevalence (by microscopy and/or PCR) and more recently to age-stratified patterns of clinical disease incidence across 23 sites with varying transmission intensity in Africa (Griffin et al., 2014). Throughout I assume both human and mosquito population sizes remain constant over time (i.e. there is no movement of individuals, growth in the population or seasonality in vector abundance). This section briefly summarises the original model (Figure 14).

Individuals are born into the population susceptible to infection (state S) but with a degree of partial maternal immunity (see later). Susceptible individuals become infected at a rate Λ (the force of infection) determined by vector density relative to humans (m), the ratio of infected vectors to uninfected and the biting rate of vectors on humans (ζ) (influenced by age and exposure) as well as an individual's level of immunity which is described later.

Infection is followed by a latent liver stage infection, which is included as a delay in the force of infection of duration d_E. The infection process is identical for susceptible individuals and for those re-infected via superinfection. After parasites emerge from the liver, individuals may become clinically symptomatic with probability ϕ, influenced by both acquired immunity to disease and maternal immunity (see later). Otherwise they enter into an Asymptomatic patent (i.e. detectable) infection state (A) with probability 1-ϕ. The recovery rate from Asymptomatic to a Sub Patent state (U) is r_A; the rate by which this occurs, i.e. the detectability of the infection is altered by anti-parasitological immunity (see later). Those in the sub-patent state U are cleared at rate r_U and individuals return to the state S. Superinfection (the possibility of becoming re-infected despite the presence of an existing infection), is included in both Asymptomatic and Sub-patent states.

Clinically symptomatic infected individuals may be treated with probability f_T after which they move to a treated state (T). In the original model, this probability is fixed, and this is something that will be refined later in this thesis. Those who are treated clear their gametocytaemia at rate r_T to enter a prophylaxed state (P). Transition from being prophylaxed back to susceptible occurs at rate r_P. Those who are not treated or who fail treatment enter a diseased state D with probability 1-f_T. Those in this state eventually clear clinical symptoms and recover to the asymptomatic state A at rate r_D. The average period of prophylaxis ($1/r_P$) is assumed to be the duration of minimum inhibitory anti-malarial concentrations in the blood against blood stage parasites.

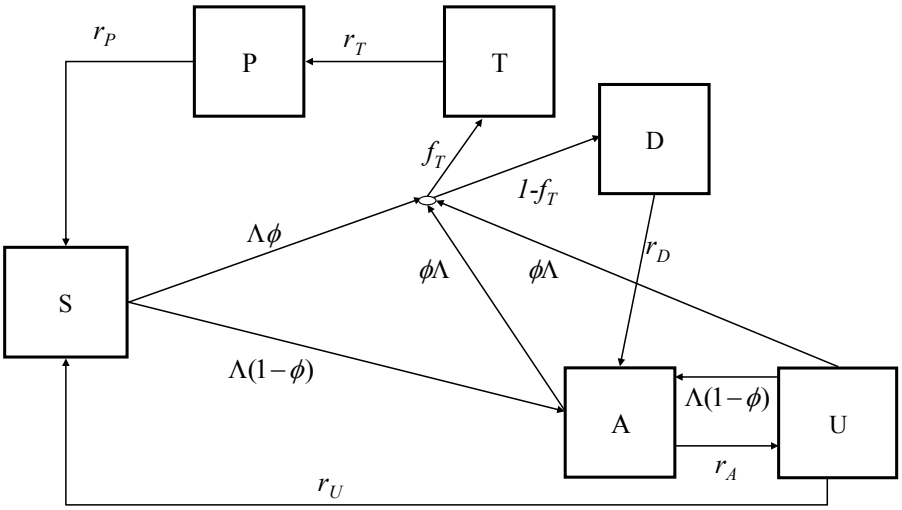


Figure 14: Baseline Transmission Model - Flow diagram for the human infection states.

S - Susceptible; T - Treated; D – untreated clinical disease; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection. People move between these states with rates/probabilities as marked on the arrows.

The partial differential equations for the model are given below, with *t* representing time and *a* representing age.

$$\frac{\delta S}{\delta t}+\frac{\delta S}{\delta a}=-\Lambda S+r_P P+r_U U$$

$$\frac{\delta T}{\delta t}+\frac{\delta T}{\delta a}=\phi f_T \Lambda(S+A+U)-r_T T$$

$$\frac{\delta D}{\delta t}+\frac{\delta D}{\delta a}=\phi(1-f_T)\Lambda(S+A+U)-r_D D$$

$$\frac{\delta A}{\delta t}+\frac{\delta A}{\delta a}=(1-\phi)\Lambda(S+U)+r_D D-\phi\Lambda A-r_A A$$

$$\frac{\delta U}{\delta t}+\frac{\delta U}{\delta a}=r_A A-r_U U-\Lambda U$$

$$\frac{\delta P}{\delta t}+\frac{\delta P}{\delta a}=r_T T-r_P P$$

Individuals in all infected states, including treated states, contribute to the infectious reservoir. Those with disease are assumed to have higher parasite densities and thus be more infectious than asymptomatic or sub-patent infections. Individuals treated with ACTs contribute a lower onward infectivity to mosquitoes.

The force of infection acting on mosquitoes (Λ_V) is the sum of the contribution to mosquito infection from the different human infectious states, as is described in Section 3.2.2.

3.2.1 Effect of Immunity

Both maternal and acquired immunity (pre-erythrocytic and blood stage) are included in the model. Acquired immunity to infection is assumed to modify the probability of infection acquisition following an infectious bite (pre-erythrocytic (PE) immunity, I_B), and is capped, irrespective of age, at a 50% relative reduction in infection risk compared with non-immune individuals (similar to that observed with high-levels of vaccine-induced PE immunity). The probability of acquisition occurring given an infectious bite is:

$$b = b_0\left(b_1 + \frac{1-b_1}{1+(I_B / I_{B0})^{\kappa_B}}\right),$$

where b_0 is the probability of acquisition of infection if no immunity exists, and $b_0 b_1$ is the minimum probability that acquisition of infection occurs with high levels of immunity. I_{BO} and κ_B are fitted scale and shape parameters.

Acquired immunity also changes the probability of developing clinical disease following infection (I_{CA}) (termed clinical immunity, representing one consequence of blood-stage immunity). In addition, blood-stage acquired immunity alters the probability of detection of infection (I_D) due to reductions in parasite density (termed anti-parasite immunity). The probability that an (asymptomatic) infection is detectable (i.e. remains patent) is given by q:

$$q = d_1 + \frac{(1-d_1)}{(1+(\mathrm{I_D}/\mathrm{I_{D\,0}})^{\kappa_D}\,\mathrm{f_D}}\ ,$$

where d_1 is the minimum probability of detection at maximum immunity and I_{D0} and κ_D are shape and scale parameters. The age dependent nature of anti-parasite immunity is determined by the parameter f_D.

Maternal immunity (I_{CM}) determines the probability of developing clinical disease following infection in young infants. At birth it is assumed to be a proportion (P_M) of the acquired immunity accumulated by a 20 year old in the same transmission setting and then decays at a rate $1/d_M$. Therefore the probability of developing clinical disease when infected is modified by both maternal immunity (I_{CM}) and acquired clinical immunity (I_{CA}):

$$\phi = \phi_0\left(\phi_1 + \frac{1-\phi_1}{1+(\mathrm{I}_{CA} + I_{CM} / I_{C0})^{\mathrm{K}_C}}\right)\ ,$$

where Φ_0 is the probability that clinical disease develops in the presence of no immunity against malaria infection, and $\Phi_0\,\Phi_1$ is the minimum probability that clinical disease may develop. I_{C0} and κ_C are shape and scale parameters.

All three acquired forms of immunity are modelled to increase with exposure and/or age and to wane with time. The partial differential equations for changes in acquired immunity with time (*t*) and age (*a*) are given below:

$$\frac{\delta I_B}{\delta t}+\frac{\delta I_B}{\delta a}=\frac{\varepsilon}{\varepsilon u_B+1}-\frac{I_B}{d_B}$$
$$\frac{\delta I_{CA}}{\delta t}+\frac{\delta I_{CA}}{\delta a}=\frac{\Lambda}{\Lambda u_C+1}-\frac{I_{CA}}{d_C}$$
$$\frac{\delta I_D}{\delta t}+\frac{\delta I_D}{\delta a}=\frac{\Lambda}{\Lambda u_D+1}-\frac{I_D}{d_{ID}}$$

where d_X represents the mean duration of immunity (of type X) and u_X represents a period during which immunity of type X cannot be boosted as a result of a prior boost. ε here represents EIR at age *a*.

3.2.2 Vector Model

The vector model is also based on the structure of a model developed by Griffin *et al.* and is dynamically modulated by changes in transmission from humans (Griffin et al., 2010). The differences between various malaria vector species such as *Anopheles gambiae* and *Anopheles arabiensis* have not been considered. I also do not consider seasonality here.

At any time, the vector (denoted by the subscript *v*) can be in one of three states: susceptible (S_v), latent (E_v) or infectious (I_v) after time τ_V where malaria sporozoites appear in the salivary glands. It is assumed that mosquitoes do not clear infection before death, and that the death rate of a mosquito is not affected by their infectious state. New adults emerge at a rate $\mu_v V$ and die at rate μ_v where V is the total adult population. Thus the mosquito population is assumed to remain constant over time.

The Entomological Inoculation Rate (EIR) is a measure of the number of bites by infectious mosquitoes per person per unit time. It is determined by the Human Blood Index (HBI) i.e. the proportion of blood meals taken on humans rather than animals, as well as the human biting rate of mosquitoes, i.e. the number of bites per person per day by vector mosquitoes, and the fraction of vector mosquitoes that are infectious (the "sporozoite rate"). In this model, it is assumed that there is heterogeneity in biting rates that varies with age (through body size) and between individuals. To incorporate heterogeneity, the relative biting rate (ζ_i) in category *i* follows a log-normal distribution between people with a mean of 1, and standard deviation on the log scale of σ:

$$\zeta_i=\exp(-\sigma^2/2+\sigma x_i)$$

Hence EIR (ε) for the exposure category *i* - is calculated as:

$$\varepsilon_i = \varepsilon_0 \zeta_i (1 - \rho \exp(-a / a0)) \ ,$$

where ε_0 is the mean EIR for adults, *a* refers to age, and ρ and a_0 are fixed biting parameters with respect to *An. gambiae* that are age dependent. *1-ρ* is the relative biting rate at birth compared to adults and *a0* determines the time-scale of the increase in biting rate with age. The force of infection (Λ) is therefore $\Lambda = \varepsilon b$ where *b* is the probability of infection if bitten by an infectious mosquito (see Section 3.2.1).

In the model simulations, I use the relationship between the EIR and the density of mosquitoes to humans (*m*) to generate simulations at fixed values of the EIR. The mosquito density required to achieve a given EIR is:

$$m_{v0} = \frac{\omega EIR}{I_v \alpha HBI} \ ,$$

where *ω* is a normalising constant for biting rate by age and exposure given by:

$$\omega = \frac{(1-\rho)\mu_h}{(\mu_h + \frac{1}{a_0})} \ .$$

Here μ_h is the death rate for an exponential human population distribution that has been fitted to an estimate of the population of Tanzania. The proportion of mosquitoes that are infectious, I_V , is found by calculating the human and mosquito equilibrium states conditional on the EIR, as in Griffin et al(Griffin et al., 2014).

3.2.3 Infectiousness to Mosquitoes

Mosquitoes become infected at a rate Λ_v , the force of infection acting on mosquitoes. This is the sum of the contribution to mosquito infection from the different human infectious states. Onward infectiousness (*c*) is dependent on parasite density and detectability (*q*), i.e. the probability of an infection remains patent as defined in section 3.2.1.

Infectiousness varies with host state e.g. c_D for infectiousness of state D and is estimated through the relationship between asexual parasite density (Ross et al., 2006a). Treatment with ACTs results in reduced onward infectiousness to mosquitoes within the model.

$$\Lambda_v = \zeta (1 - \rho \exp(-a / a_0)) [c_D D + c_A A + c_U U + c_T \mathrm{T}] \ ,$$

where c_D, c_T, c_A and c_U are the onward infectivity to mosquitoes of these different states. The expression includes a time-lag between parasitemia with asexual parasite stages and gametocytaemia (infectivity to mosquitoes) in the host to account for the lag in gametocyte development characteristic of *P. falciparum,* but has not been expanded here for simplicity. The expression $\zeta(1-\rho\exp(-a/a_0)$ was defined earlier in this chapter.

3.3 MODEL 1: INCLUSION OF TREATMENT ACCESS AND SEVERE DISEASE

The model developed by Griffin *et al* assumes a constant rate of treatment for those who are clinically symptomatic (Griffin et al., 2010). However, as outlined in Chapter 2, the actual probability of receiving an ACT for an episode of malaria is known to be variable (estimated to be less than 50%) across sub-Saharan Africa depending on where treatment is sought (WHO, 2013). Hence my aim in this first extension of the original transmission model is to incorporate the two main community sources of treatment - public sector health facilities and private sector informal outlets. I capture how access to healthcare and the quality of care received varies through the following parameters:-

(i) Following onset of symptoms, the probability of not seeking treatment (i.e. lack of access), the probability of attending a health facility and the probability of accessing a private drug shop (sector preference)

(ii) time taken to seek treatment at either a private outlet or a public facility, by those who do access care (i.e. delays to access)

(iii) probability of receiving an ACT for malaria infection in the public and private sectors (i.e. quality of care)

3.3.1 Model 1: Mathematical Details

In this first iteration, the main transmission model structure is maintained (grey section in Figure 15) but the clinical disease states are expanded to consider potential pathways for treatment seeking (black section in Figure 15). The process of infection and clinical symptoms is represented in two steps - becoming infected under the force of infection (Λ) and the probability of becoming clinically symptomatic once infected (Φ) - for greater clarity. Infections that are asymptomatic occur with probability $1-\Phi$ and this is similarly represented as two steps. The effect of immunity, both acquired and maternal, is maintained as in the original model.

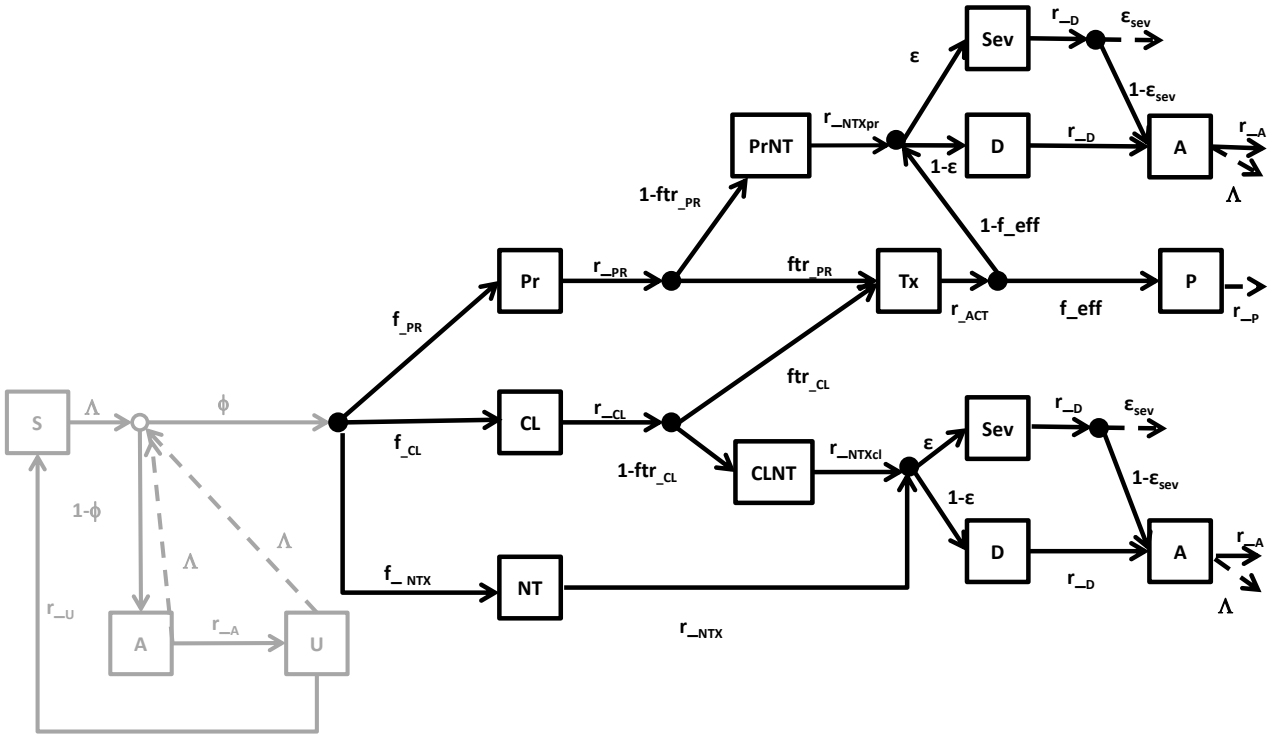


Figure 15: Flow diagram for the Health systems model 1.

S - susceptible; NT – not seeking treatment; Pr – Seeking treatment at private outlet/drug seller; CL – Seeking treatment at primary care health facility/government clinic; PrNT – not treated at private outlet/drug seller; CLNT – not treated at primary care health facility/government clinic; Tx – On treatment; D – untreated clinical disease; Sev – Severe disease; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection. People move between these states with rates/probabilities as marked on the arrows

Symptomatic individuals may choose to attend a public sector primary health facility (CL) with probability $f\__{CL}$ or seek treatment at a private sector drug shop or retail outlet (Pr) with probability $f\__{PR}$. As described in Chapter 2, the private sector may vary from accredited drug shops such as the ADDOs (Accredited Drug Dispensing Outlets) in Tanzania to general stores and itinerant drug peddlers (Goodman et al., 2007a). In this model, I have not considered each potential type of private drug outlet separately due to a lack of comparability and different nomenclature of sub-categories across the region. Instead I have used only one category for the private sector, and parameterised this using data regarding all forms of private informal sources of care except private doctor surgeries. Individuals who do not seek treatment with the probability $f\__{NTX} = 1 - (f\__{CL} + f\__{PR})$ pass into an untreated state (NT).

Delays in accessing care and treatment are known to increase risks of morbidity and mortality (Greenwood et al., 1987). I therefore incorporate a delay from the onset of symptoms to when care is received; for those seeking care from the private sector, treatment is received at the rate r_{PR} (i.e. the inverse of the average duration in days of the time taken to receive treatment at a drug shop from the time clinical disease developed) and for those attending public sector health facilities, treatment is received at the rate r_{CL}. The probability of receiving an ACT is assumed to differ by source, with ftr_{CL} denoting the probability of receiving an ACT at a public facility and ftr_{PR} the probability of receiving an ACT at a private outlet or shop. Once treated (defined as receiving an ACT at either a public or private outlet), individuals pass to a treated state Tx.

Those who are treated go on to clear gametocytaemia at rate r_{ACT} and recover to enter a prophylaxis state (P), with a probability of f_{EFF}. Transition from prophylaxis back to susceptible occurs at rate $r\__P$. No other antimalarials except ACT are included in the model, and treatment with any other antimalarial is considered in the context of the model as equivalent to non-treatment. Although levels of SP administration may still be high (Littrell et al., 2011a), this was not modelled as affording a potential prophylactic effect given reports of SP resistance in many settings (Gesase et al., 2009, Pearce et al., 2013, Ogouyemi-Hounto et al., 2013).

As in the original model, super-infection is included for both Asymptomatic and Sub-patent states, with similar probabilities of clinical symptoms dependent on immunity. Individuals moving into one of the "waiting for treatment" states i.e. CL and Pr as well as the not treated state NT are assumed to be no longer susceptible to super-infection.

Most malaria deaths can be prevented when clinical cases are promptly diagnosed and effectively treated, and studies suggest that major factors affecting the outcome of clinical malaria and the

onset of severe disease are health-seeking behaviour and determinants of access to health services (WHO, 2012c, Getahun et al., 2010, Dillip et al., 2009). I have attempted to capture this through three different pathways:

1. If no treatment is sought (with probability f_{NTX}) hence moving to state NT
2. If individuals do not receive ACTs at the source of treatment or are incorrectly treated (with probability $1\text{-}ftr\_{CL}$ at the health facility or $1\text{-}ftr\_{PR}$ at a private outlet) moving to waiting states CLNT or PrNT respectively. The reasons this may occur are explored in Chapter 4.
3. If ACT treatment fails (with probability $1\text{-}f\_{EFF}$) moving to either the Diseased (D) state or the Severe disease (Sev) state

The probability of accessing more than once source of healthcare is not included at this stage.

Those individuals who do not seek treatment exit the state NT at a rate r_{NTX}. Those leaving CLNT and PrNT do so at a rate r_{NTXPR} or $r\_{NTXCL,}$ which is adjusted by the times taken to seek treatment (r_{PR} *or* r_{CL}) to ensure that overall duration along all routes is the same.

All those who are not treated or incorrectly treated (with other anti-malarials or following ACT treatment failure) may either develop severe disease (Sev) with probability ε or pass to a clinical disease state (D) with probability 1 – ε. Individuals eventually recover from state D (at rate r_{D}) to become patently asymptomatic (A) as in the original model. The probability ε is set to vary only with age since the impact of immunity has already been included in the probability of developing clinical disease.

In this first model, no specific management is included for severe cases. It is assumed that the majority of severe cases die, with probability ε_sev. The proportion of severe cases that survives, i.e. 1 - ε_sev, eventually go on to recover from clinical symptoms and move to the asymptomatic state A at the rate r_{D}.

All deaths, from each state and from severe disease are reborn to maintain a stable population.

The equations for the human infection cycle in this model are in Appendix A.

The force of infection acting on mosquitoes in this model is simply extended to reflect the additional disease states, which are all assumed to have transmission probability c_D:

$$\Lambda_v = \zeta(1-\rho\exp(-a/a_0)[c_D D + c_A A + c_U U + c_D Pr + c_D CL + c_D NT + c_D CLNT + c_D PrNT + c_D Sev + c_{TX}\,\mathrm{Tx}]$$

As previously, individuals treated with ACTs contribute a lower onward infectivity to mosquitoes

3.3.2 Model 1: Parameters

Parameter estimates for the vector model and underlying transmission models match those used in the fitted model developed by *Griffin et al.* (Griffin et al., 2014) and are summarised in Table 4. Parameters for the health systems components are based on the literature review presented in Chapter 2 and are described in this section.

Table 4: Model 1 – Vector; Immunity and Transmission; Host infection &clinical disease parameters

4A. Vector parameters (Griffin et al., 2014, Griffin et al., 2010)

Name	Definition	Value Range	Value Used	References
HBI	proportion of blood meals on humans	0.73 - 1.0 - varies by species	0.92	(Griffin et al., 2010, Dabire et al., 2008, Dia et al., 2003, Ndiath et al., 2008, Tirados et al., 2006, Griffin et al., 2014)
A	biting rate per day	0.02-0.465	0.33	(Gillies, 1953, Bruce-Chwatt, 1960, Killeen et al., 2000, Griffin et al., 2010, Griffin et al., 2014)
$1/\mu_V$	Lifespan of vector (days)	5.6-25.0	15	(Dawes et al., 2009, Anderson RM, 1991, Griffin et al., 2010, Griffin et al., 2014)
τ_V	Latent period in mosquitoes (days)	9 – 11	10	(Anderson RM, 1991, Molineaux and Gramiccia, 1980, Griffin et al., 2010, Griffin et al., 2014)
a_0	Age-dependent biting parameter	Fixed	8 years	(Griffin et al., 2010, Griffin et al., 2014)
P	Age-dependent biting parameter	Fixed	0.85	(Griffin et al., 2010, Griffin et al., 2014)
σ^2	Variance of log of heterogeneity in biting rates	Fixed	1.67	(Griffin et al., 2010, Griffin et al., 2014)
M	Ratio of mosquitoes to humans (V/H)	0-500 (varied to determine EIR for a	-	(Griffin et al., 2010, Griffin et al., 2014)

		setting)		

4B Immunity and Transmission parameters (Griffin et al., 2014, Griffin et al., 2010)

Name	Definition	95% credible interval	Value Used	References
c_D	Probability of transmission from disease state to vector: not including immunity	0.039-0.123	0.067	(Griffin et al., 2010)
c_A	Probability of transmission from asymptomatic state to vector	As above	0.067	(Griffin et al., 2010)
c_U	Probability of transmission from subpatent state to vector	0.00056 – 0.018	0.0.0062	(Griffin et al., 2010)
c_{Tx}	Probability of transmission from an ACT treated Human TO vector on biting	0.044-0.583 x c_D	0.05094 x c_D	(Bousema et al., 2006, Okell et al., 2008a, Okell et al., 2008b, Chen et al., 1994, Cairns et al., 2011)
γ_I	Relates infectiousness to probability of detection	t ½: 0.16 – 15 (3.6) time: 0.6-8.48	1.84	(Griffin et al., 2010)
Immunity reducing probability of detection (detection immunity I_D).				
d_1	Probability with maximum immunity: decays with age	0.088 – 0.237	0.158	(Griffin et al., 2010)
d_{ID}	Duration of decay	Fixed	10 years	(Griffin et al., 2014)
I_{D0}	Scale parameter	0.2-6.17	1.51	(Griffin et al., 2014)
κ_D	Shape parameter	0.270-0.786	0.456	(Griffin et al., 2014)
u_D	Duration in which immunity is not boosted	3.66-19.4	9.61 days	(Griffin et al., 2014)
a_D	Scale parameter relating age to immunity	19.2-25.2	21.9 years	(Griffin et al., 2014)
f_{D0}	Parameter relating age to immunity	0.00055-0.0305	0.00959	(Griffin et al., 2014)
γ_D	Shape parameter relating age to immunity	3.73-6.2	4.75	(Griffin et al., 2014)
Immunity reducing probability of infection (pre-erythrocytic immunity, I_B)				
b_0	Probability of infection following infectious bite with no immunity	0.409-0.868	0.615	(Griffin et al., 2014)
b_1	Maximum relative reduction	Fixed	0.5	(Griffin et al., 2014)
d_B	Duration of decay	Fixed	10 years	(Griffin et al., 2014)
I_{B0}	Scale parameter	24.8 – 140	70.3	(Griffin et al., 2014)

κ_B	Shape parameter	1.20 – 2.88	2.10	(Griffin et al., 2014)
u_B	Duration in which immunity is not boosted	2.17 – 13.9	6.17 days	(Griffin et al., 2014)
Immunity reducing probability of clinical disease: modulated by acquired clinical immunity (I_{CA}) and maternal immunity (I_{CM})				
I_{C0}	Scale parameter	10.2 – 23.1	15.6	(Griffin et al., 2014)
κ_C	Shape parameter	1.86 – 2.6	2.16	(Griffin et al., 2014)
u_C	Duration in which immunity is not boosted	3.03 – 11.4	6.32 days	(Griffin et al., 2014)
P_M	New-born immunity relative to mother's (P_M): calculated as a 20 year old in this setting	0.744 – 0.998	0.939	(Griffin et al., 2014)
d_M	Duration of decay of maternal immunity from birth	33.3 – 46.7	39.1 days	(Griffin et al., 2014)

4C Host infection and clinical disease parameters (Griffin et al., 2014, Griffin et al., 2010)

Name	Definition	95% credible interval	Value Used	References
Φ	Probability of developing clinical symptomatic disease		Fitted as Griffin model to 23 African sites: age and immunity structured	(Griffin et al., 2010, Griffin et al., 2014)
Φ_0	Probability of developing clinical disease following infection with no immunity	0.56 - 0.963	0.8	(Griffin et al., 2014)
Φ_1	Maximum relative reduction (assumed through acquisition of anti-parasite immunity)	0.00004 – 0.0025	0.00071	(Griffin et al., 2014)
d_C	Average duration of decay	Fixed	30 years	(Griffin et al., 2014)
T	Average human latent period (days)		12	(Griffin et al., 2010, Griffin et al., 2014)
1/r_D	Average time taken to progress for an uncomplicated symptomatic episode with no treatment to asymptomatic (days)	4.2 - 13.1	5	(Griffin et al., 2010, Griffin et al., 2014)

recA	Average time taken to progress from asymptomatic to sub-patent infection (days): structured to increase with acquired anti-parasite immunity	195 (Calculated from other parameters)	Fitted as Griffin model to 23 African sites: age and immunity structured	(Bekessy et al., 1976, Griffin et al., 2010, Griffin et al., 2014)
$1/r_U$	Average duration of sub-patent infection (days)	87-131	110	(Griffin et al., 2010, Griffin et al., 2014)
$1/\mu_h$	Mean of cross-sectional age distribution (years)		21	(Griffin et al., 2010, Griffin et al., 2014)

3.3.2.1 Additional human infection parameters

The time taken for a severe episode without treatment to become asymptomatic was assumed to be the same as the length of time of an uncomplicated episode ($1/r\_{D}$), given that severity is a clinical state in the model and not defined by parasitaemia levels.

Lubell *et al* (Lubell et al., 2011) undertook a Delphi survey with malaria experts on the consequences of untreated malaria to estimate the probability of developing severe disease if untreated or the probability of death from untreated severe disease for comparison of malaria case management for low and medium/high transmission settings. The survey produced consensus on some probabilities given below in Table 5 as follows:

Age	Probability of developing severe disease if malaria untreated		Probability of severe malaria leading to death	
	Low Transmission	Medium/High transmission	Low Transmission	Medium/High transmission
U5	30% (10–58%)	13% (7–30%)	73% (50–85%)	60% (45–80%)
Adult	18% (5–25%)	3% (1–5%)	70% (50–80%)	45% (30–71%)

Table 5: Delphi survey estimates for children under 5 years of age and adults: median and interquartile range

(Lubell et al., 2011)

These were higher than those estimated in a report for Roll Back Malaria produced by Shilcutt *et al* (Shillcutt et al., 2008) (5 -10%), in which there is an acknowledgement that in a medium transmission setting by the time a child reaches the age of 5 they would have experienced and survived at least malaria infection and would have developed immunity to subsequent infections. In such settings however the levels of all-cause under five mortality is high (WHO, 2012a).

Based on these surveys, I assumed that in low transmission settings, there is a higher probability of developing the symptoms of severe malaria, and a higher probability of death from severe malaria. The role of immune modulation has already been included in the likelihood of developing disease, and thus ε and $\varepsilon_{\_SEV}$ are modelled as a constant proportion of those with untreated clinical disease (albeit with different values for under-fives and over-fives). These parameters are summarised in Table 6.

Table 6: Additional Human infection and clinical disease parameters

Name	Definition	Value Range	Value Used	References
ε	Proportion of untreated infections that progress to severe disease	0.05 - 0.58	U5: 0.13 Adult: 0.03	(Shillcutt et al., 2008, Lubell et al., 2011, Gupta et al., 1999b)
$\varepsilon_{\_SEV}$	Proportion of untreated severe infections that progress to death	0.15 - 0.85	U5: 0.6 Adult: 0.45	(Lubell et al., 2011, Shillcutt et al., 2008)

3.3.2.2 Treatment and drug parameters

Limited data exist on the duration of reduction in gametocytaemia (i.e. infectiousness) and the duration of minimum inhibitory anti-malarial concentrations of ACTs against blood stage parasites. A pooled analysis (Okell et al., 2008b) ,as well as other studies (Ezzet et al., 2000, White, 2005) and (2005), show a trend of reduced duration of infectivity in those treated with ACTs compared with other gametocytocidal and gametostatic antimalarials, i.e. ACTs induce a faster rate of reduction in gametocytaemia than non-ACT antimalarials. Bousema *et al* estimated the duration of gametocyte carriage using molecular methods to be an average of 55 days (95% CI 28.7 - 107.7) for non-ACT treatment compared to 13.4 days (95% CI 10.2-17.5) in those receiving ACT treatment, i.e. a 75% reduction in duration (Bousema et al., 2010).

Estimates of the probability of onward infectiousness of ACT treated individuals range from 0.044 - 0.583 (Okell et al., 2008a, Bousema et al., 2006, Chen et al., 1994), and of non-ACT treated individuals from 0.014 – 0.259 (Chen et al., 1994, Bousema et al., 2006, Okell et al., 2008a, Okell et al., 2008b) or 0.05 – 0.17 derived from Garki data (Griffin et al., 2010). In this model, the relative infectiousness of a treated individual (in any state) is assumed to be reduced compared to their untreated infectious state by a factor of 0.05, i.e. a 95% reduction. For simplicity the onward infectivity of individuals treated with non-ACT treatments is assumed to be the same as in non-treated individuals

The duration of post-treatment prophylaxis is dependent on the partner drug used in the combination of the ACT, and has been estimated to range from 8.5 – 12.4 days for ACT, in particular

Artemether-Lumefantrine, the most commonly used ACT in Africa (Ezzet et al., 2000, Sinclair et al., 2009). In the original model, the average period of prophylaxis is estimated to be 25 days assuming that the ACT is partnered with other drugs such as SP with a longer prophylactic time (Griffin et al., 2010). Here I used the average duration of ACT-induced prophylaxis alone which is estimated to be 10 days (Bousema et al., 2010, Okell et al., 2008b) due to reported high levels of SP resistance in many areas of sub-Saharan Africa (Ogouyemi-Hounto et al., 2013, Iriemenam et al., 2012, Gesase et al., 2009).

Differences in the impact of ACT by formulation or means of administering were not included. ACT, when given correctly as per protocol, is assumed to be 95% efficacious on the basis of a Cochrane review (Sinclair et al., 2009). The parameters relating to the impact of ACT treatment are summarised in Table 7.

Table 7: Drug related parameters

Name	Definition	Value Range	Value Used	References
f_{EFF}	ACT efficacy	0.95 – 0.97	0.95	(Sinclair et al., 2009)
$1/r\_{ACT}$	Average duration of gametocytaemia after treatment with ACT treatment (days)	10.2-17.5 (unpublished 6.3: AS - 14.9:AL)	13.4	(Okell et al., 2008b, Bousema et al., 2010)
$1/r\_{P}$	Average uration of prophylaxis after ACT treatment (days)	8.5-12.4 (AL)	10	(Okell et al., 2008b, Ezzet et al., 2000, Sinclair et al., 2009, Bousema et al., 2010)
cTx	% reduction in average infectiousness compared to state occupied prior to treatment	80.6% * cD	0.05	(Griffin et al., 2014)

3.3.2.3 Health system parameters

Baseline values for these parameters were derived from the literature but their impact is explored by varying them in sequence. A full review of this literature is presented in Chapter 2.

Several sources indicate that distance to healthcare impacts on treatment seeking behaviour (O'Meara et al., 2009, Feikin et al., 2009, Noor et al., 2003, Gething et al., 2004, Stock, 1983, Al-Taiar et al., 2008). The distance to healthcare beyond which access decreases more rapidly varies by setting, with some studies suggesting 5-6km (Gething et al., 2004, Noor et al., 2003) whilst others report a threshold of 2km (Amin et al., 2003, Alba et al., 2010a, Hetzel et al., 2008). The probability of treatment seeking for fever independent of distance was estimated to be 50%, based on Chuma's

review (Chuma et al., 2009) of barriers to access to ACTs and studies reported by Zurovac *et al*. (Zurovac et al., 2008d, Zurovac et al., 2008b) across both private and public sectors. The probability of accessing treatment was the main rate-limiting step in Krause's analysis of barriers to effectiveness (21%) (Krause and Sauerborn, 2000). Many studies report a patient preference for private drug sellers as a first action, although this does vary by region, distance and provision (Sumba et al., 2008). I therefore assumed 60% of those who seek care for a febrile illness attend private drug sellers and 40% attend public sector government health facilities (Mangham et al., 2012, Mangham et al., 2011, Alba et al., 2010a). The average delay to access a public sector clinic was assumed to be longer than a private drug seller, based on durations reported by Chuma: 86% attended a health facility in 2 days (Chuma et al., 2010), Amin: median delay of 2 days to seek care at public sector facilities (Amin et al., 2003) and al-Taiar (Al-Taiar et al., 2008).

As described in Chapter 2, distance from health care not only reduces the probability of seeking care but can also lead to delays in seeking treatment, which in turn may influence clinical outcomes. Studies by al-Taiar (Al-Taiar et al., 2008), Feikin (Feikin et al., 2009) and Rutemberwa (Rutebemberwa et al., 2009) showed that a distance greater than 1-2km was associated with an increased risk of severe disease, and O'Meara *et al* found that the incidence of severe (hospitalised) malaria more than doubled as travel time and delays increased (O'Meara et al., 2009). I incorporated this effect by doubling the probability of developing severe disease if there are delays in seeking care of greater than the average time set for untreated cases to develop severe disease i.e. greater than 3 days. These parameters relating to access to healthcare both in the public and private sectors are summarised in Table 8.

Table 8: General healthcare access parameters

Name	Definition	Value Range	Value Used	References
f_{NTX}	Probability of not seeking or accessing early treatment if infected and symptomatic (1-f_{PR}– f_{CL})	0.3 – 0.77	0.5	(Noor et al., 2003, Amin et al., 2003, Al-Taiar et al., 2008, Littrell et al., 2011a, Kangwana et al., 2011, Mangham et al., 2012, Mangham et al., 2011, Chuma et al., 2010, Chuma et al., 2009, de Savigny et al., 2004, Getahun et al., 2010, Rutebemberwa et al., 2009, Hetzel et al., 2008, Sumba et al., 2008)
f_{CL}	Probability of accessing care at a primary care clinic/public sector health facility for a mild	0.14 - 0.67	0.4*(1-f_{NTX})	(Chuma et al., 2009, Rutebemberwa et al., 2009, Chuma et al., 2010, Krause and

	episode (1-f_{NTX} – f_{PR})			Sauerborn, 2000, Amin et al., 2003, Noor et al., 2003, Sumba et al., 2008)
f_{PR}	Probability of accessing care at a private trader/ informal outlet for a mild episode (1-f_{NTX}-f_{PR})	0.17 - 0.83	0.6*(1-f_{NTX})	(Marsh et al., 2004, Gupta et al., 1999b, Alba et al., 2010a, Alba et al., 2010b, Krause and Sauerborn, 2000, Rutebemberwa et al., 2009, Amin et al., 2003, Sumba et al., 2008, Goodman et al., 2007a)
$1/r_{CL}$	Average time taken to seek treatment at clinic/formal sector (days)	24h – 7 days	2	(Chuma et al., 2009, Chuma et al., 2010, Sumba et al., 2008, Rutebemberwa et al., 2009, Amin et al., 2003, Al-Taiar et al., 2008)
$1/r_{PR}$	Average time taken to seek treatment seeking at informal/private trader (days)	2h -5days	1	(Chuma et al., 2009, Chuma et al., 2010, Sumba et al., 2008, Rutebemberwa et al., 2009, Amin et al., 2003, Al-Taiar et al., 2008)
r_{NTX}	Average time taken to enter disease (D) or Severe states if untreated	1.8-3	3	(Greenwood et al., 1987, Greenwood et al., 1991, Miller, 1958)
$1/r_{NTXPR}$	Average time taken to enter disease (D) or Severe states if not treated with an ACT at informal/private trader (days) from the time of consultation		$1/r_{NTX}$ - $1/r_{PR}$	
$1/r_{NTXCL}$	Average time taken to enter disease (D) or Severe states if not treated with an ACT at clinic/formal sector (days) from the time of consultation		$1/r_{NTX}$ -$1/r_{CL}$	
ε	Proportion of untreated infections that progress to severe disease	0.05 - 0.58	U5: 0.13/ 0.26 if delays>3 days Adult: 0.03/ 0.06 if delays > 3days	(Shillcutt et al., 2008, Lubell et al., 2011, Gupta et al., 1999b, O'Meara et al., 2009, Al-Taiar et al., 2008, Feikin et al., 2009, Rutebemberwa et al., 2009)

3.3.2.4 Quality of care parameters

The parameters for access to care in the public and private settings were taken from the outputs from Chapter 4. These are summarised in Table 9.

Table 9: Clinic parameters

Name	Definition	Value Range	Value Used	References
ftr_{CL}	Probability of receiving ACTs at	0 – 1	Baseline: 0.5	See

	a public sector/government health clinic for clinical malaria episode			Chapter 4
ftr_{PR}	Probability of receiving ACT treatment at private sector drug shop or outlet for clinical malaria episode	0 - 1	Baseline: 0.05	See Chapter 4

3.4 MODEL 1: RESULTS

3.4.1 Relationship between EIR, prevalence and disease incidence

When considering the management of malaria, it is important to understand the epidemiology of the infection in the population to appreciate which age groups are likely to be infected, symptomatic or at risk of progression to complications. Figure 16 shows the modelled relationship between EIR and parasite prevalence in different age groups. As observed elsewhere, the model captures the non-linear relationship between these two quantities, with parasite prevalence greatest in the 2-10 year age group at high values of EIR.

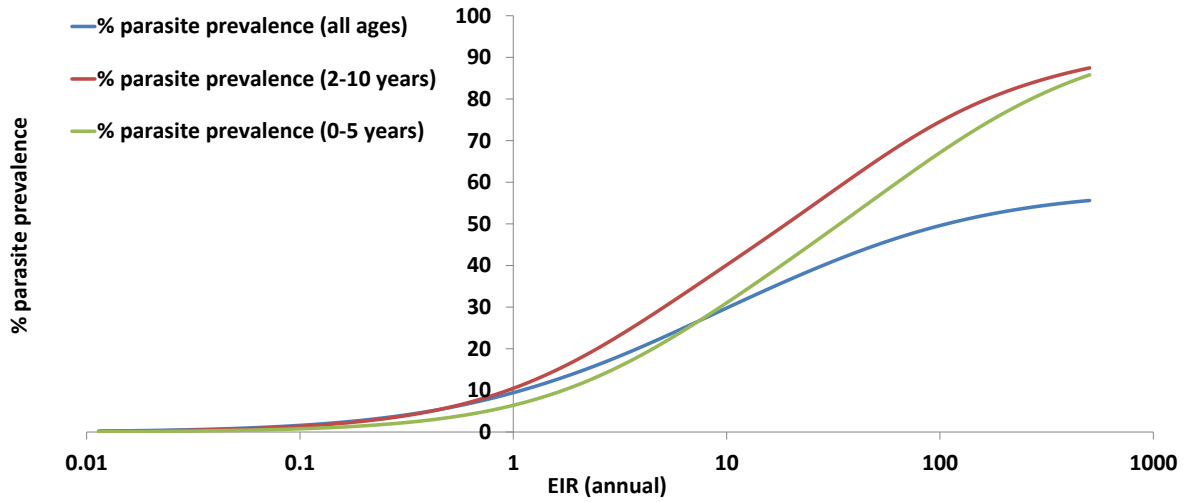


Figure 16: Model 1 – Relationship of Entomological Inoculation Rate (EIR) to the prevalence of malaria infection (% parasite prevalence in the age groups 0 – 5 years, 2 – 10 years and all ages)

The age-pattern of parasite prevalence in Figure 16 may be understood through Figures 17-19. In higher transmission settings, there is more clinical (symptomatic) infection in 0-5 year olds than older age groups. It follows that symptomatic infections are more likely to get treated, and hence infection durations are reduced. Therefore prevalence is higher in those between 2-10 years, who are less able than older age groups of clearing their infection but less likely to be symptomatic and treated than 0-5 year olds (Warrell, 2002, Carneiro et al., 2010).

Figure 17 shows the modelled incidence of symptomatic episodes of clinical malaria per 1000 persons per year in various age groups plotted against total parasite prevalence (all ages). The model captures the peak of clinical disease in the youngest age group at high transmission intensity, with incidence rates of approximately 2.5 episodes per child per year when all-age parasite

prevalence is greater than 50%. In contrast, at lower transmission, the incidence of disease is more evenly distributed across age-groups, albeit at a much lower rate.

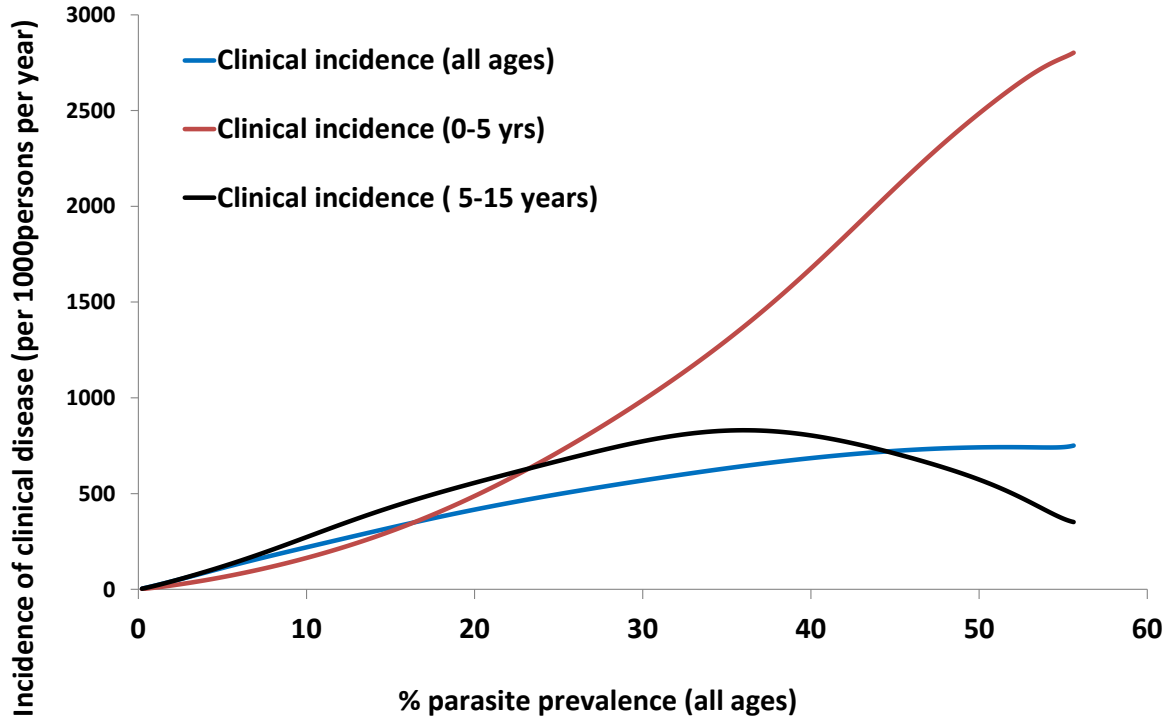


Figure 17: Model 1 – Relationship of prevalence of malaria infection in the population (all ages) to the incidence of clinically apparent or symptomatic infection episodes per 1000 persons per year (in age groups 0 - 5 years, 5 – 15 years and all ages)

3.4.2 Relationship between age, prevalence and disease incidence

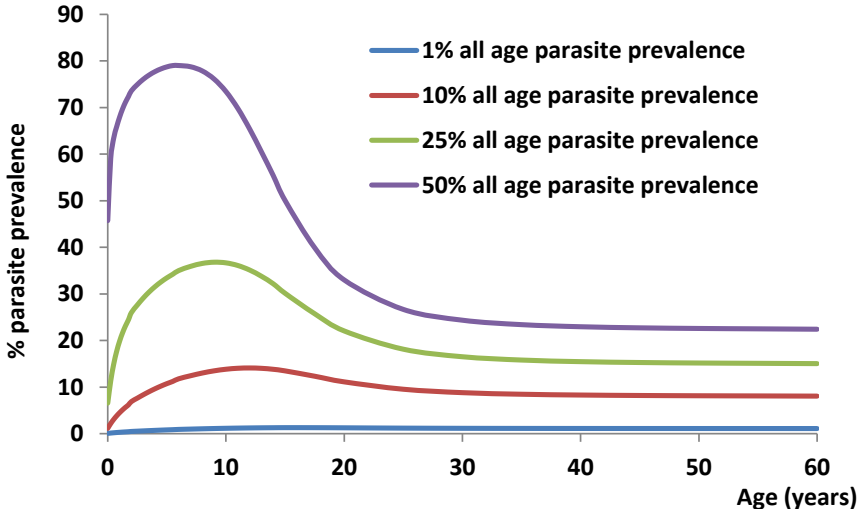


Figure 18: Model 1 – Age-prevalence curves at the 4 different transmission settings

Figures 18 and 19 depict parasite prevalence , incidence of clinical disease and incidence of severe disease in 4 different transmission settings, namely overall (i.e. over all ages) slide prevalence of 1%, 10%, 25% and 50% given baseline assumptions regarding treatment effectiveness. Slide prevalence is highest in all transmission settings in the 2-10 year old age groups, rising from birth and falling in adolescence. In high transmission settings, the incidence of clinical episodes and severe disease both peak at an early age (0-5 years) and then fall to low levels after the age of 15. In lower transmission settings, clinical and severe disease incidence rises with age and falls after 20 years. Malaria related mortality shows a similar pattern using this model. The age-patterns of the model outputs are similar to those described in a systematic analysis by Carneiro *et al* with respect to severity and transmission intensity (Carneiro et al., 2010).

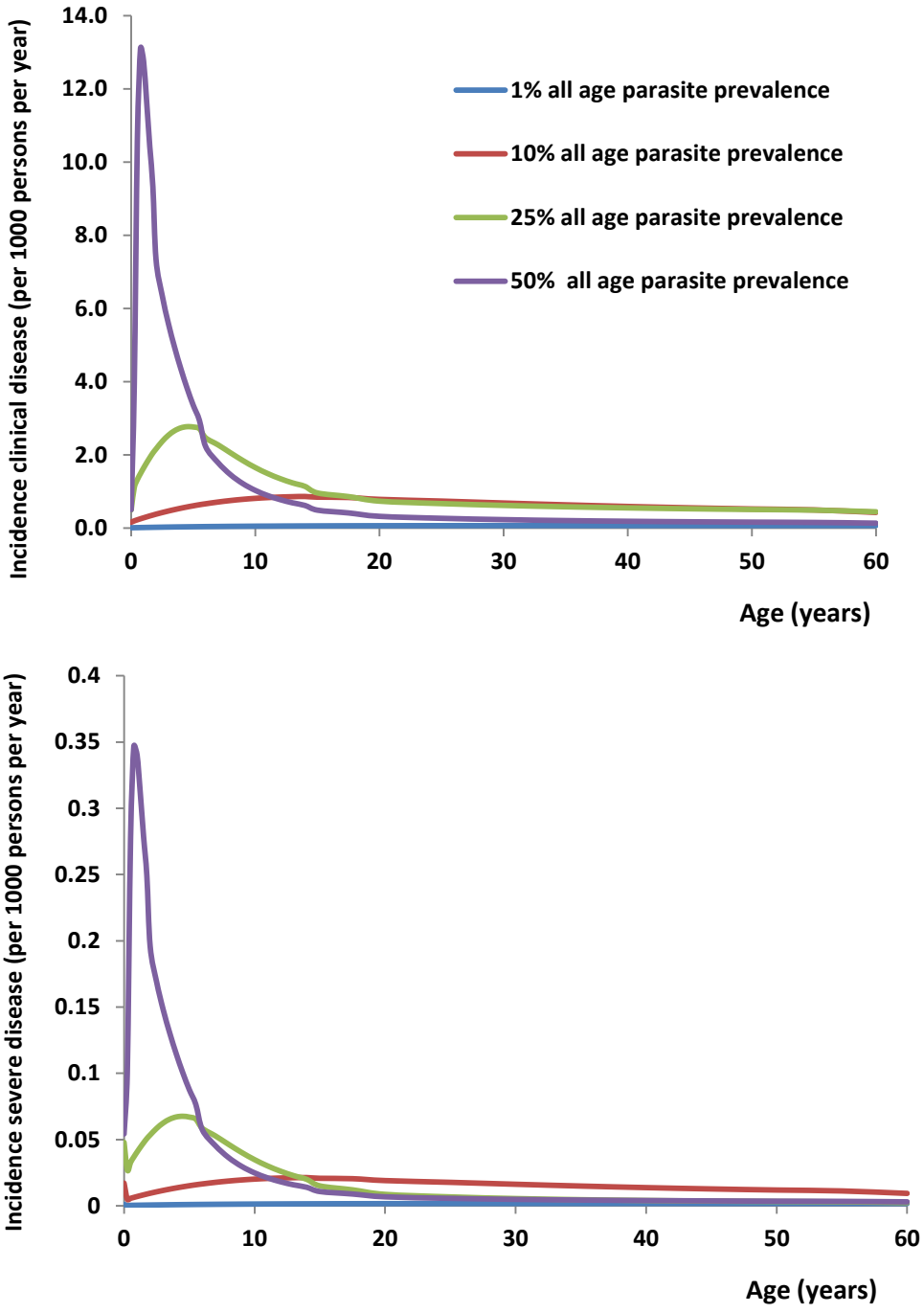


Figure 19: Model 1 – Age-incidence curves at 4 different transmission settings - 19A) Incidence of clinical disease (per 1000 persons per year); 19B) Incidence of severe disease (per 1000 persons per year)

3.4.3 Impact of health system parameters on transmission and clinical outcomes

Figure 20 shows the impact of access to treatment on transmission as captured by the EIR in 4 different transmission settings (1%, 10%, 25% and 50% all-age parasite prevalence). Improved access to healthcare, modelled here as a reduction in the probability of not seeking treatment, is

associated with a modest absolute decrease in EIR, though this is higher in high transmission settings. For example, at 50% all-age parasite prevalence (baseline EIR 109) this results in an absolute reduction of 0.72 whereas at all-age parasite prevalence of 1% (baseline EIR 0.06) this gives an absolute reduction of 0.05. However, this represents a relative reduction of 73% at 1% slide prevalence but less than 1% relative reduction in EIR at 50% parasite prevalence. A similar pattern is seen when considering the impact on parasite prevalence (not shown).

At baseline, the probability of receiving ACTs for a malaria episode at either treatment source is not high (50% at public clinics and 5% at private sector outlets). I have assumed that 40% of those who seek treatment do so in the public sector and 60% attend a private outlet. Hence overall less than 25% of all malaria cases that seek treatment actually receive ACTs. It is therefore not surprising that at the assumed probabilities of a malaria infection being treated with an ACT, varying levels of treatment seeking does not noticeably impact on malaria transmission in high transmission settings.

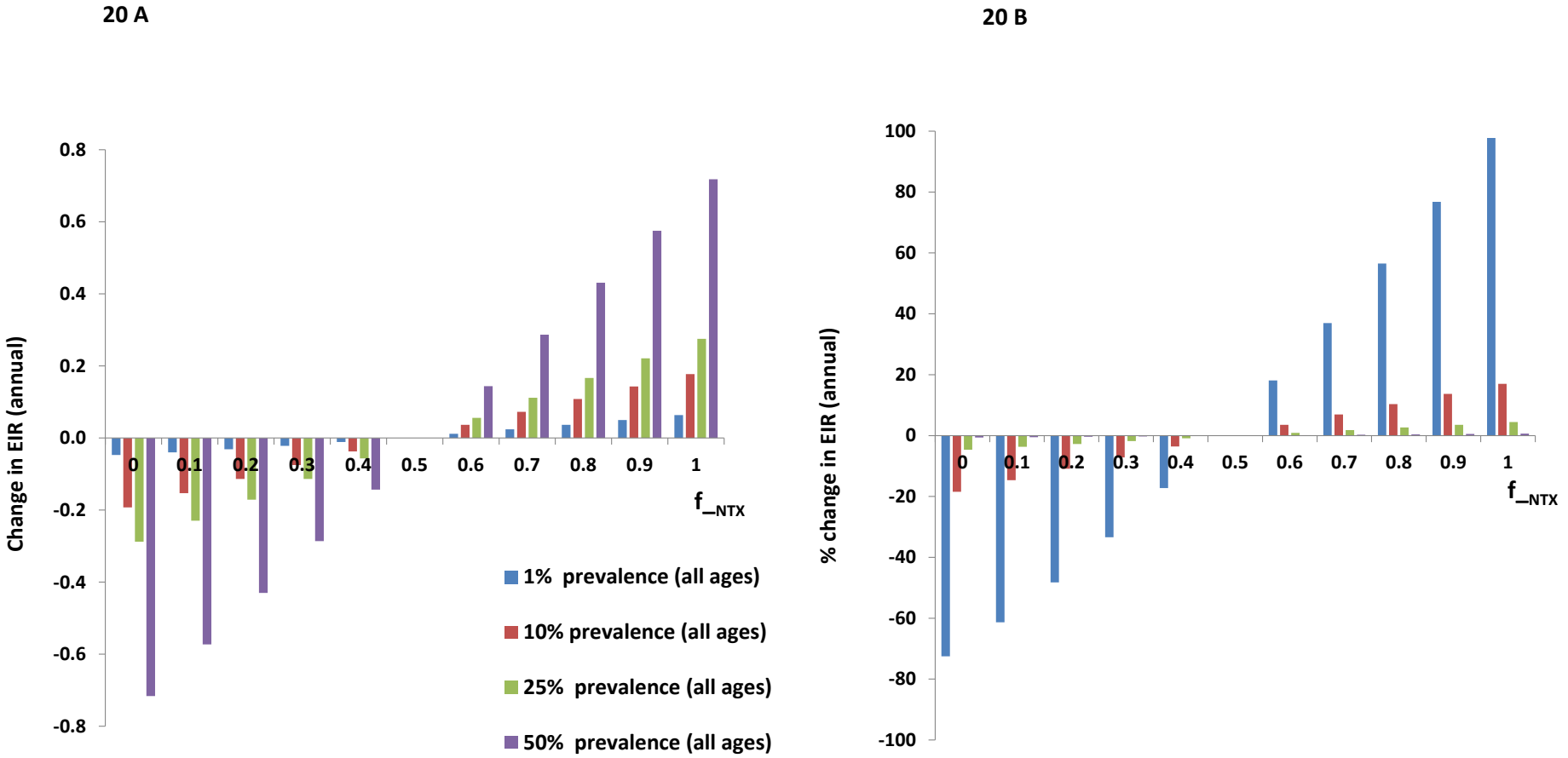


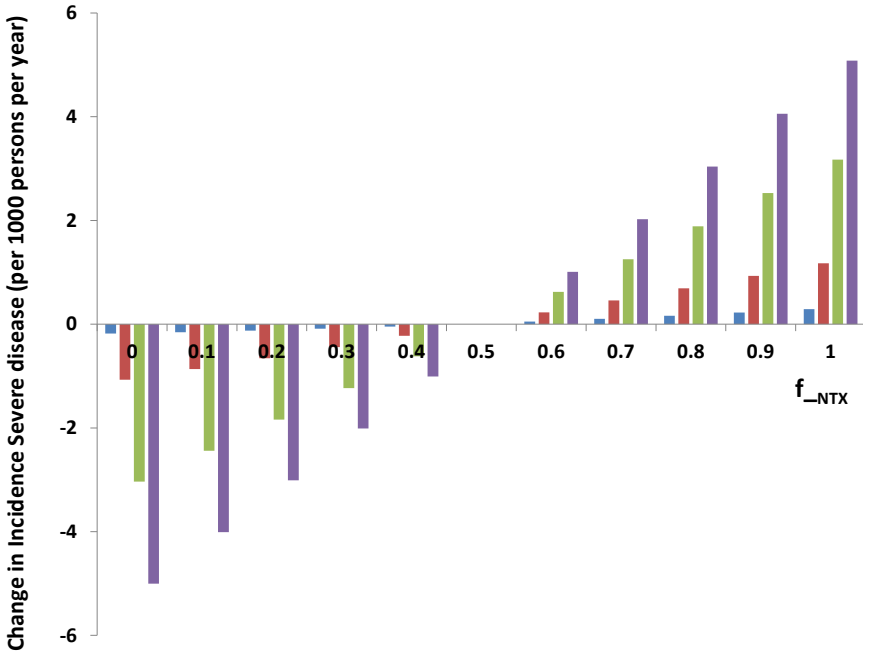
Figure 20: Model 1 - The impact of access to treatment on EIR at 4 different transmission settings.

The probability of not seeking treatment - f_NTX is varied from a probability of 0 (i.e. all cases seek treatment) to 1 (no treatment seeking). A probability of f_NTX = 0.5 is the baseline value. 20A) absolute change in EIR at the 4 prevalence settings considered and 20B) the change relative to the EIR at baseline. The ratio of f_CL and f_PR in those that do attend remains the same. Baseline EIR values using Model 1 are: 0.06 at 1% prevalence; 1.04 at 10% prevalence; 6.22 at 25% prevalence and 109.2 at 50% prevalence.

Figure 21 shows the change in incidence of severe malarial disease in 0-5 year olds as the probability of not seeking treatment (f_{NTX}) is varied. At a prevalence of 50% (all ages), at baseline health systems assumptions the model predicts 39 cases of severe disease per 1000 persons per year, compared with 0.24 cases per 1000 persons per year at 1% slide prevalence.

In this model, severe disease occurs at low levels, and only as a complication of untreated disease, inadequate treatment or delayed treatment. As expected the incidence of severe disease cases increases if access to healthcare is limited and cases do not seek treatment, with up to 5 cases of severe disease per 1000 persons per year potentially averted in high prevalence settings if treatment access is 100%. As before, the absolute impact is greater in high transmission settings but the relative impact greatest in low transmission settings.

21 A



21 B

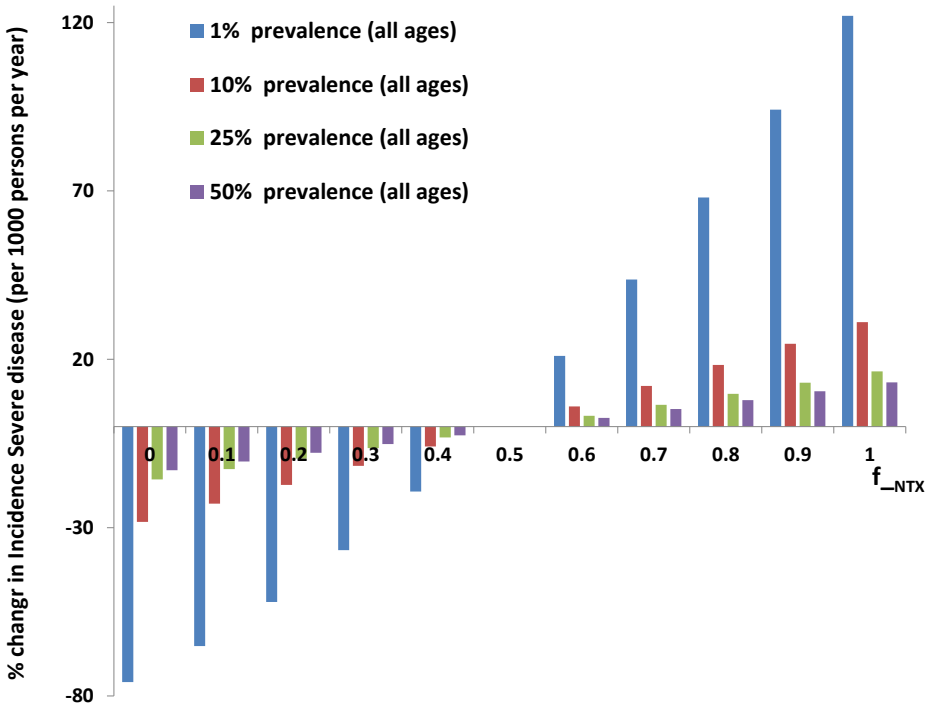


Figure 21: Model 1 - The impact of access to treatment on severe disease episodes in 0-5 year olds (per 1000 persons per year) at 4 different transmission settings.

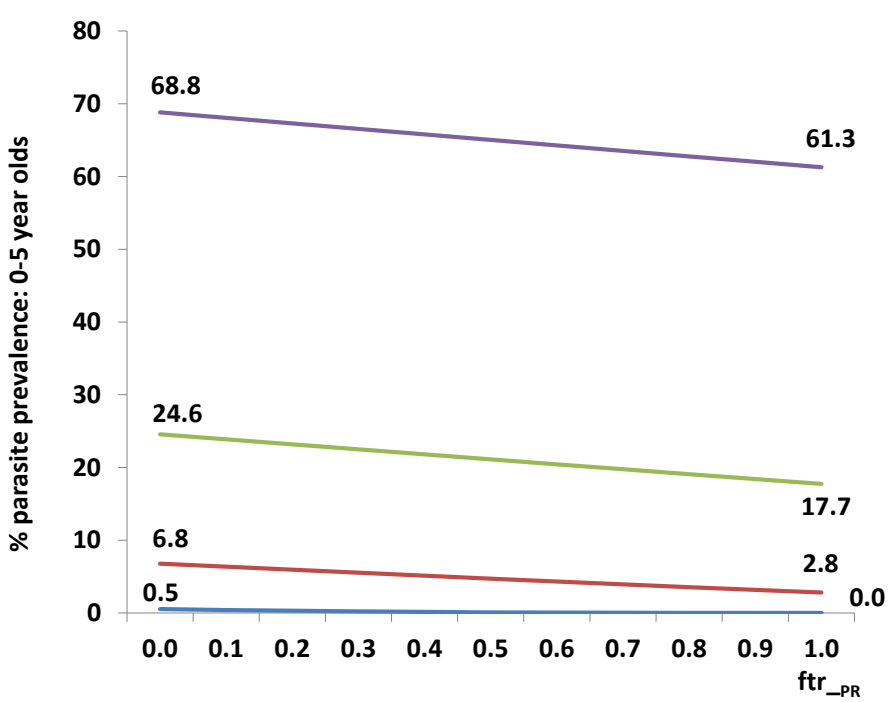
The probability of not seeking treatment - $f\__{NTX}$ is varied from a probability of 0 (i.e. all cases seek treatment) to 1 (no treatment seeking). 21A) depicts the absolute change in incidence of severe disease episodes in 0 – 5 year olds at the 4 prevalence settings considered and 21B) depicts the change relative to the severe disease episodes at baseline assumptions for each context. Baseline values for incidence of severe disease (per 1000 persons per year) using Model 1 are: 0.24 at 1% prevalence; 3.8 at 10% prevalence; 19.4 at 25% prevalence and 39 at 50% prevalence.

Figure 22A shows the impact of improved quality of care in the private sector (i.e. increasing the probability of receiving an ACT for clinical malaria - $ftr_{\_PR}$) on parasite prevalence in 0-5 year olds. In the highest transmission setting (50% all-age slide prevalence), increasing the probability of receiving an ACT for malaria at a private outlet from 0 to 1 is predicted to decrease slide prevalence in 0-5 year olds from 68.8% to 61.3%. In the lowest transmission setting (1% all-age slide prevalence), this increase is predicted to interrupt transmission. Figure 22B shows the associated impact on the incidence of severe disease in 0-5 year olds. In the highest transmission setting (50% all-age slide prevalence), increasing care quality could reduce incidence by 12.9 cases per 1000 population per year. Compared to the baseline value for the quality of care in the private sector, the model predicts a 31.5% relative reduction in severe disease incidence in the highest transmission setting and a 99.7% relative reduction in the lowest transmission setting. The relative reduction in severe disease incidence in 0-5 year olds is greater than the relative reduction in slide prevalence in 0-5 year olds in all transmission settings, indicating that quality of care may have a larger impact on clinical outcomes than on transmission. A similar pattern is seen for mortality in the same age group.

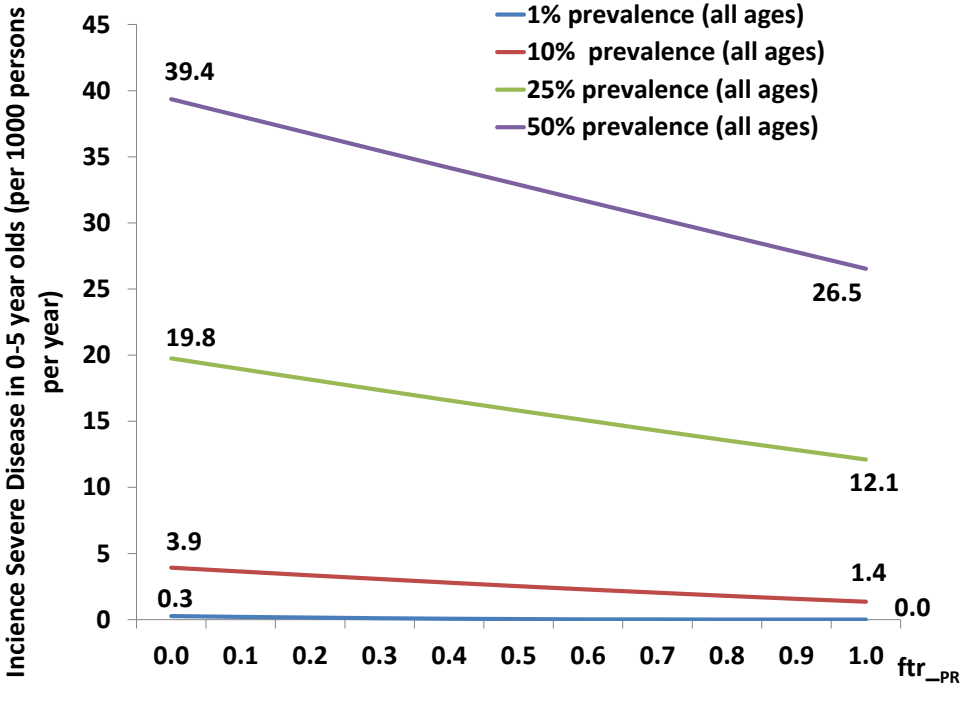
Figure 23 shows the same outcomes in 0-5 year olds when the quality of case management in the public sector i.e. $ftr_{\_CL}$ is varied (baseline probability = 0.5). For both outcomes, the impact of improving care in the public sector is predicted to be less than the equivalent impact in the private sector. This is due to the better baseline level of care currently in the public sector and a lower level of utilisation compared with the private sector. However, substantial improvements in outcomes are still observed by improving the quality of case management in the public sector.

Figure 22: Model 1 - Parameter plot showing the impact of increasing the probability of malaria cases receiving ACTs in the private sector (ftr_{PR} varied from 0-1) on 22A) the prevalence in 0-5 year olds and 22B) on the incidence of severe disease in 0-5 year olds (per 1000 persons per year).

Both plots show the decline in the relevant outcome. The baseline value for ftr_{PR} = 0.05. 22A) Baseline values for % slide prevalence in 0-5 year olds using Model 1 are: 0.47% at 1% all age prevalence; 6.58% at 10% prevalence; 24.2% at 25% prevalence and 68.4% at 50% e prevalence. 22B) Baseline values for incidence of severe disease (per 1000 persons per year) using Model 1 are: 0.24 at 1% prevalence; 3.8 at 10% prevalence; 19.4 at 25% prevalence and 39 at 50% prevalence.



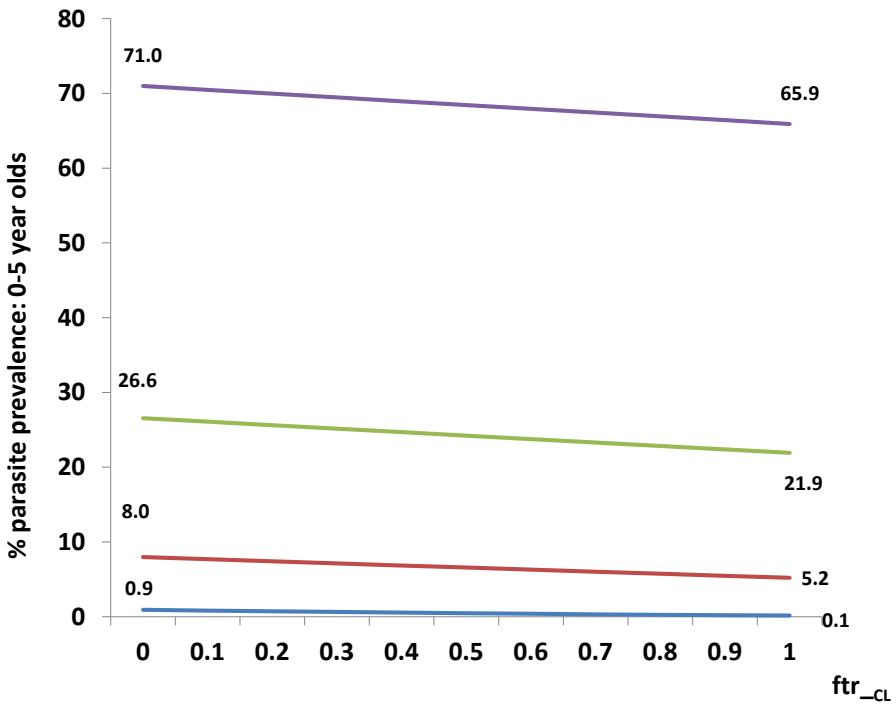
22A



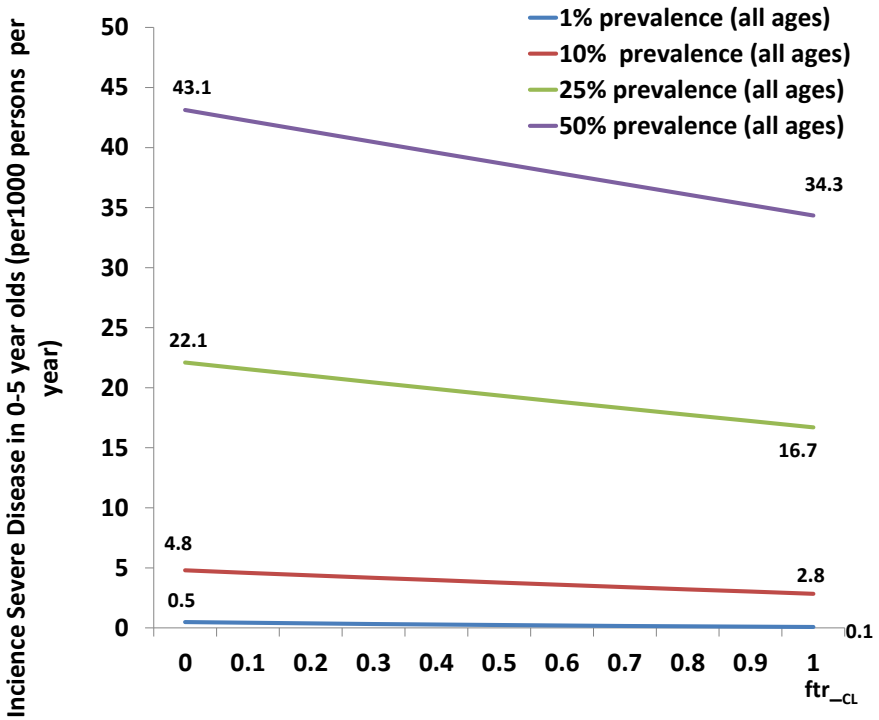
22B

Figure 23: Model 1 - Parameter plot showing the impact of increasing the probability of malaria cases receiving ACTs in public sector health facilities (ftr_CL varied from 0-1) on 23A) prevalence in 0-5 year olds and 23B) incidence of severe disease in 0-5 year olds (per 1000 persons per year).

Both plots show the decline in the relevant outcome. The baseline value for ftr_ CL = 0.5. 23A) Baseline values for % prevalence in 0-5 year olds using Model 1 are: 0.47% at 1% all age prevalence; 6.58% at 10% prevalence; 24.2% at 25% prevalence and 68.4% at 50% prevalence. 23B) Baseline values for incidence of severe disease (per 1000 persons per year) using Model 1 are: 0.24 at 1% prevalence; 3.8 at 10% prevalence; 19.4 at 25% prevalence and 39 at 50% prevalence.



23A



23B

3.5 MODEL 2: INCLUSION OF OVERTREATMENT OF NON-MALARIAL FEBRILE ILLNESS

A limitation of Model 1 is that it assumes that only the symptomatic malaria cases receive ACTs. However, until recently, presumptive treatment and syndromic management of all fevers as malaria was advocated in WHO guidelines and national policies, especially U5s. As described in Chapter 2, this has resulted in 47% - 95% of patients with non-malarial febrile illness (NMFI) receiving antimalarials unnecessarily (Zurovac et al., 2008b, Okebe et al., 2010, Bastiaens et al., 2011, Nicastri et al., 2009, Reyburn et al., 2004, Nankabirwa et al., 2009, Nyandigisi et al., 2011). Overtreatment is often with non-recommended antimalarials, although may sometimes also involve first-line ACTs (Okebe et al., 2010, Rowe et al., 2009a, Hamer et al., 2007, Nyandigisi et al., 2011, Zurovac et al., 2008b).

Although this inappropriate management of NMFI with antimalarials occurs in both public and private sectors, it is known to be prevalent within the private sector (Littrell et al., 2011b, O'Connell KA et al., 2011). The results from Model 1 highlight the potential value of inclusion of the private sector in malaria control efforts but the impact of potential excessive antimalarial use may also have consequences. Okell *et al.* (Okell et al., 2008a) showed that presumptive treatment may allow the prophylactic effect to extend to individuals without malaria and therefore reduce transmission.

However the management of NMFI has become an increasingly important policy issue since the case-fatality rate in malaria test-negative patients treated with anti-malarials can be higher than the case-fatality rate in malaria cases (Reyburn et al., 2004), as well as worries regarding the costs of wasting of ACT and the ability to meet future global demand (WHO, 2013). In addition, there is some anxiety about the potential spread of resistance to ACTs due to overtreatment, which may occur if sub-therapeutic levels of the ACT coincide with a new incoming infection, and particularly concerns the partner drug in the combination (which has a longer half-life)(Klein, 2013).

I therefore extended the model to investigate the clinical and transmission outcomes arising from policies of:-

1. Presumptive treatment in the private sector
2. Improved levels of diagnostic-led management (and hence quality of care) in private and public sectors.

I included the probability of febrile individuals (any cause) without malaria receiving ACTs at both private outlets and public health facilities. There are three main groups involved in the overtreatment of NMFI cases with ACTs:-

1. Febrile cases with no malaria infection
2. Febrile cases with subpatent malaria infection (i.e. undetectable by standard malaria testing)
3. Febrile cases with asymptomatic malaria infection (i.e. detectable by malaria testing).

3.5.1 Model 2: Mathematical Details

I extended the structure of the model to include a rate of developing a febrile illness not due to malaria (r_{NMFI}) which is structured by age. The same rate of developing NMFI is assumed to apply to those in the susceptible state (S) and to those in the two infected states A (Asymptomatic) and U (sub-patent). The probability of seeking care (1-f_{NTX} or ftr_{CL} + ftr_{PR}), and the preference for private sector or public sector health facilities for NMFI cases is assumed to be the same as for febrile illness due to malaria i.e. f_{CL} or f_{PR}.

Figure 24 demonstrates the additional pathways in this mode, i.e. how individuals asymptomatic for malaria but febrile from other causes (NMFI) enter the care-seeking pathway at the age-related rate (r_{NMFI}) and with a probability of 1-f_{NTX}. Those that do not seek treatment remain in the asymptomatic state A.

As these individuals have patent (detectable) infection, they have the same probability of receiving an ACT at either source as a clinically symptomatic malaria case i.e. ftr_{CL} and ftr_{PR}; any treatment administered is not considered overtreatment but instead as opportunistic treatment.

Asymptomatic malaria cases that are not successfully treated with an ACT do not enter the pathway that may lead to severe disease but instead re-enter the asymptomatic compartment. Asymptomatic malaria cases that are treated opportunistically with ACTs progress to a prophylaxed state at rate r_{ACT} and then return to the susceptible state S.

For clarity, the treatment of uncomplicated symptomatic malaria, whether from state S, or via super-infection from U or A has not been included in the diagrams however it is included in the model and is given in the equations in Appendix A.

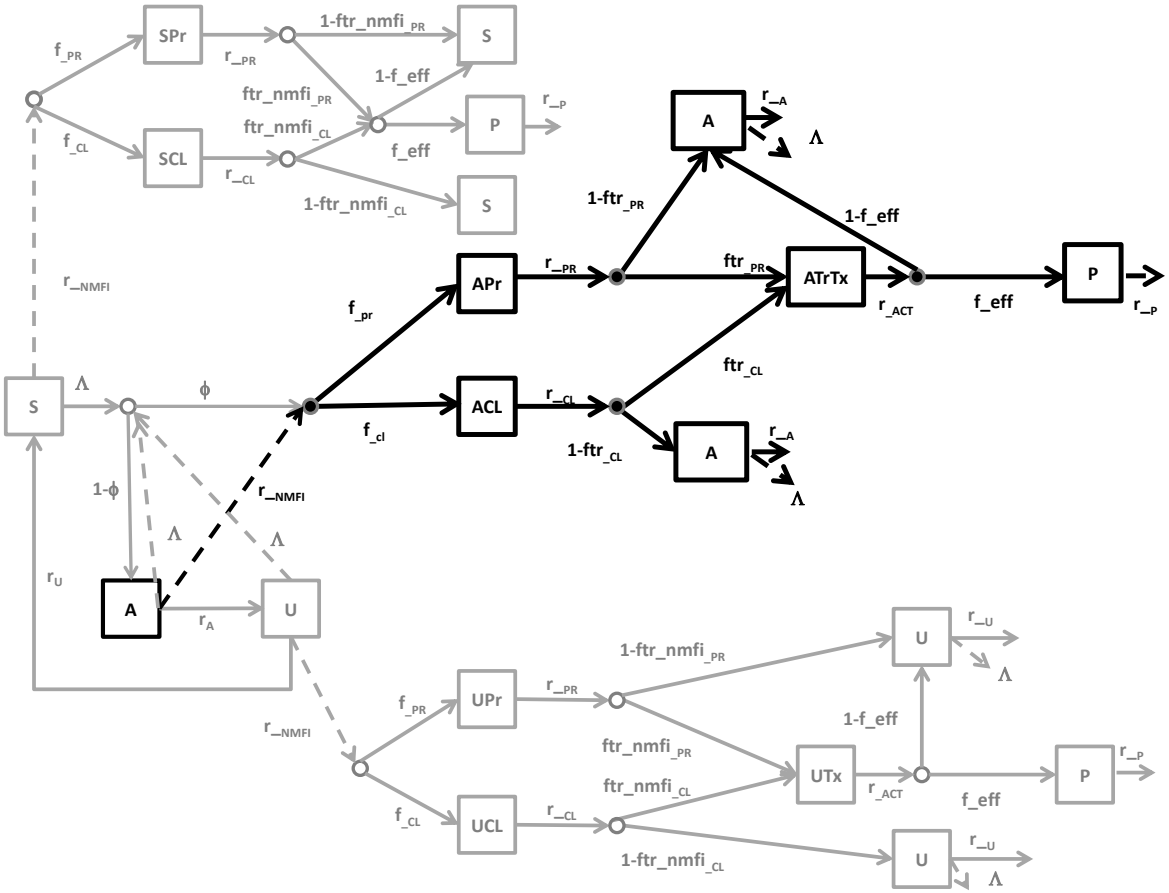


Figure 24: Model 2 - Flow diagram for the Overtreatment model: Asymptomatic NMFI cases opportunistically treated

S - susceptible; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection. UPr – Sub-patent seeking treatment for NMFI at private outlet/drug seller; UCL – Sub-patent seeking treatment for NMFI at primary care facility; UTx: Sub-patent treated with ACTs; SPr – NMFI seeking treatment at private outlet/drug seller; UCL – NMFI seeking treatment at primary care facility; APr – Asymptomatic malaria case with NMFI seeking treatment at a private outlet/drug seller; ACL – Asymptomatic malaria case with NMFI seeking treatment at a primary care facility; ATrTx – Asymptomatic malaria case with NMFI treated with ACT. People move between these states with rates/probabilities as marked on the arrows

The pathway for cases of subpatent disease that develop NMFI at r_{NMFI} is shown in Figure 25. Individuals leave the sub-patent state at the age-related rate of developing an NMFI and with the probability of seeking treatment f_{CL} or f_{PR}. Those that do not seek treatment remain in the sub-patent state U.

The probability of receiving an ACT is denoted by ftr_{NMFICL} and ftr_{NMFIPR} for those seeking care in the public and private sectors respectively. Sub-patent malaria cases are assumed to be undetectable by standard diagnostic techniques at community level. The parameters that contribute to their probability of receiving ACT are outlined in Chapter 4. They relate to the quality of care at each outlet including the presence and use of, as well as compliance with, diagnostic tools to reflect the probability of overtreatment since there is no detectable parasitaemia. If treated, NMFI cases move to the new state UTx.

If an NMFI case who is subpatently infected with malaria receives a course of ACT, then the individual is assumed to be treated and prophylaxed in a similar fashion to malaria cases treated for *P. falciparum* infection. Thus the individual moves to the state P at a rate r_{ACT} reflecting the rate of reduction in gametocytes as previously explained in Model 1. Those that do not receive an ACT or are unsuccessfully treated ($1-f\_{EFF}$) return to the sub-patent state U.

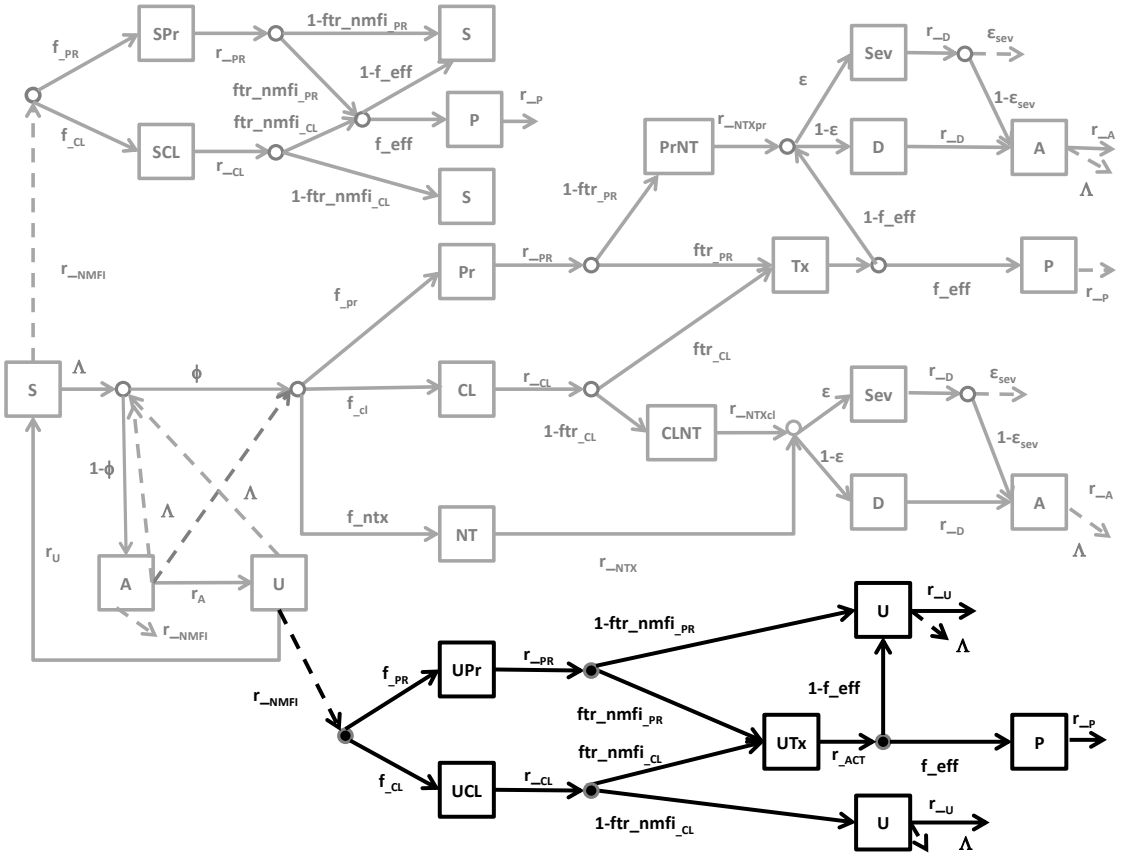


Figure 25: Model 2 - Flow diagram for the Overtreatment model. Sub-patent NMFI cases opportunistically treated

S - susceptible; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection. UPr – Sub-patent seeking treatment for NMFI at private outlet/drug seller; UCL – Sub-patent seeking treatment for NMFI at primary care facility; UTx: Sub-patent treated with ACTs; SPr – NMFI seeking treatment at private outlet/drug seller; UCL – NMFI seeking treatment at primary care facility; APr – Asymptomatic malaria case with NMFI seeking treatment at a private outlet/drug seller; ACL – Asymptomatic malaria case with NMFI seeking treatment at a primary care facility; ATrTx – Asymptomatic malaria case with NMFI treated with ACT. People move between these states with rates/probabilities as marked on the arrows.

Unnecessary treatment with ACTs is also included for individuals who are not infected with malaria, i.e. in state S. Cases leave the susceptible state at the same age-related rate of developing an NMFI and with the probability of seeking treatment f_{CL} or f_{PR}. As previously, the probability of receiving an ACT is denoted by ftr_{NMFICL} and ftr_{NMFIPR} for those seeking care in the public and private sectors respectively. If an NMFI case who is not infected with malaria receives an effective (i.e. f_{EFF}) course of ACT, then the individual is assumed to be prophylaxed immediately, i.e. moves directly to state P. Those that do not receive an ACT return to the susceptible state S. The pathway for uninfected cases with NMFI is similar and shown in Figure 26.

The new set of equations for the human component of this model is included in Appendix A.

The infectivity of the extended set of states is

$$\Lambda_v = \zeta(1-\rho\exp(-a/a_0)[c_D D + c_A A + c_U U + c_U UPr + c_U UCL + c_U UTx + c_D Pr + c_D CL + c_D NT + c_D CLNT + c_D PrNT + c_D Sev + c_{TX}\,\mathrm{Tx}]$$

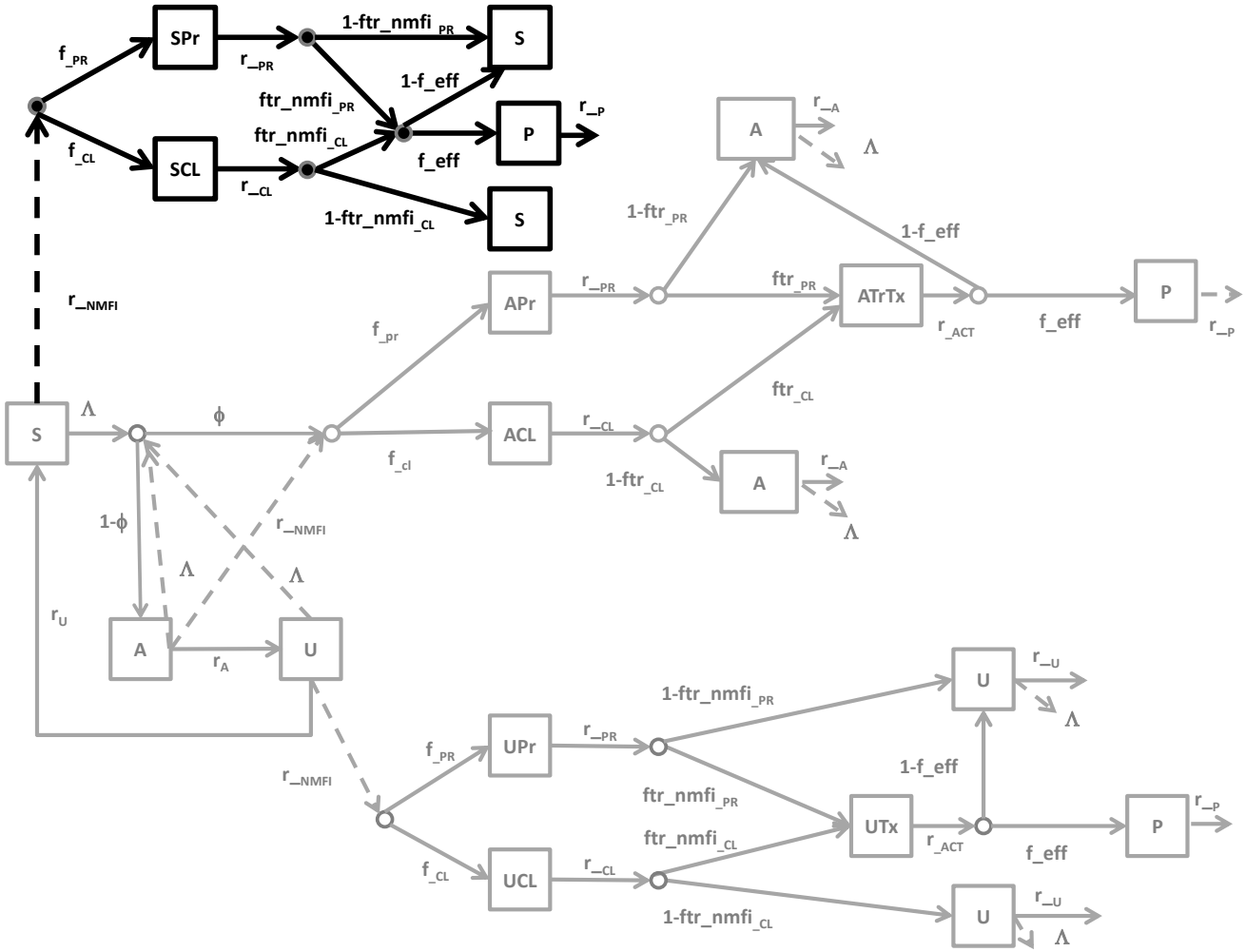


Figure 26: Model 2 - Flow diagram for the Overtreatment model. Susceptible NMFI cases over treated

S - susceptible; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection. UPr – Sub-patent seeking treatment for NMFI at private outlet/drug seller; UCL – Sub-patent seeking treatment for NMFI at primary care facility; UTx: Sub-patent treated with ACTs; SPr – NMFI seeking treatment at private outlet/drug seller; UCL – NMFI seeking treatment at primary care facility; APr – Asymptomatic malaria case with NMFI seeking treatment at a private outlet/drug seller; ACL – Asymptomatic malaria case with NMFI seeking treatment at a primary care facility; ATrTx – Asymptomatic malaria case with NMFI treated with ACT. People move between these states with rates/probabilities as marked on the arrows.

3.5.2 Additional Parameters for Model 2

3.5.2.1 Non-malarial febrile illness

To estimate the rate of non-malarial febrile illness, unpublished data from two cross-sectional surveys (n=11,532)(Drakeley et al., 2005) in the Kilimanjaro and Tanga regions of Tanzania from ages 1-45 years were used. Demographic and clinical information was collected during the short and long rainy seasons (short rains in Nov-Dec versus long rains in March-May), as well as samples for malaria microscopy. An unpublished analysis has estimated the relationship between non-malarial fever and age (Okell, 2014). The prevalence of fever by yearly age groups up to age 45 years was standardised into relative age-specific prevalence by dividing by the total prevalence of fever in the surveys. Survey data were grouped by season and subdivided by parasite-prevalence in U5s (<5%, 5-10%, 10-20%, 20-40%, >40%). The model developed by Griffin *et al.* (Griffin et al., 2010) was used to estimate the incidence of clinical malaria by age, taking account of seasonality by adjusting the mean annual EIR to match the slide-prevalence in under-fives at the time of year that the survey was done. The authors then used the model output to estimate the age-specific fever prevalence due to malaria during this time by calculating the proportion of people with symptomatic (clinical) malaria during the average fortnight. It was assumed that each new malaria infection would not cause a fever that was longer than 2 weeks. The age-specific fever prevalence due to malaria was then subtracted from total fever prevalence, giving an estimated prevalence of fevers due to other causes. They estimated 13% of the population (age up to 45 years) reported NMFI in the preceding 2 weeks, averaged in the two rainy seasons and over low to high transmission intensities. This translates into an average of 3.38 NMFI episodes per person per year.

I then used these reported fever rates and demographic data from DHS/MIS Tanzania to calculate an age structured estimate of NMFI per person from the age of 0-44 years. Ages of 45 year and older were assumed to be the same rate as 44 years.

The rates of treatment seeking and sector preference for NMFI are assumed to be the same as for malarial fevers, i.e. f_{NTX}, f_{CL} and f_{PR} remain the same for all febrile illness.

The calculation of the probability of receiving an ACT unnecessarily for NMFI at a clinic or at a private outlet is fully described in Chapter 4. The probability of overtreatment with an ACT relates to the probability of receiving presumptive (i.e. not on the basis of testing) antimalarial treatment. Unnecessary treatment of NMFI with antimalarials is known to be high at private outlets; however it is often the case that other non-ACT antimalarials are dispensed in these cases (Mangham et al., 2012, Noor et al., 2009, Uzochukwu et al., 2010). Overtreatment is also a significant issue at public

sector facilities (Bastiaens et al., 2011, Okebe et al., 2010). This may be due to non-compliance with diagnostic test results (Nyandigisi et al., 2011, Nankabirwa et al., 2009), or test quality (sensitivity and specificity) as well as ACT stockouts. My baseline parameter estimates are based on studies reviewed in Chapter 2 and summarised in Table 10.

Table 10: Parameters regarding Non-malarial Febrile Illness rates and treatment

Name	Definition	Value Range	Value Used	References
r_{NMFI}	Rate of non-malarial febrile illness per person per year	2.3 – 4.95 (age dependent)	Age-specific rates: overall 3.38	(Drakeley et al., 2005),(Okell, 2014)
ftr_{NMFICL}	Probability of receiving ACTs for NMFI at public sector clinic/health facility	0-1	Baseline: 0.5	See Chapter 4
ftr_{NMFIPR}	Probability of receiving ACTs for NMFI at private outlet (drug shop or general shop)	0-1	Baseline: 0.05	See Chapter 4

3.5.2.2 Treatment parameters

The relative infectiousness of a treated individual (in any state) is reduced compared to their infectious state as in Model 1. The infectiousness of any sub-patent malaria infections opportunistically treated with ACTs when attending with an NMFI is also reduced (Table 11).

Table 11: Treatment parameters for sub-patent infections

Name	Definition	Value Range	Value Used	References
UTx	% reduction in average infectiousness compared to state occupied prior to treatment	80.6% * cD	0.05	(Dunyo et al., 2006), (Griffin et al., 2014)

3.6 MODEL 2: RESULTS

The probability of receiving an ACT for an NMFI at a public sector clinic was set at baseline at 0.5 and the probability of receiving an ACT for an NMFI at a private sector outlet at 0.05; these estimates are based on the decision-tree modelling in Chapter 4.

3.6.1 Impact of treating with ACTs NMFI on transmission and clinical outcomes

Figure 27 depicts the impact of increasing the probability of receiving ACT treatment for an NMFI at public sector health facilities (solid line) or private informal outlets (dashed lines) on severe disease incidence in 0-5 year olds and parasite prevalence in 0-5 year olds in the 4 transmission settings. It was anticipated that reduction in overtreatment would cause a rise in malaria prevalence due to the lack of prophylactic protection afforded by unnecessary ACTs.

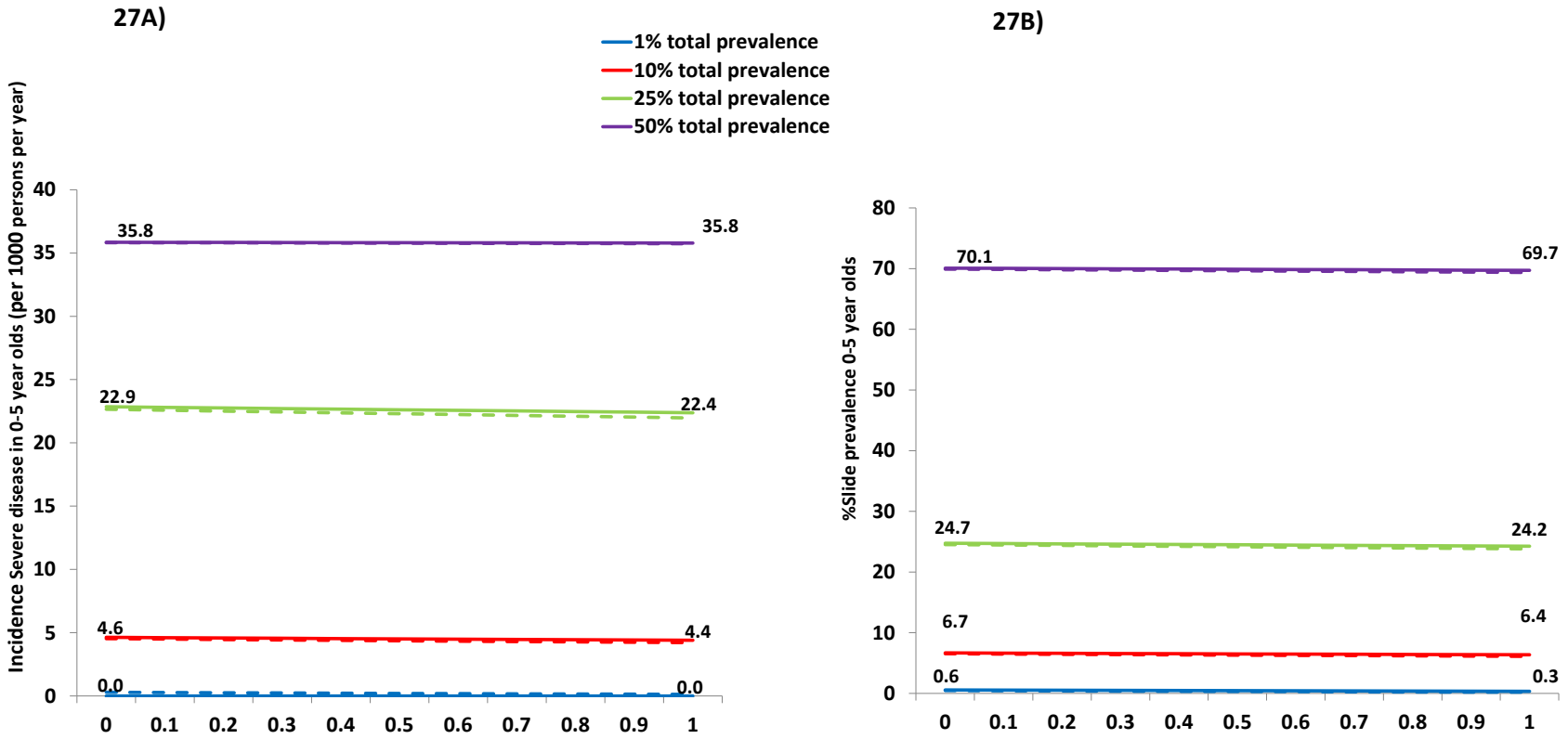
However, the results indicate that if all other parameters are maintained, there may be negligible impact on slide prevalence or severe disease incidence in 0-5 year olds, even in low prevalence settings. At 1% all-age prevalence, eliminating all overtreatment in the private sector (but maintaining baseline levels of malaria case management with ACTs) may lead to a less than 0.5% reduction in prevalence in 0-5 year olds relative to baseline, whilst eliminating all overtreatment at the public sector may lead to a 13% relative reduction, despite higher levels of treatment seeking in the private sector. However, as seen in Figure 27 the absolute changes seen are very limited, and relative impact is small even at 1% prevalence.

This finding is due to assumed higher levels of overtreatment with ACTs at public sector facilities, whereas overtreatment in the private sector is assumed to be with other antimalarials (as described in Chapter 4), although this may change in the future with the onset of AMFm. The results are similar for the incidence of severe malaria (Figure 27).

Hence if overtreatment of NMFI is reduced in either sector, for example through the mandatory use of diagnostic testing and if all negative tests were not treated, the impact on reducing transmission and severe disease would be very limited, given assumed baseline levels of malaria treatment.

Figure 27: Model 2 - Parameter plot showing the impact of increasing the probability of NMFI cases receiving ACT treatment

Solid line: ACT treatment of NMFI at public sector health facilities for a non-malarial febrile illness (ftr_{NMFICL}) and dashed lines: ACT treatment of NMFI at private outlets (ftr_{NMFIPR}) (dashed lines) on 27A) incidence of severe malaria in 0-5 year olds (per 1000 persons per year) & 27B) % prevalence in 0-5 years olds



3.6.2 Combinations of interventions

I next compared the potential impact of single and combinations of interventions to the health system for the 4 transmission settings, namely:

1. 100% access (i.e. 100% treatment seeking : f_{NTX} = 0 - keeping sector preference and probability of treatment the same as baseline),
2. Perfect clinic treatment: 100% chance of receiving ACTs for malaria at public sector clinics (ftr_{CL} = 1) and 0% overtreatment at clinics (ftr_{NMFICL} = 0)
3. 100% access (f_{NTX} = 0) and perfect clinic treatment
4. 100% presumptive treatment in public and private sectors: i.e. all fevers treated as malaria (ftr_{CL} = 1; ftr_{NMFICL} = 1; ftr_{PR} = 1; ftr_{NMFIPR} = 1)
5. 100% access and 100% Presumptive (clinic and private) treatment
6. 100% Presumptive private treatment: all fevers in private sector given an ACT (ftr_{PR} = 1; ftr_{NMFIPR} = 1)
7. 100% access and 100% Presumptive private treatment
8. Perfect treatment (clinic and private): 100% chance of receiving ACTs for malaria and 0% overtreatment in all sectors (ftr_{CL} = 1; ftr_{NMFICL} = 0; ftr_{PR} = 1; ftr_{NMFIPR} = 0)
9. 100% access and Perfect treatment (clinic and private)

The results from a 1% (low) transmission setting indicate that each of the above list of interventions reduce parasite prevalence in 0-5 years olds to 0% and have a similar effect on severe disease incidence in 0-5 years olds. Figure 28 shows relative changes compared to baseline for each group of interventions for the 10%, 25% and 50% total prevalence settings.

The juxtaposed figures indicate that various health systems interventions have differing relative impacts on slide prevalence and severe malaria incidence in 0-5 year olds due to the dynamics of age groups affected by the disease and its consequences. Introducing 100% access to healthcare in the 1%, 10% and 25% settings is predicted to have a greater relative impact on slide prevalence than severe disease incidence. However at the highest transmission setting (50% all-age prevalence) this intervention led to a 14% relative decrease in severe disease incidence but only a 7% reduction in parasite prevalence in 0-5 year olds. This is because at a higher prevalence, symptomatic clinical disease is mainly seen in the youngest age groups, whilst the main reservoir of parasites is in older age groups (2-10 years) as seen in Figures 17-19. Therefore through increased levels of treatment, the consequence of untreated disease i.e. severe malaria is averted but the transmission outcomes such as parasite prevalence are less affected. In the other prevalence settings, the epidemiology of

clinical disease and prevalence may overlap more i.e. those that are parasitaemic are also likely to be symptomatic and so increased treatment does impact on prevalence.

At the 10% setting, improving access alone without improvements in the quality of healthcare may not sufficiently reduce the transmission of malaria or severe disease incidence. Perfect care in the public sector clinic alone has less impact than improving access (i.e. the probability of treatment seeking) to any source.

Presumptive treatment of all fevers (malaria and NMFI) in the private sector at 25% slide prevalence may reduce both outcomes by 50%, and by 62% if this policy of presumptive treatment is applied in both sectors. Slide prevalence and severe disease incidence are not reduced by improvements in quality of care alone in this setting but may approach nearly 100% reductions if in combination with 100% access to healthcare.

At the highest prevalence setting, no combination of interventions of care quality and access cause greater than a 45% reduction in parasite prevalence in 0-5 year olds. However important reductions in severe disease incidence in this age group may be possible with 100% treatment of all malaria cases (in both sectors) along with 100% access. As indicated by Figure 28, there is little increase in the impact of either outcome if all NMFI cases are treated with ACTs (presumptive treatment) compared with the impact if no NMFI cases are given ACTs as long as all malaria cases are given ACTs (perfect treatment).

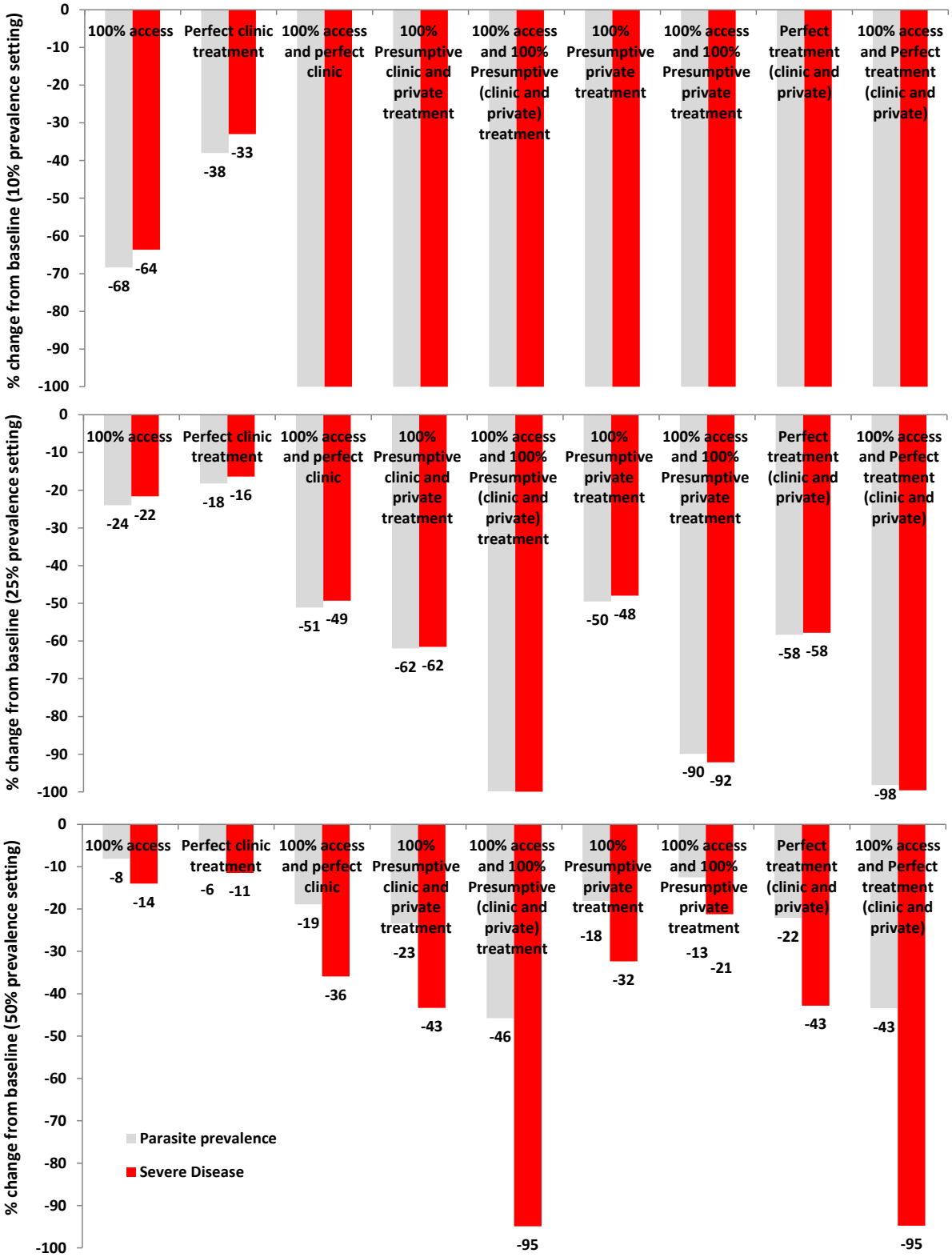


Figure 28: Model 2 Figure depicting impact of combinations of interventions in 3 transmission settings (10%; 25%; 50% parasite prevalence in all ages)

Impact on % parasite prevalence in 0-5 year olds (grey bars) and Severe disease incidence in 0-5 year olds (red bars) in the 10%, 25% and 50% total prevalence settings. The change relative to baseline values for each is shown. Values for all except 100% change indicated.

3.6.3 Inclusion of Management of Severe Disease: Model 3

Models 1 and 2 concern management of malaria only at community level and do not include any management of severe malaria. In these earlier iterations, severe disease occurs as a result of a lack of ACT treatment, whether not sought, delayed or ineffective. Severe cases either progress to death or recover to an asymptomatic state.

In Model 3 I aim to investigate:

1. The impact of health systems on the morbidity and mortality associated with malaria
2. The role of tertiary level health institutions e.g. district hospitals in the management of severe malaria and its consequences

I expand the model to include two pathways by which severe malaria may develop and incorporate the treatment of severe malaria both at community and tertiary level.

Prompt diagnosis and timely malaria treatment can reduce illness progression to severe stages and, therefore, decrease mortality (Warsame et al., 2007, Getahun et al., 2010, Byakika-Kibwika et al., 2009). As in Models 1 and 2, delayed or unsuccessful treatment is included here as a potential route to develop severe malaria. However treatment delay may not be the only cause of severe malaria. The risk of developing acute severe malaria is known to diminish with repeat infections of *P. falciparum* (Gupta et al., 1999b), but the rate of acquisition of immunity is still poorly understood (Langhorne et al., 2008b). Manifestations of severe malaria have been shown to vary with age and transmission setting (Langhorne et al., 2008b, Reyburn et al., 2005, O'Meara et al., 2008b, Carneiro et al., 2010, Ross et al., 2006b). In Model 3 I have attempted to reflect this risk of acute severe malaria by including the possibility that some individuals are more likely to develop severe malaria at presentation, i.e. that severe cases do not only occur from delay in treatment of non-complicated malaria. To capture this I included a new pathway from those who develop clinical disease. A proportion of these individuals θ are assumed to have severe disease on presentation. This is determined by levels of acquired immunity, whilst the remainder follow the pathway previously described in which severe disease may occur as a result of delayed treatment.

The WHO guidelines for management of the small percentage of *Plasmodium falciparum* infections that progress to severe malaria promote intravenous administration of artesunate as first-line followed by a course of ACTs (WHO, 2010a, Dondorp et al., 2010). In Model 3 I extended the previous models to incorporate the possibility of treatment of severe malaria infections at an appropriate level facility (e.g. district hospital or tertiary level facilities). Patients may reach the

hospital as a first source of care, following referral from a community source of care or following unsuccessful treatment at a community source of care.

A study by Gomes *et al.* (Gomes et al., 2009) suggests that very early administration of rectal artesunate may prevent death and disability in those at risk of severe malaria. There is concern regarding the effect of such an intervention if administered more than 6 hours after onset of symptoms (Grobusch, 2009), however it reiterates the importance of early access. The original trial used rectal artesunate as a pre-referral tool, however in the model this has been incorporated as an assumption that early administration of artesunate (intravenous or rectal) with a course of ACTs will prevent progression to fulminant severe disease in these individuals. Early administration of artesunate may occur at the health facility or private outlet level especially since early evaluation suggests a reluctance of caretakers to take children to hospital after a suppository of artesunate (Simba et al., 2010).

In summary, in Model 3 the management of severe malaria is included in three different ways:

1. Prevention of progression to fulminant severe disease in those at risk of early acute severe malaria by treatment with rectal artesunate and ACTs – which may occur at public facilities or private outlets
2. Referral of those at risk of early acute severe malaria to hospital/tertiary level facilities – which may occur from public facilities or private outlets
3. Treatment of severe malaria at a hospital/tertiary level facility with artesunate and ACTs – which may be early acute severe malaria or those uncomplicated symptomatic malaria cases that may not have sought treatment or were unsuccessfully treated either at a public facility or private outlets.

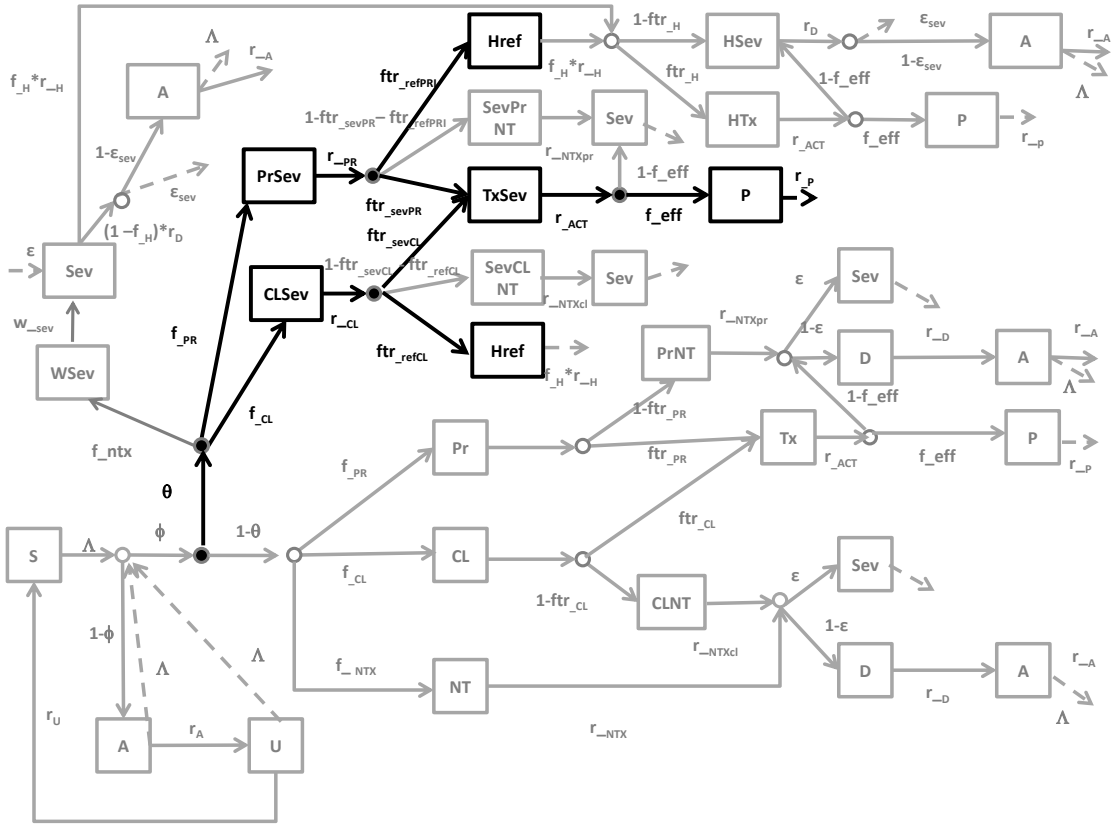


Figure 29: Model 3 - Flow diagram for the Severe treatment model: Community management of acute severe malaria risk

S - susceptible; NT – not seeking treatment; Pr – Seeking treatment at private outlet/drug seller; CL – Seeking treatment at primary care health facility/government clinic; PrNT – not treated at private outlet/drug seller; CLNT – not treated at primary care health facility/government clinic; Tx – On treatment; D – untreated clinical disease; Sev – Severe disease; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection; WSev – untreated progressing early severe PrSev – Severe case seeking treatment at private outlet/drug seller ; CLSev – Severe case seeking treatment at primary care facility; Href – Severe case referred to hospital or tertiary facility by either health facility or private outlet; TxSev – Severe case that has received treatment at clinic/health facility or private outlet; CLSevNT – severe case not treated at primary care facility/government clinic; PrSevNT – severe case not treated at private outlet/drug seller;- HTx – Sever case treated in hospital or tertiary facility; HSev – untreated severe case in hospital or tertiary facility. People move between these states with rates/probabilities as marked on the arrows

In this model, a symptomatic individual has a risk of developing severe disease early (θ). This is a proportion of those who have clinical symptoms and is determined by maternal and acquired immunity. However if the individual accesses treatment at this stage (with probability $1\text{-}f\__{NTX}$) then progression to fulminant severe disease may be avoided, provided correct treatment is administered.

This is depicted in Figure 29. For clarity, the treatment of NMFI, whether from state S, U or A has not been included in the diagrams however it is included in the model and is given in the equations in Appendix A.

I assume that the probability of seeking care at community/primary level (i.e. either a private outlet or a government facility) for these acute severe cases is similar as previously defined i.e. $f\__{CL}$ or $f\__{PR}$ leading to state CLSev and PrSev respectively. I assume the delay in accessing care is also similar (that is, progression from seeking treatment to accessing care occurs at a rate $r\__{CL}$ and $r\__{PR}$ for the public and private sectors respectively).

For those at risk of early severe disease who seek care at the primary level (clinic or drug shop), there are three possible outcomes at each source of care:

1. Referral to hospital (with probabilities $ftr\__{REFCL}$ and $ftr\__{REFPR}$ for public and private sectors respectively) moving to Href state
2. Correct treatment at each source of care, which is modified to incorporate the presence and use of rectal or intramuscular artesunate, thus giving the probabilities *ftr_sevcl* and *ftr_sevpr* for public and private sectors respectively, subsequently moving to the TxSev state. This treatment may be successful with a probability of *f_eff*, and so individuals progress at rate *r_ACT* to recovery and into the prophylaxed state (P).
3. To neither receive treatment or referral (with probability *1-ftr_refcl – ftr_sevcl* or *1-ftr_refpri-ftr_sevpri* respectively). We will consider those who are not treated or not referred later in this chapter.

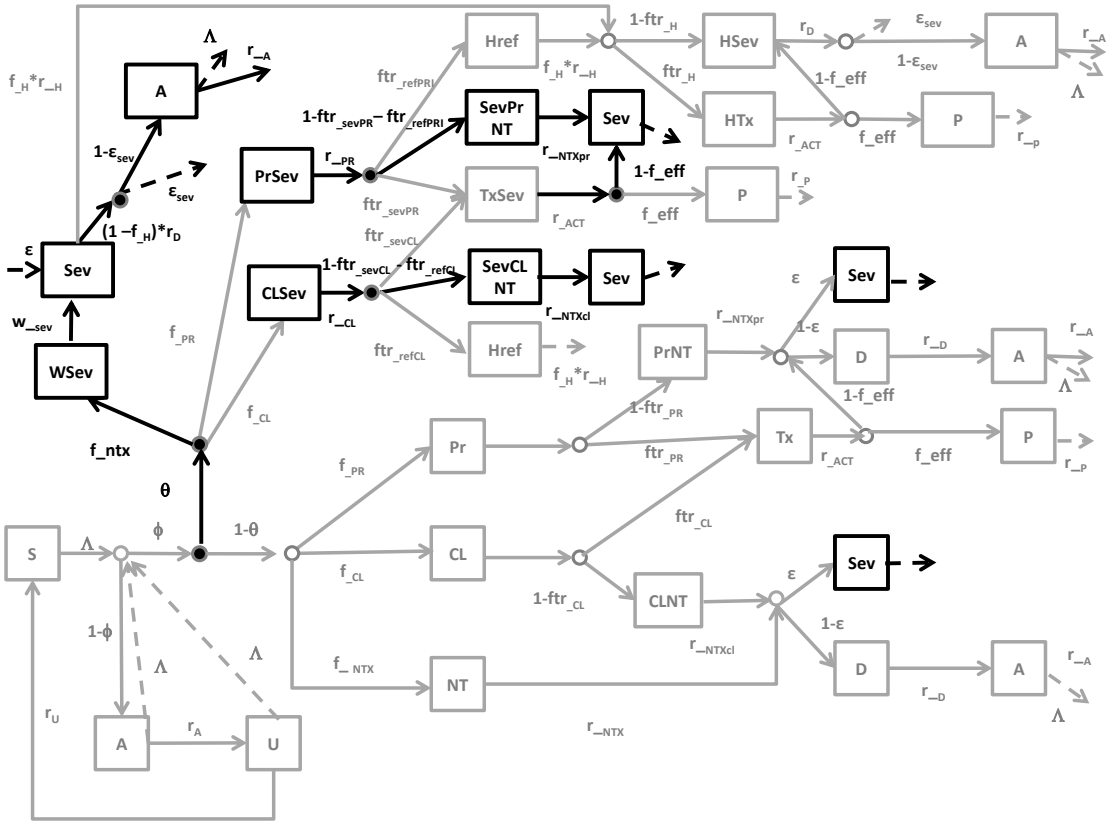


Figure 30: Model 3 - Flow diagram for the Severe treatment model: Pathways to develop Severe disease

S - susceptible; NT – not seeking treatment; Pr – Seeking treatment at private outlet/drug seller; CL – Seeking treatment at primary care health facility/government clinic; PrNT – not treated at private outlet/drug seller; CLNT – not treated at primary care health facility/government clinic; Tx – On treatment; D – untreated clinical disease; Sev – Severe disease; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection; WSev – untreated progressing early severe PrSev – Severe case seeking treatment at private outlet/drug seller ; CLSev – Severe case seeking treatment at primary care facility; Href – Severe case referred to hospital or tertiary facility by either health facility or private outlet; TxSev – Severe case that has received treatment at clinic/health facility or private outlet; CLSevNT – severe case not treated at primary care facility/government clinic; PrSevNT – severe case not treated at private outlet/drug seller;- HTx – Sever case treated in hospital or tertiary facility; HSev – untreated severe case in hospital or tertiary facility. People move between these states with rates/probabilities as marked on the arrows

As shown in Figure 30, a symptomatic individual with a risk of developing severe disease early (with probability θ) who does not access early treatment (with probability f_ntx) then enters a waiting state WSev (to ensure times are equivalent on all pathways to enter Severe disease state).

Figure 30 also highlights that, in contrast to the earlier models, those with uncomplicated clinical malaria who do not receive treatment at the initial source, or who fail treatment, enter into the same severe disease compartment with the probability ε. In previous models there was no further treatment opportunity for these cases – but in Model 3, they have the opportunity to seek hospital treatment with the probability $f\__H$. Those who do not seek treatment, (1-$f\__H$), either die (ε_sev) or those that survive (1 - ε_sev) eventually clear clinical symptoms and move to the asymptomatic state A at the rate $r\__D$.

In addition, those symptomatic patients at risk of early severe disease who enter the PrSev and CLSev compartments but

a. who are not treated promptly or referred (i.e. $1\text{-}ftr\__{REFCL} - ftr\__{SEVCL}$ or $1\text{-}ftr\__{REFPRI} - ftr\__{SEVPRI}$) or
b. who fail treatment (1-$f\__{EFF}$)

also enter the severe disease compartment. Waiting states PrSevNT and CLSevNT have been included to ensure times to develop severe disease are consistent in all pathways at rates r_NTXPR and r_NTXCL respectively.

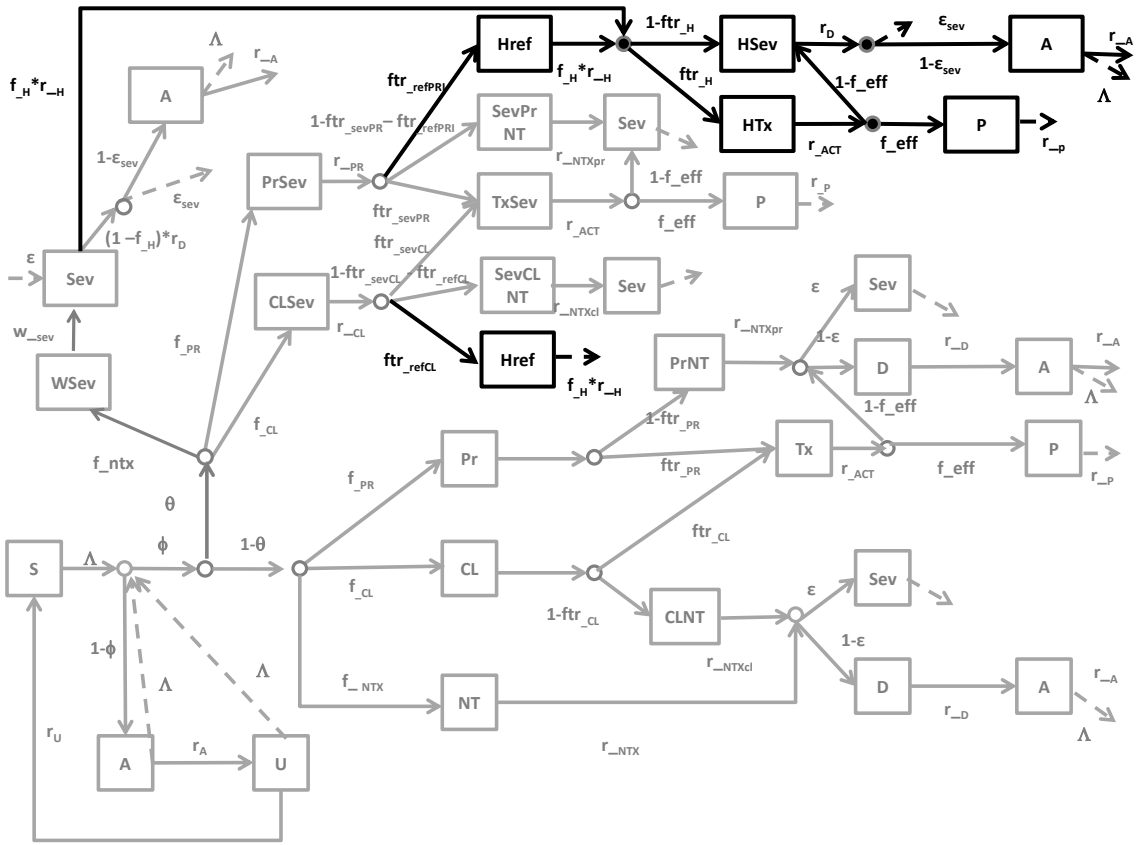


Figure 31: Model 3 - Flow diagram for the Severe treatment model: Management of severe malaria at hospital/tertiary care level

S - susceptible; NT – not seeking treatment; Pr – Seeking treatment at private outlet/drug seller; CL – Seeking treatment at primary care health facility/government clinic; PrNT – not treated at private outlet/drug seller; CLNT – not treated at primary care health facility/government clinic; Tx – On treatment; D – untreated clinical disease; Sev – Severe disease; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection; WSev – untreated progressing early severe PrSev – Severe case seeking treatment at private outlet/drug seller ; CLSev – Severe case seeking treatment at primary care facility; Href – Severe case referred to hospital or tertiary facility by either health facility or private outlet; TxSev – Severe case that has received treatment at clinic/health facility or private outlet; CLSevNT – severe case not treated at primary care facility/government clinic; PrSevNT – severe case not treated at private outlet/drug seller;- HTx – Sever case treated in hospital or tertiary facility; HSev – untreated severe case in hospital or tertiary facility. People move between these states with rates/probabilities as marked on the arrows

Figure 31 details the potential treatment pathways for severe disease. Following onset of severe symptoms, cases may seek treatment at a hospital or a tertiary centre (with probability f_{H}) at a rate r_{H}. In addition cases at risk of early severe disease that have been referred from either private vendors or government health facilities (Href) seek treatment at hospitals or tertiary care centres at rate r_{H}. It is assumed that the probability of attending a hospital as a first choice source of treatment (f_{H}) is the same as the probability of attending following referral.

If cases are correctly treated at the higher level health facility, with a probability of ftr_{H}, they then enter the treated state HTx. These cases progress to being prophylaxed (P) at rate r_{ACT} with a probability that the treatment is effective (f_{EFF}). First-line treatment of severe malaria at hospital is assumed to be with Artesunate as per the WHO guidelines(WHO, 2010a). Those who are not treated (with probability $1-ftr\_{H}$) or who fail treatment then progress to a late severe disease stage (HSev). Patients leave this state at rate r_{D} and either die with a probability of ε_{SEV}, or slowly clear the disease entering the asymptomatic state A with a probability of $1-\varepsilon\_{SEV}$.

The equations for the full model are given in Appendix A.

The force of infection acting on mosquitoes in this model is simply extended to reflect the additional disease states, which are all assumed to have transmission probability c_D. Hence the infectivity of the extended set of states is:-

$$\Lambda_v = \zeta(1-\rho\exp(-a/a_0)[c_D D + c_A A + c_U U + c_U UPr + c_U UCL + c_U UTx + c_D Pr + c_D CL$$
$$+c_D NT + c_D CLNT + c_D PrNT + c_D Sev + c_D WSev + c_D CLSev + c_D PrSev + c_D CLSevNT + c_D PrSevNT$$
$$+c_D Href + c_D Hsev + c_{TX} SevTx + C_{TX} HTx + c_{TX}\ \mathrm{Tx}]$$

3.6.4 Additional Parameters for Model 3

3.6.4.1 Human infection parameters

Community level risks of acute severe malaria are difficult to assess since most studies present hospital level data and case fatality rates. Gupta *et al.* modelled the risk of acute severe disease in hospitalised cases decreasing with progressive exposure to infections (Gupta et al., 1999b). Ross *et al*. constructed an epidemiologic model of severe morbidity and mortality caused by *P. falciparum*, and predict that the risk of severe disease decreases with exposure, but that other factors also affect the risk of acute severe presentation including age, presence of co-morbidities and transmission setting such that severe disease can occur in older individuals at low transmission settings (Ross et al., 2006b). In this model, I use estimates for Θ fitted by Griffin *et al.* using hospital data from Tanzania (Griffin et al., 2014).

It is known that at low transmission intensities, once infected there is a higher probability of developing severe symptoms and a greater risk of death from severe malaria. The role of immune modulation has already been included in the likelihood of developing disease, and thus ε and $\varepsilon_{\_SEV}$ are modelled as a constant proportion of under and over fives with untreated clinical disease. As previously described, there is a higher risk of developing disease if there is a delay in treatment seeking.

The time taken to progress to developing severe disease in those at risk if untreated, $w_{\_SEV}$, is set at 3 days in order to make this time equal to other pathways that result in severe disease.

Table 12: Severe disease Host infection and clinical disease parameters

Name	Definition	Value Range	Value Used	References
Θ	Probability of presenting with severe disease (i.e. not due to treatment delay or failure)	0.03-0.15	Fitted to hospital data from Tanzania	(Griffin et al., 2014)
$w_{\_SEV}$	Time taken to progress to severe illness if no treatment (days)	1.8 - 3	3	(Miller, 1958, Greenwood et al., 1987)

3.6.4.2 Treatment and drug parameters

The traditional parenteral treatment for severe malaria is intravenous quinine. However the WHO 2010 guidelines on management of severe malaria now recommend the use of intravenous

artesunate for both adults and children due to the rapid clearance of parasitaemia leading to reduced mortality and reduced incidence of complications such as hypoglycaemia as well as its gametocidal activity discussed previously in section 3.3.2.2 (WHO, 2010a). The guidance suggests that this treatment should be given for 24 hours and thereafter, the patient should receive a full course of the locally recommended ACT (WHO, 2010a). Thus I have used the same values for the reduction in parasitaemia and reduction in infectiousness due to gametocytaemia as previously outlined in section 3.2.3.5. I have not included the use of quinine in the models, since I am considering the impact of ACTs and also because the guidelines recommend a second oral agent should be added if using quinine therapy - there are little data regarding how this is implemented (WHO, 2010a).

As summarised earlier, a study by Gomes *et al*. investigated the use of early administration of rectal artesunate in cases of severe malaria as a pre-referral tool and found that it may prevent death and disability (Gomes et al., 2009). There is uncertainty regarding the effect of such an intervention if given more than 6 hours after the onset of symptoms (Grobusch, 2009), highlighting the importance of early access to treatment.

In this model I assume that early administration of artesunate (intravenous or rectal) with a course of ACTs will prevent progression to fulminant severe disease in these individuals, and may occur at the health facility or private outlet level.

Table 13: Severe Disease Drug related parameters

Name	Definition	Value Range	Value Used	References
cSevTx/HTx	% reduction in average infectiousness compared to state occupied prior to treatment	80.6% * c_D	0.05	(Dunyo et al., 2006), (Griffin et al., 2014)

3.6.4.3 Clinic Health system parameters

The use of pre-referral rectal or intramuscular artesunate is included at community level in order to prevent progression to severe disease in those at risk of developing early severe disease. Given the recent change in guidance regarding the use of pre-treatment with artesunate, very little data are available on the frequency of its use. A study in Uganda (Sears et al., 2013) found that amongst patients who were given a diagnosis of severe malaria or who were referred for admission due to

the severity of their symptoms, the most frequently prescribed antimalarial was still quinine. Only 6.5% were given ACTs (Sears et al., 2013). Also from Uganda Kyabayinze *et al*. noted that at tertiary level facilities, 70% of the patients referred from lower level health facilities had received pre-referral antimalarial drugs but none had been prescribed pre-referral rectal artesunate (Kyabayinze et al., 2012).

Hence I estimated the probability of the treatment of severe disease (ftr_{SEVCL}) at clinical level, i.e. using rectal artesunate and ACTs, by multiplying the probability of receiving ACTs at a public sector clinic (ftr_{CL}) and the probability of having artesunate stock. The method for deriving ftr_{CL} is described in Chapter 4.

Stocks of rectal or intravenous artesunate are not commonly reported. In Uganda, Kyabayinze surveyed 125 primary care clinics across 11 districts and found rectal artesunate for pre-referral medication was only available in one health centre (Kyabayinze et al., 2012). I estimated the probability of artesunate availability at public facilities using the AMFm evaluation (AMFm Independent Evaluation Team, 2012) which reports on both the proportion of outlets with artemisinin monotherapy (all forms) in stock and the proportion of outlets with oral artemisinin monotherapy in stock, across 8 countries. I assumed that the difference accounts for rectal and intravenous preparations of artesunate.

There is little published data on the probability of severe cases being referred to tertiary care facilities and hospitals for in-patient care from public sector health facilities. The IMPACT 2 study in Tanzania, described in greater detail in Chapter 5, did not record any referrals from clinics to hospitals. Kyabayinze documents that of 186 patients that were referred to hospitals for severe malaria, only 10% had received adequate referral care including notes and transport support (Kyabayinze et al., 2012). Hence I used this figure to estimate the probability of referral for severe disease to higher level facilities.

Table 14: Severe disease Clinic parameters

Name	Definition	Value Range	Value Used	References
ftr_{SEVCL}	Probability of severe case receiving Artesunate and ACT at a public sector/government health clinic	Artesunate in stock: 0 – 0.38	0.2*0.5 = 0.1 (See Chapter 4 for ftr_{CL})	(AMFm Independent Evaluation Team, 2012, Mangham et al., 2012, Kyabayinze et

				al., 2012)
ftr_{REFCL}	Probability of a severe case seen at public sector/government health clinic being referred to in-patient/tertiary care/hospital for treatment		0.1	(Kyabayinze et al., 2012, Berendes et al., 2012)

3.6.4.4 Informal sector parameters

I estimated the probability of receiving rectal or intravenous artesunate and ACTs at a private sector outlet (ftr_{SEVPR}) by multiplying the probability of suitable artesunate preparations in stock with the probability of receiving ACTs for malaria at a private outlet (ftr_{PR}). The method by which ftr_{PR} is estimated is described in Chapter 4. Estimates of artesunate stocks in the private sector were used from surveys in Nigeria (Berendes et al., 2012, Okeke and Uzochukwu, 2009, Mangham et al., 2011) and Cameroon(Mangham et al., 2012) as well as the AMFm evaluation. Reducing the use of oral artemisinin monotherapy at private sector outlets has been identified as a target for the AMFm initiative, and this policy objective may have affected the reporting, use and stock of other artesunate monotherapy preparations at drug and general shops.

Private sector outlets are increasingly included within national malaria control strategies, especially through subsidy schemes such as AMFm. Hence it is a quality of care concern that private outlet staff are able to recognise the symptoms of severe disease and understand the urgency of referral to a health facility or tertiary level clinic. A recent study in Kenya found that over a quarter of interviewed drug shop owners knew to ask about at least one symptom of severe disease. However only 1% knew what the appropriate actions were if a child did not recover or was vomiting their medication (Kangwana et al., 2013). Similar results were seen in a study in Nigeria by Berendes *et al*, who estimated that after training, 14% (CI: +/- 7.63%) of shop owners could recognise the symptoms needing referral (Berendes et al., 2012).

Table 15: Severe Disease Informal sector parameters

Name	Definition	Value Range	Value Used	References
ftr_{SEVPR}	Probability of severe case receiving ACT at private sector drug shop or outlet	Artesunate in stock: 0 – 0.57	0.2*0.05 = 0.01 (See Chapter	(Mangham et al., 2012, Mangham et al., 2011,

			4 for ftr_{PR})	AMFm Independent Evaluation Team, 2012, Berendes et al., 2012, Okeke and Uzochukwu, 2009)
ftr_{REFPR}	Probability of a severe case seen at private sector drug shop or outlet being referred to in-patient/tertiary care/hospital for treatment	0.002 – 0.26	0.01	(Kangwana et al., 2013, Berendes et al., 2012) Unpublished data (IMPACT 2 study)

3.6.4.5 Hospital parameters

The SEAQUAMAT (Dondorp et al., 2005) and AQUAMAT (Dondorp et al., 2010) trials have favourably compared the use of intravenous artesunate to quinine for the treatment of severe malaria and the most recent WHO guidance recommends artesunate followed by ACTs as first line treatment (WHO, 2010a). Yet data regarding the care capacity and quality at a hospital level in sub-Saharan Africa is limited. A study by Achan *et al.* surveyed case management of severe malaria in Uganda at 83 lower level facilities and 22 in-patient facilities, before the change in guidance recommending artesunate as first-line treatment for severe malaria (Achan et al., 2011). Microscopy was available in 77.3% of inpatient hospital units and 51% of the higher level clinics. In the preceding 3 months only 54% of the hospital and higher level facilities had consistent availability of parenteral quinine, while fewer had consistent stocks of oral quinine (16.2%) and ACTs (33.3%). None of the inpatient facilities had consistent availability of all seven components of a basic care package for severe malaria management (parenteral quinine, intravenous fluids, 50% dextrose, blood for transfusion, transfusion sets, IV giving sets and syringes). The most common stockouts were for blood (only in 4.5% units), 50% dextrose (32% units) and 5% dextrose and transfusion sets (35.4%). The majority of the staff at inpatient and higher level facilities were nurses/midwives, with only 2 doctors noted on survey days. Approximately 52% of workers at the higher level facilities were able to write an appropriate prescription for a child with severe malaria, and only 22% had received in service training on severe malaria or supportive supervision. Whilst over 90% of patients prescribed IV

quinine were prescribed it correctly, the dose of IV artesunate was incorrect in all 8 of the patients it was given to. Overall only 16.9% of patients hospitalised with severe malaria were given full correct management: initial parenteral antimalarial medicine, dosing regimen, and mode of administration, although the actual dosage of quinine and regimen was correct in 70%, administration in the correct volumes of dextrose etc. was only correct in 18%.

Noor *et al.* in Somalia found that at hospital facilities 95.5% of health workers reported use of ACTs as first line treatment (as opposed to 0% in the peripheral health posts) and 91% used quinine for severe malaria or treatment failure (Noor et al., 2009). However 54.5% of hospitals had stockouts on the day of survey of the first-line treatment. Given the paucity of evidence at this level, I have therefore assumed that the probability of receiving artesunate and ACTs for malaria at a tertiary level facility (ftr_H) is the probability of having these preparations in stock.

Manongi *et al.* found that in rural Tanzania the mortality impact of poor access to tertiary care for severe disease was potentially substantial, but constrained by uncertainty in the quality of in-patient care (Manongi et al., in submission). Treatment seeking at a hospital for severe disease was estimated from unpublished data from the IMPACT 2 study in Tanzania (described in Chapter 5) as well as data describing hospital visits following attendance at another facility first (Agyepong and Kangeya-Kayonda, 2004): 9% surveyed attended hospital as a first choice for fever where as 43% attended as a second choice if their symptoms became worse. I assumed that the probability of attending a hospital as a first choice source of treatment (f_H) is the same as the probability of attending following referral.

Table 16: Hospital Parameters

Name	Definition	Value Range	Value Used	References
f_H	Probability of accessing care at a hospital-level facility per severe episode	0– 0.43	0.1	(Noor et al., 2009, Achan et al., 2011, Agyepong and Kangeya-Kayonda, 2004), Unpublished data IMPACT 2
$1/r_H$	Average time taken to seek treatment at appropriate level facility for severe malaria	1.3 - 7.25 (data from hospitalised	2	(Feikin et al., 2009, Al-Taiar et al., 2008, Rutebemberwa

		patients: time from start of infection)		et al., 2009) Unpublished data IMPACT 2
ftr_H	Probability of receiving correct treatment at hospital or high level facility for severe malaria (i.e. probability of artesunate and ACTs in stock)	0.28-0.82	0.5	Unpublished data IMPACT 2

3.6.5 Results from Model 3: Severe disease and Hospital model

3.6.5.1 Impact of public sector health interventions on clinical outcomes

Model 3 includes pathways for those at risk of acute severe disease as well as those who develop severe disease after failing to be successfully treated for uncomplicated malaria. Figure 31 shows the impact on malaria mortality in 0-5 year olds of altering:

1. probability of an uncomplicated malaria case receiving an ACT at a public sector clinic ($ftr_{\_CL}$)
2. probability of a malaria case at risk of acute severe disease receiving an ACT and pre-referral rectal or intramuscular Artesunate at a public sector clinic as per WHO guidelines ($ftr_{\_SEVCL}$)
3. probability of a potentially severe malaria case being referred to hospital or tertiary care facility from a public sector clinic ($f_{\_REFCL}$)
4. the probability of a severe malaria case seeking care at a hospital or tertiary care facility ($f_{\_H}$)
5. probability of a severe malaria case being treated at a hospital or tertiary care facility with artesunate and ACTs as per WHO guidelines ($ftr_{\_H}$)

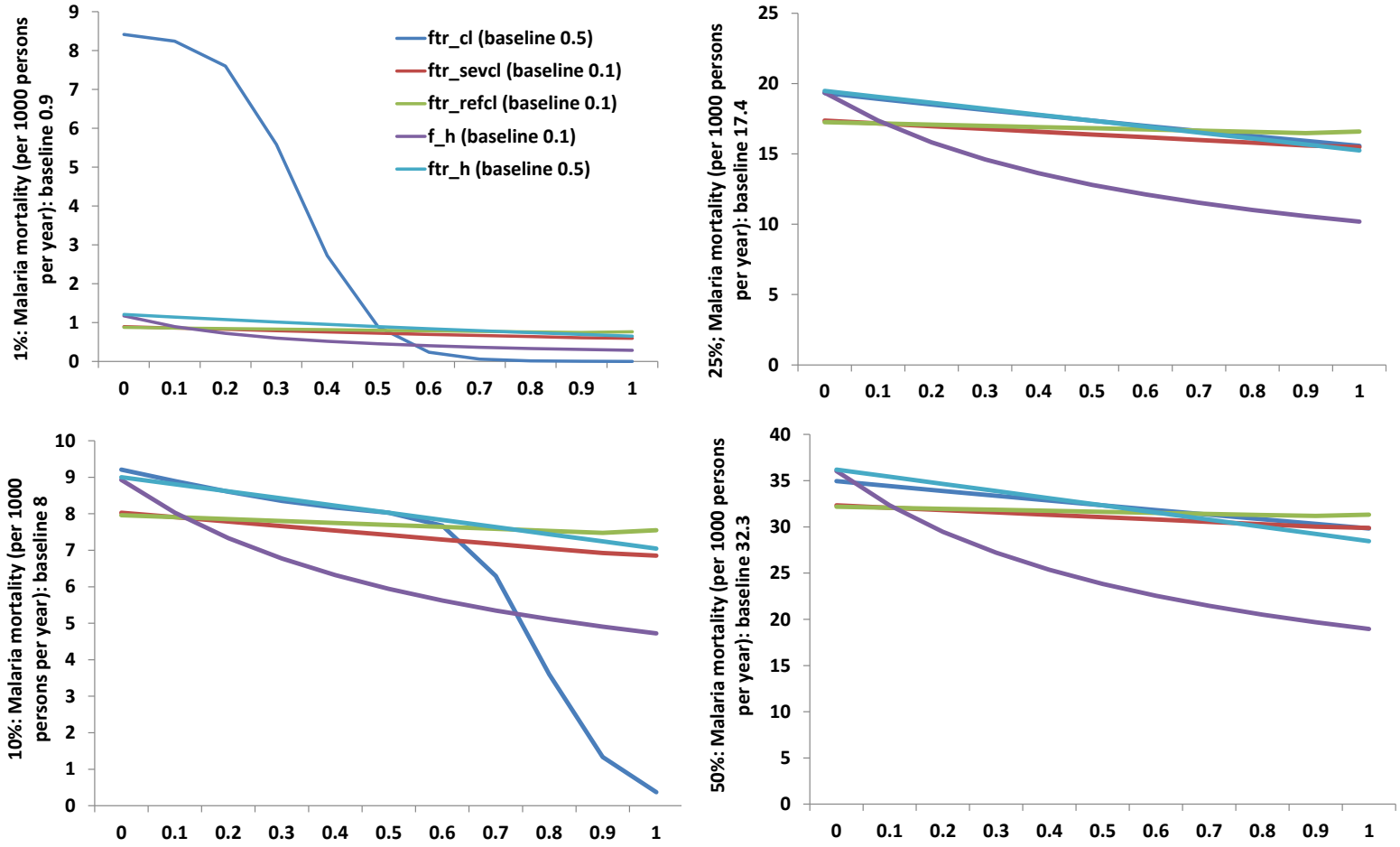


Figure 32: Model 3 - The impact on malaria mortality, in 0-5 year olds at 4 prevalence settings, of varying the probability of being treated at clinic, being referred to hospital, accessing hospital care and receiving Artesunate plus ACTs at hospital/tertiary care.

1) probability of uncomplicated malaria case receiving an ACT at a clinic ($ftr_{\_CL}$: dark blue); 2) probability of a malaria case at risk of severe disease receiving an ACT and rectal /IM Artesunate ($ftr_{\_SEVCL}$: red); 3) probability of a potentially severe malaria case being referred to hospital from clinic ($f_{\_REFCL}$: green); 4) the probability of seeking care at a hospital ($f_{\_H}$: purple); 5) probability of being treated for severe malaria at a hospital or tertiary care facility with artesunate and ACTs as per guidelines access to treatment ($ftr_{\_H}$: light blue).

At low transmission settings, varying the quality of community (health facility) treatment of uncomplicated malaria impacts most greatly on malaria mortality, whereas altering the access to and quality of tertiary care does not greatly affect this outcome. At higher transmission settings, the quality of treatment for uncomplicated malaria does not appear to drive rates of malaria mortality as much as access to tertiary care where IV artesunate is assumed to be available. This is further demonstrated in Table 17 which lists the maximal reduction relative to baseline achieved with each of the 5 interventions (i.e. when each parameter is equal to 1) on severe disease incidence and malaria mortality in 0-5 years olds.

Table 17: Relative change (%) in malaria mortality and severe disease incidence from baseline in each prevalence setting

	1% slide prevalence		10% slide prevalence		25% slide prevalence		50% slide prevalence	
	Mortality	Severe Disease	Mortality	Severe Disease	Mortality	Severe Disease	Mortality	Severe Disease
$ftr_{\_CL}=1$	-99.9	-99.9	-95.4	-95.3	-10.3	-11	-7.7	-9.4
$ftr_{\_SEVCL}=1$	-33.6	-35.5	-14.6	-16.7	-10.8	-10.3	-7.6	-5.2
$f_{\_REFCL}=1$	-14.8	-26.3	-6	-17.8	-4.4	-10.9	-3.1	-5.5
$f_{\_H}=1$	-68	-66.5	-41.2	-38.4	-41.4	-36	-41.4	-34
$ftr_{\_H}=1$	-27.3	-17.3	-12.3	0.2	-12.2	-0.1	-12	-0.02

Improving the probability of receiving ACTs for uncomplicated malaria (from 50% at baseline to 100%) is the most effective of the interventions considered here in reducing both malaria mortality and severe disease incidence in this age group at lower transmission settings.

At 25% and 50% prevalence settings, ensuring cases seek treatment at a hospital (from baseline 10% to 100%, and thus are treated there (even at baseline assumed levels of hospital treatment with ACTs) may decrease malaria mortality by up to 40%. This also impacts the incidence of severe disease. This is due to the structure of the model, whereby acute severe disease cases referred from clinics or drug shops to the hospital bypass the severe disease state. Hence severe disease is averted so long as appropriate treatment at hospital occurs. Improving the quality of treatment at hospital does not affect the incidence of severe disease (as cases arrive to hospital either from the severe disease state or via referral from community, bypassing the severe disease state) but may reduce malaria mortality.

Further results using Model 3 are described in Chapter 5.

3.7 CONCLUSION

This chapter defines a model investigating the effect of first-line antimalarial delivery on malaria transmission and clinical outcomes at varied malaria prevalence settings. The model was iteratively constructed incorporating (a) access to primary level or community sources of ACTs, i.e. public sector health facilities and informal private sector outlets, and (b) the quality of care in the different sectors, i.e. the probability of a malaria case receiving an ACT and NMFI unnecessarily receiving ACTs. In addition, the final model reflects the role of health systems on the incidence of severe malaria and the different pathways by which the development of severe disease may be prevented or treated in the community and at tertiary level health facilities.

The results from the initial model incorporating severe disease as a consequence of absent, delayed or ineffective treatment in addition to public and private sources of antimalarials suggest that improvements in the quality of care (i.e. the probability of receiving an ACT for a malaria infection) in either sector may have a larger impact on clinical outcomes than on transmission. The model outputs indicate the relative reduction in severe disease incidence in 0-5 year olds is greater than the relative reduction in slide prevalence in 0-5 year olds in all transmission settings, with a similar pattern for malaria-related mortality in this age group. This is likely to be due to the age distribution of clinically symptomatic malaria infections, i.e. in young children in medium-high transmission settings who are therefore treated as quality of care improved, whilst those who are infected but not symptomatic (i.e. over 5 years) continue to function as an infection reservoir.

The second iteration of the model included the treatment of NMFI with ACTs, including asymptomatic and sub-patent malaria infection as well uninfected individuals. Eliminating NMFI treatment with ACTs in both the private and public sectors had negligible impact on parasite prevalence and severe disease incidence, at baseline levels of malaria treatment. This suggests that addressing the treatment of NMFI as a policy issue may not lead to unwanted rises in infection as feared, at present levels of quality of care.

The final model, extended to capture tertiary level treatment of severe disease as well as early management of acute disease at a community level to avert fulminant severe disease, demonstrates that improved management of uncomplicated disease at community level is sufficient to reduce levels of malaria mortality at low transmission settings. However at medium-high prevalence levels, investment in tertiary care both in terms of access and the ability to treat with artesunate is required to improve treatment of severe malaria and its complications and in turn reduce malaria-related mortality.

The model is limited by the assumption that I only considered ACTs as treatment, and hence assumed that any other antimalarials do not exert an effect on clinical outcomes or transmission. Furthermore the parameter values regarding the efficacy of ACTs are based on AL (Artemether Lumefantrine), and thus may vary for other combinations. The average period of prophylaxis (1/rP) is assumed to be the fixed duration of minimum inhibitory anti-malarial concentrations in the blood against blood stage parasite, although this may also vary with immunity. In addition, the model does not account for repeat treatment-seeking in any sector, and thus may overestimate the impact of stockouts. Further work is required on health seeking behaviour, especially in the private sector to understand whether patients will attend several sources of care if drugs are unavailable or accept other non-first line medication.

The analysis finds that access to local sources of anti-malarial treatment (i.e. probability of seeking treatment) has the greatest relative impact at lower prevalence settings on both transmission-related and clinical outcomes. At higher prevalence scenarios, interventions which increase use of ACTs are most effective in addressing malaria morbidity and mortality. Reducing transmission through treatment with ACTs in higher transmission settings will require investment across private and public sectors both with respect to access to these sources of care and the ability of these sources to prescribe ACTs to those in need, whilst avoiding the treatment of those who do not.

The next Chapter will consider how to estimate the quality of care received at health facilities and private outlets and investigate which interventions are most likely to result in malaria cases receiving ACTs appropriately.

4 IMPROVING MALARIA AND NON-MALARIAL FEBRILE ILLNESS CASE MANAGEMENT

4.1 INTRODUCTION

Until recently, presumptive treatment of all fevers as malaria was advocated in WHO guidelines and national policies for malaria-endemic areas, especially for children under 5 years (U5s). As described in Chapter 2, studies estimate between 47-95% of patients with a non-malarial febrile illness (NMFI) receive antimalarials unnecessarily in both public sector health facilities and private sector outlets (Hamer et al., 2007, Reyburn et al., 2004, Zurovac et al., 2008b, Rowe et al., 2009a, Nicastri et al., 2009, Nankabirwa et al., 2009, Okebe et al., 2010, Bastiaens et al., 2011, Nyandigisi et al., 2011, Harchut et al., 2013, Mangham et al., 2012). Overtreatment is often with non-recommended antimalarials (Zurovac et al., 2008b, Noor et al., 2009, Mangham et al., 2012, Mangham et al., 2011), but may involve first-line ACTs (Okebe et al., 2010, Rowe et al., 2009a, Hamer et al., 2007, Nyandigisi et al., 2011, Zurovac et al., 2008b, Mangham et al., 2012, Mangham et al., 2011). In 2010, the WHO revised the protocols for the treatment of malaria to state that whenever possible:

"*... prompt parasitological confirmation by microscopy or alternatively by rapid diagnostic test (RDT) is recommended in all patients suspected of malaria before treatment is started. Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible*" (WHO, 2010a).

In 2012, the WHO launched "T3: Test. Treat. Track"(WHO, 2012b), an initiative to reduce routine overtreatment of NMFI with antimalarials, to expand disease surveillance and to improve quality of care for both malaria and NMFI. Though its likely impact remains a subject of debate (Graz et al., 2011, Bjorkman and Martensson, 2010, English et al., 2009, D'Acremont et al., 2009, Masanja et al., 2011), the strategy has been widely adopted in guidelines across malaria endemic countries (WHO, 2012b).

The WHO estimates that net expenditure on antimalarial treatment may decrease as a result of testing before treatment (Feachem et al., 2010). However non-compliance with test results by healthcare workers (HCWs), i.e. treating with antimalarials despite a negative test for malaria, is common (Chandler et al., 2012, Chandler et al., 2010, Chandler et al., 2008a) and can be detrimental to those patients who are not parasitaemic. For example, a Tanzanian study found the case fatality rate, in albeit hospitalised, test-negative patients treated with antimalarials, to be significantly

higher (12.1%) than for test-positive patients (6.9%), and over 60% of NMFI were not treated with antibiotics (Reyburn et al., 2004). A study, in a high malaria transmission region of Tanzania, of severe hospitalised NMFI found that half of the bacteraemic patients were not prescribed empirical antibiotics; whilst three quarters of all febrile admissions were diagnosed on admission with severe malaria, only 20% were found to be parasitaemic (Nadjm et al., 2012).

As described in Chapter 2, private outlets such as drug stores and general shops are often staffed with poorly qualified staff. Not only are antimalarials often overprescribed presumptively for fever (Kangwana et al., 2011, Ringsted et al., 2011, Littrell et al., 2011a, Littrell et al., 2011b), there is good evidence of use of substandard or counterfeit antimalarials, as well as artemisinin monotherapy or chloroquine as first-line treatments (Kaur et al., 2008, Bate et al., 2008, Newton et al., 2006, Noor et al., 2009, Alba et al., 2010b, Amuasi et al., O'Connell KA et al., 2011, Littrell et al., 2011b). Quality assured ACTs (QAACTs) as certified by organisations such as AMFm and ACTWatch represented less than 20% of the antimalarial market (O'Connell KA et al., 2011, Ringsted et al., 2011, Kangwana et al., 2011). ACTs are also priced higher in the private sector compared to other antimalarials, despite this being the most common point of access (O'Connell KA et al., 2011).

The price and quality of Artemisinin Combination Therapies (ACTs) has been a barrier to effectively expanding their use in the private sector. In 2009, the subsidy programme Affordable Medicines Facility for malaria (AMFm) was launched, seeking to reduce the price through a co-payment facility, and therefore aiming to increase access to QAACTs and drive out ineffective drugs and monotherapies(Laxminarayan R and H, 2009). As reported in Chapter 2, the price subsidy is acknowledged to have been passed widely onto customers (AMFm Independent Evaluation Team, 2012, Tougher et al., 2012) and the market share of QAACTs has increased (Tougher et al., 2012, AMFm Independent Evaluation Team, 2012). However it is not yet clear whether drug subsidies have translated into a higher standard of malaria treatment in the private sector.

Effective malaria control requires the delivery of interventions at sustained high levels of coverage and quality, ensuring those who need treatment receive it, and that those febrile patients who do not have malaria infections, are not needlessly treated. There have been relatively few modelling approaches to address the delivery of treatment for case management of malaria and NMFI (Tediosi et al., 2006, Rafael et al., 2006, Lubell et al., 2008, Zurovac et al., 2008a).

The “systems effectiveness framework” (Tanner et al., 1993) described in Chapter 2, illustrates how interacting health-systems barriers may sequentially reduce the in-field effectiveness of treatment interventions (Hetzel et al., 2008, Krause and Sauerborn, 2000, Littrell et al., 2013). This has proved

valuable as a means of analysing the steps to optimal case management. However outcomes such as the proportion of malaria cases that receive first-line treatment through all pathways (i.e. not solely via diagnostic-led management) and the levels of unnecessary treatment of NMFI with antimalarials are not addressed by this approach. Such outcomes are important given the limited budgets for the purchase and distribution of antimalarial treatment courses. The INESS project in Ghana, using this framework for delivery in the public sector, estimated that just 13.5% of simple malaria fevers were treated effectively, with the greatest loss due to failure to access care within 24-48 hours (Binka et al., 2012). Patient adherence was included in this analysis and constituted the second largest bottleneck (Binka et al., 2012). However this differs from WHO estimates of cases of malaria treated with ACTs and other published studies (Mangham et al., 2012, Sserwanga et al., 2011) in part because it does not include alternative non-recommended pathways to receiving treatment.

In Chapter 3, I defined a model investigating the effect of first-line antimalarial delivery on malaria transmission and clinical outcomes, at varied malaria prevalence settings. The model was constructed in stages incorporating access to community sources of ACTs, i.e. public sector health facilities and informal sector outlets, as well as considering the quality of care in the different sectors.

In this Chapter, I extend the systems effectiveness framework into a decision-tree tool to derive and compare estimates of the quality of care in the private and public sectors. In the model outlined in Chapter 3, quality of care parameters are ftr_{CL} and ftr_{PR}, namely the probability of a malaria case receiving an ACT at either a public sector clinic or a private outlet, and ftr_{NMFICL} and ftr_{NMFIPR}, i.e. the probability of NMFI unnecessarily receiving ACTs at a public sector clinic or a private outlet. The decision-tree outputs are used as the baseline parameters in the models described in Chapter 3.

Decision-tree approaches have previously been used to consider the role of diagnostics in reducing the burden of childhood malaria in Africa (Rafael et al., 2006, Lubell et al., 2008). Here I include considerations of treatment seeking, diagnostic availability, use and quality, as well as ACT stock in order to compare interventions to improve case management in a context specific manner. I also use this tool to undertake an early evaluation of the impact of the revised WHO guidelines on treatment outcomes for malarial and non-malarial fever, and the impact of AMFm on the management of fever in the private sector.

4.2 METHODS

4.2.1 Systems Effectiveness and Decision-Tree Approach

I consider two approaches to evaluate the impact of improvements in case management on the appropriate treatment of fevers in malaria endemic settings. The first follows the published stepwise systems effectiveness framework for case management (Tanner et al., 1993, Mumba et al., 2003, Hetzel et al., 2008, Krause and Sauerborn, 2000), whilst the second is a decision-tree approach to malaria treatment (Figure 33) extending previous similar decision-tree models for diagnostics (Lubell et al., 2008, Rafael et al., 2006). The entry point is a febrile case seeking treatment, for both public sector health facilities and private sector drug and general shops. I next stratify on their true (unobserved) cause of fever as either malaria or non-malarial febrile illness (NMFI). The case management process then involves five steps:

1. the availability of an RDT
2. whether the RDT is used
3. the outcome of the RDT given the true underlying cause of fever (based on the sensitivity and specificity of the diagnostic)
4. whether an ACT is in stock
5. whether an ACT is prescribed given the RDT result or clinical diagnosis.

I do not consider the possibility of a co-morbid condition causing fever as well as malaria at this stage.

This leads to three outcomes:

1. correct treatment – namely ACTs for malaria, and NMFI not receiving any ACT (both shown as green circles),
2. under-treatment of malaria (shown as a purple circle, i.e. not given ACTs),
3. overtreatment of an NMFI with ACTs (shown as a red circle).

In a perfect case management system there would be no under- or over-treatment. Treatment following clinical (i.e. non-diagnostic guided) diagnosis is included in the decision tree, but was not included in the published systems effectiveness framework (Tanner et al., 1993, Binka et al., 2012).

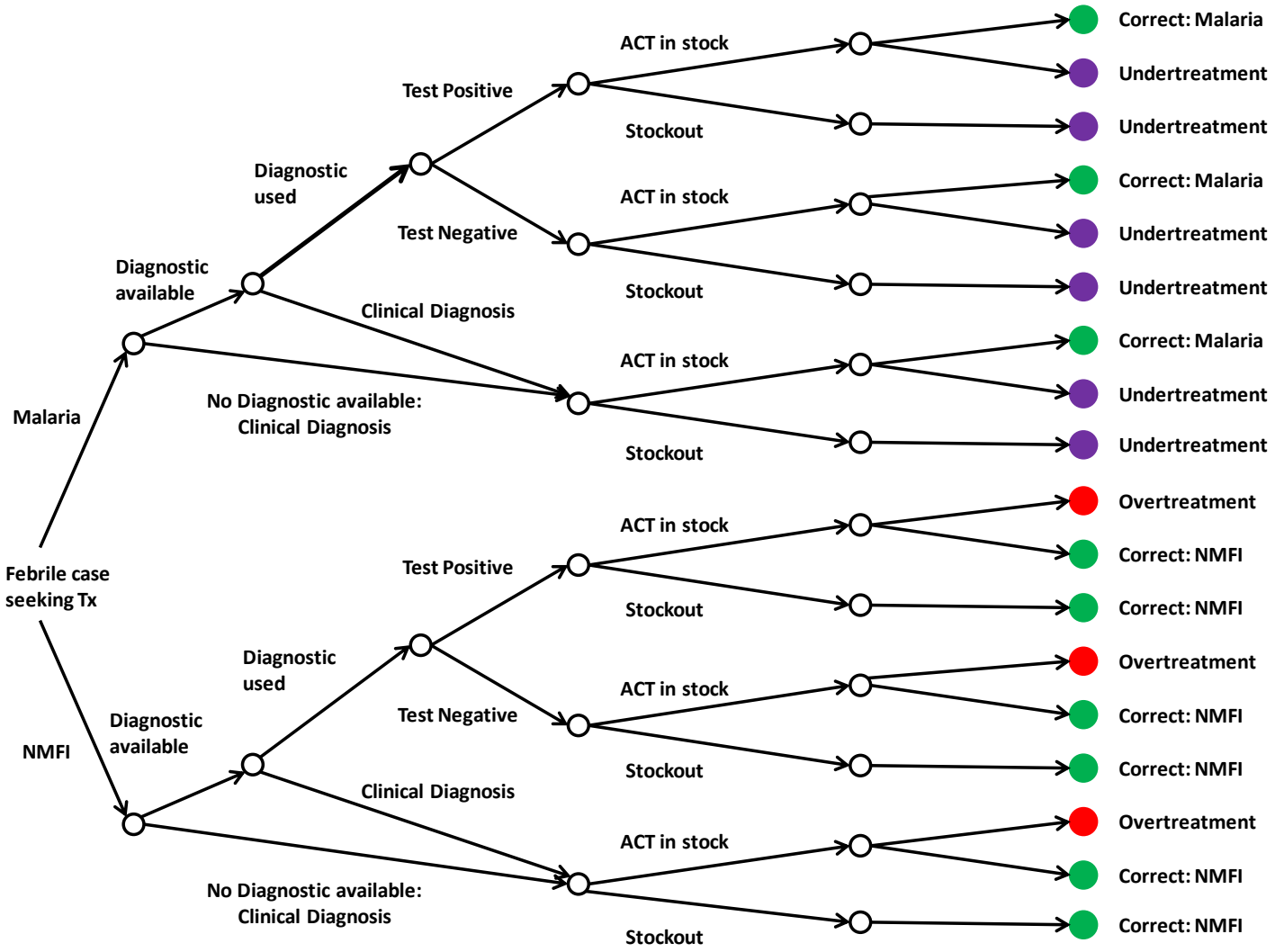


Figure 33: Decision tree modelling approach to malaria case management in the public sector.

The outcome of the systems effectiveness approach is the proportion of malaria cases that receive correct diagnostic-led treatment with ACTs. In contrast, the decision-tree allows a wider spectrum of outcomes to be evaluated:

1. Correct treatment of malaria with ACTs (diagnostic-led or clinically diagnosed)
2. Under-treatment of malaria cases (i.e. those not given ACTs)
3. Overtreatment of NMFI with ACTs
4. Overall number of febrile patients treated appropriately (i.e. both malaria cases given ACTs and NMFI not treated with ACTs).

Staff availability and training in malaria management were not included at this stage as, despite having potential impact, their effects can be difficult to quantify as described in Chapter 2 (Rao et al., 2013a) . Stockouts of treatment for NMFI were not considered given the diversity of possible bacterial and non-bacterial causes, uncertainty regarding the need for antibiotics, and the high likelihood of basic antibiotics being available. In addition the focus here is the impact of the health system, hence patient adherence to ACTs prescribed and drug failure were not included in either approach.

4.2.2 Model Parameters: Public sector/government health facility

Parameters for the moderate-high transmission setting analysis were derived from the literature review in Chapter 2 (Rao et al., 2013a). The parameters were restricted to data presented in studies published between January 2004 (following adoption of ACT as first-line treatment in most countries) and November 2012. The model parameters are shown in Table 18. For each health-systems parameter I extracted any relevant data from the papers restricting my analysis to medium-high transmission settings (as reported in the papers included). I also stratified by whether the study was conducted before or after the introduction of the WHO guidelines regarding universal rational (diagnostic-led) treatment in 2010 (WHO, 2010a). Parameters for diagnostic performance were derived from published values for the sensitivity and specificity of RDTs. I did not limit this to a specific type of RDT nor did I differentiate between the various types of RDTs or microscopy for parameters of diagnostic availability and use. In this public sector model, I used estimates for "all doses of ACT" being available assuming this to be paediatric and adult preparations. Case management values for low prevalence scenarios were limited, and so I included studies published in regions outside Africa (including Afghanistan).

For the baseline scenario I calculated the median of the extracted estimates for each parameter and the 25th and 75th percentiles for the parameter range. These ranges were chosen so as not to skew the results by sampling outliers. To calculate uncertainty intervals I generated 1000 random parameter samples, drawing each parameter independently from a Uniform distribution between the 25th and 75th percentiles.

Table 18: Parameter estimates for each process in the cascade and decision-tree models in the public sector

	Pre universal rational treatment guidelines	Post universal rational treatment guidelines	Pre universal rational treatment guidelines	Post universal rational treatment guidelines	References
	All Studies		**Tanzania**		
Probability of patient with fever seeking treatment at public sector clinic	0.28 (0.26-0.39)	0.29 (0.26-0.40)	0.28 (0.26-0.39)	0.29 (0.26-0.40)	(Littrell et al., 2011a, Tipke et al., 2009, Mangham et al., 2012, Chuma et al., 2009, Chuma et al., 2010, Sumba et al., 2008, Amin et al., 2003)
Probability fever is due to malaria	0.22 (0.13-0.33)	0.22 (0.13-0.33)	0.18	0.1	(WHO, 2010c, WHO, 2012c, Hay et al., 2004, O'Meara et al., 2010, D'Acremont et al., Carneiro et al., 2010, Leslie et al., 2012, Okebe et al., 2010)
Probability that a diagnostic is available	0.54 (0.36-0.97)	0.58 (0.50-0.83)	0.35 (0.34-0.36)	0.61 (0.55-0.68)	(Rowe et al., 2009a, Leslie et al., 2012, Mangham et al., 2012, Littrell et al., 2011a, AMFm Independent Evaluation Team, 2012, Zurovac et al., 2008b, Nyandigisi et al., 2011, Skarbinski et al., 2009, Juma and Zurovac, 2011, Noor et al., 2009, Abdelgader et al., 2012, Masanja et al., 2012b, Nankabirwa et al., 2009, Hamer et al., 2007, Uzochukwu et al., 2010)
Probability that a diagnostic is used if available	0.39 (0.29-0.58)	0.46 (0.34-0.46)	0.69 (0.47-0.71)	0.71 (0.52-0.83)	(Okebe et al., 2010, Rowe et al., 2009a, Leslie et al., 2012, Littrell et al., 2011a, Mangham et al., 2012, Zurovac et al., 2008b, Zurovac et al., 2008c, Nyandigisi et al., 2011, Skarbinski et al., 2009, Juma and Zurovac, 2011, Abdelgader et al., 2012, Masanja et al., 2012b,

					Bastiaens et al., 2011, D'Acremont et al., 2011, Nankabirwa et al., 2009, Sserwanga et al., 2011, Kyabayinze et al., 2010)
Diagnostic sensitivity	0.90 (0.78-0.92)	0.86 (0.72- 0.92)	0.82 (0.63-0.92)	0.82 (0.62-0.86)	(Abeku et al., 2008, Masanja et al., 2012b, Ishengoma et al., 2011, Mtove et al., 2011b, Msellem et al., 2009, Baiden et al., 2012)
Diagnostic specificity	0.86 (0.8-0.92)	0.91 (0.82-0.98)	0.89 (0.83-0.95)	0.98 (0.91-0.98)	(Baiden et al., 2012, Abeku et al., 2008, Masanja et al., 2012b, Ishengoma et al., 2011, Mtove et al., 2011b, Msellem et al., 2009, Leslie et al., 2012)
Probability that all dose packages of ACT are available	0.65 (0.54-0.73)	0.64 (0.62-0.68)	0.59 (0.51-0.67)	0.85 (0.81-0.90)	(Rowe et al., 2009a, O'Connell KA et al., 2011, Mangham et al., 2012, AMFm Independent Evaluation Team, 2012, Njogu et al., 2008, Zurovac et al., 2008b, Zurovac et al., 2008c, Kangwana et al., 2009, Nyandigisi et al., 2011, Juma and Zurovac, 2011, Sudoi et al., 2012, Noor et al., 2009, Mangham et al., 2011, Abdelgader et al., 2012, Masanja et al., 2012b, Zurovac et al., 2008d, Zurovac et al., 2007, Uzochukwu et al., 2010)
Probability that ACT is prescribed/dispensed if test positive	0.99 (0.91-1.0)	0.98 (0.76-0.99)	1.00 (0.99-1.00)	1.00 (0.87-1.00)	(Rowe et al., 2009a, Bisoffi et al., 2009, Mangham et al., 2012, Ansah et al., 2010, Zurovac et al., 2008b, Zurovac et al., 2008c, Nyandigisi et al., 2011, Skarbinski et al., 2009, Juma and Zurovac, 2011, Abdelgader et al., 2012, Masanja et al., 2012b, Masanja et al., 2010, Ishengoma et al., 2011, Bastiaens et al., 2011, D'Acremont et al., 2011, Kyabayinze et al., 2010, Sserwanga et al., 2011)
Probability that ACT is prescribed/dispensed if test	0.51 (0.39-0.71)	0.25 (0.11-0.53)	0.77 (0.53-0.81)	0.12 (0.08-0.20)	(Rowe et al., 2009a, Bisoffi et al., 2009, Mangham et al., 2012, Ansah et al., 2010, Zurovac et al., 2008b, Zurovac

negative					et al., 2008c, Nyandigisi et al., 2011, Skarbinski et al., 2009, Juma and Zurovac, 2011, Abdelgader et al., 2012, Nicastri et al., 2009, Masanja et al., 2012b, Ishengoma et al., 2011, Bastiaens et al., 2011, D'Acremont et al., 2011, Nankabirwa et al., 2009, Kyabayinze et al., 2010, Sserwanga et al., 2011, Okebe et al., 2010, Leslie et al., 2012)
Probability that ACT prescribed/dispensed if untested	0.67 (0.65-0.84)	0.49 (0.23-0.71)	0.89 (0.79-0.95)	0.15 (0.08-0.21)	(Zurovac et al., 2008b, Okebe et al., 2010, Bastiaens et al., 2011, Nyandigisi et al., 2011, Mangham et al., 2012, Leslie et al., 2012, Skarbinski et al., 2009, Juma and Zurovac, 2011, Abdelgader et al., 2012, Masanja et al., 2012b, Zurovac et al., 2008c, Kyabayinze et al., 2010, Zurovac et al., 2008d, Bisoffi et al., 2009, Ansah et al., 2010)

The median and interquartile range from the published studies are presented. For the probability of seeking treatment at the public sector clinic, diagnostic sensitivity and diagnostic specificity, separate values for Tanzania were not available and so the general parameters were used. The probability of fever being due to malaria was assumed the same both before and after the institution of the WHO guidelines in the aggregated analysis but set to reflect the reduction in malaria incidence seen in Tanzania from 2007 to 2011. In the Tanzanian case study, the probability of at least one dose of ACT being in stock was used rather than the probability of all doses of ACT being in stock due to limited data on the latter.

4.2.3 Model Parameters: Private outlet/drug shop

A similar approach was taken to derive model parameters for private outlets such as drugs shops and other general shops that sell antimalarials, as defined in Chapter 2, drawing from the systematic review presented in Chapter 2 (Rao et al., 2013a) as well as from evaluation of the AMFm programme in Tanzania by the IMPACT 2 study (Thomson et al., in submission, Thomson, 2011) which is described in greater detail in Chapter 5. These drug shops are known by several names across Africa, e.g. *duka la dawa baridi* (DLDB) but also include general local shops. I did not include private medical clinics staffed by doctors since these are rare and not present across the region. The model parameters are shown in Table 19.

For each health-systems parameter I extracted any relevant data from medium-high transmission settings (as reported in the papers included). In addition, I also stratified the data by whether the study was conducted before or after the introduction of the subsidised ACTs as part of the AMFm rollout (AMFm Independent Evaluation Team, 2012) if the data were from any of the eight AMFm pilot countries. Data on the dispensing practices of vendors were scarce. Hence the probability of receiving either any ACT or a QAACT when untested or test-negative at baseline was assumed to be the same due to the low levels of testing and lack of data regarding vendor compliance to test results.

The probability that a QAACT is given following a positive diagnostic result or if untested was estimated by multiplying the probability that any ACT was used by the proportion of patients known to receive QAACTs overall, i.e. market share of QAACTs. In addition, the probability of at least one dose of ACT/QAACT being in stock was used rather than the probability of all doses of ACT/QAACT being in stock due to limited data on the latter. This was felt to be reasonable since the practice of "dose stacking" is recognised, where individuals are treated with multiple lower dose packs if the correct dosage is not available. Values for diagnostic sensitivity and specificity were the same as used in the public sector models since little data have been published from this setting.

The probability of treatment seeking after the rollout of AMFm was assumed to be the same as before rollout in the absence of any evidence to suggest otherwise, and since there was little time between the studies for substantial change to have occurred.

Table 19: Parameter estimates for each process in the cascade and decision-tree models in the private sector

	Pre AMFm and drug subsidy pilots	Post AMFm and drug subsidy pilots	Pre AMFm and drug subsidy pilots	Post AMFm and drug subsidy pilots	References
	All Studies		**Tanzania**		
Probability of seeking treatment at private outlet	0.55 (0.25-0.68)	0.55 (0.25-0.68)	0.50 (0.37-0.59)	0.50 (0.37-0.59)	(Alba et al., 2010a, de Savigny et al., 2004, Littrell et al., 2011a, Kangwana et al., 2011, Mangham et al., 2012, Mangham et al., 2011, Sumba et al., 2008, Nabyonga Orem et al., 2013, Thomson, 2011)
Probability fever is due to malaria	0.22 (0.13-0.33)	0.22 (0.13-0.33)	0.1	0.1	(WHO, 2010c, WHO, 2012c, Hay et al., 2004, O'Meara et al., 2010, D'Acremont et al., Carneiro et al., 2010, Leslie et al., 2012, Okebe et al., 2010)
Probability that a diagnostic is available	0.02(0.00-0.09)	0.04 (0.01-0.12)	0.01 (0.01-0.02)	0.05 (0.04-0.05)	(Mangham et al., 2012, Mangham et al., 2011, AMFm Independent Evaluation Team, 2012, Albertini, 2012, Uzochukwu et al., 2010, O'Connell KA et al., 2011, Mbonye et al., 2013, Thomson, 2011)
Probability that a diagnostic is used if available	0.04 (0.02-0.1)	0.04 (0.02-0.1)	0.04 (0.04-0.04)	0.02 (0.02-0.02)	(Littrell et al., 2011a, Mangham et al., 2012, Uzochukwu et al., 2010, Thomson et al., in submission)
Diagnostic sensitivity	0.90 (0.78-0.92)	0.86 (0.72- 0.92)	0.82 (0.63-0.92)	0.82 (0.62-0.86)	(Baiden et al., 2012, Abeku et al., 2008, Masanja et al., 2012b, Ishengoma et al., 2011, Mtove et al., 2011b, Msellem et al., 2009, Leslie et al., 2012)
Diagnostic specificity	0.86 (0.8-0.92)	0.91 (0.82-0.98)	0.89 (0.83-0.95)	0.98 (0.91-0.98)	
Probability that any doses of QAACT are available	0.11 (0.08-0.21) Any ACTs: 0.39 (0.14-0.59)	0.35 (0.12-0.66) Any ACTs: 0.44 (0.21-0.68)	0.07 (0.05-0.05) Any ACTs: 0.29 (0.23-0.32)	0.50 (0.41-0.58) Any ACTs:0.74 (0.72-0.77)	(O'Connell KA et al., 2011, Littrell et al., 2011a, AMFm Independent Evaluation Team, 2012, Kangwana et al., 2011, Smith et al., Berendes et al., 2012, Mangham et al.,

					2012, Mangham et al., 2011, Noor et al., 2009, Alba et al., 2010a, Amuasi et al., Cohen et al., 2010, Kyabayinze et al., 2012, Mbonye et al., 2013, Thomson et al., in submission, Bruxvoort et al., 2013)
Probability that QAACT is prescribed/dispensed if test positive	0.04 (0.05-0.06) Any ACTs: 0.26 (0.26-0.26)	0.33 (0.32-0.33) Any ACTs: 0.38 (0.35-0.4)	0.02 (0.02-0.02) Any ACTs: 0.26 (0.26-0.26)	0.4 (0.28-0.38) Any ACTs: 0.38 (0.35-0.4)	(Cohen et al., 2012, Thomson et al., in submission)
Probability that QAACT is prescribed/dispensed if test negative	0.02 (0.01-0.05) Any ACTs: 0.11 (0.08-0.21)	0.09 (0.07-0.08) Any ACTs: 0.09 (0.09-0.09)	0.01 (0.01-0.01) Any ACTs: 0.19 (0.19-0.19)	0.1 (0.08-0.11) Any ACTs: 0.09 (0.09-0.09)	(Cohen et al., 2012, Thomson et al., in submission)
Probability that QAACT prescribed/dispensed if untested	0.02 (0.01-0.05) Any ACTs: 0.11 (0.08-0.21)	0.26 (0.22-0.22) Any ACTs: 0.25 (0.25-0.26)	0.01 (0.01-0.01) Any ACTs: 0.19 (0.19-0.19)	0.27 (0.25-0.3) Any ACTs: 0.26 (0.25-0.26)	(Cohen et al., 2012, Kangwana et al., 2011, Mangham et al., 2012, Mangham et al., 2011, Littrell et al., 2011a, Mbonye et al., 2013, Hansen et al., 2013, AMFm Independent Evaluation Team, 2012, Alba et al., 2010a, Uzochukwu et al., 2010, Harchut et al., 2013, Thomson et al., in submission)

The values are stratified by whether the data were collected before or after the pilot of the drug subsidy scheme – Affordable Medicines facility for malaria. Values specific to a Tanzanian case study are also shown. The median and interquartile range from the published studies is presented. For diagnostic sensitivity and diagnostic specificity, separate values for the private sector were not available and hence the same values at the public sector were used. The probability of fever being due to malaria was assumed the same in the aggregated analysis but set to reflect the malaria incidence seen in Tanzania (2011). In the private sector analysis, the probability of at least one dose of ACT being in stock was used rather than the probability of all doses of ACT being in stock as per the public sector analysis. Probability of treatment seeking was assumed to be the same for both pre and post AMFm rollout. The probability of receiving either any ACT or a QAACT when untested or test-negative at baseline was assumed to be the same due to the low levels of testing, and lack of data regarding vendor performance on test compliance.

4.2.4 Case Management Scenarios

Parameters based on the literature prior to the publication of the 2010 WHO guidelines were used as a baseline scenario representing current practice, since the rollout of guidance is in its early stage. I then investigated how improving case management at different points along the patient care-pathway impacted on the four outcomes in the decision-tree model. Table 20 summarises the set of scenarios considered.

Table 20: Scenarios for improved malaria case management.

Scenario	Modified Parameters
Baseline	
100% diagnostic availability	Probability that a diagnostic is available = 1
100% diagnostic use	Probability that a diagnostic is used = 1
100% ACT stock	Probability that all (public) or any (private) doses of ACT are available = 1
100% compliance with test results (i.e. treatment of test-positive only)	Probability that ACT is received if test positive = 1 Probability that ACT is received if test negative =0
Perfect diagnostic	Diagnostic sensitivity = 1 Diagnostic specificity = 1
100% diagnostic availability & use	Probability that a diagnostic is available = 1 Probability that a diagnostic is used = 1
100% diagnostic availability & ACT stock	Probability that a diagnostic is available = 1 Probability that all doses of ACT are available = 1
100% diagnostic use and compliance with results	Probability that a diagnostic is used = 1 Probability that ACT is received if test positive = 1 Probability that ACT is received if test negative =0
100% diagnostic availability, use & compliance	Probability that a diagnostic is available = 1 Probability that a diagnostic is used = 1 Probability that ACT is received if test positive = 1 Probability that ACT is received if test negative =0
100% diagnostic availability, use & compliance & ACT stock	Probability that a diagnostic is available = 1 Probability that a diagnostic is used = 1 Probability that all doses of ACT are available = 1 Probability that ACT is received if test positive = 1

	Probability that ACT is received if test negative =0
100% perfect diagnostic availability, use & compliance & ACT stock	Probability that a diagnostic is available = 1 Probability that a diagnostic is used = 1 Diagnostic sensitivity and specificity= 1 Probability that all doses of ACT are available = 1 Probability that ACT is received if test positive = 1 Probability that ACT is received if test negative =0
Presumptive treatment	Probability that a diagnostic used = 0 Probability that QAACT is received if untested = 1

4.2.5 Tanzania: case study

I performed the same scenarios using only data from Tanzania as a case-study, in order to compare modelled outcomes using published data from before and after the early stages of the rollout of the new WHO guidance in the public sector. I also compared outcomes in the private sector using data published prior to and following the initial implementation of the AMFm pilot in Tanzania. Due to a paucity of published information, the values from all sub-Saharan Africa studies were used for the probability of seeking treatment at a public sector clinic. In addition, in both the Tanzanian case-studies (public and private sectors), the probability of at least one dose of ACT being in stock was used rather than the probability of all doses of ACT being in stock due to limited data on the latter. Tables 18 and 19 summarise the model parameters for the Tanzanian case-study in each sector.

4.3 RESULTS: PUBLIC SECTOR HEALTH FACILITIES

4.3.1 Comparison of systems effectiveness and decision tree approaches: public sector

Figure 34 shows the outcomes from the systems effectiveness model for public sector facilities. The grey bars show the probabilities for each step for malaria case management whilst the orange line and values show the cumulative probability along this pathway. Data here is taken from studies published across sub-Saharan Africa prior to the rollout of the WHO guidelines on universal rational management.

Using the baseline parameters in the systems effectiveness model, I estimate that 4.7% (95% uncertainty interval [UI]: 2.1 – 8.8%) of all malaria cases present in the population, and 14.7% (95% UI: 6.9 – 25.6%) of those malaria cases that actually attend the health facility, will be treated correctly.

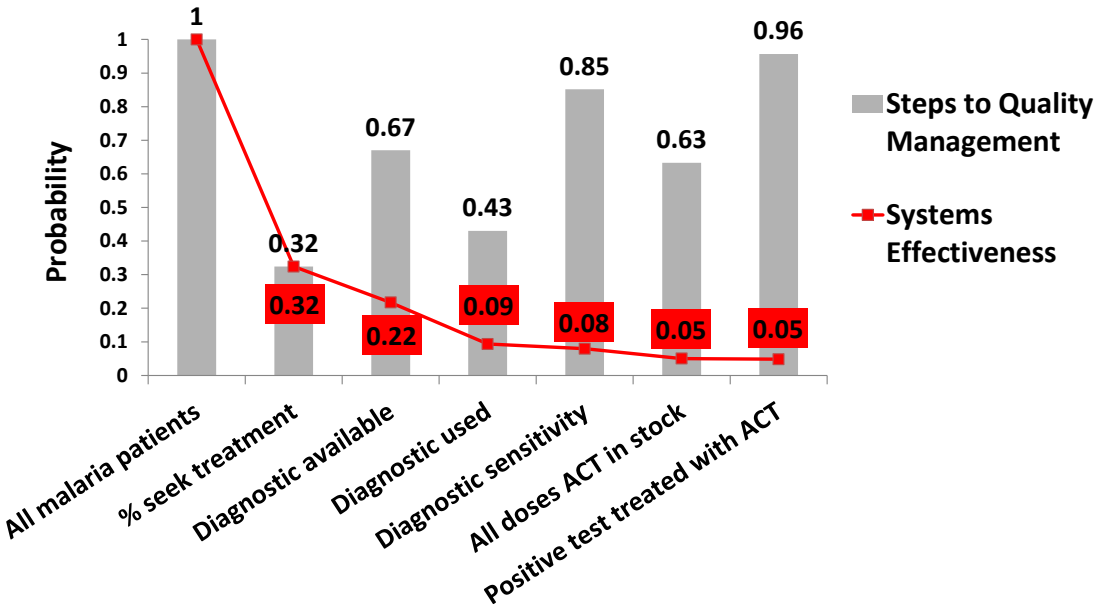


Figure 34: Estimated proportion of malaria cases at each case management point in the systems effectiveness pathway in public sector health facilities

The grey bars show the probabilities for each step for malaria case management whilst the red line and values show the cumulative probability along this pathway.

In contrast, using the decision tree model, which allows for the correct outcome being possible despite imperfect case management (e.g. a case may receive an ACT despite not being tested) I estimate that 54% (95% UI: 48.9 – 59.3%) of all febrile attendees in the public sector will be correctly managed. The decision tree calculates that 49% of malaria cases attending a public facility would

receive first line ACTs (95% UI: 40.6 – 59.2%). This is similar to the WHO estimate of malaria cases being treated with ACTs at health facilities (WHO, 2012c, WHO, 2013) and hence appears to represent a rational model for case management evaluation. I also estimate using this approach that 44% (95% UI: 35 – 54.8%) of NMFI cases attending the clinic would unnecessarily receive an ACT.

4.3.2 Case-management interventions: public sector

Modelling 100% attendance at the facility resulted in 49.6% all malaria cases in the population (95% UI: 40.9 – 58.6%) receiving an ACT compared with 16.2% (95% UI: 11.8 – 20.8%) at baseline. Increased treatment-seeking was the most effective single step in increasing the proportion of all febrile cases in the population that would be correctly managed and all malaria cases receiving an ACT. However this has little effect in improving case management of those patients attending the clinic.

Perfecting a single step in the care pathway almost always resulted in an overall predicted increase in the proportion of fever cases attending clinic that are correctly treated. The one exception was a scenario of improving ACT stock alone (i.e. 100% availability), under which our model predicted a 13% point reduction (95% UI: 5.0 – 21.6%) in correct management of all febrile cases. This is explained by a breakdown of correct overall "fever" management into the proportion of malaria cases receiving an ACT and the risk of NMFI being over-treated with an ACT as shown in Figure 35.

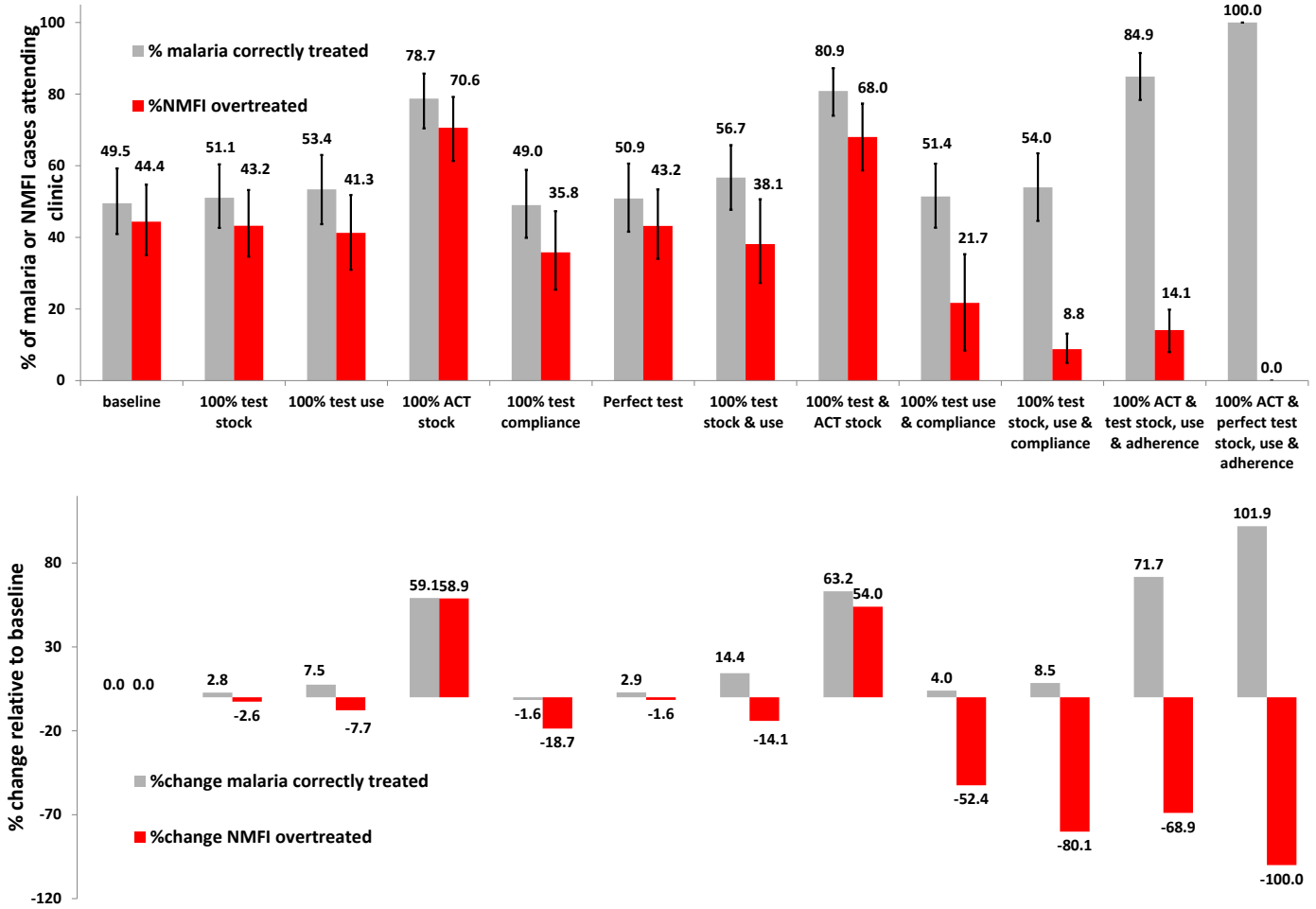


Figure 35: Results from the decision tree model for cases attending the public sector health facility in idealised case management scenarios

Figure 35A) depicts the percentage of malaria cases correctly treated with an ACT (grey bars) and percentage of NMFI overtreated with an ACT (red bars) in a variety of scenarios as defined in Table 20. Figure 35B) shows the percentage point change relative to baseline of malaria cases correctly treated with an ACT (grey bars) and NMFI overtreated with an ACT (red bars) in each of the scenarios depicted in Figure 35A).

Provision of 100% stock of ACTs predicted a 28.9% point (95% UI: 20.5 – 36.1%) increase in the proportion of malaria cases given an ACT, i.e. 59% increase relative to baseline. However, this was also accompanied by a 26% point (95% UI: 17.0 – 34.7%) anticipated increase in the overtreatment of NMFI, potentially resulting in 70% NMFI cases (95% UI: 56.4 – 79.2%) receiving an ACT. Thus the modelled decrease in correct management of all febrile cases in a scenario of 100% ACT stock is due to a larger proportion of NMFI cases predicted to receive ACTs since there is no limitation by drug stock.

Single interventions aimed at increasing availability or use of diagnostic tools, were forecast to have little effect on improving the management of malaria cases or reducing NMFI overtreatment. Modelling perfect compliance with diagnostic results without any increase in diagnostic stock or use (i.e. positive tests treated with ACTs and negative tests not treated with ACTs) led to little change in the proportion of malaria cases receiving an ACT but anticipated an 8.9% point reduction (95% UI: 2.6 – 19%) in NMFI overtreatment with ACTs (18% relative reduction). Improved diagnostic quality, (100% sensitivity and specificity) also led to small predicted improvements in malaria treatment and a decrease in NMFI overtreatment even when all other conditions were maintained at baseline.

Combinations of improvements to diagnostics deployment however did show an effect on NMFI management results. For example, increasing the availability and use of diagnostics reduced overtreatment of NMFI with ACTs to 38% (95% UI: 27.3 – 50.7%), i.e. a 14% point reduction from baseline. This scenario also improved overall management of malaria cases, with 57% (95% UI: 47.7 – 65.8%) of malaria cases receiving ACTs, i.e. a 7% point increase (95% UI: -1.4 – 16.8%).

4.3.3 Tanzania case study: WHO guidelines on diagnostic led management in public sector

Using Tanzania as a case-study, I compared predicted case management outcomes using papers published before and after the 2010 WHO guidelines. The Tanzanian HIV/AIDS and Malaria Indicator Study (THMIS) reported that malaria prevalence amongst U5s had dropped from 18% in 2007/8 (TACAIDS et al., 2008) to 9% in 2011/12 (TACAIDS et al., 2013). The data collected from studies published in the year following the guidelines rollout are summarised in Table 18, and indicate stock levels of any dose of ACTs had increased (from 59% to 85%) as well as availability of any diagnostic tools (from 35% to 61%). At this stage, levels of diagnostic usage were not seen to have substantially increased (69% compared to 71%), although compliance to test results had improved (the probability of receiving an ACT with a negative test result reduced from 67% to 14%) and treatment of untested cases had also decreased (from 86% in untested febrile cases to 15%). Using these

parameters in the decision-tree, Figure 36 depicts the predicted change in the overall proportion of all fever cases correctly treated, the proportion of malaria cases correctly treated and the proportion of NMFI over-treated in Tanzania.

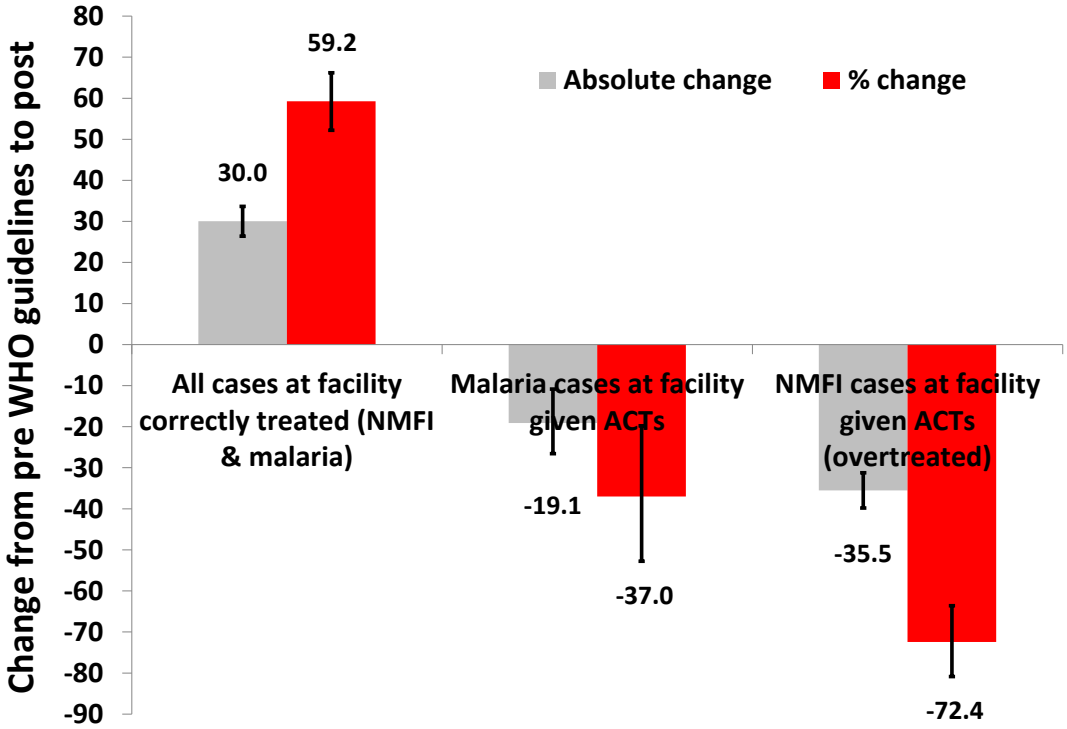


Figure 36: Change in case management outcomes at public sector health facilities after early rollout of WHO 2010 guidelines in Tanzania.

The absolute percentage point change is shown by the grey bar, and percentage change relative to the baseline scenario is depicted in red.

I estimate that a 30% point increase (95% UI: 26.5 – 33.6%) in the proportion of all attending febrile cases correctly treated would have occurred in the early stages of the implementation of the guidelines, i.e. 59% increase relative to pre-WHO guidance baseline. Contributing to this overall predicted improvement is a 35% point reduction (95% UI: 31.2 – 39.8%) in the proportion of NMFI treated inappropriately with ACTs, resulting in only 13% of NMFI patients being over-treated following the guidance rollout.

However I also predict a 19% reduction (95% UI: 11 to 27.2%) in the proportion of malaria cases receiving an ACT if they attend a clinic may have ensued following rollout of the new WHO guidelines, i.e. only 37.5% of attending malaria cases are given ACTs. Overall the percentage of all malaria cases in the community treated with ACTs is modelled to have reduced from 16.8% to 10.6%.

Thus despite improved access to diagnostics, improved ACT stock and compliance to test results (but no increase in the overall proportion tested), my results suggest a reduction in the proportion of malaria cases given ACT. This does not mean that these malaria cases were not treated at all since I have not included other antimalarials aside from ACTs in this analysis.

Exploration of the different pathways by which a malaria case may receive ACTs reveals a greater than twofold increase in the modelled probability of a malaria case being tested and receiving treatment on the basis of a positive test result (9.4% vs. 24%), i.e. rational diagnostic-led treatment. However there is greater than fourfold reduction in the predicted probability of malaria cases receiving ACTs through other pathways (42.5% vs. 8.9%), i.e. opportunistic treatment in those untested or in those who falsely test negative and are hence untreated. Similar outputs are seen when comparing the combined dataset from all countries.

4.3.4 Estimating Treatment gap and Treatment excess: public sector

Figure 37 depicts the percentage treatment gap and percentage overtreatment (treatment excess) of all febrile patients attending public health facilities using Tanzania as a case study, in the scenarios defined in Table 20. Desirable outcomes, namely malaria cases receiving ACTs and NMFI cases not being treated with ACTs are depicted in green. The malaria treatment gap i.e. cases that need ACTs but that do not receive ACTs are depicted in yellow. The percentage treatment excess i.e. cases that do not need antimalarials but are given ACTs unnecessarily are depicted in red.

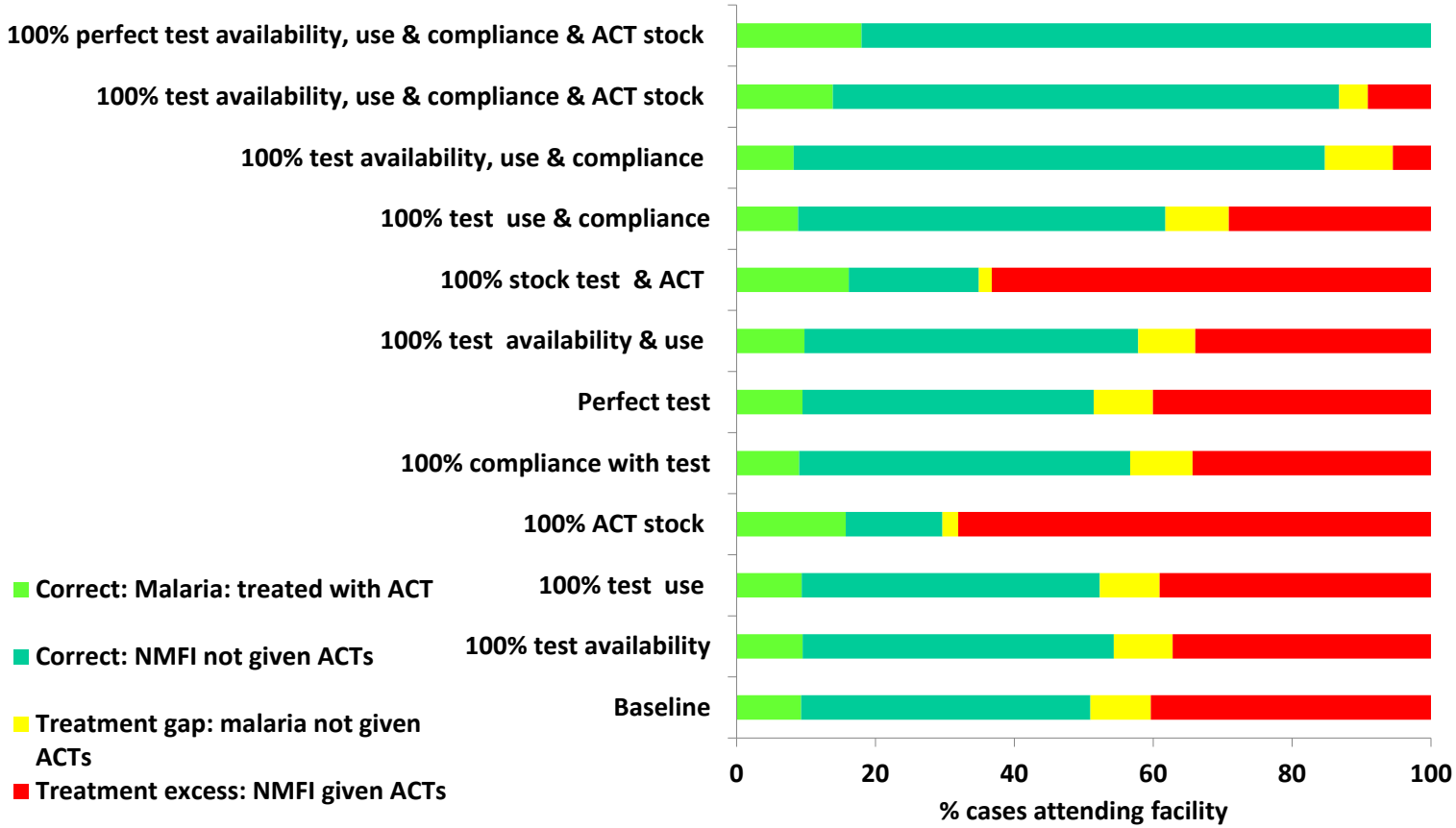


Figure 37: The percentage treatment gap and percentage overtreatment (treatment excess) of all febrile patients attending public sector health facilities in Tanzania, in the scenarios defined in Table 20.

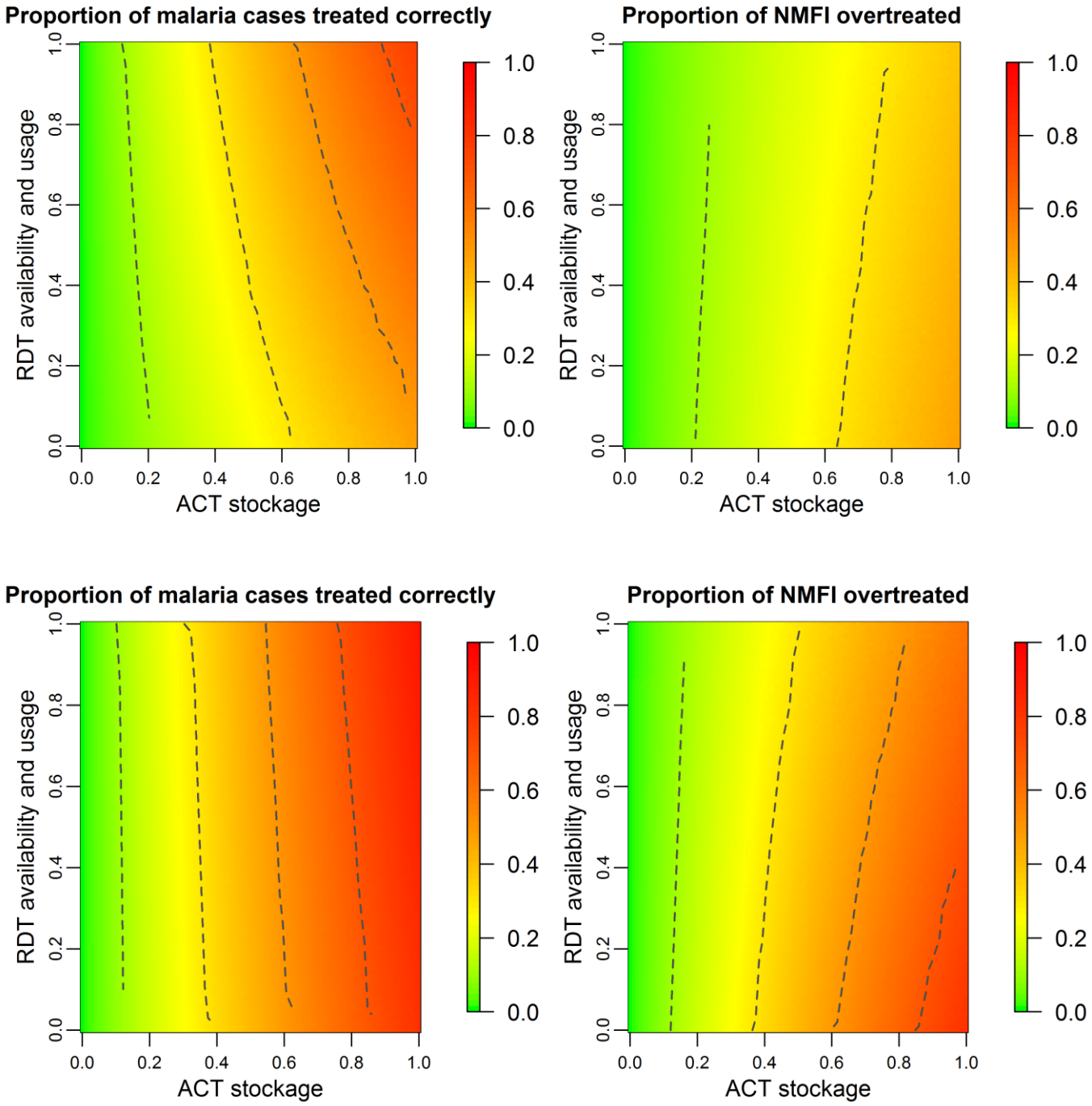
At baseline there is a high degree of NMFI overtreatment, with less than a quarter of patients that receive ACTs actually needing antimalarials, whilst there is a substantial treatment gap (i.e. malaria cases not given ACTs) with only half of patients needing antimalarial treatment forecast to actually receive ACTs. Overtreatment can be reduced by improving compliance with diagnostic results, as well as diagnostic availability; although a treatment gap may remain. In contrast high levels of ACT stock alongside high availability, use and compliance to diagnostic tests reduce the treatment gap, i.e. increase the likelihood that those in need of treatment receive ACTs. However, this may also increase over treatment (i.e. NMFI given ACTs unnecessarily). If additionally the performance of the diagnostic test is improved (i.e. assume 100% specificity and sensitivity), there is perfect case management, i.e. no further treatment gap or treatment excess.

Figure 37 illustrates the potential trade-off between increasing diagnostic use and compliance versus increasing ACT stock with respect to reducing the treatment gap and limiting treatment excess at medium-high transmission settings. Figure 38 shows the balance of promoting ACT stocks against increasing diagnostic availability and use. In this case currently reported levels of compliance to test results are kept unchanged. At medium-high transmission, improving malaria treatment is achievable with increased ACT stock, but will require high levels of diagnostic availability and usage to prevent high levels of NMFI overtreatment. Importantly, high levels of diagnostic usage allow improved malaria treatment at lower levels of ACT stock than if diagnostic use had been low.

At low transmission, data is scarce but my modelling suggests that given current assumptions of compliance to diagnostics, there is little relationship between diagnostic availability and appropriate treatment and thus reducing NMFI overtreatment is more challenging than improving levels of malaria treatment.

Figure 38: Density plot: balance of diagnostic availability and use versus ACT stock for malaria and NMFI at public sector health facilities - 38A) Medium-high prevalence malaria; 38B)

Low prevalence malaria. The colour density map depicts the percentage of malaria correctly treated and the percentage of NMFI overtreated at a) medium – high transmission scenario using values obtained from all studies published after the rollout of the WHO guidance and b) low transmission scenario using values obtained from studies published from all countries (including studies from countries outside Africa). The colour scale depicts desirable outcomes as green, i.e. high levels of malaria treatment and low levels of NMFI overtreatment, whilst undesirable outcomes are red, namely low malaria treatment and high NMFI overtreatment. Contour lines indicate similar colour densities



4.4 RESULTS: PRIVATE SECTOR OUTLETS AND DRUG SHOPS

4.4.1 Comparison of systems effectiveness and decision-tree approaches

Figure 39 shows the outcomes from the systems effectiveness model for the private sector, namely drug and general shops. In this analysis and all further results for the private sector model, I have used the stock and use of QAACTs rather than all ACTs despite the restrictively low estimates since this is the aim of AMFm. Data here is taken from studies published across sub-Saharan Africa prior to the piloting of AMFm and other drug subsidy schemes.

Using the baseline parameters in the systems effectiveness approach, I estimate that only 0.00008% (95% uncertainty interval [UI]: 0.00003-0.0028%) of all malaria cases in the population, and 0.002% (95% UI: 0.0001 – 0.01%) of those malaria cases that attend a drug or general shop will be treated correctly with a QAACT. If we consider all ACTs (i.e. not just QAACTs), then this approach estimates that 0.01% of all malaria cases in the population and 0.02% of malaria cases that attend a shop would be treated with any ACT.

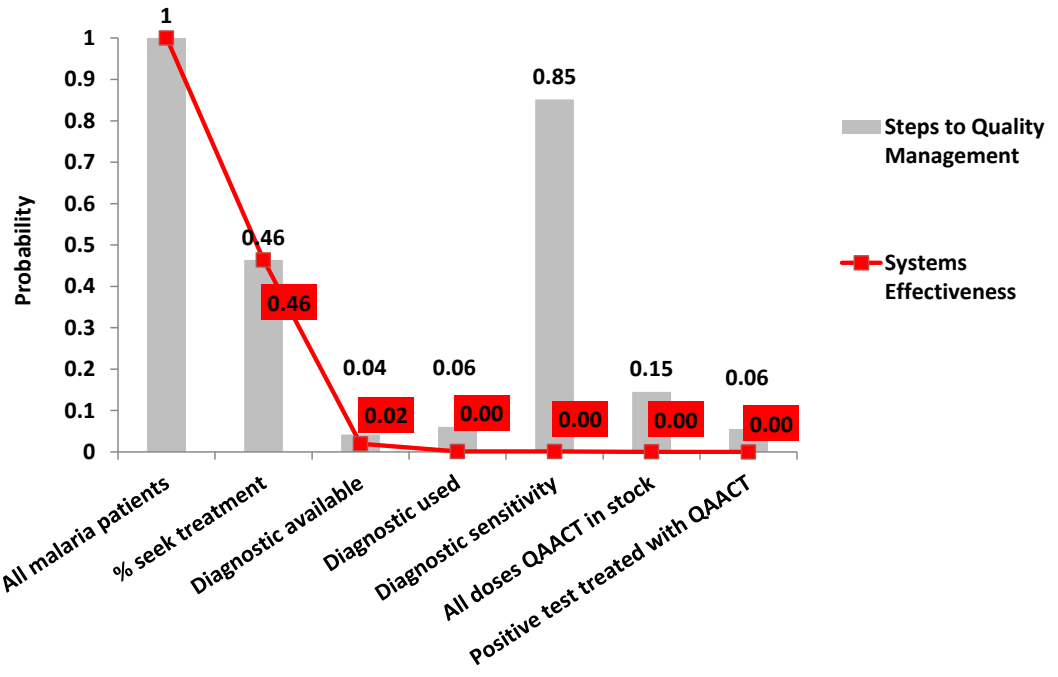


Figure 39: Estimated proportion of malaria cases at each case management point in the systems effectiveness pathway at private sector outlets (drug and general shops).

The grey bars show the probabilities for each step for malaria case management whilst the red line and values show the cumulative probability along this pathway.

In contrast, using the decision tree model, which allows for the correct outcome being possible despite imperfect case management (e.g. a malaria case may receive a QAACT despite not being

tested, and NMFI cases may not receive a QAACT), I estimate that 70.53% (95% UI: 67.3 – 86%) of any febrile cases that visit drug or general shops will be correctly managed, but that only 0.44 % of malaria cases that attend these shops would receive QAACTs (95% UI: 0.13 – 0.89%). This corresponds to just 0.2% (95% UI: 0.05 – 0.89%) of all malaria cases in the community receiving QAACTs. I also estimate that 0.44% (95% UI: 0.14 – 0.87%) of NMFI cases attending a private outlet would unnecessarily receive a QAACT. The low numbers of NMFI patients that receive QAACTs therefore contribute to the high proportion of patients being treated "correctly". These low estimates are driven by the paucity of QAACTs at baseline (i.e. pre-AMFm) in the drug shops, but may also be due to provider or purchaser preference. If we consider the use of all ACTs, I estimate that 4.75% of malaria cases that attend a shop would be treated with an ACT (95%UI: 1.26-10.47%).

It is important to note that NMFI patients may purchase other non-QAACT antimalarials and that this is not included in my analysis

4.4.2 Case management interventions: private sector

As in the public sector, increased treatment-seeking was the most effective single step in increasing the proportion of all febrile cases in the community that would be correctly managed. However unlike the public sector analysis, improving attendance was not the most effective single step to improving all malaria cases in the population receiving a QAACT. Modelling 100% attendance at the facility resulted in 0.44% all malaria cases in the community (95% UI: 0.13 – 0.9%) receiving a QAACT, i.e. double the estimate at baseline. As in the public sector, the model is structured so that that attendance does not impact upon improving case management of those patients attending a drug or general shop.

Perfecting a single step in the care pathway had little effect on the proportion of fever cases attending a drug shop that are correctly treated. The breakdown of correct fever management into the proportion of malaria cases receiving a QAACT and the risk of NMFI being over-treated with a QAACT is shown in Figure 40.

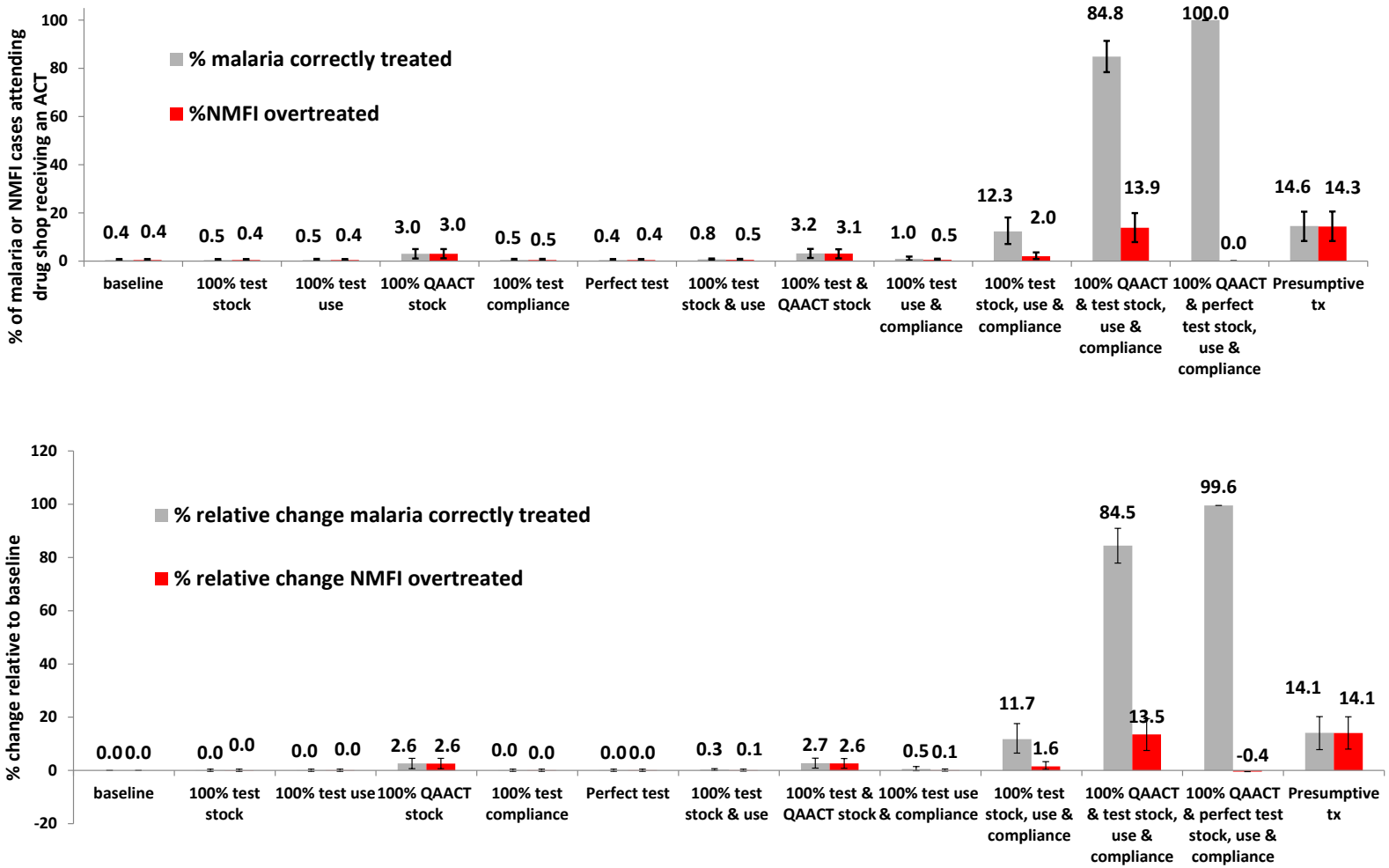


Figure 40: Results from the decision tree model for cases attending drug or general shops (private drug outlets) in idealised case management scenarios

Figure 40A) depicts the percentage of malaria cases correctly treated with a QAACT (grey bars) and percentage of NMFI overtreated with a QAACT (red bars) in a variety of scenarios as defined in Table 20. Figure 40B) shows the percentage point change from baseline of malaria cases correctly treated with a QAACT (grey bars) and change from baseline of NMFI overtreated with a QAACT (red bars) in each of the scenarios depicted in Figure 40A.

Despite the low baseline levels of correct malaria treatment with QAACTs, no single step intervention was predicted to significantly improve this outcome. Provision of 100% stock of QAACTs led to a 2.6% (95% UI: 0.66 – 4.57%) increase in the proportion of malaria cases attending a private drug shop given an ACT. However, this was also mirrored by a 2.6% point (95% UI: 0.66 – 4.56%) increase in the overtreatment of NMFI, i.e. 3% NMFI cases (95% UI: 1.13 – 5.02%) receiving a QAACT. Even with such a small increase, provision of 100% QAACT stock was still the most effective single step to improving all malaria cases in the community receiving a QAACT, from 0.2% at baseline (95%UI: 0.05-0.48) to 3.04% (95%UI: 1.1 – 5.02).

Single interventions aimed at increasing availability or use of diagnostic tools did not have significant effects on improving the management of malaria cases or reducing NMFI overtreatment in private outlets. Combinations of improvements to diagnostics deployment have the potential to show a greater effect. Perfect availability, use of, and compliance with diagnostics may increase the proportion of attending malaria cases treated with QAACTs up to 12.32% (95% UI: 7.1 – 18.1%), whilst only increasing NMFI overtreatment to 2% (95% UI: 0.87 - 3.6%). Adding 100% QAACT stock alongside 100% availability, use and compliance with diagnostic tools, increases the percentage of malaria cases receiving QAACT to 84.8% (95% UI: 78.4 – 91.4%). A scenario of presumptive treatment, i.e. no use of diagnostic testing and treatment of all untested febrile patients with QAACTs, predicted 14.6% of malaria cases at the shop would receive QAACTs (95% UI: 8.34 – 20.5%). However this would be accompanied by 14.3% (95% UI: 8.3 – 20.6%) of patients with an NMFI also being needlessly treated with QAACTs.

The poor results for baseline quality of care at private outlets or the improvement brought about by single step interventions is minimal because the baseline parameter values for the components of case management are low. Combinations of interventions, for example perfect QAACT stock, as well as use and compliance with diagnostics may give improvements in the proportion of malaria cases modelled to receive ACTs. However if even one of the component interventions is reduced back to baseline, then the results fall back to low levels.

4.4.3 Tanzania case study: AMFm and drug subsidies in the private sector

Using Tanzania as a case-study, I compared predicted case management outcomes using data before and from the initial stages of the AMFm drug subsidy scheme. Data collected from the IMPACT 2 study and other studies published in the year following the drug subsidy programme are summarised in Table 19, and indicate stock levels of any dose of QAACTs had increased (from 7% to 50%) although the availability of any diagnostic tool did not mirror this (increase from 1% to 5%). Estimates of diagnostic usage barely changed (2% compared to 1%). Although compliance to positive test results had improved (the probability of

receiving a QAACT with a positive test result increased from 2% to 40%), the treatment of negative tests and untested cases had also increased (proportion of negative tests given QAACTs rose from 1% to 10%, and untested febrile cases from 1% to 27%). Using these parameters in the decision-tree model, Figure 40 depicts the predicted change in the proportion of all fever cases correctly treated, the proportion of malaria cases correctly treated with QAACTs and the proportion of NMFI overtreated with QAACTs.

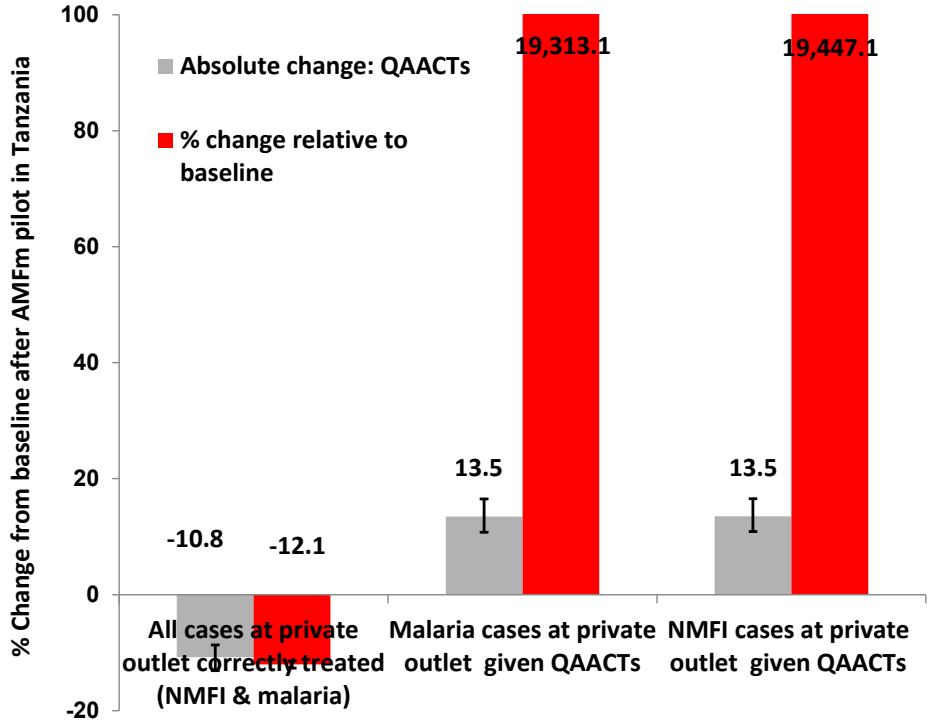


Figure 41: Change in case management outcomes after the AMFm drug subsidy pilot scheme in Tanzania.

The absolute percentage change following the introduction of the drug subsidies and the AMFm pilot in Tanzania is shown by the grey bar, and the percentage change relative to the baseline (before drug subsidies) is depicted in red in 1) estimated proportion of attending cases correctly treated (both malaria and NMFI); 2) proportion of malaria cases correctly treated with QAACTs and 3) proportion of NMFI cases given a QAACT.

Using this model, I estimate that a 10.8 % decrease (95% UI: 8.7 - 13.1%) in the proportion of all attending fever cases correctly treated may have occurred following the AMFm pilot. Contributing to this overall predicted change is a 13.5% increase (95% UI: 20.9 – 16.5%) in the proportion of NMFI treated inappropriately with QAACTs; resulting in 13.5% of NMFI patients potentially being overtreated following the drug subsidy rollout. The percentage of malaria cases treated with a QAACT rises from 0.07% at baseline to 13.6% (95% UI: 10.8 – 16.6%) following the rollout of AMFm in Tanzania at private sector outlets.

Overall, on the basis of published drug and general shop data in Tanzania and from the IMPACT 2 household and outlet surveys, the percentage of all malaria cases in the community treated with QAACTs is modelled to have increased from 0.03% to 6.8%. Similar outputs are seen when comparing the combined dataset from all countries.

4.4.4 Treatment gap and treatment excess: Private sector

In Figure 42, desirable outcomes, namely malaria cases receiving QAACTs and NMFI cases not being treated with QAACTs are depicted in green. The treatment gap i.e. cases that need QAACTs but that do not receive QAACTs are depicted in purple. The treatment excess i.e. cases that do not need antimalarials but are given QAACTs unnecessarily are depicted in red.

At baseline I predict that there is a large treatment gap (purple), with the great majority of those assumed to need QAACTs failing to receive them, whilst in contrast there is only a low level of treatment excess (i.e. NMFI cases unnecessarily given QAACTs). The treatment gap in the private sector can be reduced by high levels of diagnostic availability and use coupled with improved compliance with test results. This is further increased with 100% probability of QAACTs being in stock. However this may elevate levels of treatment excess. The figure suggests that improving levels of malaria treatment with QAACTs, i.e. narrowing the treatment gap in the private sector, would require strengthening all components of the case management chain simultaneously, rather than just one or two areas of focus as per the AMFm strategy. A policy of presumptive treatment, previously advocated in high transmission settings, may serve to increase NMFI overtreatment much more than reducing the treatment gap for malaria cases

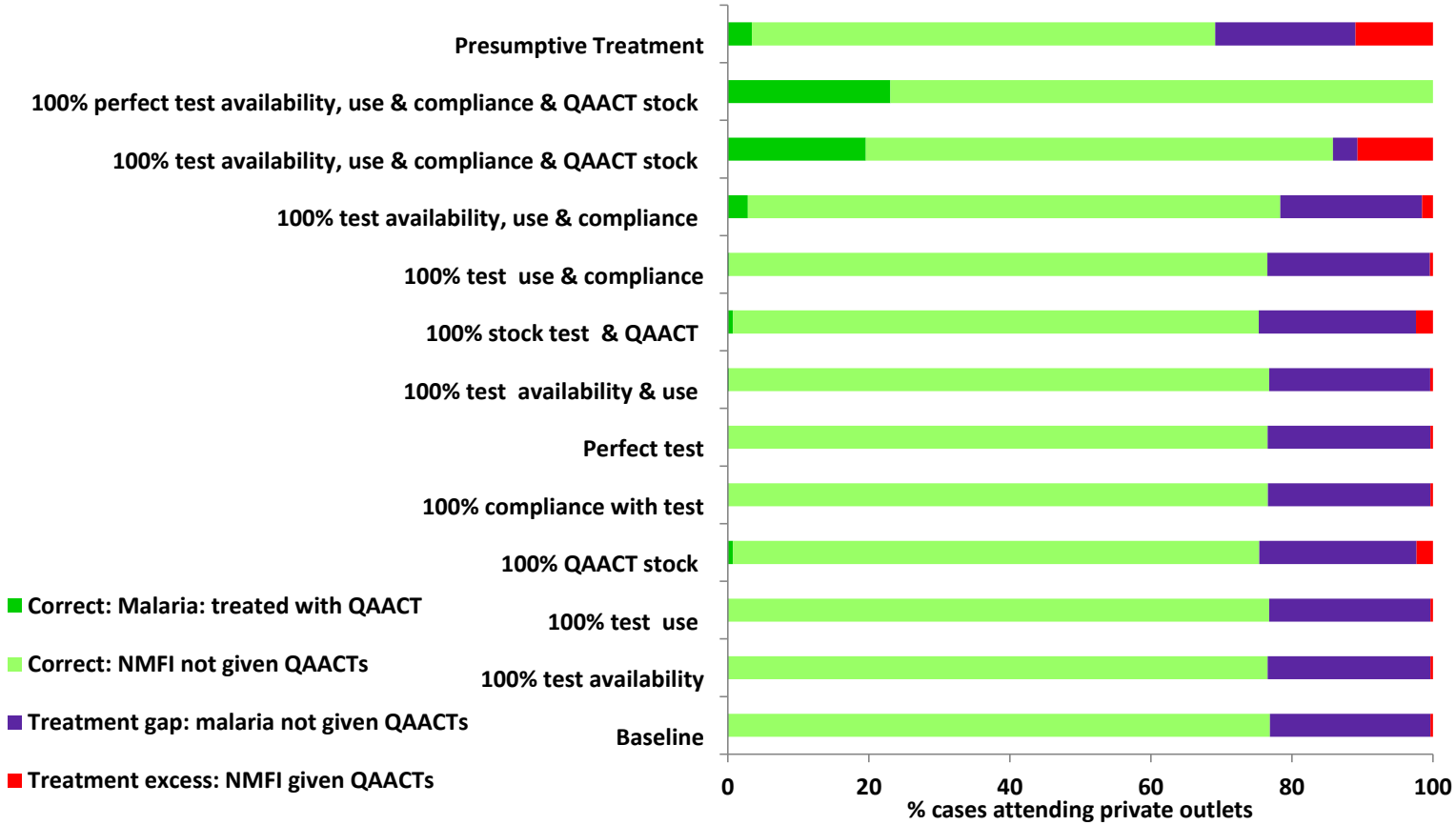


Figure 42: The percentage treatment gap and percentage overtreatment (treatment excess) of all febrile patients attending drug or general shops using aggregated sub-Saharan data as baseline, in the scenarios defined in Table 20.

4.5 DISCUSSION

This simple decision-tree model can provide insight into the aspects of delivering care most likely to impact on care quality and programme efficiency, and can quantify the intuitive qualitative effects of refining different steps of the care pathway in order to help to inform decisions and guide investments in improving fever management.

Both models suggest that improving timely attendance whether at a health facility or at a drug shop, would be the most important single intervention to increase the overall percentage of all febrile cases managed correctly, and improving attendance at the health facility would also increase the proportion of all malaria cases in the community treated with ACTs.

Considering only those who attend a primary health facility, increased ACT stock level was the most critical intervention in potentially improving in the proportion of febrile malaria cases receiving treatment with ACTs. In contrast, the greatest predicted reduction in NMFI cases being overtreated at a primary care clinic following a single health system intervention was due to improved compliance with diagnostic results. However this was also associated with a reduction in the proportion of malaria cases receiving ACTs. Multi-pronged intervention strategies were most effective in balancing possible improvements in malaria treatment with the risks of NMFI overtreatment. Substantial improvements in malaria case treatment were not predicted without increasing ACT stock levels. Modelling interventions targeted at diagnostic tool availability, use and compliance improved NMFI management rather than significantly impacting on malaria treatment.

The results of the private sector model indicate that at baseline there are very low levels of malaria cases receiving QAACTs (drug subsidy schemes had barely started) but also negligible amounts of overtreatment of NMFI with first-line QAACTs, although other antimalarials may be prescribed. If the use of any ACT (i.e. QAACTs and non-assured ACTs) are considered in the analysis then estimates of the probability of receiving appropriate treatment are naturally higher. Single interventions, whether diagnostic-related or QAACT stock, appeared to not result in any significant improvements in case management, due to the low baseline parameter estimates for the private sector. Emphasis on diagnostic tool availability, use and compliance did not produce reductions in the malaria treatment gap. Modelling solely improved levels of QAACT stock was not as effective in the private sector as in the public sector with respect to expanding the proportion of malaria cases receiving first-line treatment. This is due to the baseline parameter indicating low provider preference in prescribing QAACTs even when present at drug shops. However it is unclear whether the basis of this in the literature is actually prescriber preference, or may also be due to the preference of particular patients that attend private outlets. I have not included the role of patients in deciding which antimalarial they request, whether due to price or familiarity, nor accounted for the perverse incentive for retailers to

satisfy their customer's requests, e.g. selling antimalarials whether a patient needs them or not irrespective of a diagnostic result (Chandler et al., 2011).

A combination of diagnostic and QAACT stock interventions are predicted to narrow the treatment gap in the private sector. However my assumptions regarding test performance, i.e. using sensitivity and specificity estimates for RDTs for all diagnostic tests, mean that the NMFI treatment excess is also increased. The model suggests that whilst improving case management in the private sector is possible, significant investments across the entire treatment-pathway would be needed, rather than individual interventions.

The Tanzanian public sector case study explored the impact of the recent WHO guidance advocating diagnostic-led therapy for malaria. Despite published reports of improved access to diagnostics and compliance with their results, as well as expanded ACT stocks, the model predicted the proportion of malaria cases treated with ACTs to have reduced following rollout of new WHO guidelines. The levels of NMFI overtreatment are predicted to have decreased. This is due to a large modelled reduction in the numbers of malaria cases that previously were untested yet still received ACTs (i.e. presumptive treatment) and in those who test falsely negative and hence are not given ACTs. The model did not differentiate between the likelihood in receiving ACTs if untested due to healthcare/provider choice or lack of diagnostic availability. However, this result highlights the need for improved quality of testing, and also proper communication of the new WHO guidance to healthcare workers to prevent any malaria under-treatment if diagnostics are unavailable. My analysis did not include patients receiving antimalarials other than ACTs.

In contrast, the Tanzanian private sector case study considered the potential impact of the AMFm pilot. Early reports confirm that the programme had met its target of increasing coverage of QAACTs with an increased proportion of outlets stocking the first-line antimalarials (AMFm Independent Evaluation Team, 2012, Littrell et al., 2011a, Tougher et al., 2012). However, there are limited data to suggest that any training as part of the AMFm scheme has also led to an increase in use of diagnostic tools, although this was not a stated target of the programme (AMFm Independent Evaluation Team, 2012). The modelled results suggest that the scheme may have successfully expanded the use of QAACTs to treat malaria in the Tanzanian private sector from 0.41% to 18.2% (Figure 9); however this still represents less than 20% of malaria cases that attend drug shops and hence a large treatment gap remains. I have not included other ACTs or antimalarials in this analysis as the objective was to consider the consequences of the AMFm drug subsidy scheme on treatment delivery. Levels of any ACT distribution are likely to be higher, and I will use this more inclusive measure (i.e. QAACTs and non-assured ACTs) when exploring transmission and clinical impact in Chapter 5. Non-ACTs are not included as they are not the recommended first line therapy.

Health system interventions for case management of malaria must be guided by whether the priority is improvement in malaria cases receiving ACTs, i.e. reducing the treatment gap, reducing ACT waste through

unnecessary treatment of NMFI, i.e. treatment excess, increasing appropriate treatment of all febrile illness or expanding the most cost-effective solution for that particular epidemiological environment.

The decision tree results shown here suggest that the recent emphasis on rollout of RDTs and the WHO guidance may be effective in reducing ACT waste, but also highlight the need to focus on stock-management and improving HCW training in diagnostics to improve the quality of care dispensed to malaria cases. These priorities and the most cost-effective way to manage fevers may vary by transmission setting. Lubell *et al.* used a decision-tree cost modelling approach to demonstrate that use of diagnostics at moderate and low levels of transmission was more cost-beneficial than presumptive treatment (providing compliance to test results was high), but that this was less clear in high transmission settings (Lubell et al., 2008). I found a paucity of data on case management indicators in low malaria prevalence settings, but our results mirror intuitive assumptions that the high levels of diagnostic use and compliance with results may have an important role to play in reducing levels of overtreatment with ACTs of NMFI cases especially when malaria cases are scarce.

In the private sector, this trade-off between treating malaria cases whilst avoiding overtreatment of those not infected with malaria, is highlighted by the model outputs in the presumptive treatment scenario. The results suggest malaria treatment gap would be reduced by a policy of treating all fevers with an ACT without testing at drug shops to such an extent that it could only be surpassed with high levels of diagnostic availability, use, and compliance along with QAACT stock. Although presumptive treatment would naturally increase NMFI unnecessary treatment, this may be acceptable in settings where this was not considered a priority.

A limitation of this decision-tree approach is the assumption that the parameters are independent of each other. For example it is recognised that improved drug stock levels can motivate treatment seeking (Alba et al., 2010a), or increased treatment seeking may increase HCW workload leading to reduced time for performing diagnostics and dispensing appropriate treatment. It would seem likely that the availability and use of diagnostics are related to each other, and stock levels of ACTs may also influence whether testing occurs, but there is little data to parameterise such an association. I did not include staff or shopkeeper training in this analysis at this stage, as there is much uncertainty about the impact of training on HCW performance especially in the public sector (Chandler et al., 2008a, Chandler et al., 2008b, Chandler et al., 2012). In addition I used the same probability of receiving ACTs when untested irrespective of the presence of diagnostics, which may not reflect reality and will need further study of HCW and provider behaviour. In the literature review in Chapter 2, I used aggregated data from several countries from across Africa (and outside Africa for a low prevalence scenario), but these are unlikely to be comparable between countries, given there was substantial variation in data collection methods, sample sizes and the nature of the data

collected. However data from Tanzania, used as a single country case study did give similar pattern of results for both the private and public sector models as the aggregated data. I chose only to include drug and general shop data in my private sector analysis but there is also significant variation in the standards of these across Africa. In addition there were extremely limited data on the performance of drug or general shop keeper behaviour with respect to compliance with test results, and so several parameters have been derived from estimates of drug use and market share. In the analysis of the impact of AMFm, much of the data used were from the official evaluation of the programme and some of this may also have been reproduced in country specific publications, which were counted separately. In addition there is very limited data on provider behaviour compliance to tests and anti-malarial preference. Despite these limitations, the results demonstrate the feasibility of such a decision-tree approach to quantify the effects of investing in changing health systems parameters, which could be made site-specific if such data were available.

Further work is required to explore the most cost-effective targets to expand the delivery of antimalarials and reduce ACT waste, given limited malaria control budgets and the potential rise of ACT resistance. The results concerning the potential impact of interventions in the private sector to improve overall care illustrate the need to understand the ability, cost and acceptability of such improvements across the chain of delivery in drug and general shops, especially in the context of the future of programmes such as AMFm. In addition, this approach could be extended to delivery through other sectors including community health care workers. I will consider whether improving access to and the performance of public and private health systems may allow reductions in malaria transmission intensity and disease mortality and morbidity in Chapter 5 by using these estimates, i.e. the probability of a malaria case receiving an ACT and the probability of an NMFI cases receiving an ACT in both the public and private sectors, within the models outlined in Chapter 3. As malaria transmission declines and appropriate treatment for NMFI becomes of increasing importance, it will become necessary to adopt a holistic approach to investing in improving fever management, improving our understanding of both malaria and NMFI, taking into consideration the particular characteristics of the health systems, including the contributions of public, private and community delivery.

5 THE IMPACT OF HEALTH SYSTEMS INTERVENTIONS ON TRANSMISSION AND CLINICAL OUTCOMES IN TANZANIA

5.1 INTRODUCTION

Over the past decade, global funding and commitment to malaria control have led to malaria mortality rates almost halving, especially in children under five, and a 30% drop in malaria infections overall (WHO, 2013) (O'Meara et al., 2010). Malaria modelling estimates up to 3.3 million malaria deaths may have been averted between 2001 and 2012, the majority of which are in areas of high burden (WHO, 2013). However in the 18 countries with the highest burden of disease, which account for 80% of malaria cases, surveillance data is still not sufficient to robustly assess trends. If transmission is not addressed in these high prevalence countries, it is unlikely that the global reductions in incidence and mortality will continue their trajectory to reach 2015 targets and may even reverse with declining funding levels (Feachem et al., 2010, WHO, 2013).

Model estimates suggest that the rate of decline in malaria mortality may have slowed more recently. This may in part be due to a levelling off in ITN coverage and IRS over the same period (2011-2012)(WHO, 2013) . Although delivery of ACTs increased from 11 million courses in 2005 to 331 million in 2012, and the numbers of procured rapid diagnostic tests (RDTs) have increased, many people with confirmed infections do not receive appropriate treatment with a quality assured antimalarials (AMFm Independent Evaluation Team, 2012, WHO, 2013), although estimating this proportion is challenging.

The World Malaria Report 2013 (WHO, 2013) acknowledges that predicting the percentage of patients with malaria that receive antimalarials is limited by the quality of surveillance data, but estimates that in 2012 this had risen to 60% across both private and public sectors. In a subset of 9 African countries surveyed, 68% of children under five that received an antimalarial were given an ACT, i.e. approximately 40% of under-fives with malaria attending healthcare receive an ACT, and other surveys suggest even lower estimates (WHO, 2013). As described in Chapters 2 and 4, this may be due to a sequence of health systems barriers, which vary by region both between countries and within.

Whilst national malaria control strategies must rely on international guidelines and policy, decisions as to what package of interventions are required need to be tailored to local vector patterns and epidemiology. Similarly, interventions to improve case management of malaria need to also be steered by the healthcare provision mix in the region and directed towards the local, national or international priority, whether limiting malaria transmission, preventing the development of parasite drug resistance, or reducing malaria related morbidity and mortality. The development and evaluation of such tailored malaria control strategies would require considerable input of evidence and resources. Randomised controlled trials of health systems

interventions or novel methods of intervention delivery would require impractical numbers of participants to achieve statistical significance. Mathematical modelling therefore offers the opportunity to estimate the potential impact of such policies at scale.

In this chapter I aim to demonstrate the need to adapt health systems improvements of ACT treatment programmes to local needs and epidemiology. To do this, I first use data collected by the IMPACT 2 study group at government health facilities and private drug shops in 3 regions of Tanzania (mainland) in 2010 and 2012 to estimate the probability of malaria and NMFI cases receiving an ACT in the private and public sectors employing the decision tree approach described in Chapter 4. I use these parameters in the model outlined in Chapter 3 to identify points in the implementation pathway in each region which have a critical impact on the effectiveness of ACTs in reducing transmission and preventing malaria mortality. I then consider the potential impact of single and combinations of health systems interventions to overcome the critical barriers for each region in order to develop strategies to improve malaria control.

5.2 COUNTRY CONTEXT: MAINLAND TANZANIA

Mainland Tanzania has a population of approximately 47.8 million, spread across 950 thousand square kilometres but predominantly living in the areas surrounding Dar-es-Salaam, Lake Victoria and in the Northern and Southern Highlands (WorldBank, 2013: accessed February 2014, NBS/ICF, 2011). Data were obtained from three regions, namely Lake (Mwanza), Southern Highlands (Mbeya) and Southern (Mtwara).

The Gross National Income per capita was $570 in 2012, and Tanzania ranks 177 out of 194 countries worldwide by per capita Gross Domestic Product (WorldBank, 2013: accessed February 2014). Life expectancy at birth is estimated at 58.9 years; with a median age of 17.5 years, and the mean years of schooling are 5.1. The economy is primarily agricultural and over 50% of the population lives on less than $2 a day (WorldBank, 2013: accessed February 2014).

1.1.1 Health Services

The WHO estimates that the government annual per capita expenditure on healthcare in 2011 was $42.4 (PPP: purchasing power parity), representing 11% of all government expenditure (WHO, 2012a). The annual per capita total expenditure on health was $107.4 (PPP), i.e. 60% of expenditure on health is private (WHO, 2011b). Healthcare provision is typically pyramidal, as depicted in Figure 43A, structured around primary care provision through health posts and health centres. These are often staffed by village health workers and clinical assistants especially in rural areas, with limited in-patient capacity (Kwesigabo et al., 2012). The WHO African Health Observatory estimated nurses and midwives comprise 27% of the health workforce (50% is the average for Africa) and trained doctors constitute 1.7% of the health workforce compared to 9.7% in the rest of Africa (WHO, 2010b). The chronic shortage of healthcare workers affects all levels of healthcare but particularly primary care (Figure 43B).

43A

43B

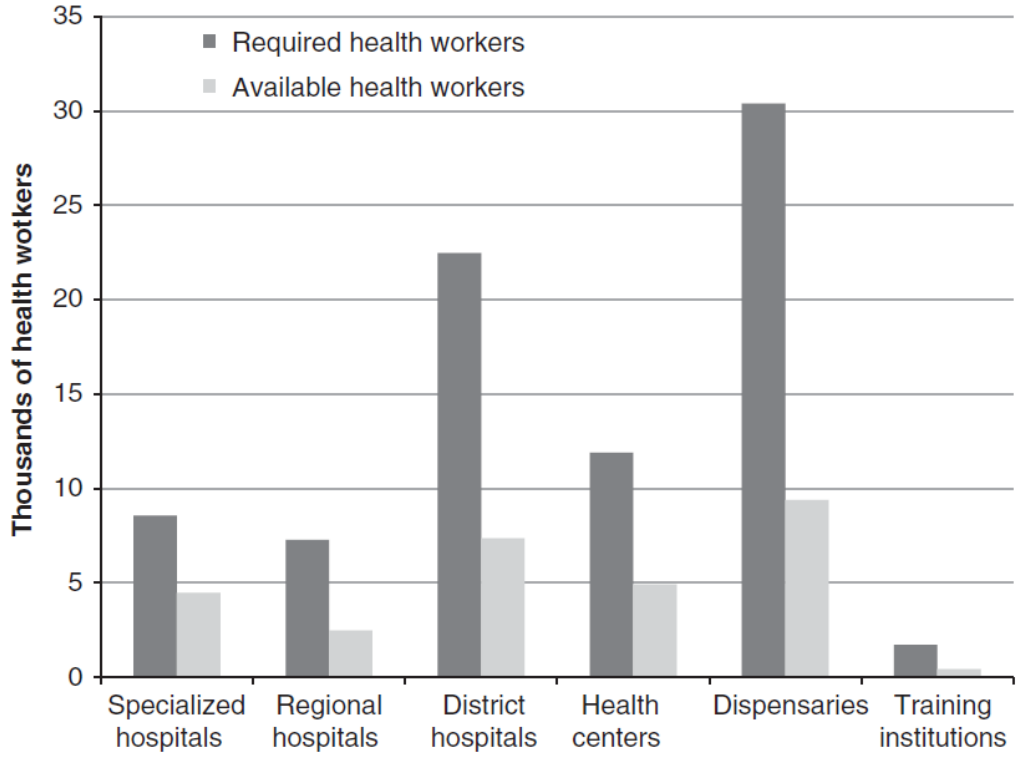


Figure 43 Health Services provision in Tanzania

43A) Hierarchy or health service provided in Mainland Tanzania B) Healthcare workers available and required in government facilities *(Kwesigabo et al., 2012)*

5.2.1 Malaria in Mainland Tanzania

Plasmodium *falciparum* accounts for almost 100% of malaria infections in mainland Tanzania, transmitted mainly by *Anopheles gambiae* and *Anopheles funestus* mosquitoes (WHO, 2013).

Transmission patterns vary with the geography of Tanzania (Hay et al., 2009). The Malaria Atlas Project estimates that 91% of the population lives in an area where malaria is endemic, and the risk of malaria transmission is stable (MAP (Malaria Access Project), acccessed February 2014). Areas of high altitude (greater than 2000m) such as Arusha and Kilimanjaro are at very low risk of malaria (Hay et al., 2009). High transmission intensity with seasonal variation occurs along coastal regions, near Lake Victoria and in the southern lowlands, which includes two of the sites used in the analysis: Mwanza (Lake Victoria) and Mtwara (Southern)(Hay et al., 2009). The 2011-2012 Tanzania HIV/AIDS and Malaria survey (THMIS) estimates an overall prevalence by RDT of 9% in children aged 6-59 months, varying from greater than 30% near Lake Victoria to less than 1% in the highlands (Figure 44) (TACAIDS et al., 2013), and represents a 50% reduction from an estimated 18% prevalence in children under 5 in the 2008 survey (TACAIDS et al., 2008).

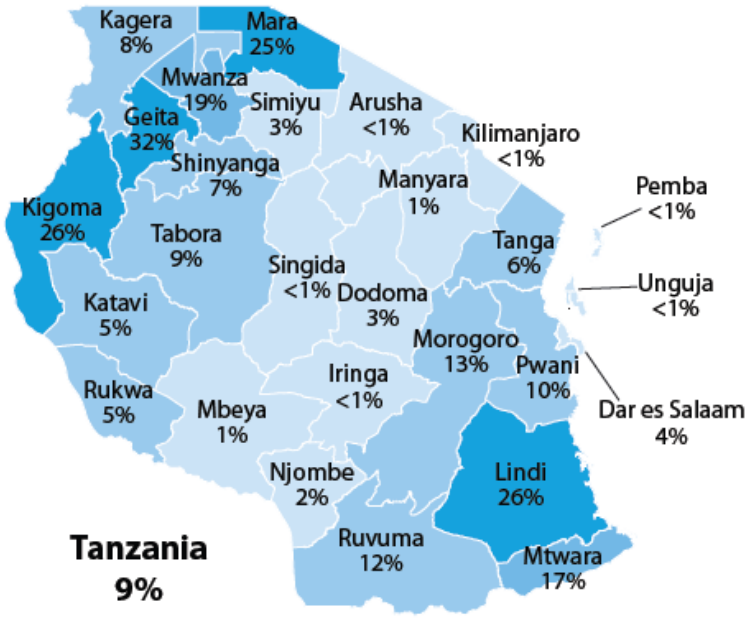


Figure 44: Malaria prevalence in young children by region: % of children 6-59 months testing positive by RDT (TACAIDS et al., 2013)

The World Malaria Report 2013 estimates that there were almost 11 million cases of malaria in 2013 (including all suspected, presumed and confirmed cases), and approximately 40 confirmed cases per 1,000 population (WHO, 2013). Calculating malaria-attributable mortality is difficult and estimates vary from 7,812

inpatients deaths in 2012 (World Malaria Report 2013) to an annual death toll across all ages of 60,000-80,000 deaths in the mainland in 2009 according to the Tanzanian National Malaria Control Programme (NMCP) (NBS/ICF, 2011). Although malaria related mortality has declined over the past decade (Figure 44) (TMIERG, 2012), it is still the primary cause of death in children under 5 with 24% of deaths directly attributed to malaria; under-five mortality is Tanzania is high at approximately 81 deaths per 1000 live births (TMIERG, 2012, WHO, 2012a). This figure excludes indirect malaria mortality through chronic anaemia or exacerbation of other co-morbidities.

5.2.1.1 Diagnostics and Treatment for malaria in Tanzania

Chloroquine was the first-line treatment in Tanzania up to 2001. The national guidelines were subsequently changed to Sulphadoxine-Pyrimethamine (SP) for uncomplicated malaria, due to chloroquine drug resistance, and intravenous quinine recommended for severe malaria. Resistance to SP emerged rapidly, and in 2006, ACTs (Artemether-Lumefantrine) were adopted as the new first line therapy. This was rolled out in the public sector in 2006/2007 (TMIERG, 2012). Government policy stipulates that malaria treatment at all public sector facilities, whether community or hospitals, is free of charge for children and pregnant women, however this is not always observed (Njau et al., 2006).

Presumptive treatment for all ages at a community level, with the use of malaria microscopy limited to tertiary level facilities, was standard practice until 2006. In line with WHO guidance, the NMCP changed their protocol to advocate presumptive diagnosis in the U5s only in 2006. Since 2010, Tanzania has adopted the policy of diagnostic-led malaria treatment in all age groups with a phased rollout of RDTs along with the T3 (Test, Treat, Track) Initiative (Bruxvoort et al., 2013).

5.2.1.2 Burden of malaria on primary healthcare

Health service statistics for Tanzania are scanty, and there are limited national data regarding the burden of confirmed malaria on health services, especially since improved diagnostics were introduced. The 2011-2012 THMIS estimated that 77% of febrile U5s sought treatment at any source (TACAIDS et al., 2013). Khatib *et al.* reported that between 36-41% of febrile U5s in Tanzania had access to an authorised provider of ACTs within 24 hours of the onset of fever (Khatib et al., 2013). Similarly, THMIS reports that a quarter of febrile children in Tanzania that attended public facilities were tested, and 54% of U5s with a fever were administered an antimalarial, of whom a third were treated either the same day or the next following the onset of their illness (within 24-36 hours) (TACAIDS et al., 2013, NBS/ICF, 2011).

In 2011/2012, of the children who received an antimalarial, 66% received an ACT, 19% quinine, 16% amodiaquine and 4% SP. Overall 38% of those who were treated with antimalarials actually took an ACT

within 24-36 hours of fever onset, i.e. approximately 19% of all febrile under-fives. The average price of an ACT was 1,372 Tanzanian Shillings (less than £1.00)(TACAIDS et al., 2013). In the 2007/2008 survey, 14% of children were treated with a first-line antimalarial within 24-36 hours (TACAIDS et al., 2008).

5.2.1.3 Burden of malaria on tertiary healthcare

Earlier surveys estimate that 40% of under-five outpatient consultations and inpatient admissions are diagnosed with malaria (TMIERG, 2012). The World Malaria Report 2013 (Figure 45) reports 500 admissions for malaria per 100,000 population across all ages, down from approximately 1000 per 100,000 in the 2012 Report (WHO, 2013, WHO, 2012c). The 2012 evaluation from the Tanzania Malaria Impact Evaluation Research Group considered admissions in the U5s at two hospitals, namely Ifakara and Bagamoyo District hospitals. In Ifakara District, 30% of cases of admissions tested positive for malaria with an increasing trend from 2006 -2010 (although reduced from prior to 2006), whereas in Bagamoyo slide positivity of admissions declined from 60% (2006) to 23% (2010). Over diagnosis of malaria in children and adults with severe febrile illness is common (Nadjm et al., 2012, Reyburn et al., 2004). Mtove *et al.* noted that the incidence of severe malaria declined amongst cases referred to Muheza hospital from 2006 to 2010 but that the age of cases admitted also increased from 1.7 years to 2.5 years ($p<0.0001$) as malaria prevalence fell (Mtove et al., 2011a). This age-shift in severe malaria incidence in Tanzania has also been described by Okiro *et al.* and similarly in other east African sites (Okiro et al., 2009, O'Meara et al., 2008a, O'Meara et al., 2010).

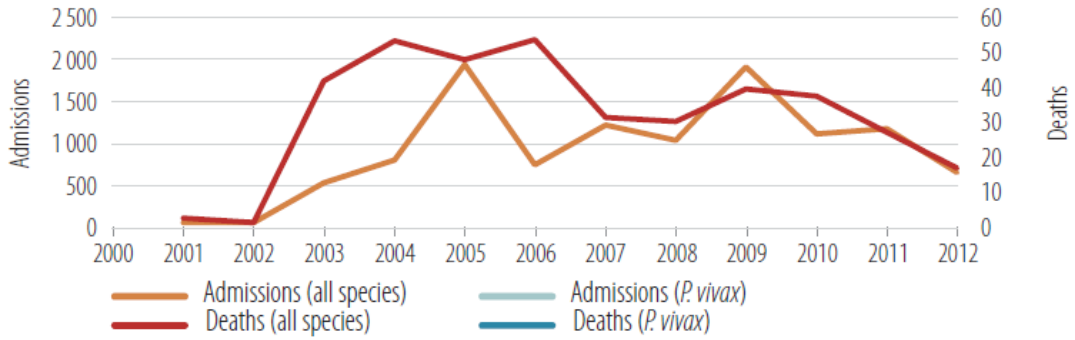


Figure 45: World Malaria Report 2013: Tanzania profile. Microscopically confirmed cases, admissions and deaths per 100,000 population *(WHO, 2013).*

5.2.1.4 Private sector and Affordable Medicines for Malaria (AMFm) in Tanzania

Aside from the government funded public sector healthcare, the Tanzania mainland has various other private sector outlets, which are registered by the government to provide medical care services to the population. These registered private sources of antimalarials include drug shops (Part Two drug shops

known locally as Duka la Dawa Baridi - DLDB), Accredited Drug Dispensing outlets (ADDOs) and Part One pharmacies (POPs) (Alba et al., 2010b, Alba et al., 2010a, Thomson, 2011, Tougher et al., 2012). Other sources of medicines do exist such as general shops as in other African countries (Goodman et al., 2004), but it is now not legal for these to sell ACTs and they are becoming increasingly less common (Thomson, 2011, Tougher et al., 2012).

DLDBs are registered to sell only a limited subset of drugs, medicines and cosmetics, including antimalarials. They are common nationally but not staffed by qualified pharmacists. Accredited Drug Dispensing Outlets (ADDOs) are upgraded DLDB with dispensers that are qualified to dispense a wider range of medications. Part One pharmacies (POPs) are staffed by fully trained pharmacists, and are less common in rural areas (Thomson, 2011).

Tanzania hosted the original AMFm pilot (Sabot et al., 2009) and one of the eight national-scale programmes introduced in 2010. The first co-paid ACTs, designated by a green-leaf logo as a mark of quality assurance, were distributed in October 2010. Interventions to support the rollout of AMFm were added in early 2011, including mass media campaigns at national and local levels to improve awareness of the logo, understanding of co-paid drugs and their recommended pricing. An independent evaluation of the initial phase of the national rollout (conducted in 2010 and 2011) showed that 10.7% of private for profit outlets had a quality-assured ACT (QAACT): 65% of POPs stocked QAACTs but less than 10% of DLDBs and drug shops. Availability was higher in urban populations and stockists close to major transport links and roads (Thomson, 2011, Cohen et al., 2010). The median price of an adult equivalent treatment dose (AETD) was $4.93, although higher in urban areas ($7.04) compared to rural ($1.41) (Thomson, 2011, Tougher et al., 2012). This early data and data from surveys conducted by the IMPACT 2 team once the AMFm initiative was more established (Thomson et al., in submission) are included in my analysis and described further in Section 5.3.

5.3 MONITORING INTERVENTIONS TO IMPROVE ARTEMISININ-BASED COMBINATION TREATMENT (ACT) ACCESS AND TARGETING IN TANZANIA THROUGH HOUSEHOLD AND HEALTH FACILITY SURVEYS (IMPACT 2 STUDY)

In order to explore the role of regional health systems in malaria control and ACT programme planning, I used data collected by the IMPACT 2 study in Tanzania. This study commenced in 2010 and aimed to evaluate the operational success of two programmes, namely the introduction of RDTs in government facilities and of subsidised ACTs in private retail outlets as the national rollout commenced in three regions: Mwanza, Mtwara and Mbeya. Funding for the study was provided through the Bill and Melinda Gates Foundation through the ACT Consortium, based at the London School of Tropical Medicine and Hygiene with sub-grants to Ifakara Health Institute in Tanzania and the US Centres for Disease Control. The protocol consisted of

1) household and facility surveys (Bruxvoort et al., 2013, Thomson et al., in submission)
2) national outlet survey (Thomson et al., in submission) (which informed the early evaluation of AMFm Tanzania report (Thomson, 2011))
3) drug availability inventory
4) qualitative study of sociocultural factors influencing the implementation of malaria prevention, diagnosis and treatment interventions
5) additional quantitative studies of treatment availability and adherence

Mwanza region is located near Lake Victoria with a population of 3,771,000; 20.8% of whom lie in the poorest national wealth quintile. Mbeya is a southern highland region, with a population of 2,822,000 (7.7% in the poorest wealth quintile). Mtwara lies along the southern border with Mozambique and is the poorest region with 35.5% of its 1,375,000 population in the lowest wealth quintile (Bruxvoort et al., 2013, NBS/ICF, 2011). The estimated regional prevalence of malaria in under-fives is: Mwanza 18.6%, Mtwara 17.4, Mbeya 0.5% (TACAIDS et al., 2013).

Outlet surveys were conducted across Tanzania within the independent evaluation of AMFm (Thomson, 2011, Thomson et al., in submission, Tougher et al., 2012). Baseline data were collected from September – November 2010 and endline from October 2011 – January 2012 (Figure 46). In the regions selected, every outlet that had the potential to sell antimalarials, including private and public health facilities, drug shops, ADDOs, and general kiosk stores was surveyed. Data presented here are from the three selected regions as well as all Tanzania, for all private outlets except private health facilities staffed by trained doctors.

The protocol of the household surveys is fully described by Thomson *et al.* (Thomson et al., in submission). Baseline collection of household data occurred in June to October 2010. Endline surveys were conducted in May – September 2012. Participants were questioned on household demographics and if any reported a fever in the 14 days prior to the interview, they were then questioned about whether care was sought and at which source as well as other questions regarding testing and treatments obtained. RDTs were performed on those who consented.

The protocol for the health facility surveys is described by Bruxvoort *et al.* (Bruxvoort et al., 2013). Baseline surveys were conducted in 2010 and endline post-implementation surveys in 2012; in Mwanza: April –May, Mbeya: May-June and Mtwara: June-July. In each region 35 health facilities were surveyed at baseline and 60 in 2012 (Figure 46). Patients attending with a fever were questioned, and also tested by the study team by both RDT and microscopy for malaria. Health facility staff were interviewed and the facility itself audited for stock and other components of case management.

The ADDO programme for upgrading drug shops (DLDB) was implemented prior to 2010 (baseline data collection) in Mtwara and Mbeya regions but not in the Mwanza area until after the endline surveys in 2012 (Thomson et al., in submission). The public sector rollout of RDTs occurred in Mwanza and Mbeya in February 2011 but only in May 2012 in Mtwara, i.e. just prior to the endline survey (Bruxvoort et al., 2013) (Figure 46).

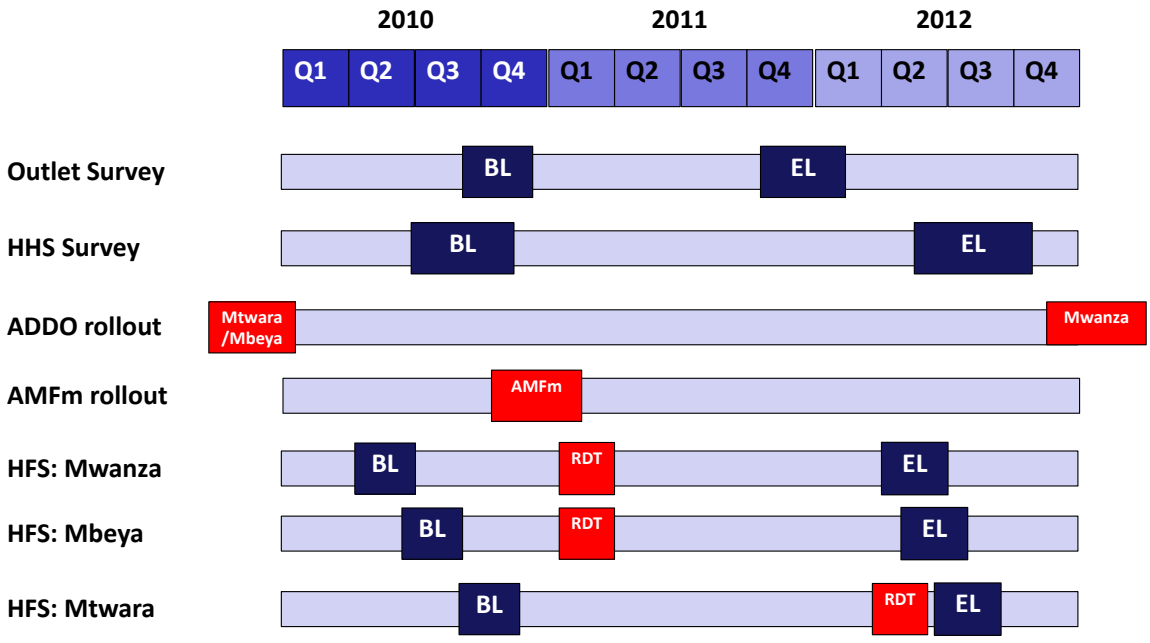


Figure 46: Timeline for IMPACT 2 study data collection at baseline (BL) and endline (EL)

Timeline for outlet survey, household survey (HHS) and health facility survey (HFS) as well as the rollout of Accredited Drug Dispensing Outlets (ADDOs) and the Affordable Medicines facility for malaria (AMFm).

5.4 IMPACT 2 STUDY DATA SUMMARY

5.4.1 Data

Data were used from the IMPACT 2 study as described in section 5.3 (in the form of summary statistics). Sampling, data collection methods and questionnaires used as well as other results have been published by the IMPACT 2 group (Bruxvoort et al., 2013, Thomson et al., in submission). The data were analysed by the IMPACT 2 team using Stata 11.0 (Stata Corporation, College Station, USA), using survey commands to account for the two-stage survey design (Bruxvoort et al., 2013, Thomson et al., in submission).

In total, 138 facilities were surveyed at baseline (11 hospitals, 24 health centres and 105 dispensaries) in May-October 2010 and 176 health facilities (13 hospitals, 31 health centres, 132 dispensaries) at endline in April-July 2012. The initial household survey interviewed 20,874 household members of whom 1,410 (369 under-five) reported a fever in the past 2 weeks (6.75%). At endline 1,683 of 20,102 interviewees (424 under-five) gave a history of febrile illness in the preceding fortnight (8.37%)(Thomson et al., in submission).

In this analysis, to assess the performance of the private sector, and to avoid overlap with the public sector health facilities, I included only drugs shops, pharmacies and general stores that sold medicines, but not private health facilities staffed by medical personnel. At baseline, of 602 outlets that met the IMPACT study criteria, staff at 559 outlets were interviewed. 535 of these outlets had the full range of information required for the analysis in this thesis and so were included for an all-Tanzania analysis: 33 were in Mwanza, 17 in Mbeya and 9 in Mtwara. At endline, 708 met the IMPACT 2 criteria, 707 were interviewed of which 700 outlets had sufficient information to be included in the all-Tanzania analysis: 77 were in Mwanza, 43 in Mbeya and 3 in Mtwara (Thomson et al., in submission).

5.4.1.1 Slide prevalence of malaria in febrile care-seekers

The prevalence of malaria in febrile patients attending a health facility who consented to be tested with an RDT and blood slide is shown in Table 21. As previous studies have shown, the parasitaemia prevalence among febrile patients in the same area is similar in both age groups at both health facilities and private outlets (Kachur et al., 2006). These values were used in decision-tree modelling for both sectors. As only summary statistics were available from the IMPACT 2 study, the means of the two samples (baseline and endline) were compared using the 2 sample z-test, with a two-tailed comparison; significance was defined as $p<0.05$ (assuming a Normal approximation). The methodology is described in the Oxford Handbook of Medical Statistics (Peacock and Peacock, 2010), and implemented through the web-based tool: http://epitools.ausvet.com.au/content.php?page=z-test-

2&p1=0.14&p2=0.02&n1=138&n2=176&Conf=0.05&tails=2&samples=2). The validity of regional sample differences is limited by small sample sizes.

The under-five population parasite prevalence values estimated by THMIS are 9% nationwide; 17% in Mtwara; 19% in Mwanza and 0.5% in Mbeya. The study values in febrile patients seeking treatment are higher than the population estimates for Mtwara and Mbeya but less in Mwanza, and have increased in the time period; this is contrast to the overall population estimates which are estimated to have decreased from the 2007/8 THMIS and 2011/12 THMIS surveys (TACAIDS et al., 2008, TACAIDS et al., 2013).

Table 21: Mean malaria parasite prevalence in under-fives and over-five years of age (children and adults) in the three regions surveyed in the Health Facility Survey from IMPACT 2.

95% confidence intervals in brackets; significant difference (p<0.05) between the means of baseline and endline samples is indicated by an asterix

Malaria Prevalence		**All 3 regions**			**Mtwara**			**Mwanza**			**Mbeya**		
	Age	Baseline 138	Endline 176	***Sig diff***	**Baseline 44**	**Endline 59**	***Sig diff***	**Baseline 39**	**Endline 60**	***Sig diff***	**Baseline 55**	**Endline 57**	***Sig diff***
Probability fever is due to malaria	<5 years	0.12 (0.1-0.16)	0.16 (0.13-0.2)		0.27 (0.21 - 0.33)	0.3 (0.24 - 0.37)		0.09 (0.06 - 0.15)	0.12 (0.08 - 0.17)	*	0.01 (0.02 - 0.04)	0.04 (0.01 - 0.12)	
	>5 years	0.05 (0.03-0.11)	0.17 (0.14-0.21)	*	0.11 (0.06 - 0.19)	0.35 (0.28 - 0.42)	*	0.02 (0.01 - 0.05)	0.08 (0.04 - 0.15)		0.02 (0.01 - 0.05)	0.07 (0.03 - 0.13)	*

5.4.1.2 Access to healthcare: public health facilities, private outlets and tertiary care

In Chapter 2, I presented the evidence that access to treatment, whether determined by distance or travelling time, as well as the source of treatment were important determinants of the effectiveness of a treatment programme. Table 22 shows IMPACT 2 study summary estimates of the probability that febrile patients seek care for their illness, as well as their preferred sector.

I have only included private and public sector preferences in this analysis and have not considered other sources of treatment such as traditional healers or drugs from family members. The data are taken from the household surveys, which allowed multiple sources of treatment to be selected. For example, a patient may attend a health facility first then subsequently go to a drug shop to purchase medications that had been out of stock at the initial source of care. Therefore the sum of the probabilities from the original IMPACT 2 study regarding seeking at either private or public sector sources do not equal one. As I am not including the chance of a patient attending multiple sources of primary-level care, I have used both IMPACT 2 data and data from THMIS (TACAIDS et al., 2008, TACAIDS et al., 2013) to estimate the probably that a febrile individual who seeks treatment does so in either at a private retail outlet or public sector health facility. These values that are used in the transmission model are given in italics in the table.

Overall, more than 80% of children under-five years (U5) and over 60% of those over-five seek treatment for fever. In Mbeya (low prevalence) and Mwanza (medium-high) there was a marked preference for the private sector both at baseline and endline whereas is Mtwara (medium-high prevalence) the difference is less clear at baseline but changes to private preference at endline. The probability of attending a hospital for a severe febrile illness is low throughout.

The time taken to access each source of care indicates that overall individuals take longer to access care in the public sector than the private although the difference in unlikely to be significant since the 95% confidence intervals overlap.

ACCESS		All		Mtwara		Mwanza		Mbeya	
		Baseline	Endline	**Baseline**	**Endline**	**Baseline**	**Endline**	**Baseline**	**Endline**
	HFS	138	176	**44**	**59**	**39**	**60**	**55**	**57**
	OS	535	700	9	3	33	77	17	43
	HH	1510 (U5: 369, O5: 1141)	1653 (U5: 424, O5: 1228)	375 (U5: 93, O5: 282)	345 (U5: 74, O5: 270)	786 (U5: 196; O5: 590)	940 (U5: 268, O5: 671)	349 (U5:80; O5:296)	368 (U5: 81; O5: 287)
Probability of patient with fever seeking treatment	<5 years of age	0.81 (0.75-0.86)	0.84 (0.78-0.88)	0.87 (0.82 - 0.91)	0.76 (0.63 - 0.86)	0.8 (0.7 - 0.88)	0.87 (0.82 - 0.91)	0.83 (0.72 - 0.9)	0.65 (0.58 - 0.71)
	5 years and over	0.66 (0.62-0.69)	0.7 (0.66-0.73)	0.73 (0.69 - 0.77)	0.63 (0.56 - 0.7)	0.67 (0.62 - 0.72)	0.73 (0.69 - 0.77)	0.62 (0.55 - 0.87)	0.65 (0.58 - 0.71)
Probability of patient with fever seeking treatment at public sector clinic	<5 years of age	0.62 *(0.6)* (0.55-0.68)	0.71 *(0.6)* (0.65-0.77)	0.58 *(0.65)* (0.43 - 0.72)	0.32 *(0.4)* (0.19 - 0.48)	0.28 *(0.35)* (0.21 - 0.37)	0.28 *(0.35)* (0.21 - 0.35)	0.11 *(0.3)* (0.06 - 0.2)	0.15 *(0.35)* (0.1 - 0.23)
	5 years and over	0.8 *(0.7)* (0.76-0.83)	0.88 *(0.6)* (0.8-0.86)	0.27 *(0.35)* (0.19 - 0.35)	0.15 *(0.25)* (0.1 - 0.2)	0.15 *(0.2)* (0.12 - 0.2)	0.1 *(0.15)* (0.08 - 0.13)	0.29 *(0.35)* (0.21 - 0.37)	0.15 *(0.25)* (0.1 - 0.23)
Time taken to seek treatment at clinic (days)	<5 years of age	1.4 (1.1-1.7)	1.9 (1.7-2.1)	1.3 (0.8 - 1.8)	1.7 (1.1 - 2.4)	1.3 (0.9 - 1.7)	2 (1.7 - 2.3)	1.6 (0.9 - 2.3)	1.8 (1.2 - 2.3)
	5 years and over	2.1 (1.7-2.4)	2.2 (1.8-2.5)	1.9 (1.5 - 2.3)	2.5 (1.6 - 3.4)	1.9 (1.4 - 2.5)	2.3 (1.7 - 2.8)	2.4 (1.7 - 3)	1.8 (1.2 - 2.3)
Probability of patient with fever seeking treatment at private outlet	<5 years of age	0.46 *(0.4)* (0.39-0.42)	0.55 *(0.4)* (0.48-0.61)	0.28 *(0.35)* (0.17 - 0.42)	0.48 *(0.6)* (0.34 - 0.62)	0.57 *(0.65)* (0.48 - 0.65)	0.58 *(0.65)* (0.49 - 0.66)	0.34 (*0.7)* (0.22 - 0.44)	0.45 *(0.65)* (0.31 - 0.59)
	5 years and over	0.63 *(0.3)* (0.58-0.67)	0.69 *(0.4)* (0.65-0.73)	0.56 *(0.65)* (0.47 - 0.65)	0.61 *(0.75)* (0.58 - 0.68)	0.71 *(0.8)* (0.66 - 0.72)	0.73 *(0.85)* (0.68 - 0.77)	0.47 (*0.65)* (0.37 - 0.57)	0.62 *(0.75)* (0.53 - 0.7)
Time taken to seek treatment at private outlet(days)	<5 years of age	1 (0.8-1.2)	1.6 (1.3-1.8)	0.6 (0.1 - 1)	1.1 (0.8 - 1.4)	1 (0.8 - 1.3)	1.5 (1.3 - 1.7)	0.9 (0.4 - 1.4)	1.9 (0.9 - 3)
	5 years and over	1.4 (1.2-1.5)	1.6 (1.5-1.7)	1 (0.8 - 1.2)	1.5 (1.2 - 1.9)	1.5 (1.3 - 1.8)	1.6 (1.4 - 1.8)	1.1 (0.6 - 1.6)	1.6 (1.4 - 1.7)

Hospital n	Age	All 3 regions Baseline 11	 Endline 13	Mtwara Baseline 5	 Endline 5	Mwanza Baseline 2	 Endline 3	Mbeya Baseline 4	 Endline 5
Probability of patient with fever seeking treatment at a hospital	<5 years of age	0.43 (0.4-0.53)	0.35 (0.29-0.41)	0.67 (0.53 - 0.78)	0.36 (0.23 - 0.53)	0.35 (0.27 - 0.43)	0.16 (0.13 - 0.2)	0.57 (0.44 - 0.7)	0.22 (0.15 - 0.3)
	5 years and over	0.27 (0.23-0.31)	0.18 (0.15-0.21)	0.33 (0.25 - 0.43)	0.21 (0.16 - 0.24)	0.21 (0.17 - 0.25)	0.16 (0.13 - 0.2)	0.33 (0.27 - 0.46)	0.22 (0.15 - 0.3)
Time taken to seek treatment at hospital (days)	<5 years of age	1.5 (1.1-1.8)	1.9 (1.7-2.1)	1.3 (0.9 - 1.8)	1.7 (1.1 - 2.3)	1.5 (0.9 - 2.1)	2.3 (1.9 - 2.7)	1.5 (0.9 - 2)	2.3 (1.5 - 3.2)
	5 years and over	2.1 (1.8-2.4)	2.3 (1.9-2.3)	1.8 (1.4 - 2.2)	2.3 (1.8 - 3)	2.1 (1.5 - 2.6)	2.3 (1.9 - 2.7)	2.3 (1.7 - 2.9)	2.3 (1.5 - 3.2)

Table 22: Access to healthcare: public health facilities, private outlets and hospital using household, health facility and outlet surveys from IMPACT 2

Mean and 95% confidence intervals in brackets. The values used in the transmission model for the probability that a febrile individual that decides to seek treatment goes to a public facility or a private retail outlet are estimated from both IMPACT 2 and THMIS data and are given in italics in the table.

5.4.1.3 Quality of care in public sector facilities

As discussed in Chapter 4, the probability of receiving an ACT (whether for malaria or NMFI) in the public sector depends not only on the availability of stocks of ACTs but also on diagnostics and healthcare worker compliance with test results. The decision tree approach showed that ACTs may be prescribed through a variety of pathways, and not solely via the diagnostic-led route recommended by the T3 guidance. Quality of care estimates in government primary care facilities (from urban clinics facilities to village health posts) from the IMPACT 2 Health Facility baseline and endline surveys are shown in Table 23.

As previously described, the difference between the means of the two samples (baseline and endline) were compared using the 2 sample z-test, with a two-tailed comparison; significance was defined as $p<0.05$ (assuming a Normal approximation). The validity of regional sample differences is limited by small sample sizes.

Values regarding the sensitivity and specificity of malaria diagnostic tools are derived from the endline health facility survey in 2012. Facility blood smears and RDTs were compared to reference blood smears, which were double-read at the Ifakara Health Institute by two blinded microscopists, with contradictory readings read by a third microscopist. Facility smears gave a sensitivity and specificity of 70.6% and 63.7% respectively (n=119 patients). In contrast the sensitivity and specificity of RDTs performed at the facility compared with reference blood smears were 91.3% and 88.0%, respectively (n = 746). Overall the RDT positive predictive value was 69.3% and the negative predictive value of 97.3%. Due to the numbers involved, these estimates were not broken down by region, although some studies suggest that the performance of some RDTs may vary by age and malaria prevalence (Laurent et al., 2010). In the transmission model I have used the sensitivity and specificity values for RDTs in both baseline and endline respectively, since estimates were only derived at endline, when most of the tests performed were by RDT. At baseline although the majority of tests performed were by microscopy, there were very low levels of testing overall.

Mwanza suffered more complete stock outs of ACTs than the other regions in both surveys, and also of RDTs in the endline survey in 2012. This was despite the rollout of RDTs in this region in February 2011. Both stock and use of diagnostics increased from baseline to endline, as well as adherence to test results. Artesunate stocks were low in all regions and no referral of severe patients to tertiary level facilities was recorded.

Values are given for the use of RDTs and ACTs overall for each regions and also for use if each commodity is in stock, e.g. use of RDTs overall and use of RDTS if RDTS are in stock. The use of ACTs is stratified by whether an individual has tested positive, negative or has not been tested.

The stock and use of diagnostics increased significantly in all regions, as did the percentage of tests performed that used an RDT. In addition, the treatment of negative test results or those who were untested with ACTs decreased significantly in Mtwara and Mbeya, but not in Mwanza despite the rollout of T3 guidance and RDTs in this region.

These stock-dependent values were used in a decision tree model, as described in Chapter 4, to estimate the probability of a malaria case receiving an ACT and an NMFI case being treated with an ACT. I used the probability of at least one dose of ACT being present, as the phenomena of dose "stacking" and "splitting" were observed during the IMPACT 2 study surveys. The probability of an acute severe case receiving rectal or intramuscular artesunate as well as ACTs, as per WHO guidelines, is calculated as the product of the probability of a febrile malaria case being treated with an ACT and the probability that artesunate is in stock, as described in Chapter 3.

PUBLIC SECTOR FACILITIES		All 3 regions			Mtwara			Mwanza			Mbeya		
	Age	Baseline 138	Endline 176	*Sig diff*	**Baseline 44**	**Endline 59**	*Sig diff*	**Baseline 39**	**Endline 60**	*Sig diff*	**Baseline 55**	**Endline 57**	*Sig diff*
Probability that a diagnostic is available	<5 years	0.12 (0.08-0.18)	0.74 (0.66-0.8)	*	0.25 (0.13 - 0.44)	0.89 (0.77 - 0.95)	*	0.12 (0.05 - 0.26)	0.6 (0.46 - 0.73)	*	0.05 (0.03 - 0.11)	0.79 (0.64 - 0.88)	*
	>5 years	0.12 (0.08-0.18)	0.74 (0.66-0.8)	*	0.25 (0.13 - 0.44)	0.89 (0.77 - 0.95)	*	0.12 (0.05 - 0.26)	0.79 (0.64 - 0.88)	*	0.05 (0.03 - 0.11)	0.79 (0.64 - 0.88)	*
Probability that a diagnostic is used	<5 years	0.15 (0.1-0.21)	0.55 (0.48-0.62)	*	0.32 (0.19 - 0.49)	0.72 (0.58 - 0.83)	*	0.04 (0.01 - 0.11)	0.5 (0.39 - 0.62)	*	0.11 (0.06 - 0.2)	0.48 (0.34 - 0.62)	*
	>5 years	0.18 (0.12-0.26)	0.54 (0.47-0.61)	*	0.3 (0.18 - 0.46)	0.7 (0.55 - 0.82)	*	0.13 (0.05 - 0.3)	0.44 (0.33 - 0.56)	*	0.15 (0.07 - 0.29)	0.48 (0.34 - 0.62)	*
Probability that a diagnostic is used if available	<5 years	0.45 (0.32 – 0.6)	0.69 (0.62-0.76)	*	0.71 (0.53 - 0.85)	0.83 (0.72 - 0.9)		0.06 (0.01 - 0.38)	0.67 (0.53 - 0.78)	*	0.33 (0.18 - 0.53)	0.47 (0.63 - 0.33)	
	>5 years	0.47 (0.32-0.62)	0.66 (0.58-0.74)	*	0.64 (0.46 - 0.78)	0.8 (0.65 - 0.9)		0.27 (0.07 - 0.63)	0.65 (0.49 - 0.78)	*	0.5 (0.25 - 0.75)	0.47 (0.63 - 0.33)	
Diagnostic sensitivity	<5 years	0.93 (0.86-0.96)	0.93 (0.86-0.96)	n/a	0.93 (0.86-0.96)	0.93 (0.86-0.96)	n/a	0.93 (0.86-0.96)	0.93 (0.86-0.96)	n/a	0.93 (0.86-0.96)	0.93 (0.86-0.96)	n/a
	>5 years	0.91 (0.78-0.96)	0.91 (0.78-0.96)	n/a	0.91 (0.78-0.96)	0.91 (0.78-0.96)	n/a	0.91 (0.78-0.96)	0.91 (0.78-0.96)	n/a	0.91 (0.78-0.96)	0.91 (0.78-0.96)	n/a
Diagnostic specificity	<5 years	0.89 (0.83-0.93)	0.89 (0.83-0.93)	n/a	0.89 (0.83-0.93)	0.89 (0.83-0.93)	n/a	0.89 (0.83-0.93)	0.89 (0.83-0.93)	n/a	0.89 (0.83-0.93)	0.89 (0.83-0.93)	n/a
	>5 years	0.87 (0.81-0.91)	0.87 (0.81-0.91)	n/a	0.87 (0.81-0.91)	0.87 (0.81-0.91)	n/a	0.87 (0.81-0.91)	0.87 (0.81-0.91)	n/a	0.87 (0.81-0.91)	0.87 (0.81-0.91)	n/a
Probability that all dose packages of ACT are available	<5 years	0.57 (0.45-0.68)	0.49 (0.41-0.58)		0.58 (0.37 - 0.76)	0.19 (0.1 - 0.34)	*	0.35 (0.2 - 0.55)	0.43 (0.3 - 0.58)		0.72 (0.54 - 0.85)	0.52 (0.38 - 0.67)	*
	>5 years	0.41 (0.28-0.55)	0.27 (0.2-0.36)	*	0.52 (0.23 - 0.8)	0.12 (0.05 - 0.24)	*	0.23 (0.1 - 0.43)	0.16 (0.08 - 0.31)		0.53 (0.32 - 0.73)	0.52 (0.38 - 0.67)	
Probability at least one dose	<5 years	0.77 (0.75-0.86)	0.71 (0.62-0.78)		0.91 (0.76 - 0.97)	0.57 (0.39 - 0.74)	*	0.56 (0.38 - 0.73)	0.57 (0.43 - 0.71)		0.84 (0.7 - 0.92)	0.96 (0.85 - 0.99)	*

package of ACT is available	>5 years	0.78 (0.68-0.85)	0.78 (0.78-0.85)		0.94 (0.79 - 0.98)	0.8 (0.6 - 0.92)	*	0.56 (0.38 - 0.73)	0.61 (0.47 - 0.74)		0.86 (0.72 - 0.93)	0.98 (0.85 - 1)	*
Probability that ACT prescribed/dispensed if test positive	<5 years	0.67 (0.52-0.79)	0.5 (0.37-0.64)	*	0.81 (0.57 - 0.93)	0.63 (0.47 - 0.77)	*	0.17 (0.01 - 0.84)	0.16 (0.06 - 0.36)		0.93 (0.53 - 0.99)	0.9 (0.55 - 0.99)	
	>5 years	0.61 (0.4-0.0.79)	0.68 (0.53-0.8)		0.52 (0.23 - 0.8)	0.76 (0.6 - 0.88)	*	0.21 (0.01 - 0.85)	0.25 (0.08 - 0.56)		0.85 (0.52 - 0.97)	0.9 (0.55 - 0.99)	
Probability that ACT prescribed/dispensed if test positive and ACT is in stock	<5 years	0.82 (0.69-0.8)	0.77 (0.63-0.86)		0.84 (0.62 - 0.95)	0.82 (0.74 - 0.89)		0.2 (0.01 - 0.81)	0.45 (0.15 - 0.79)	*	0.93 (0.61 - 0.99)	0.9 (0.57 - 0.98)	
	>5 years	0.86 (0.63-0.96)	0.88 (0.75-0.95)		0.67 (0.39 - 0.86)	0.91 (0.8 - 0.97)	*	0.27 (0.02 - 0.85)	0.63 (0.16 - 0.94)	*	0.85 (0.58 - 0.96)	0.9 (0.57 - 0.98)	
Probability that ACT prescribed/dispensed if test negative	<5 years	0.43 (0.37-0.5)	0.07 (0.1-0.04)	*	0.34 (0.13 - 0.65)	0.04 (0.02 - 0.11)	*	0	0.06 (0.03 - 0.12)		0.33 (0.1 - 0.7)	0.16 (0.08 - 0.3)	*
	>5 years	0.33 (0.27-0.4)	0.08 (0.04-0.14)	*	0.12 (0.04 - 0.32)	0.07 (0.02 - 0.23)		0	0.02 (0.01 - 0.1)		0.33 (0.13 - 0.62)	0.16 (0.08 - 0.3)	*
Probability that ACT prescribed/dispensed if test negative and ACT is in stock	<5 years	0.63 (0.55-0.67)	0.07 (0.05-0.11)	*	0.35 (0.14 - 0.64)	0.05 (0.02 - 0.12)	*	0	0.07 (0.03 - 0.14)		0.33 (0.11 - 0.66)	0.16 (0.08 - 0.3)	*
	>5 years	0.45 (0.37-0.53)	0.09 (0.17-0.05)	*	0.13 (0.05 - 0.32)	0.08 (0.02 - 0.25)		0	0.04 (0.01 - 0.15)		0.29 (0.1 - 0.57)	0.16 (0.08 - 0.3)	
Probability that ACT prescribed/dispensed if untested	<5 years	0.43 (0.35-0.5)	0.21 (0.14-0.3)	*	0.63 (0.52 - 0.72)	0.4 (0.19 - 0.65)	*	0.25 (0.15 - 0.38)	0.11 (0.06 - 0.19)		0.52 (0.4 - 0.64)	0.33 (0.19 - 0.51)	*
	>5 years	0.33 (0.27-0.4)	0.19 (0.12-0.29)	*	0.54 (0.42 - 0.66)	0.3 (0.13 - 0.55)	*	0.15 (0.08 - 0.26)	0.07 (0.02 - 0.18)		0.26 (0.3 - 0.39)	0.33 (0.19 - 0.51)	
Probability that ACT prescribed/disp	<5 years	0.63 (0.56-0.69)	0.31 (0.22-0.42)	*	0.66 (0.57 - 0.74)	0.47 (0.25 - 0.7)	*	0.55 (0.4 - 0.69)	0.23 (0.15 - 0.35)	*	0.66 (0.56 - 0.75)	0.33 (0.2 - 0.51)	*
	>5	0.48	0.29	*	0.58	0.42		0.27	0.14		0.54	0.33	*

ensed if untested and ACT is in stock	years	(0.4-0.56)	(0.19-0.4)		(0.46 - 0.68)	(0.21 - 0.66)		(0.16 - 0.41)	(0.06 - 0.31)		(0.39 - 0.68)	(0.2 - 0.51)	
Probability that diagnostic used is an RDT	<5 years	0.08 (0.03-0.21)	0.8 (0.7-0.87)	*	0.08 (0.02 - 0.27)	0.87 (0.72 - 0.94)	*	0.14 (0.01 - 0.7)	0.76 (0.55 - 0.89)	*	0.06 (0.01 - 0.39)	0.81 (0.64 - 0.91)	*
	>5 years	0.05 (0.02 – 0.13)	0.82 (0.74-0.88)	*	0.06 (0.01 - 0.2)	0.88 (0.74 - 0.95)	*	0.08 (0.01 - 0.41)	0.75 (0.59 - 0.86)	*	0	0.81 (0.64 - 0.91)	*
Probability that Artesunate (rectal or intramuscular) is in stock	All	0.14 (0.07-0.24)	0.02 (0.01-0.08)	*	0.18 (0.08 - 0.26)	0	*	0.18 (0.07 - 0.38)	0.03 (0.01 - 0.21)	*	0.09 (0.03 - 0.25)	0.02 (0.07 - 0.01)	
Probability a severe case is referred to hospital	All	0	0		0	0		0	0		0	0	

Table 23: Care Quality indicators in public sector health facilities: IMPACT 2 Health facility Survey

Mean with 95% confidence intervals in brackets. A significant difference ($p<0.05$) between the means of baseline and endline samples is indicated by an asterix

5.4.1.4 Quality of care in private sector outlets

The decision-tree approach to estimating the probability of receiving an ACT for a malaria infection or NMFI is described in Chapter 4. In order to calculate this quality of care value for the private sector (from general stores and DLDB to part one pharmacies with qualified pharmacists) in the three regions of Tanzania being considered, the component from the IMPACT 2 Household and outlet surveys are shown in Table 24.

As stated in section 5.4.1.1, given that only summary statistics were available from the IMPACT 2 study, the difference between the means of the two samples (baseline and endline) were compared using the 2 sample z-test, with a two-tailed comparison; significance was defined as $p<0.05$ (assuming a Normal approximation). The validity of regional sample differences is limited by small sample sizes.

Levels of test stock and testing were universally poor. Values regarding whether individuals were treated if they test positive are based on individuals in the household survey who recalled being tested and treated, and not from observation at the outlet survey itself. Thus, these values of private sector prescription performance are not dependent on stock levels at the outlet. For example, there were no outlets surveyed in Mtwara with ACT stock however in the household survey individuals reported attending an outlet in the past 14 days and being treated with an ACT. Due to low numbers of tests performed, estimates of treatment probability are not stratified by age for each region, for example only 27 patients recalled having a positive test at a private outlet in the household study.

Table 24 gives values for ACT stock and use, which includes both quality assured ACTs (QAACTs) and non-quality assured ACTs; which were almost always Artemether-Lumefantrine in both cases. Stocks were low in all three regions in retail outlets at baseline but improved significantly in Mbeya and Mwanza by endline, to the extent that there was a higher probability of an outlet having ACTs stocks than a health facility in Mwanza.

In Mtwara, at endline, none of the outlets surveyed carried any ACT stock, but the number of outlets was very small. Artesunate stocks were low in all regions and no referral of severely ill patients to tertiary level facilities was recorded from a private retail outlet. The structure of the survey did not capture whether severely ill patients then sought care elsewhere. The household and outlet surveys did not ask any questions regarding stock or use of ACTs with the AMFm “green-leaf” logo at baseline. Table 25 shows nationwide estimates at endline for stocks of QAACTs with the AMFm logo, and their use on patients with a positive test (n=27) and in those who were untested. 19% of test positive patients received a QAACT compared with 9% of those who were untested. These are lower than the estimates for use of any ACT. It is unclear whether this is due to provider or patient preference.

As described in Section 5.4.1.3, these values were used in a decision tree model to estimate the probability of a malaria case receiving an ACT for their fever as well as an NMFI unnecessarily being treated with an ACT. The probability of at least 1 dose of an ACT in stock was used here rather than the probability of all doses being present as the practices of dose stacking and splitting were observed. Of the few patients who were tested, only one negative test was recorded in the survey. Hence I used the same probability of receiving an ACT if untested as for those who test-negative in the decision-tree model.

Table 24: Care Quality indicators in private outlets (Drug shops including DLDB and ADDOs, pharmacies including POP and general stores): from IMPACT 2 Household and Outlet surveys

Mean with 95% confidence intervals in brackets. A significant difference (p<0.05) between the means of baseline and endline samples is indicated by an asterix

		All 3 regions			Mtwara			Mwanza			Mbeya		
N	**OS HH**	**Baseline 535 1510 (U5: 369*0.4, O5: 1141*0.3)**	**Endline 700 1653 (U5: 424*0.4, O5: 1228*0.4)**	***Sig diff***	**Baseline 9 375 (U5: 93*0.35, O5: 282*0.65)**	**Endline 3 345 (U5: 74*0.6, O5: 270*0.75)**	***Sig diff***	**Baseline 33 786 (U5: 196*0.65; O5: 590*0.8)**	**Endline 77 940 (U5: 268*0.65, O5: 671*0.85)**	***Sig diff***	**Baseline 17 349 (U5:80*0.7; O5:296*0.65)**	**Endline 43 368 (U5: 81*0.65; O5: 287*0.75)**	***Sig diff***
Probability that a diagnostic is available	All	0 (0 - 0.01)	0.03 (0.01-0.05)	*	0	0		0	0		0	0.03 (0.01 - 0.08)	
Probability that a diagnostic is used	<5 years	0.04 (0.02-0.09)	0.02 (0.01-0.05)		0	0		0	0.02 (0.01 - 0.05)		0	0.05 (0.01 - 0.2)	
	>5 years	0.03 (0.02-0.06)	0.02 (0.01-0.03)		0	0		0	0.02 (0.01 - 0.05)	*	0	0	
Probability that all dose packages of ACT are available	<5 years	0.03 (0.02-0.06)	0.33 (0.24-0.42)	*	0	0		0	0.35 (0.56 - 0.19)	*	0.15 (0.05 - 0.38)	0.2 (0.09 - 0.4)	
	>5 years	0	0.1 (0.06-0.14)	*	0	0		0	0.05 (0.02 - 0.13)		0	0.05 (0.01 - 0.15)	
Probability at least one dose package	<5 years	0.03 (0.02-0.06)	0.33 (0.24-0.42)	*	0.11 (0.11 - 0.11)	0		0.03 (0.01 - 0.17)	0.71 (0.59 - 0.8)	*	0.3 (0.26 - 0.34)	0.68 (0.67 - 0.7)	*

of ACT is available	>5 years	0.18 (0.11-0.27)	0.70 (0.61-0.78)	*	0.11 (0.11 - 0.11)	0		0.03 (0.01 - 0.17)	0.71 (0.59 - 0.8)	*	0.3 (0.26 - 0.34)	0.68 (0.67 - 0.7)	*
Probability that ACT prescribed/dispensed if test positive	<5 years	0.26 (0.09-0.55)	0.43 (0.21-0.69)	*	0.26 (0.09 - 0.55)	0.43 (0.21 - 0.69)	n/a	0.26 (0.09 - 0.55)	0.43 (0.21 - 0.69)	n/a	0.26 (0.09 - 0.55)	0.43 (0.21 - 0.69)	n/a
	>5 years	0.61 (0.4-0.79)	0.43 (0.21-0.69)	*									
Probability that ACT prescribed/dispensed if test negative	<5 years	0.18 (0.14-0.23)	0.32 (0.25-0.4)	*	0.22 (0.14 - 0.31)	0.27 (0.19 - 0.35)		0.18 (0.13 - 0.24)	0.24 (0.2 - 0.29)	*	0.17 (0.09 - 0.29)	0.21 (0.14 - 0.29)	
	>5 years	0.18 (0.14-0.23)	0.2 (0.17-0.25)										
Probability that ACT prescribed/dispensed if untested	<5 years	0.20 (0.13-0.3)	0.32 (0.25-0.4)	*	0.22 (0.14 - 0.31)	0.27 (0.19 - 0.35)		0.18 (0.13 - 0.24)	0.24 (0.2 - 0.29)	*	0.17 (0.09 - 0.29)	0.21 (0.14 - 0.29)	
	>5 years	0.18 (0.14-0.23)	0.2 (0.17-0.25)										
Probability that Artesunate (rectal or intramuscular) is in stock	All	0	0.0 (0-0.01)		0	0		0	0		0	0.21 (0.14 - 0.29)	*
Probability a severe case is referred to hospital	All	0.01 (0-0.01)	0.01 (0-0.01)		0	0		0	0		0	0	

Table 25: Estimates of stocks and usage of QAACTs (with the AMFm green leaf logo) in private outlets at endline: IMPACT 2 Outlet and household surveys (mean with 95% confidence intervals in brackets)

Survey (All regions)	N	Probability that all dose packages of QAACT are available	Probability at least one dose package of QAACT is available	Probability that QAACT prescribed/dispensed if test positive (n=27)	Probability that QAACT prescribed/dispensed if test negative (n=1)	Probability that QAACT prescribed/dispensed if untested
Endline **OS: 700** **HHS: 1653**	<5 years: 424	0.3 (0.22-0.4)	0.33 (0.24-0.42)	0.19 (0.048-0.52)	0	0.094 (0.074-0.12)
	>5 years: 1228	0.09 (0.06-0.13)	0.66 (0.57-0.74)			

5.4.1.5 Quality of care in tertiary care facilities

As discussed in Chapter 3, access to and quality of tertiary care may be an important determinant of mortality, especially in medium to high transmission settings.

Table 26 describes data from the Health Facility survey that pertains to hospitals and other tertiary care facilities. The numbers here are small since only 11 hospitals were included in the baseline survey and 13 hospitals in the endline interviews.

Diagnostic availability increased in all regions at endline, and quinine stock levels were high both at baseline and endline throughout. However the probability of artesunate being in stock on a given day never exceeded 50%.

Table 26: Quality of care in hospitals and other tertiary care facilities from the IMPACT 2 Health facility survey

Hospital		All 3 regions		Mtwara		Mwanza		Mbeya	
	Age	Baseline	Endline	Baseline	Endline	Baseline	Endline	Baseline	Endline
n		11	13	5	5	2	3	4	5
Probability of diagnostic availability in hospital	All	0.38 (1.1-1.7)	100	0	100	0.48 (0.07 - 0.91)	100	0.16 (0.03 - 0.76)	100
Probability of artesunate in stock in hospital	All	0.29 (0.64-0.86)	0.38 (0.16-0.82)	0.26 (0.05 - 0.73)	0	0.37 (0.03 - 0.91)	0.48 (0.07 - 0.92)	0.24 (0.03 - 0.76)	0.16 (0.02 - 0.65)
Probability of quinine in stock in hospital	All	100	0.83 (0.46-0.97)	100	0.8 (0.28 - 0.98)	100	0.85 (0.32 - 0.99)	100	0.8 (0.02 - 0.97)

5.4.2 Mathematical model

I aim to use mathematical modelling techniques to estimate the impact made by changes in health systems factors such as access to healthcare and the components of delivering ACTs on the clinical outcomes of malaria (e.g. malaria mortality) as well as parasite prevalence on a national and regional basis. This modelling approach allows analysis of the effects of packages of interventions that would be difficult to explore through other study methods such as randomised controlled trials.

The IMPACT 2 data summarised in the previous section was used to obtain parameters for Model 3 in Chapter 3, shown in full in Figures 47 and 48.

ACTs may be prescribed on the basis of a positive diagnostic test, however as demonstrated in Chapter 4 there are several pathways through which an individual with malaria may receive an ACT. In both the public and private sectors, febrile cases not infected with malaria may also be prescribed or purchase ACTs. Hence, parameters for the probability of receiving an ACT for a malaria infection (including an asymptomatic infection) or an NMFI (including sub-patent infections) in both public health facilities and private outlets are calculated using IMPACT 2 data in the decision-tree model described in Chapter 4. Scenarios in which the steps of treatment delivery are optimised were run using the decision tree for both public and private sectors separately for U5s and over fives, in the three regions of Tanzania. These case management scenarios are summarised in Table 30 (Section 5.5.6). The values derived from the decision tree results were then used to consider the impact of these interventions on malaria transmission and clinical sequelae.

In addition I investigated how improving hospital access and severe disease management affected these model outcomes. Table 31 (Section 5.5.7) summarises the set of tertiary care scenarios considered and the relevant parameterisation.

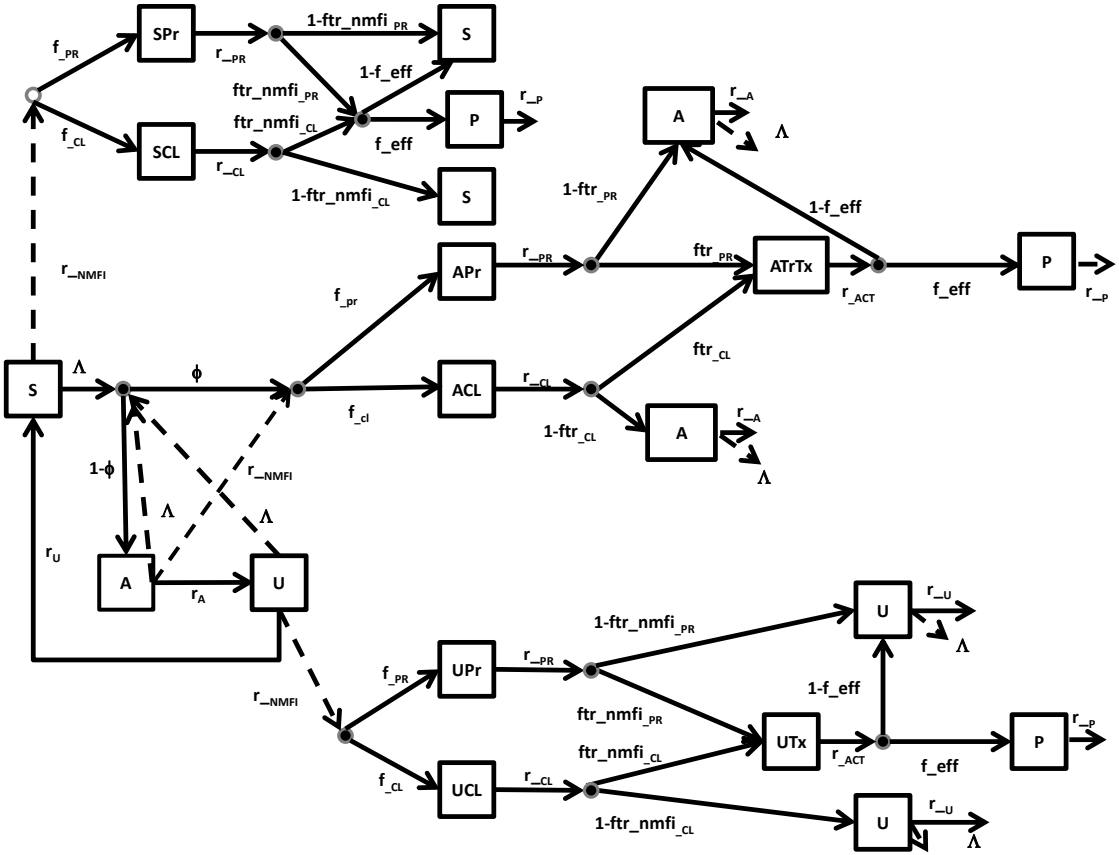


Figure 47: Flow diagram for the final health systems malaria transmission model (Model 3): Treatment of NMFI pathways

S - susceptible; NT – not seeking treatment; Pr – Seeking treatment at private outlet/drug seller; CL – Seeking treatment at primary care health facility/government clinic; PrNT – not treated at private outlet/drug seller; CLNT – not treated at primary care health facility/government clinic; Tx – On treatment; D – untreated clinical disease; Sev – Severe disease; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection. UPr – Sub-patent seeking treatment for NMFI at private outlet/drug seller; UCL – Sub-patent seeking treatment for NMFI at primary care facility; UTx: Sub-patent treated with ACTs; SPr – NMFI seeking treatment at private outlet/drug seller; UCL – NMFI seeking treatment at primary care facility; APr – Asymptomatic malaria case with NMFI seeking treatment at a private outlet/drug seller; ACL – Asymptomatic malaria case with NMFI seeking treatment at a primary care facility; ATrTx – Asymptomatic malaria case with NMFI treated with ACT. People move between these states with rates/probabilities as marked on the arrows

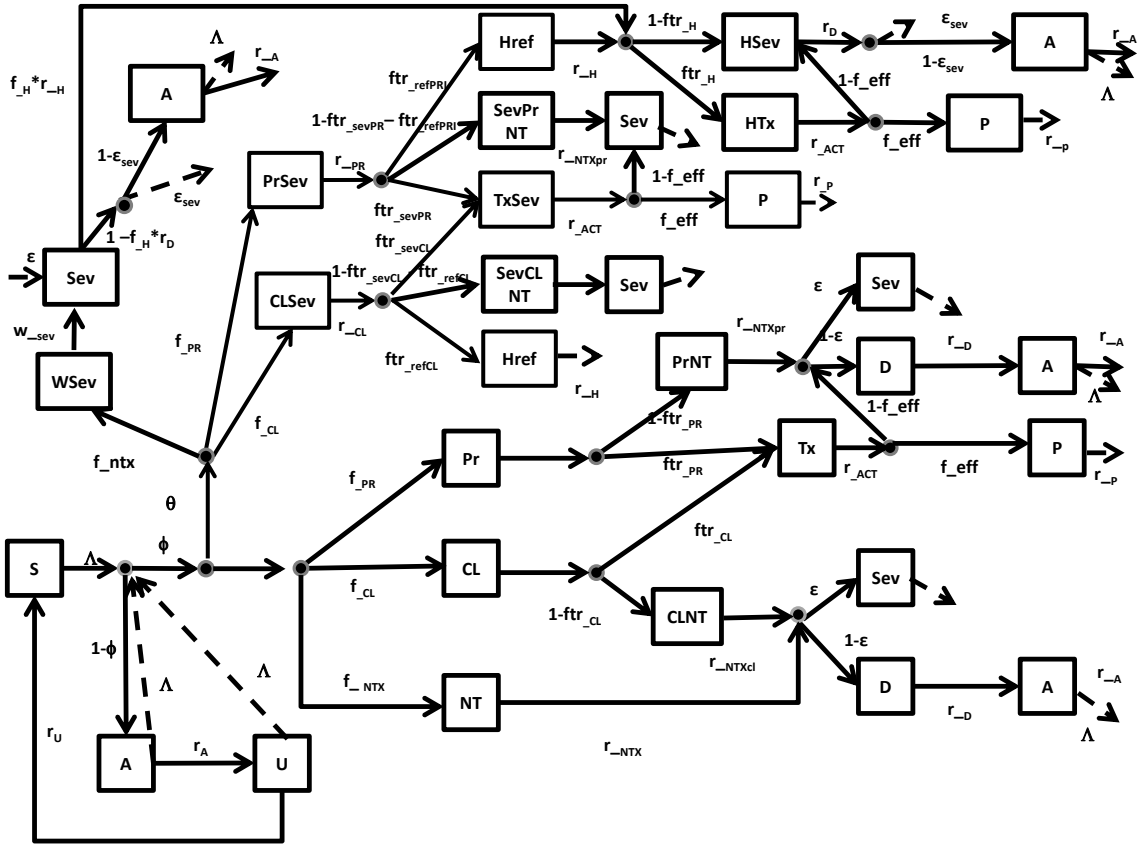


Figure 48: Flow diagram for the final health systems malaria transmission model (Model 3): Pathways for treating symptomatic malaria (uncomplicated and severe)

S - susceptible; NT – not seeking treatment; Pr – Seeking treatment at private outlet/drug seller; CL – Seeking treatment at primary care health facility/government clinic; PrNT – not treated at private outlet/drug seller; CLNT – not treated at primary care health facility/government clinic; Tx – On treatment; D – untreated clinical disease; Sev – Severe disease; P - prophylaxis; A - asymptomatic patent infection; U - asymptomatic sub-patent infection; WSev – untreated progressing early severe PrSev – Severe case seeking treatment at private outlet/drug seller ; CLSev – Severe case seeking treatment at primary care facility; Href – Severe case referred to hospital or tertiary facility by either health facility or private outlet; TxSev – Severe case that has received treatment at clinic/health facility or private outlet; CLSevNT – severe case not treated at primary care facility/government clinic; PrSevNT – severe case not treated at private outlet/drug seller;- HTx – Severe case treated in hospital or tertiary facility; HSev – untreated severe case in hospital or tertiary facility. People move between these states with rates/probabilities as marked on the arrows

5.5 RESULTS

5.5.1 Probability of receiving an ACT: comparison of Decision tree outputs to IMPACT 2 study data

The decision tree approach, described in Chapter 4, was used to derive the probability that a malaria or NMFI case would receive an ACT (in both public and private sectors). These values were compared to the same probabilities estimated in the IMPACT 2 study. The health facility survey collected finger prick blood samples on all enrolled consenting patients attending each health facility. In the household study an RDT was performed on all consenting members who had a fever in the past fortnight.

Table 27 shows the estimated probability that a patient who was malaria test positive or negative by RDT had received an ACT in the IMPACT 2 study, using data from all regions. As previously, the means of the two samples (baseline and endline) were compared using the 2 sample z-test, with a two-tailed comparison; significance was defined as $p<0.05$ and shown in the table using an asterix.

These estimates are compared with the outputs from the decision-tree model parameterised using IMPACT 2 data, estimating the number of malaria cases that have been treated with an ACT (whether tested or not) and the number of NMFI cases that have been treated unnecessarily. Through bootstrapping the decision tree outputs, I generated a distribution for the difference between baseline and endline estimates for the 2 outcomes (i.e. the probability of receiving an ACT for a malaria case and for an NMFI case) in U5s and over-fives in both public and private sectors. The difference between endline and baseline was assumed to be significant if the distribution of the difference did not cross zero, and this is depicted in Figure 49. Only the probability of a malaria case over-five receiving an ACT in the public sector did not change significantly at endline. This is likely due to a more long-standing practice of diagnostic-led treatment in this age group.

The proportions treated in the private sector are significantly different between the two approaches, with confidence intervals that do not overlap for any age group at baseline or endline. For example, using the decision-tree I estimate 0.8% (95% UI: 0.28-1.51%) of U5s with malaria at baseline are given ACTs at a private outlet compared to an estimate of 24% (95%CI: 12.2-41.7) from the IMPACT 2 study. The most likely explanation for these differences is that the decision-tree estimates are based on the reported probabilities of ACT stock levels for a given survey day and thus do not account for patients visiting several treatment sources in order to obtain drugs. Differences may also be due to provider preference, customer preference to use other antimalarials or to the ability of the patients to search other sources of ACTs as well as patient recall regarding their treatment which is known to be sub-optimal in other settings (Eisele et al., 2013).

In the private sector, the decision tree outputs suggest that the probability of being treated with an ACT (malaria and NMFI) was approximately 9% greater at the endline survey for both age groups. In the IMPACT 2 survey, this was estimated to be a difference of up to 12% in the U5s. In contrast to the decision tree

estimates, there was little change in the percentage of over-five malaria cases treated in the private sector observed for those over-five, despite increased levels of over-treatment.

In the public sector, the estimated proportion of NMFI cases treated with an ACT using the decision-tree was similar to the percentage of study test negatives that received an ACT in the IMPACT 2 study at both baseline and endline. However the estimated proportion of malaria cases that receive an ACT obtained from the decision-tree model was lower than the proportion of study test positive patients given an ACT at the health facility in both the baseline and endline surveys; although the confidence intervals do overlap between the estimates of the IMPACT 2 study and the decision tree approach. The difference between the IMPACT 2 study estimates and the decision tree outputs may be due to sampling bias at the facility or more likely due to a dependency between input variables that is not captured in the decision tree, e.g. the probability of prescribing an ACT may be associated with test availability as well as ACT availability. This may also contribute to the differences seen in the private sector decision tree outputs and those from the household survey.

In both the decision-tree outputs and the IMPACT 2 study estimates, the probability of an NMFI case being treated with an ACT decreases from baseline to endline, by almost 30% in U5s and approximately 15% in over-fives. The difference in prescribing behaviour between age groups may be due to the practice of presumptive treatment in U5s being more prevalent than in over-fives as a result of previous guidelines.

Additionally, in both the IMPACT 2 and decision-tree estimates, the probability of an U5 malaria case being treated with an ACT reduces by approximately 12% in each case compared to baseline. Thus the decision tree estimates that only 35% (95%UI: 28.3-43%) of U5s receive an ACT at a health facility, whilst IMPACT 2 estimates that only 45% (95%CI: 34-56%) are treated with a first-line antimalarial at endline. In contrast, 42% (95%UI: 35-49.5%) of over fives are treated with an ACT using the decision tree, and 60% (95%CI: 47-71% using the IMPACT 2 data.

This undertreatment of malaria cases at health facilities is likely due to stockouts of ACTs, especially in the Mwanza region. However even at facilities where ACTs were in stock, ACTs were still not prescribed in approximately 20% of cases where the case was facility-test positive, which is similar to that reported in an evaluation of the RDT rollout in a single Tanzanian district (Masanja et al., 2012a). This rationing may have been due to a past history of poor stock levels - Wasunna *et al* have documented withholding of ACTs in fear of future stockouts but few other studies have identified similar levels of undertreatment in other countries (Wasunna et al., 2008).

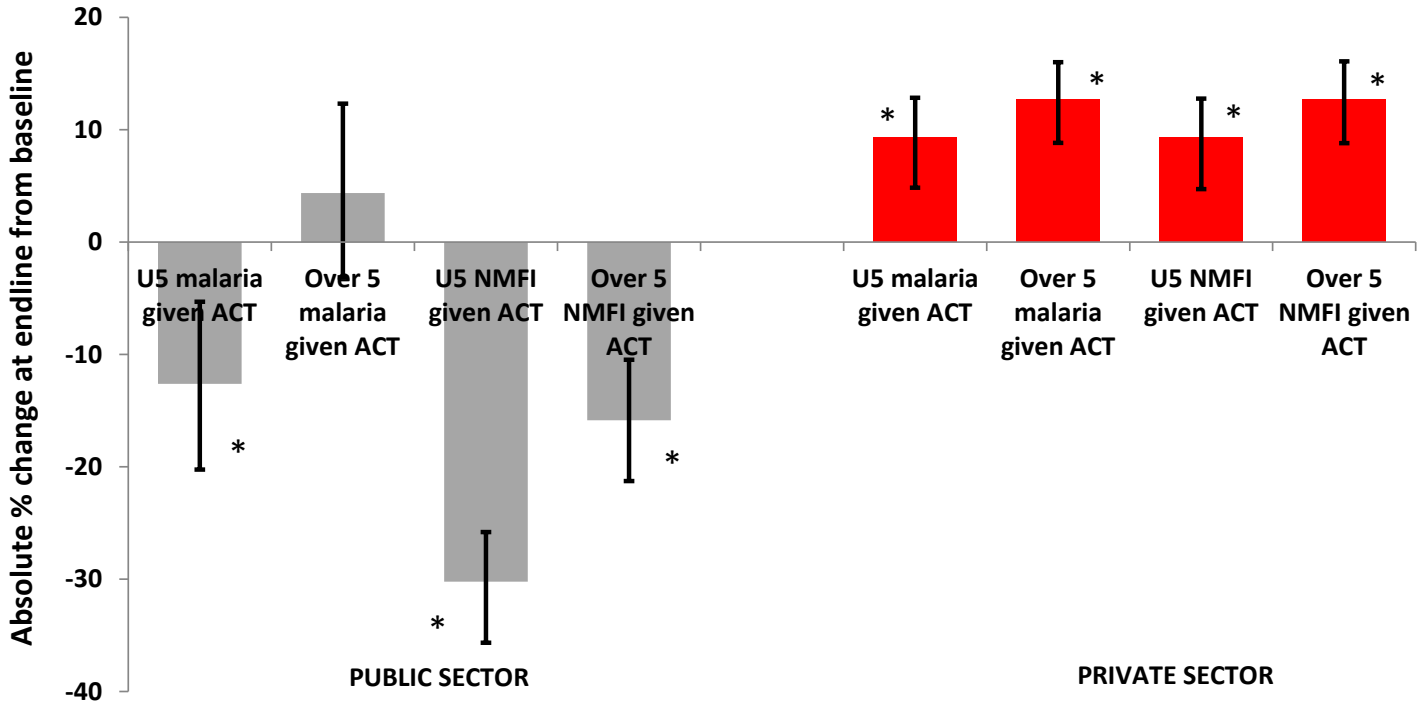
Table 27: Estimates derived from the decision tree approach and the IMPACT 2 study for the probability of receiving an ACT for a malaria infection or an NMFI in the public and private sectors, using IMPACT input data for all regions of Tanzania considered.

Mean with 95% uncertainty intervals given in brackets. A significant difference (p<0.05) between the means of baseline and endline IMPACT 2 survey samples is indicated by an asterix

	Age	Decision Tree (Public)		IMPACT 2 (Public)		Decision Tree (Private)		IMPACT 2(Private)	
		% Malaria given ACT	% NMFI given ACT	% Study + given ACT	% Study - given ACT	% Malaria given ACT	% NMFI given ACT	% Study + given ACT	% Study - given ACT
Baseline	U5	47.78 (40.53 - 56.02)	47.06 (39.82 - 55.22)	67 (51 - 79)	43 (36 - 50)	0.8 (0.28 - 1.51)	0.8 (0.28 - 1.52)	24 (12.2 - 41.7)	19.1 (11.6 - 30)
Endline	U5	35.25 (28.3 - 43.18)	16.69 (12.36 - 21.7)	45 (34 - 56)	15 (11 - 20)	10.02 (6.48 - 14.44)	10.14 (6.17 - 14.32)	36.7 (23.7 - 51.9)	30.5 (22.6 - 39.7)
Difference between endline and baseline		**-12.62* (-4.98 -19.93)**	**-30.23* (-24.79 -34.64)**		*	**9.30* (5.76 13.75)**	**9.31* (5.85 13.89)**	*	*
Baseline	Over 5	38 (30.44 - 46.28)	36.78 (29.52 - 44.77)	61 (40 - 79)	33 (27 - 40)	1.99 (1.29 - 2.82)	1.97 (1.27 - 2.83)	16.4 (10.6 - 24.7)	19.4 (14.8 - 25)
Endline	Over 5	42.15 (35 - 49.49)	21.09 (15.7 - 26.55)	60 (47 - 71)	15.7 (12.1 - 22)	14.63 (11.3 - 18.53)	14.71 (11.3 - 18.42)	14 (7.4 - 24.8)	30.5 (22.6 - 39.7)
Difference between endline and baseline		4.36 (11.86 -3.62)	**-15.85* (-10.43 -21.22)**		*	**12.67* (9.3 16.48)**	**12.71* (9.32 16.61)**		*

Figure 49: Difference between endline and baseline estimates derived from the decision tree approach on the probability of receiving an ACT for a malaria infection or an NMFI: "all-Tanzania" scenario

The absolute percentage change is shown for the public sector (grey) and private sectors (red). Significant difference is indicated by an asterix.



5.5.2 Comparison of Baseline and Endline parameters in transmission model: Impact on parasite prevalence and clinical outcomes using decision-tree and IMPACT 2 estimates

In order to estimate the effect of health systems changes seen from baseline to endline surveys on prevalence and clinical outcomes, the values listed in Table 28 were input into the transmission model as the parameters: ftr_{CL} and ftr_{PR} for the probability of a malaria case being treated at a clinic or private outlet and ftr_{NMFICL} and ftr_{NMFIPR} representing the probability of an NMFI case receiving ACTs at each respective source. The transmission model was then used to compare the expected impact of the changes in access to care on transmission (parasite prevalence and EIR) and clinical outcomes (clinical disease, severe disease incidence and malaria mortality). All other parameters regarding probability of treatment seeking, sector preference and hospital case management were taken from the IMPACT 2 data summarised in Tables 22-26. In order to compare the impact of the changes in ACT delivery, the model was run to equilibrium using the parameters from the baseline survey and then the run from this point to the new equilibrium using the parameters from the endline survey. I assumed that the baseline population parasite prevalence in under-fives was 9% (TACAIDS et al., 2013), representing Tanzania as a whole.

Using the IMPACT 2 study derived parameters, the model predicted an increase in all clinical and transmission outcomes at endline compared with the baseline scenario, as summarised in Table 28. In contrast, using the decision-tree generated parameters for the probability of receiving treatment led to a modest decrease in all modelled outcomes from baseline except the incidence of severe disease, assuming these systems changes were sustained. These results using the decision-tree outputs in the transmission model follow the pattern of reductions in prevalence and mortality described in recent reports, both in Tanzania and globally (WHO, 2013, WHO, 2012c). The effects were greatest in the U5 age-group, which is the group most likely to be symptomatic and attend a source of care.

Table 28: Percentage change relative to baseline in modelled outcomes using IMPACT 2 study estimates and Decision-tree generated outputs to parameterise the transmission model

	Prevalence: all ages	Prevalence: 2-10 years	Prevalence: 0-5 years	EIR	Clinical Incidence: 0-5 years	Severe incidence: 0-5 years	Malaria Mortality: 0-5 years
% change:							
IMPACT 2	6.5	8.1	9.5	5.8	5.6	19.2	9.6
% change:							
Decision-tree	-12.0	-14.9	-16.1	-10.7	-10.2	2.7	-5.4

5.5.3 Regional comparison of Baseline and Endline health systems surveys: Impact on parasite prevalence and clinical outcomes

Figure 50: Age-incidence and Age-prevalence curves depicting the impact of changes in malaria treatment delivery from baseline to endline in 3 regions of Tanzania on clinical and severe disease incidence (per 1000 persons per year) and %population parasite prevalence.

Baseline is indicated in blue and endline in red.

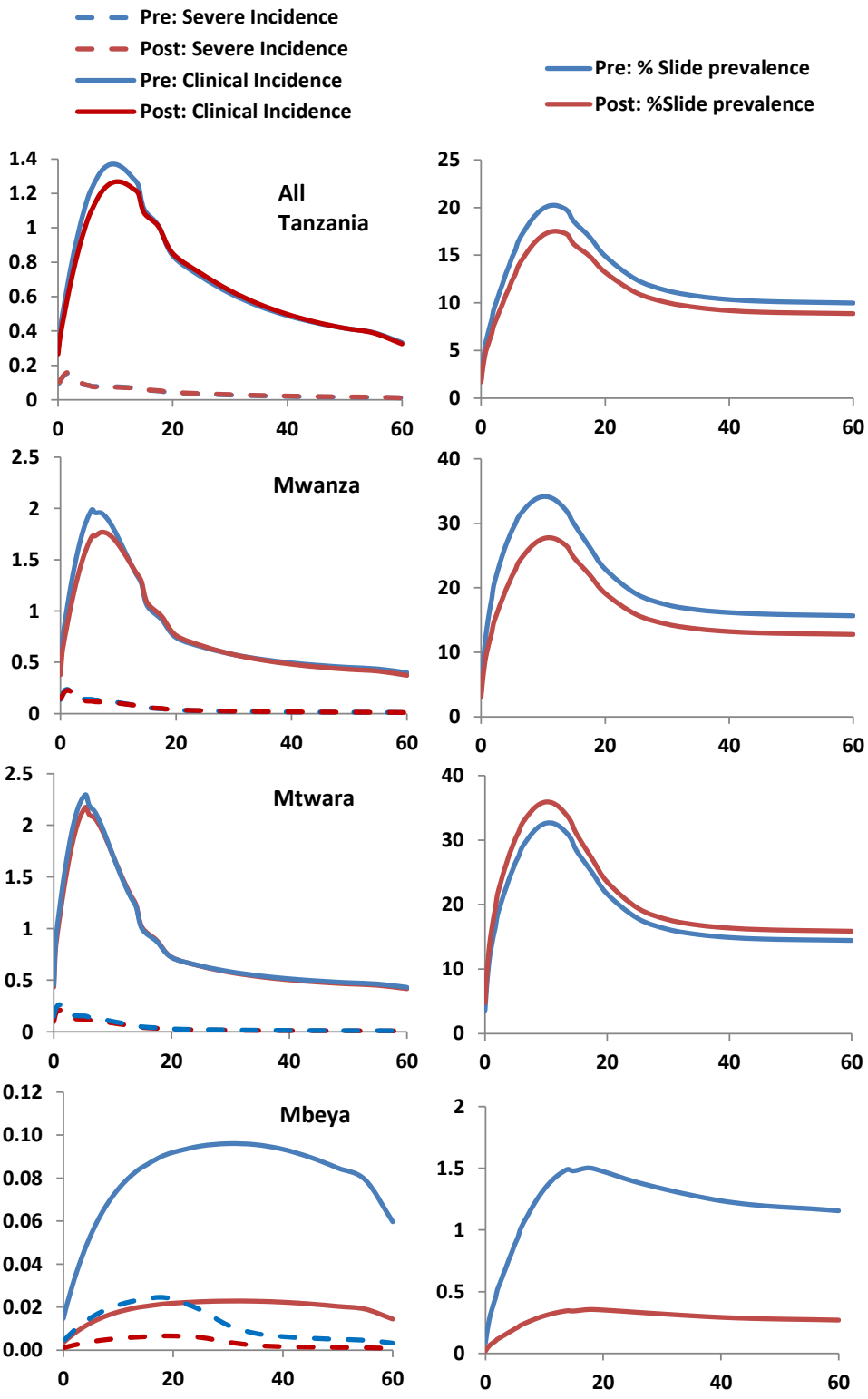


Figure 50 depicts the baseline and endline age-incidence and age-prevalence curves for each of the three regions considered. The baseline models were parameterised to match the 2011 parasite prevalence for U5s for each region obtained in the THMIS survey (TACAIDS et al., 2013). Parameter values were generated from the decision-tree approach, using the regional IMPACT 2 data in table 22-26, and are listed in Table 29. Baseline curves are in blue and endline in red. The baseline curves are as expected for medium to high prevalence settings (Mwanza and Mtwara) and for low prevalence settings (Mbeya) (Griffin et al., 2014, Griffin et al., 2014). In Mwanza, the model predicts that parasite prevalence in all ages would be reduced by the health systems changes to ACT delivery reported by IMPACT 2. Clinical incidence is predicted to be reduced in the young, but to a lesser extent in older ages. Severe disease incidence is not predicted to change substantially. Mortality curves are not shown here but malaria mortality is not discernibly impacted (less than 10% change relative to baseline).

In Mbeya, a low prevalence setting, the model predicts a reduction in parasite prevalence as a result of the improvements in case management with ACTs seen from baseline to endline in the IMPACT 2 study. Severe disease and malaria mortality are low and are predicted to be further reduced in all ages, with mortality levels in those under-15 years particularly impacted; approximately 3 fewer children per 1000 per year are predicted to die.

The baseline prevalence in Mtwara in 0-5 years was 17.4% in 2011 according to THMIS (TACAIDS et al., 2013). Here the model predicted an increase in parasite prevalence in all age-groups, with a 3% increase in those aged 0-5 years and 3.5% increase in the 2-10 year age group. Despite this I estimated very little change in malaria morbidity or mortality would have occurred due to any changes in ACT delivery from baseline to endline. This rise in prevalence is due to high levels of preference for the private sector in this region combined with a complete stockout of ACTs reported at endline. Hence no treatment was given to the estimated 75% of over-fives and 60% of U5s with fever that seek care at drug shops, whether for malaria or NMFI. Severe disease and mortality levels are less affected in this medium to high transmission setting since community level barriers to treatment of uncomplicated malaria only affect one pathway by which severe disease is captured in the model, as discussed further in the results Section 5.5.6.

Table 29: Decision tree estimates: for the probability of receiving an ACT for a malaria infection or an NMFI in the public and private sectors for the three regions of Tanzania. Mean with 95% confidence intervals in brackets.

Probability of receiving an ACT		All		Mtwara		Mwanza		Mbeya	
		% Malaria given ACT	% NMFI given ACT	% Malaria given ACT	% NMFI given ACT	% Malaria given ACT	% NMFI given ACT	% Malaria given ACT	% NMFI given ACT
Public sector (baseline)	U5	47.78 (40.53 - 56.02)	47.06 (39.82 - 55.22)	58.13 (47.9-69.76)	52.77 (42-64.7)	29.9 (17.79-44.41)	29.27 (17.27-44.15)	53.51 (42.42-65.71)	52.64 (4.97-64.95)
	Over 5	38 (30.44 - 46.28)	36.78 (29.52 - 44.77)	50.66 (39.82-62.52)	45.68 (34.98-56.76)	16.03 (8.27-26.24)	15.18 (7.58-25.57)	44.78 (31.97-59.08)	29.94 (19.77-41.77)
Private sector (baseline)	U5	0.8 (0.28 - 1.51)	0.8 (0.28 - 1.52)	2.52 (1.62-3.37)	2.49 (3.37-1.67)	1.64 (0.18-3.38)	1.6 (0.17-3.41)	5.73 (2.86-9.02)	5.73 (2.76-8.96)
	Over 5	1.99 (1.29 - 2.82)	1.97 (1.27 - 2.83)	2.49 (1.62-3.37)	2.5 (1.61-3.38)	1.59 (0.18-3.36)	17.06 (12.98-21.86)	5.76 (2.81-8.88)	5.71 (2.84-8.9)
Public sector (endline)	U5	35.25 (28.3 - 43.18)	16.69 (12.36 - 21.7)	37.74 (25.53-51.41)	14.24 (8.35-22.92)	18.26 (9.41-29.38)	11.52 (6.9-17.46)	49.33 (38.15-60.53)	52.64 (41.97-64.95)
	Over 5	42.15 (35 - 49.49)	21.09 (15.7 - 26.55)	50.85 (37.18-66.5)	22.97 (13.35-34.85)	19.77 (7.91-34.67)	9.93 (4.8-16.14)	44.57 (31.43-58.86)	29.94 (19.77-41.17)
Private sector (endline)	U5	10.02 (6.48 - 14.44)	10.14 (6.17 - 14.32)	0	0	16.94 (12.8-21.93)	17.08 (12.89-21.85)	14.79 (9.92-19.75)	14.77 (9.89-19.6)
	Over 5	14.63 (11.3 - 18.53)	14.71 (11.3 - 18.42)	0	0	16.96 (12.97-21.84)	17.06 (12.98-21.86)	14.88 (9.81-19.72)	14.8 (9.94-19.67)

5.5.4 Treatment seeking, sector preference and access to hospitals

The IMPACT 2 data gives an estimate of between 63% - 87% of febrile patients seeking treatment across all ages, a figure that is consistent with national surveys (TACAIDS et al., 2013). In all three regions, there was a preference for private sector outlets expressed in the endline survey, especially in the over-five age group. Overall the probability of seeking care at a tertiary facility was low.

The potential impact of overcoming barriers of access to healthcare was investigated using three separate scenarios:

A) 100% access i.e. all febrile cases (malaria and NMFI) seek treatment: $f\_{NTX} = 0$

B) 100% clinic treatment only i.e. all of those who seek community treatment have access to public health facilities only (i.e. no private outlets supply care): $f\_{CL} = 1 - f\_{NTX}$ (i.e. $f\_{PR} = 0$/ f_{NTX} = baseline)

C) 100% access to a hospital/tertiary level care whether referred or direct: $f\_{H} = 1$

The results are shown in Figure 51. In low prevalence Mbeya, increased attendance at any source of care (Scenario A, B or C) reduced levels of parasite prevalence, clinical (uncomplicated) and severe disease incidence and malaria-related mortality. In Mwanza, eliminating barriers to accessing care, i.e. here through increased treatment seeking to any source (Scenario A) had a greater impact on parasite prevalence in both the U5 and 2-10 years age groups than if febrile cases that sought treatment did so only at a clinic (Scenario B i.e. the private sector is eliminated). This is due to the fact that Mwanza's public sector clinics had a greater probability of stockouts than other regions, and thus the probability of a malaria case receiving an ACT at a health facility was low and similar to that in the private sector, whereas the probability of an NMFI receiving an ACT in the health facility was lower than the private sector. Hence in this region, increasing the proportion of treatment-seeking febrile patients attending public clinics has a limited impact on prevalence. In contrast in Mtwara at the endline survey, the private outlets had no stocks of ACTs. In this setting the model predicts improved clinical and transmission outcomes under Scenario B; this is greater than that expected from the average across all regions.

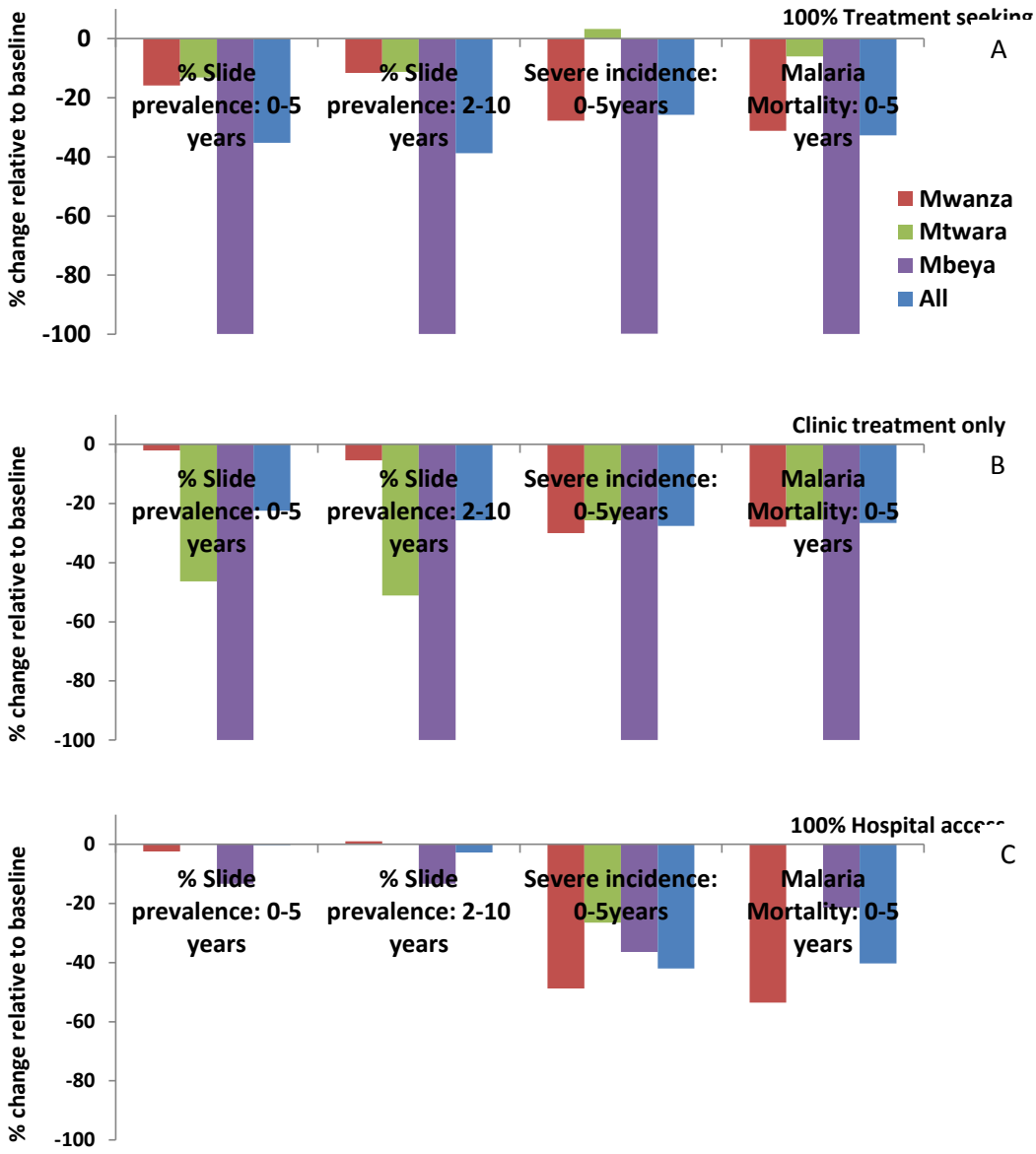


Figure 51: The percentage change relative to baseline under three idealised conditions A) 100% treatment seeking; B) Access only to clinic treatment in the community; C) 100% access to hospital care, with respect to four outcomes: slide prevalence in 0-5 years; slide prevalence in 2-10 years; severe disease incidence in 0-5 years and malaria mortality in 0-5 years.

In order to reduce the risk of severe disease and mortality, malaria programmes are often evaluated on the proportion of malaria patients that were able to access care within 24 hours. I therefore considered a scenario in which the time taken to access either private or public sector care in each region was reduced to half a day i.e. on average those seeking treatment access care the same day as symptoms arise. This could be achieved through a programme of community healthcare workers, as described in Chapter 2. In Mbeya, this was predicted to have little impact, with less than a 2% change relative to baseline in the parasite prevalence, disease incidence or malaria mortality in U5s. In Mtwara and Mwanza, the impact in the population as a whole was also limited. However mortality in the youngest age group, which has a greater

probability of continuing to severe disease or death if untreated (Lubell et al., 2011), was estimated to be reduced by approximately 25% relative to baseline. This was predicted to occur in both private and public sectors in Mwanza. However in Mtwara, since the private outlets are assumed to have no ACT stock, there was no predicted change in either outcome. Overall modelling this scenario predicted a greater impact on morbidity than other community-level interventions (see sections 5.5.5 and 5.5.6) but had only limited impact on parasite prevalence since it does not affect the proportion of those treated. Thus reducing the delay in accessing care is most relevant in areas of high morbidity.

Finally I modelled a scenario of perfect access to a hospital, whether referred from a community source for being at risk of severe malaria or if severe cases attend directly (Scenario C). As expected, this intervention had little impact on parasite prevalence. Severe disease levels were predicted to be reduced. This is due to the structure of the model that allows patients with the potential to develop acute severe malaria to by-pass the Severe state and enter either the Hospital treated state (HTx) or the Hospital untreated/failed treatment Severe state (HSev) if they are referred from a community treatment source. Hence the reduction in severe disease seen here represents the individuals referred from a private sector outlet or government health facility that would avoid progression to severe disease if they could be appropriately treated in a hospital.

Improving access to hospitals within the model predictably also leads to reductions in malaria mortality, except in the case of Mtwara where at endline the hospitals surveyed did not have stocks of artesunate. This does not suggest severe disease patients were untreated as 80% of the hospitals had stock of intravenous quinine, which is not included as an appropriate treatment in this model.

5.5.5 Treatment vs. Diagnostics

Two major malaria control initiatives introduced over the past 3 years are the emphasis on diagnostic-led management and the focus on stocks of quality ACTs, especially in the private sector but also in public health facilities. In Chapter 4 I discussed the balance of the use of RDTs and improved ACT stocks with respect to the probability of a malaria case receiving an ACT (whether tested or not) and the probability of an NMFI being unnecessarily treated with an ACT.

To evaluate the likely impact of these initiatives I considered the two scenarios of perfect ACT stock and 100% diagnostic stock and use. Using the decision tree I generated probabilities for each region of malaria cases and NMFI receiving an ACT. I then explored the impact of these changed values in the transmission model and compared the outcomes to those generated at endline of the IMPACT study, in essence considering the further effect such interventions may have on the existing setting. From this point onwards, the endline of the IMPACT 2 scenarios will be considered as baseline. The probability of malaria being treated with an ACT will also affect asymptomatic cases presenting with an NMFI since these infections are patent. The probability of an NMFI receiving an ACT will affect sub-patent malaria infections presenting with an NMFI since these are assumed to not be detectable by current diagnostics.

The impact of overcoming ACT stockouts in the public sector (solid bars) in the three regions is predicted to be less than that of improving stocks in the private sector (hatched bars) since the private sector is preferred in all three settings (Figure 52A). In the "all-Tanzania" scenario (where the household survey data is from more than just the three regions and is also derived from the THMIS data (TACAIDS et al., 2013)), the public sector is preferred overall and hence increased availability of ACT leads to greater reductions in prevalence and mortality.

In relative terms, the impact on prevalence is greater than the impact on mortality. This is likely to be due to the treatment of asymptomatic cases and subpatent infections with NMFI, which are thought to constitute a reservoir for transmission (Okell et al., 2012, Manjurano et al., 2011). In the model, improving ACT stock may prevent uncomplicated malaria progressing to severe states by increasing treatment, but does not affect the acute severe cases that in the model require artesunate or referral to hospital. The exception to this is the "all Tanzania" scenario, where 100% ACT stock in the private sector is predicted to result in an 18% relative reduction in mortality compared with a 4% reduction in parasite prevalence. This is due to the fact that a greater proportion of the "all-Tanzania" population is assumed to preferentially seek treatment in the public sector. Therefore increasing ACT availability in the private sector does not impact on the treatment of NMFI with asymptomatic and sub-patent infections that drive infection transmission. However since the quality of treatment in the private sector is less than that in the public sector, a greater proportion of severe disease cases are generated through this pathway as a result of a lack of or delayed treatment. Improving drug stock

in the private sector (in this setting of public sector preference) averts severe disease and mortality, which occurs as a consequence of private sector stockouts, to greater relative extent than affecting parasite prevalence.

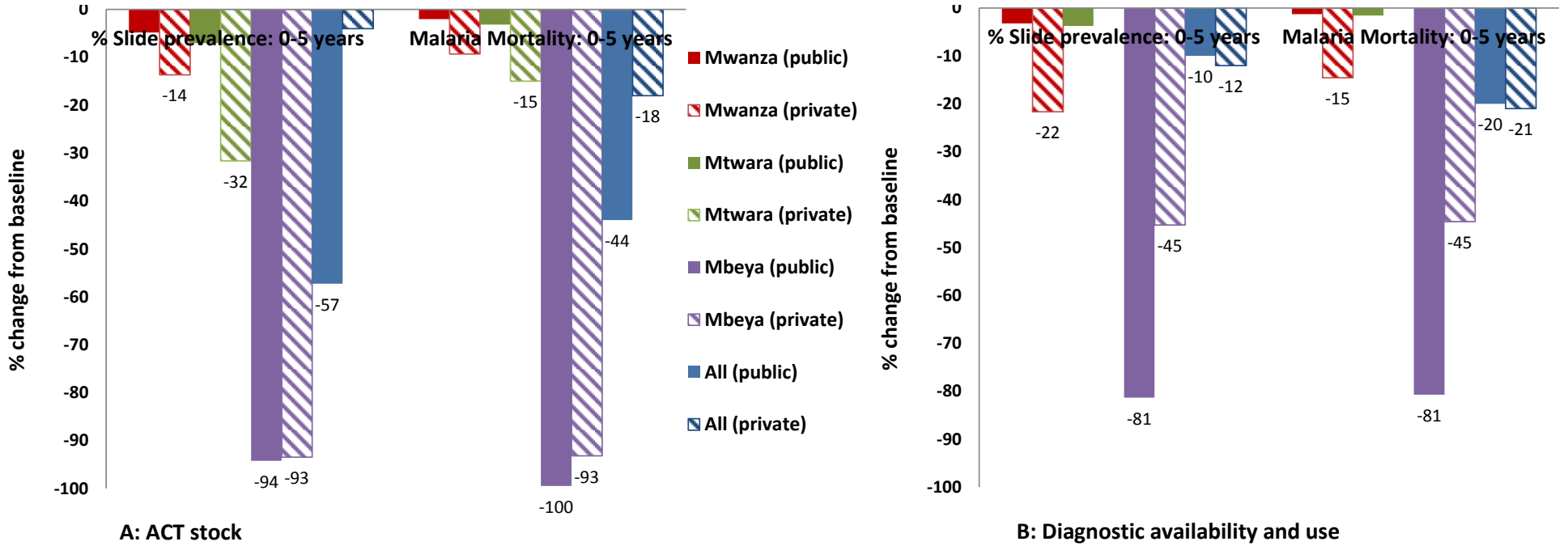
Figure 52B depicts the potential relevant reductions in slide prevalence and malaria mortality due to improved stock of diagnostics and their use in all febrile patients. Compliance with test results has not been varied here. The relative impact of diagnostic deployment is less than that predicted to occur following the improved stocks of ACTs in each matching scenario except when comparing the effect of diagnostics on parasite prevalence and malaria mortality in the Mwanza private sector.

The relative reduction in these two outcomes is higher for the private sector in Mwanza with increased diagnostic deployment compared with 100% ACT stock. This is due to Mwanza's private outlets having adequate levels of ACT stock; hence the change relative to baseline is less. In addition in the private outlets in Mwanza's drug shops, compliance with positive test results is not constrained by a lack of ACT stock. Hence addition of diagnostics improves levels of under-treatment, thereby avoiding progress to clinical sequelae. In Mtwara, outcomes in the private sector are unaffected by diagnostic deployment due to lack of ACT stock in this setting.

Modelling improved access to and use of testing is not predicted to increase malaria mortality, as compliance with positive test results is high. I have assumed here, due to scanty data, that compliance with negative test results is low (i.e. there is the same probability of being treated if not tested). Multiple interventions simultaneously implemented as packages of improvement together are considered in Section 5.5.6.

Figure 52: Reduction relative to baseline in population parasite prevalence and malaria mortality in the under-fives under conditions of A) perfect ACT stock B) 100% stock of RDTs and 100% use in all febrile patients.

Results are shown for each region in public (solid) and private (hatched) sectors Data labels are shown for values greater than 10% relative reduction.



5.5.6 Impact of packages of multiple interventions at community level

The full potential impact of a single intervention to address a systems barrier may not be realised until it is delivered in combination; the value of diagnostic testing may be enhanced by improving levels of compliance to test results. Using the decision-tree, I generated the probabilities of malaria cases and NMFI receiving ACTs in the private and public sectors for both age groups for each of the scenarios summarised in Table 30.

Table 30: Scenarios for improved malaria case management in public and private sectors using IMPACT 2 data

Scenario for primary care (private and public sectors)	Decision tree Parameters
Baseline	
100% diagnostic availability & ACT stock	Probability that a diagnostic is available = 1 Probability that all doses of ACT are available = 1
100% diagnostic use and compliance with results	Probability that a diagnostic is used = 1 Probability that ACT is received if test positive = 1 Probability that ACT is received if test negative =0
100% diagnostic availability, use & compliance	Probability that a diagnostic is available = 1 Probability that a diagnostic is used = 1 Probability that ACT is received if test positive = 1 Probability that ACT is received if test negative =0
100% diagnostic availability, use & compliance & ACT stock	Probability that a diagnostic is available = 1 Probability that a diagnostic is used = 1 Probability that all doses of ACT are available = 1 Probability that ACT is received if test positive = 1 Probability that ACT is received if test negative =0
Presumptive treatment	Probability that a diagnostic used = 0 Probability that QAACT is received if untested = 1

Figure 53A shows the predicted relative reduction in two outcomes: parasite prevalence in U5s and malaria mortality in U5s for each of the 6 packages of case management interventions using the "All Tanzania" scenario. In this "All Tanzania" model, the impact on prevalence of 100% ACT stock in the public sector (Figure 53A) is only surpassed by a policy of presumptive ACT treatment for all fevers in clinic (ACT stock allowing) or with a scenario of 100% stock and 100% diagnostic stock, use and adherence, which is associated with less overtreatment of NMFI. In the private sector 100% use and compliance with diagnostic tests is predicted to result in a small increase in prevalence, likely due to a reduction in the prophylactic effect of treating uninfected individuals and the lack of treatment of sub-patent infections with NMFI.

Figures 53B to D shows the missing impact in each region if a package is implemented nationally, i.e. the difference between the effects anticipated on the basis of all Tanzania predictions and the effect in each region for these outcomes. Positive values indicate the impact is less than anticipated (i.e. missing) and negative values indicate impact greater than anticipated.

All interventions in Mbeya whether private sector or public sector exceed the anticipated relative nationwide effects, as although the absolute changes are small their relative impact in a low prevalence setting is large. The exception to this is the scenario of under-five presumptive treatment, i.e. treating all febrile under-fives with ACTs, as per the previous international treatment guidance before the T3 initiative (WHO, 2012b). This is most likely due to the fact that most clinical cases at low prevalence occur in ages above five and thus mortality is not impacted by presumptive treatment of under-fives, whilst that for over-fives remains unchanged.

In Mwanza and Mtwara the predicted impact of interventions in the public sector is less than predicted nationally, both in relative terms but also in absolute terms despite having higher parasite prevalence. This is due to sector preference i.e. patients are more likely to go to the private sector when febrile in these regions, and therefore the anticipated impact of public sector interventions is diminished.

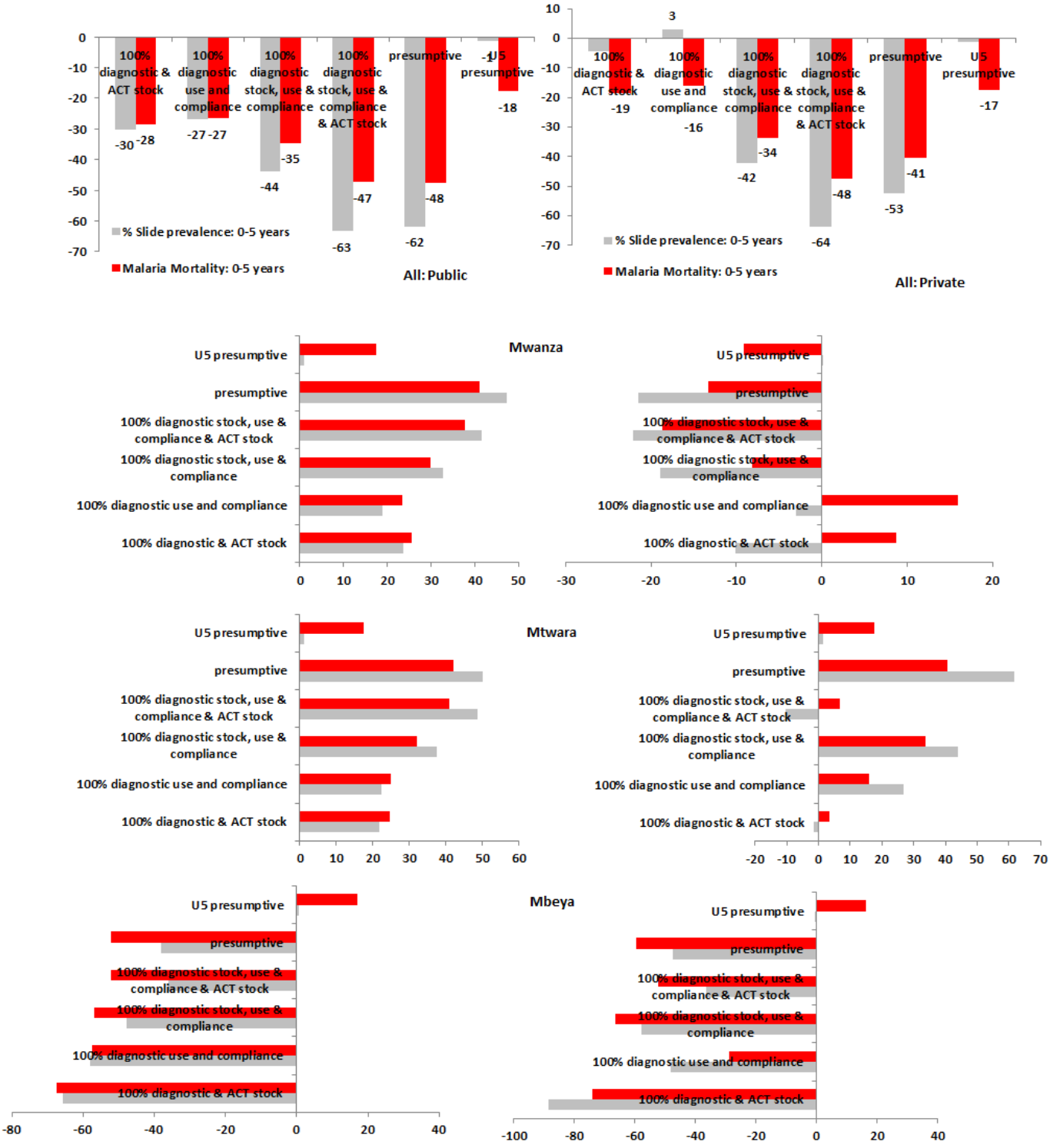
In Mtwara, private sector interventions that do not include ACT stock are not predicted to have any effect since the outlets surveyed by IMPACT 2 in this region all reported stockouts.

Improvements made to treatment delivery in Mwanza through the private sector all exceed the anticipated nationwide relative effect on slide prevalence in the U5s, but are less than expected with respect to U5 mortality with the packages of 1) 100% diagnostic and ACT stock and 2) 100% diagnostic use and compliance.

Within the structure of this model, malaria mortality is avoided by increasing the probability of an uncomplicated malaria case receiving ACTs, by a potentially severe case being treated with ACTs and rectal or intramuscular artesunate or being referred to hospital. In a medium-high prevalence setting, improving diagnostic use and compliance in the private sector is an insufficient intervention to increase proportions of malaria cases following the three pathways above, since although uncomplicated cases may have a higher chance of being treated with an ACT, management of the potential acute severe cases is not affected.

Figure 53: Impact of package of interventions on parasite prevalence and malaria morbidity in under-fives.

A) depicts the relative reduction compared to baseline if these packages are introduced in the private and public sectors using All Tanzania setting. Figures B-D depict the missing impact: i.e. the difference between the effect anticipated (all Tanzania) and the effect in each region for these outcomes. Positive values indicate the impact is less than anticipated (i.e. missing) and negative values indicate impact greater than anticipated.



Increasing the stock in drug shops of ACTs and diagnostics alone, without improving diagnostic use or compliance (given that these are not dependent on stock), overcomes the constraints of stock levels hence reducing the proportion of untreated uncomplicated disease that may progress to severe disease but does not avert the risk of those with early severe disease.

Thus in a medium-high transmission setting a larger package of interventions than just improving supply-chains is needed to match the relative impact expected in lower transmission settings. Therefore when striving to meet international targets such as the Roll Back Malaria targets of a 75% reduction in malaria mortality by 2015, a broader suite of interventions will be needed in higher transmission settings, addressing both community level management of uncomplicated malaria but also the pathways by which severe disease and mortality may be averted.

In Mwanza (medium-high prevalence), modelling referral of all potentially severe cases for hospital management decreased the incidence of malaria mortality in under-fives by 28% relative to baseline (clinic referral) and 37% relative to baseline (private referral). There was negligible impact on slide prevalence as community level treatment especially of NMFI is not affected. In Mtwara (medium-high prevalence) this effect was not seen as the hospitals surveyed did not have artesunate in stock, and hence within the model no effective hospital treatment was possible.

As described previously in Chapters 2 and 4, until recently a policy of presumptive treatment for febrile U5s was internationally recommended. Modelling this policy in the “all-Tanzania” scenario decreases mortality levels in the U5s but has little impact on parasite prevalence levels in the same age group in comparison to a policy of presumptive treatment for all ages, which reduces prevalence in U5s by approximately 40% whether in the private or public sector. At a regional level, this strategy of paediatric presumptive treatment also has minimal effect on parasite levels, whereas the effectiveness of all-age presumptive treatment is constrained by regional preferences for the private sector and high levels of ACT stockouts in the private sector (Mtwara) and the public sector (Mwanza). The results show that to reduce prevalence and transmission targeting just the U5 age group, which is not the main reservoir for parasite infection, is not effective. In contrast this strategy does appear to be effective in reducing levels of U5 mortality, by prevention of uncomplicated disease progressing to severe disease if left untreated, in the medium-high settings where most clinical disease is in this age group. However as seen in the Mwanza public sector and Mtwara private sector, ACT stockouts are a barrier to this potential effect.

5.5.7 Impact of packages of multiple interventions at hospital/tertiary level

Table 31 summarises 11 scenarios that I explored for each region considering their impact on the incidence of severe disease and malaria mortality. The impact of increased treatment seeking for febrile illness has been described in Section 5.5.3 and the effects of increased referrals for potentially acute severe cases from private and public community sources discussed in Section 5.5.6.

Table 31: Scenarios for improved access and severe malaria case management

Scenario for access and severe case management	Model Parameters
100% access/treatment seeking	$f\_{NTX} = 0$
100% hospital access/treatment seeking	$f\_{H} = 1$
100% treatment of all hospitalised severe malaria patients with ACTs and artesunate	$ftr\_{H} = 1$
Duration of delay to seek care/access hospital	$1/r\_{H} = 0.5$
100% referral of severe cases to hospital from clinic	$ftr\_{REFCL} = 1$ (and hence $ftr\_{SEVCL} = 0$)
100% referral of severe cases to hospital from private outlets	$ftr\_{REFPR} = 1$ (and hence $ftr\_{SEVPR} = 0$)
100% stock of artesunate in clinics for potential acute severe malaria treatment	$ftr\_{SEVCL} = 1 * ftr\_{CL}$
100% treatment of all potential acute severe malaria in clinic	$ftr\_{SEVCL} = 1$ (and hence $ftr\_{REFCL} = 0$)
100% referral of acute severe patients from private and public sectors & 100% treatment of all hospitalised severe malaria	$ftr\_{REFCL} = 1$ (and hence $ftr\_{SEVCL} = 0$) $ftr\_{REFPR} = 1$ (and hence $ftr\_{SEVPR} = 0$) $ftr\_{H} = 1$
100% treatment seeking at hospital & reduced duration of delay to seek care at hospital	$f\_{H} = 1$ $1/r\_{H} = 0.5$
100% referral of acute severe patients from private and public sectors & 100% treatment of all hospitalised severe malaria & 100% access to hospitals	$ftr\_{REFCL} = 1$ (and hence $ftr\_{SEVCL} = 0$) $ftr\_{REFPR} = 1$ (and hence $ftr\_{SEVPR} = 0$) $f\_{H} = 1$ $ftr\_{H} = 1$

The health systems interventions considered here have little effect on parasite prevalence levels since they do not concern the majority of infections that are either uncomplicated, asymptomatic or subpatent. Due to the structure of the model, severe infections may be prevented by referral of those at risk of acute severe malaria if they are then treated successfully at hospital.

Increasing the probability of receiving treatment at hospital is effective only in reducing malaria mortality, but not preventing severe disease. In this work, I have assumed that treatment for severe disease is the recommended first-line regime of Artesunate plus ACTs and have considered quinine equivalent to non-treatment. Figure 54 illustrates the impact of single and packages of interventions in preventing severe disease incidence and reducing malaria-related mortality by age for each region.

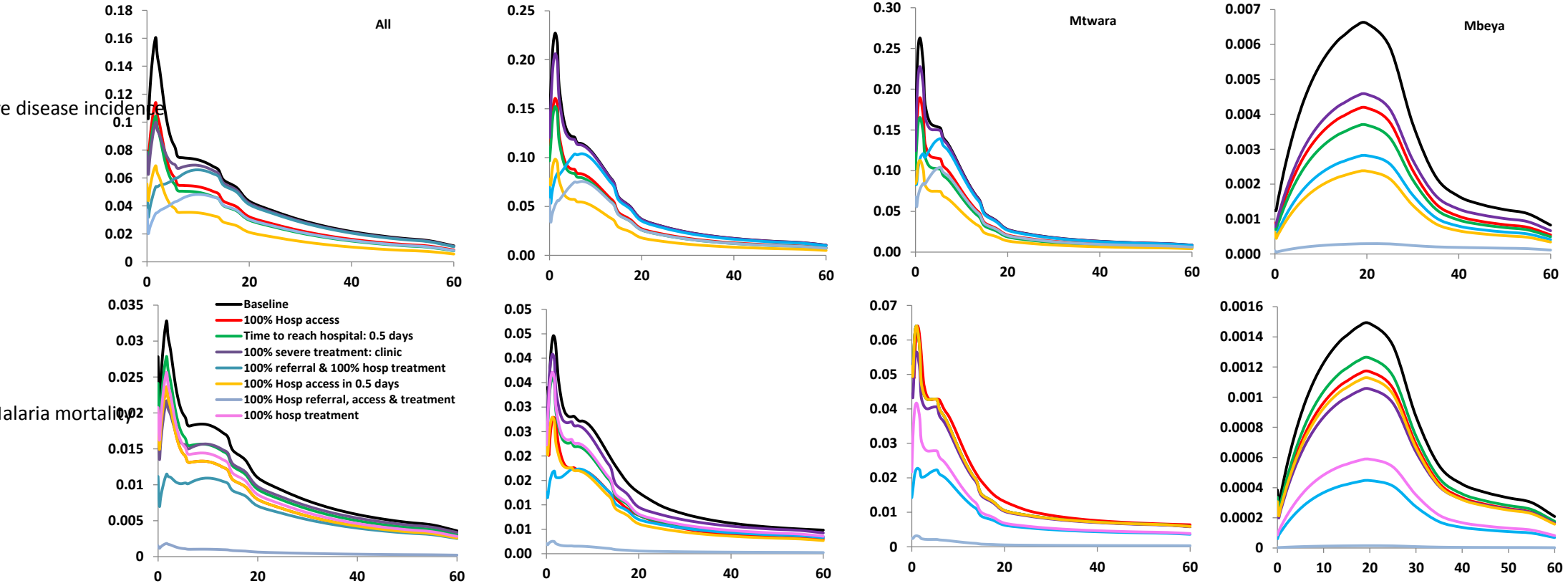
The most effective single interventions to prevent the incidence of severe disease in U5s are improved probability of seeking treatment at a hospital and reducing the time taken to access a hospital (52% reduction from baseline in Mwanza; 35% in Mtwara and 47% all regions). As discussed previously, these figures represent malaria cases that are referred from the community to hospital and thus bypass the severe disease state in the model. If they are not appropriately treated, individuals enter the hospitalised severe (HSev; figure 48) state with a high probability of death. With increased delay to seek care, levels of severe disease rise as expected.

Combinations of intervention such as 100% referral to hospital from both community sectors or 100% referral with 100% probability of attending a hospital, also affect the group of patients who could potentially avoid severe disease and its consequences if treated appropriately at the hospital. These combinations could result in a shift in the pattern of severe disease away from a peak at early ages (greater than 70% relative reduction in 0-5 year olds in Mwanza) towards a more sustained lower incidence pattern across 0-20 years of age similar to that seen in Mbeya and low prevalence settings. This is not an effect of immunity but of health systems interventions potentially preventing the development of severe disease in those that are at risk.

If effective treatment in a hospital could be provided, then these cases would be averted. In the model, if these cases are not successfully treated they enter the HSev compartment where they are still infectious (in the model, the state HSev is as infectious as Sev). Hence, in these two scenarios there is no change in population prevalence seen in these age groups, as the probability of being treated remains unchanged.

Impact on malaria mortality follows a similar pattern but significant reduction requires improvement in hospital-based treatment; here related to the stock levels of artesunate. This is especially the case in Mtwara where no hospital reported artesunate stocks. Under conditions of 100% referral of potential severe cases from the community, 100% access or probability of seeking care at a hospital and 100% treatment at hospital, the model predicted over 96% reduction in malaria mortality even in high prevalence settings. 100% referral and 100% hospital treatment halved mortality in Mtwara and Mwanza in the under-five age group. The potential reduction in U5 mortality with this strategy was greater than the potential reduction achieved by improving the treatment of potentially severe cases in clinic with rectal/IM artesunate (9.5% relative reduction in Mtwara; 32% in Mwanza). This is because of higher levels of private sector preference in these regions, but also because developing hospital capacity also allows treatment of those patients who develop severe disease as a result of delayed or ineffective treatment of uncomplicated malaria (which is not affected by community severe disease treatment in this model). Thus placing specific interventions to target malaria mortality may be more effective in some contexts through a hospital-based strategy rather than a community-based strategy, provided high levels of referral and hospital access can be achieved.

Figure 54: The impact of single and packages of interventions in preventing severe disease incidence and reducing malaria-related mortality on age-incidence curves for each region.



5.5.8 Hierarchy of packages and addressing local priorities

The results presented so far have highlighted the need to consider the barriers posed by local health system structures and prevailing population preferences as well as malaria epidemiology to the implementation of ACT treatment programmes. In addition regional control priorities, for example reducing parasite prevalence versus preventing severe disease, should determine interventions to bolster the ability of the programme to meet its objectives.

Clinical interventions based on treatment of infected cases are dependent on many health systems variables, as demonstrated above, but also on the probability of an individual becoming symptomatic. In high transmission settings, this is most likely in children under the age of 5, as depicted in Figure 50, but this is not the age group in whom slide prevalence is greatest. Few of the interventions considered in this analysis exert a greater relative effect on the parasite prevalence in this older age group compared with the under-fives. This occurred in the Mtwara region, a high transmission setting where levels of treatment seeking in the over 5 age group are higher than that in other regions as shown in Table 32.

In Table 32 I rank for each region, as well as for all regions of Tanzania, the 5 interventions that produce the largest relative reduction in the three outcomes listed, namely parasite prevalence in the 0-5 years and 2-10 years age groups and mortality in the under 5s. In addition, I include an estimate of the probability of NMFI receiving an ACT in that scenario (low, baseline or high) to indicate whether this strategy might also result in inappropriate treatment with anti-malarials.

The hierarchy for reduction of parasite prevalence in each region was the same for both age groups, and all the interventions were community-based. The most effective intervention in all settings for affecting transmission and parasite prevalence was overhauling the provision of care through the private sector by achieving 100% diagnostic availability, use and compliance alongside ACT stock. This is due to a combination of individuals preferring to access antimalarials through the private sector and low baseline levels of quality at drugs shops and pharmacies. In Mtwara, where the population prefer seeking treatment at the private sector but which at the time of the survey experienced complete ACT stockouts in drug shops, prevalence is predicted to be reduced by greater than 70% relative to baseline. In Mwanza where drug shops had ACT in stock, this improvement from baseline is predicted to be greater than 80% due to a very strong private sector preference.

In Mwanza the top 3 intervention packages were all in the private sector. Presumptive treatment at drug shops for all ages ranked second, lower than the package of 100% diagnostic availability, use and compliance alongside ACT stock, for the reduction of parasite prevalence indicating that ACT stocks did act as a small

constraint here. However the third most effective package to impact on prevalence levels was 100% diagnostic availability, use & compliance. This suggests that improved identification of malaria cases, when stock levels are only a minor constraint, can prove a successful means of achieving ACT effectiveness. The fourth and fifth most useful packages in the Mwanza region, as regards addressing parasite prevalence, are much less effective than the top 3 (less than 25% relative reduction compared with 65-85% reductions described earlier).

In Mtwara, the success of packages to reduce parasite prevalence levels is influenced by the lack of ACTs in drug shops in the endline survey. Hence whilst the most effective package is in the private sector though 100% availability, use and compliance with diagnostics as well as 100% ACT stock, the second most effective intervention would be to eliminate any care at the private sector and ensure only public sector treatment, thereby halving the parasite prevalence in U5s. In Mtwara, the success of the third most effective intervention package drops to 28%, suggesting that barriers in terms of access and sector preference as well as quality need to be addressed in this region.

Considering the "all-Tanzania" scenario, the second to fourth most effective packages for the reduction of malaria prevalence were all health facility based, which can be explained by the assumed preference for public sector care overall. 100% diagnostic availability, use and compliance alongside 100% ACT stock in a facility gave similar reductions as the same intervention in the private sector. Each of the top five intervention packages in the "all-Tanzania" setting were predicted to lead to a greater than 60% relative reduction in parasite prevalence.

This is likely to have been skewed by the results obtained for the Mbeya setting where all of the top 5 interventions modelled led to 100% reduction in parasite prevalence levels. Mbeya is a low transmission setting, so although the actual predicted reductions may have been small, they may be sufficient to eliminate the malaria parasite. These results suggest that in low prevalence areas, the health systems barriers to achieving the full effectiveness of ACTs in reducing transmission may be achievable through health systems improvements, such as ensuring all febrile patients attend a source of treatment even if the quality of treatment provided is not actually improved.

Table 32: Hierarchy of interventions for each region with respect to relative reduction in parasite prevalence (in under-fives and 2-10 years) and mortality (under-fives)

	% reduction in parasite prevalence from baseline					% reduction in mortality from baseline			
	Source	Intervention	f_{NMFI} @ source	0-5 years	2-10 years	Source	Intervention	f_{NMFI} @ source	0-5 years
All Tz	Private	100% diagnostic availability, use & compliance & ACT stock	Low	63.8	60.6	Hospital	100% referral, access & treatment	N/A	95.4
	Clinic	100% diagnostic availability, use & compliance & ACT stock	Low	63.4	60.2	Hospital	100% referral & treatment	N/A	67.9
	Clinic	Presumptive treatment	High	61.8	58.3	Private	100% diagnostic availability, use & compliance & ACT stock	Low	47.6
	Clinic	100% ACT	High	57.3	53.8	Clinic	Presumptive treatment	High	47.5
	Private	Presumptive treatment	High	52.6	49.1	Clinic	100% diagnostic availability, use & compliance & ACT stock	Low	47.3
Mbeya	Private	100% diagnostic availability, use & compliance & ACT stock	Low	100.0	100.0	Private	100% diagnostic availability, use & compliance & ACT stock	Low	100
	Private	Presumptive treatment	High	100.0	100.0	Private	Presumptive treatment	High	100
	Clinic	100% diagnostic availability, use & compliance	Low	100.0	100.0	Clinic	100% diagnostic availability, use & compliance	Low	100
	Clinic	Access to clinic only	Baseline	100.0	100.0	Clinic	Access to clinic only	Baseline	100
	Clinic	Presumptive treatment	High	99.9	99.9	Clinic	Presumptive treatment	High	100
Mtwara	Private	100% diagnostic availability, use & compliance & ACT stock	Low	69.8	73.9	Hospital	100% referral, access & treatment	N/A	95.1
	Clinic	Access to clinic only	High	46.4	51.1	Hospital	100% referral & treatment	N/A	58.9
	Private	100% diagnostic availability & ACT stock	High	28.0	31.8	Private	100% diagnostic availability, use & compliance & ACT stock	Low	40.9
	Private	100% ACT	High	27.8	31.6	Hospital	100% Hospital Treatment	N/A	36.3
	Clinic	100% diagnostic availability, use & compliance & ACT stock	Low	12.4	14.6	Clinic	Access to clinic only	Baseline	25.6
Mwanza	Private	Private: 100% diagnostic availability, use & compliance & ACT stock	Low	85.9	83.6	Private	100% diagnostic availability, use & compliance & ACT stock	Low	66.3

	Private	Presumptive treatment	High	74.1	70.3	Private	Presumptive treatment	High	53.8
	Private	100% diagnostic availability, use & compliance	Low	61.0	-56.8	Private	100% diagnostic availability, use & compliance	Low	41.7
	Clinic	100% diagnostic availability, use & compliance & ACT stock	Low	21.9	19.2	Private	100% diagnostic stock & use	Low	14.6
	Private	100% diagnostic stock and use	Low	21.6	19.0	Clinic	100% diagnostic availability, use & compliance & ACT stock	Low	9.5

Table 32 also lists the five packages of interventions predicted to most successfully reduce malaria mortality in the U5s. Across Tanzania, improving hospital referral, access and treatment reduces mortality in this age group by 95%, which exceeds the targets set by Roll Back Malaria to be achieved by 2015 (WHO, 2013). Community level interventions such as the top three packages to impact on prevalence are predicted to halve mortality rates.

Hospital-based interventions are also the most effective packages in Mtwara to reduce U5 mortality from malaria. In this setting where there is a low probability of receiving an ACT in the community due to private sector stockouts, mortality may be prevented through improvements at hospital level. Whilst ensuring 100% hospital referral, access and treatment is predicted to reduce mortality by 96%, the top intervention to reduce parasite prevalence (namely 100% diagnostic availability, use and compliance alongside 100% ACT stock in the private sector) can only decrease U5 mortality by 41% relative to baseline. In contrast, instituting 100% treatment of all severe cases in hospital with artesunate and ACTs alone can decrease mortality in U5s by a third. Eliminating all private sector treatment, i.e. ensuring all treatment seekers are diverted to the health facility, may reduce mortality by 25% compared to baseline.

In contrast to these two settings, in Mwanza, a medium-high transmission setting, the most effective packages are all at community level, particularly in the private sector. This is because the baseline high probability of hospital treatment at the Mwanza hospital is higher than other settings, thus the relative impact of interventions is less, in combination with poor probabilities of receiving an ACT in either sector at baseline due to stockouts. Therefore the interventions that relatively affect childhood mortality levels are those that address the greatest barriers, namely community level treatment. In Mwanza the most successful packages to tackle U5 malaria mortality are also those that are most effective in relatively reducing parasite levels, and these private sector packages also have a greater relative impact in Mwanza than they do in other regions. Thus driving control efforts through drug shops and pharmacies in Mwanza is predicted to decrease malaria mortality by 40-60% whilst reducing malaria prevalence in the U5s by up to 80%. The relative reductions are less profound than those predicted with hospital-based interventions in other settings as expected as these intervention packages do not directly impact on the management severe disease but instead on preventing progression to morbidity and mortality.

In Mbeya, as community level interventions are predicted to eliminate parasite prevalence, they similarly reduce mortality to zero.

5.6 DISCUSSION

Using IMPACT 2 study data in a decision-tree and then in a malaria transmission model extended to incorporate access and quality of healthcare, I have demonstrated that health systems pose barriers to realising the potential effectiveness of ACTs in both treating clinical disease and reducing transmission. These constraints are often region-specific and need to be considered in conjunction with local epidemiology in order to maximise the impact of using ACTs as both treatment and prevention.

In the examples used here, the hierarchy of intervention packages at an "all-Tanzania" level are different to those for the low transmission setting of Mbeya and the medium-high settings of Mwanza and Mtwara when addressing malaria parasite prevalence or mortality in children under 5. Stockouts and the local population's preference for buying anti-malarials at drug shops when febrile, as well as differences in provider behaviour with respect to the use of diagnostics, lead to varying predicted outcomes for the Mwanza and Mtwara settings despite similar parasite prevalence levels.

In low prevalence scenarios, such as Mbeya, some single interventions such as ensuring all health facilities have stocks of ACTs or that all cases of fever seek care at any source, if implemented ideally are modelled to eliminate malaria in the region and thus also any ensuing mortality. However a policy of presumptive treatment for U5s alone, in either sector, does not reduce malaria mortality due to the epidemiology of clinical malaria in low transmission: most symptomatic disease occurs above the age of five years.

Intervention packages in higher prevalence scenarios are more complicated, and need to be formulated with careful consideration to local priorities as well as health systems. For example, improving access through promotion of treatment seeking or a programme of community healthcare workers is not effective if drug shops or facilities have stock outs of ACTs. In addition, aiming to increase the proportion who seek care within 24 hours can reduce malaria mortality in U5s but has little impact on parasite prevalence or transmission.

Improvements in the quality of care received, by addressing barriers such as ACT stockouts or the use of diagnostics, need to be broad ranging and in the sector preferred by the local population in order to have significant effect. This means in Mwanza and Mtwara that innovative ways may need to be found of including the private sector in malaria control efforts. The ADDO programme had been rolled out in Mtwara before the time of the IMPACT 2 baseline survey. However only small sample of outlets were surveyed here and at endline reported no ACT stock, which would have prevented the effects of this being seen in this analysis. The ADDO programme was implemented in the Mwanza region after the IMPACT 2 study data collection, but the modelling of packages shows that if this private sector improvement had been rolled out here earlier there might have been important clinical gains. The AMFm initiative in private outlets did lead to

significant improvements in stock levels in Mwanza and Mbeya as well as overall across Tanzania. In these areas decreases in slide prevalence were observed in study data and predicted by the model (Figure 35). However changes over this time period were also being made in the public sector health facilities, including the roll out of RDTs and increase in availability of other malaria interventions, and so the reductions in prevalence cannot entirely be attributed to private sector drug subsidies.

I also examined the competing policies of improving ACT stocks and improving diagnostic availability and use. RDT use has been advocated in the T3 strategy (WHO, 2012b) to reduce overtreatment of non-malarial febrile illness, and the IMPACT 2 study data suggests that there is improved compliance to test results, when RDTs are used. The model predicts that a holistic testing strategy, in the absence of better ACT stocks, would have limited effect on transmission (especially if RDT quality was poor and did not identify asymptomatic infections) but could reduce mortality levels, through improved identification of malaria cases. IMPACT 2 study data highlights that malaria undertreatment, i.e. cases not receiving ACTs, does occur even when ACTs were present, and so further underlines the value of including testing in treatment guidelines.

As explained previously, the model is structured so that severe disease occurs through the lack of effective or delayed treatment of uncomplicated malaria, or may follow an acute course with severe disease on presentation. Severe disease may therefore be averted by improved timely community treatment (private or public sector). It may also be averted by administration of artesunate and ACTs in the community or by referral to hospital. The model therefore counts cases referred as not having disease, if they are not appropriately treated at hospital then they enter a separate hospitalised severe state alongside established severe disease that is not treated with a higher risk of mortality (HSev). The results from the model demonstrate that the potential to avert severe disease (provided hospital treatment can be administered) is greater with improved access to hospitals, i.e. increased probability of attending a hospital and increased rates of referral of acute severe cases than relying on community management. Hospital-based strategies in the all-Tanzania and Mtwara settings were also the most effective means of reducing malaria mortality. In Mwanza, the quality of hospital treatment was better than in other regions, and in this setting the model predicted that addressing mortality through community health systems interventions would be more effective.

However community based interventions have the advantage of also impacting transmission, because it is in the community that clinical cases as well as sub-patent and asymptomatic reservoirs of infection (Manjurano et al., 2011, Okell et al., 2009a) may be treated. Okell et al suggested that presumptive treatment may allow the prophylactic effect to extend to individuals without malaria and therefore reduce transmission (Okell et al., 2008a), and this is also shown here when modelling the impact of a policy of presumptive treatment in either sector with high rates of NMFI treatment with ACTs. However, in all the settings, instituting

diagnostic-led treatment with good stocks of ACTs in the sector that the local population preferred was more or equally effective as a policy of presumptive treatment in that sector. Thus improved targeting of malaria clinical cases and asymptomatic NMFI cases treated opportunistically (but not sub-patent infections) may allow similar levels of transmission reduction as administration of ACTs to all with a fever. This is based on the assumption that RDT specificity and sensitivity did not vary across the settings, which may cause this strategy to be less effective in cases of poor quality diagnostic procedure.

The model is limited by its dependence on data collected through 3 different surveys. In particular the household and outlet surveys were based on recall data that is subject to recall bias, and has been shown to be unreliable (Eisele et al., 2013). Small sample numbers in some regions, for example just 3 outlets in the Mtwara outlet survey at endline, none of whom stocked ACTs, can skew the inputs and hence the model outcome, and reduce the applicability of the regional results. In addition, the surveys did not control for the "Hawthorne effect" (McCambridge et al., 2014), and so the presence of a survey team may alter the behaviour of staff or outlet owners as well as attracting the interest of individuals who may have otherwise not attended. This could alter estimates for the probability of testing and adherence to guidelines as well as potentially overestimating the numbers of NMFI attending. A lack of control areas in the surveys and timing proximity to multiple interventions, e.g. AMFm and facility-based RDT rollout, mean that it is difficult to attribute the impacts seen to any particular health systems intervention.

In addition, the decision-tree analysis was only able to capture dependencies between variables for some parameters in the public sector, for example the probability of receiving an ACT for a positive test if ACT was in stock. This was not possible in the private sector analysis due to using an amalgamation of outlet and household surveys. In addition I did not include the possibility of individuals attending multiple sources of treatment in case of stockouts at the initial point of care. Other potential dependencies, for example the probability of testing provided ACTs were in stock or the impact of recent stockouts on current prescribing were not accounted for, and may be important as seen where ACTs were not prescribed for a positive test despite stock in place.

Tanzania has made great progress over the past decades in addressing malaria control through a variety of innovative local (e.g. ADDO programmes) and global (e.g. AMFm) initiatives. This research has attempted to bring together both quality of care, community coverage and access interventions at primary and tertiary levels to model and quantify their predicted combined impact. It highlights that key policy considerations should include local patterns of health system utilisation as well as epidemiology, in order to develop targeted and nuanced malaria control plans for each region to maximise the potential of ACTs as treatment and to reduce transmission.

6 DISCUSSION

This thesis has described the development of a mathematical malaria transmission model to explore the impact of health systems barriers on the effectiveness of an ACT (Artemisinin Combination Therapy) treatment programme on clinical outcomes such as malaria related morbidity and mortality as well as transmission outcomes such as parasite prevalence. It considers public and private sector sources of care, as well as tertiary care for severe illness. A decision-tree model was developed to estimate the probability of malaria and NMFI case management with ACTs. In addition, it examines the potential gains to be made through alleviating these health systems barriers, and considers optimal packages of interventions for different transmission settings. Discussion of the detailed findings is included in the relevant Chapters. This Chapter provides an overall summary of the key findings, describes some of the main limitations of the thesis, considers the implications of the findings within the wider context of malaria control and makes some suggestions regarding work which would further this stream of research.

6.1 SUMMARY OF FINDINGS

In Chapter 1, I outlined the epidemiology and clinical features of malaria infection, and the role of ACTs as first-line treatment. I summarised the evidence for the use of ACTs in malaria control through successful treatment programmes (symptomatic case management) in South Africa, Ethiopia and Zanzibar , and also more recent attempts using ACTs to reduce transmission through mass drug administration (MDA) and mass screening and treatment (MSAT). Although mathematical modelling of such strategies has shown promise (Okell et al., 2011), field trials have proved less successful in delivering sustainable change. A potential cause for such policies not proving as effective as predicted through modelling, is achieving the necessary coverage in a sustained fashion. Although as described in Chapter 1, health systems in many malaria endemic countries are recognised as impoverished and weak, there has been little modelling of the role of health systems factors in reducing transmission. Tediosi *et al.* used a decision-tree modelling approach to predict incidence and mortality, and integrated this into a malaria transmission model to predict the cost-effectiveness of treatment in different prevalence and coverage scenarios (Tediosi et al., 2006). Cost-effectiveness analysis has been used to evaluate the use of RDTs to reduce childhood mortality in different transmission settings (Rafael et al., 2006). However previous studies modelling health systems effects on malaria transmission were not identified.

The literature review in Chapter 2, used the "systems effectiveness" framework to identify potential systems constraints to the effectiveness of ACT treatment programmes, summarized in two main categories:

a) ensuring timely access to healthcare, i.e. distance to sources of care, the costs of travel, delays and the probability of seeking treatment
b) the quality of care received at a source of treatment, dependent on several components including shortage of trained staff, drug stockouts, and the overtreatment of non-malarial febrile illness (NMFI) with ACTs due to presumptive treatment of fevers which occurred especially in the private sector.

The same approach was used to review the evidence for interventions to address these barriers to successful implementation of ACT case management. The studies reviewed suggested that some strategies that have traditionally formed a part of health systems strengthening such as training may have less impact than intended. However novel use of mobile phones to enable improved stock-management and task shifting to community health care workers to reduce delays and promote treatment seeking whilst still providing quality care were reported to show promising results. Few of these interventions had been implemented at scale. However AMFm (Affordable Medicines Facility-malaria) a multi-national scheme to harness the private sector, i.e. drug shops and pharmacies, as well as the public sector into national control efforts through the provision of subsidised and quality assured ACTS (QAACTs), has proved successful. When evaluated in the initial malaria endemic countries to implement the scheme, drug subsidy to the end user was found to have been passed on and stocks of QAACTs in formerly poorly regulated outlets had improved.

In Chapter 3, a deterministic compartmental model of malaria transmission previously developed (Griffin et al., 2010, Griffin et al., 2014) was extended in stages to incorporate dimensions of access to primary level or community sources of ACTs i.e. public sector health facilities and private retail outlets, and the quality of care received at each source. Quality of care was assumed to be the probability of receiving an ACT, and this was iteratively expanded to address the issue of NMFI treatment, including for the opportunistic treatment of asymptomatic malaria infections. From a public health perspective, the effectiveness of a treatment programme must also be considered with respect to averting morbidity and mortality and not only impact on transmission. Therefore different pathways by which the development of severe malaria could be avoided or treated in the community or at tertiary levels facilities were also integrated. At this stage parameters were sought from the literature. Model outputs identified that systems interventions have a proportionately greater clinical impact than epidemiological impact in all settings, and that both have a larger relative impact at low transmission levels. Although the prophylactic effects of treatment potentially may have an impact on transmission, modelling a reduction in NMFI overtreatment did not lead to unwanted rises in infection, at assumed baseline levels of malaria care. Whilst at low transmission settings,

improved provision of community level care was modelled to reduce the incidence of severe disease and mortality, in higher transmission scenarios developing tertiary care, both in terms of access and quality, is required to decrease malaria-related mortality.

Chapter 4 sought to develop an approach to estimate the key quality of care parameters, i.e. the probability of a malaria case receiving an ACT and the probability of an NMFI receiving an ACT when attending a health facility or buying drugs from a private pharmacies and retail outlets. A decision-tree framework, incorporating the chief steps of case management, was used to account for the multiple pathways by which a febrile case attending a source of care may receive an ACT, whether they are tested or untested. At this stage, the decision tree was parameterised using values sourced from the literature. In the public sector, the most critical step to improving malaria cases receiving treatment was the presence of ACT stocks (29% increase; 95% UI: 20.5-36.1%). Interventions targeting diagnostic use reduced NMFI mismanagement, but had less effect on malaria treatment. In the private sector, the probability of malaria cases receiving QAACTs was very low, and required a large spectrum of interventions to improve case management.

Using Tanzania as a case study, the probability of receiving an ACT was compared before and soon after the rollout of the T3 guidelines promoting diagnostic led management of fever at all ages. The model predicted that overall the proportion of malaria cases receiving an ACT would have reduced by 19.5% (95%UI: 11-27%), despite a doubling in cases tested and treated appropriately. However this was outweighed by a fourfold reduction in malaria cases receiving ACTs through other pathways, e.g. if untested. Tanzania was also used as a case study to assess the AMFm initiative. The model predicted that the proportion of malaria cases treated with QAACTs would increase from 0.07% to 13.6% (95% UI: 10.8-16.6%), but that NMFI overtreatment would also similarly increase, as testing and prescribing practices were not concurrently reported to improve.

The decision-tree approach was used to consider how case management interventions could reduce the treatment gap whilst decreasing treatment excess, e.g. at baseline in the Tanzania public sector case study only half the patients that need ACTs were predicted to actually receive them, whilst only 20% of those who were treated with ACTs needed this treatment. The results from modelling interventions to improve this balance suggest a tension between addressing issues of stock or provision or ACTs and the use of diagnostic tools, depending on local priorities.

Chapter 5 integrated the model developed in Chapter 3 and the decision-tree approach from Chapter 4 to predict the impact of changes in health systems factors and case management on clinical outcomes and malaria prevalence. The model used data collected by the IMPACT 2 study in baseline (mid-late 2010) and endline (late 2011-mid 2012) household, health facility and outlet surveys in three regions of Tanzania with

differing transmission settings (Mbeya, Mtwara and Mwanza). The IMPACT 2 study aimed to evaluate the operational success of the rollout of RDTs in government health facilities and AMFm in private outlets. The model outcomes demonstrate that the optimal packages of interventions at a national level are not always the ideal interventions at a regional level, but that success depends on local epidemiology, prevailing health systems and population preference for either government-funded primary care or private drug shops and pharmacies.

In low prevalence scenarios (e.g. Mbeya) modelling some single interventions, such as increased ACTs stocks or improved access to any source of anti-malarials, if implemented at high levels of coverage may reduce prevalence of malaria sufficiently to eliminate transmission and clinical complications. A policy of presumptive treatment of U5s, as per international guidance prior to 2010, was not predicted to be as effective in this setting, presumably because symptomatic disease occurs in older children and adults. Modelling interventions in medium-high transmission settings (e.g. Mwanza and Mtwara) required combinations of health systems strengthening to impact clinical and transmission outcomes, depending on the baseline state of healthcare provision and the local community's preference for private or public care. For example, improving access to health facilities, e.g. through increased health posts or community health workers, is limited in its effect if ACT stocks are the constraint to treatment. The rollout of the T3 guidance promoting diagnostic-led treatment in the public sector was predicted to have had a limited effect on parasite prevalence, but could reduce mortality levels through identification of malaria cases (and reducing under-treatment) assuming high quality tests.

In medium-high prevalence scenarios (with a private sector preference in both) improving diagnostic use and compliance in the private sector was insufficient to impact severe disease incidence noticeably. Similarly improving ACT stock in drug shops (as per AMFm) without improving diagnostic use or compliance (given that these are not dependent on stock), overcame the constraints imposed by stock levels hence reducing the proportion of uncomplicated disease that if untreated can progress to severe disease but did not avert the risk of progression those with early severe disease, which was assumed to require artesunate. Improving access to tertiary care is modelled to be more effective in averting severe disease, if treatment with artesunate and ACTs can be administered at hospital, than management of those at risk of early severe disease at a primary care level (i.e. with rectal or intramuscular artesunate), although in reality both strategies may be needed.

Combinations of interventions such as 100% referral to hospital from both primary care sources, or 100% referral with 100% probability of attending a hospital, was modelled to result in a shift in the pattern of severe disease away from a peak at early ages (greater than 70% relative reduction in 0-5 year olds in Mwanza) towards a more sustained lower incidence pattern across 0-20 years of age similar to that seen in

Mbeya and low prevalence settings. This was not an effect of immunity but demonstrates the impact of health systems interventions potentially preventing the development of severe disease in those that are at risk. Hospital-based strategies were also the most effective means of reducing mortality, through the treatment of severe hospitalized disease in these settings.

However primary care based interventions were more effective as regards impact on transmission. Diagnostic-led therapy in association with adequate stocks of ACTs were as effective in all settings as a policy of presumptive treatment of all fevers as malaria, reducing parasite prevalence in U5 in Mwanza by 86% when implemented in the private sector compared with 74% reduction with a policy of presumptive treatment in the private sector. This suggests that potential opportunistic benefits of NMFI treatment of asymptomatic cases and the prophylactic effect associated with ACTs may be matched by a policy of targeting and treating symptomatic cases across all settings.

6.2 LIMITATIONS OF THE THESIS

Mathematical modelling is inherently limited by the complexity of vector-borne disease dynamics, reliance on input data and uncertainty of underlying assumptions especially regarding the applicability across settings.

6.2.1 Model limitations

The structure of the transmission model was based on a previously developed model (Griffin et al., 2010, Griffin et al., 2014, Griffin et al., 2014), which incorporates acquisition and loss of malaria immunity in order predict age-related patterns of disease. The extensions made regarding sources of ACT treatment simplified the sectors to only public health facilities and private retail outlets at community level, as well as larger health centres or hospitals with inpatient capacity for management of severe disease. In reality the spectrum of sources of antimalarials at primary level is wide (Littrell et al., 2011a) and varies between rural and urban settings, as well as between countries. This simplification may lead to the model outputs not reflecting some of the nuances of health systems particular to these different scenarios, as well as either over or underestimating the impact of interventions implemented through a sector e.g. the impact of drug subsidies may be greater in urban areas (Cohen et al., 2010) where there is a greater density of accredited pharmacies than in rural areas.

Chapter 2 summarised the potential effect that distance to a treatment source and the ability to access care (e.g. costs of travel) may have on the effectiveness of a treatment programme. These dimensions of access were aggregated into a single parameter, namely the probability of seeking treatment which does not capture the contributions that each of these dimensions individually but was more readily available in the literature and through survey data. It would be interesting to disaggregate the interaction of distance and cost in future work, especially to model the impact of schemes aimed at addressing the barrier of access such as Community Health Workers. In addition the structure of the model did not allow for treatment seeking at more than one source of treatment, which could account for the higher levels of ACT treatment estimated in the IMPACT 2 study than within this analysis and reduce the predicted impact of stockouts.

A further limitation is the absence of seasonality in the model, not only in the transmission model itself but also with respect to seasonal changes in access to care or quality of care. IMPACT 2 study collected data in both the rainy season in Tanzania but also throughout drier seasons. It is unclear whether treatment seeking varies with the weather, but also if individuals recognise varying probability that a fever is due to malaria in the face of seasonal peaks in malaria transmission. During drier seasons, the rate of clinical episodes is less and so the impact of ACT may also be limited. However this model and other studies (Tediosi et al., 2006) predict that the impact of improving ACT delivery is proportionately greater in low transmission settings since infections are more likely to develop symptoms. A greater understanding of the relationship of

seasonality and health seeking behaviour would help guide implementation of interventions at different times of the year.

The model did not include adherence to treatment, instead assuming all patients took the prescribed treatment. The INESS study in Ghana found that adherence to treatment was one of the most important factors in determining effectiveness (Binka et al., 2012), however a systematic review of how patients take antimalarial drugs found that variations in adherence relates not only to patient characteristics, but also the nature of their interaction with the source of care, which may in itself be distorted by study procedures (Littrell et al., 2011b). Given that it is still unclear what levels or features of adherence are required for ACTs to maintain their efficacy, this thesis focused on the upstream features of ACT delivery. Although the review found that most studies reported high levels of adherence, estimates of the percentage of patients adherent ranged from 1.5% to 100%, and so considerations of whether patients do take their prescribed drugs will be important in realising the full efficacy of ACTs.

I have assumed a fixed duration of minimum inhibitory ACT concentration (10 days) and reduction in onward infectiousness (95%) in this model, based on literature review. These are based in particular on studies using Artmether Lumefantrine (AL), but may vary with other partner-drugs especially in the case of duration of prophylaxis. I have not accounted for the impact of immunity on the prophylactic or treatment effects nor have I included any consideration of anti-malarial resistance. This may lead to overestimated impact of treatment, and the model should be recalibrated as resistance patterns in this region become better defined.

Estimates for the probability a malaria case or NMFI of receiving treatment at any particular outlet through the decision-tree approach did not match those from the IMPACT 2 study. The differences for estimates in the private sector have been previously discussed in Section 5.5.1, due to combining different survey data sets. The health facility estimates however were based on the same input data. Despite accounting for some dependencies, for example the probability of prescribing an ACT provided ACTs were in stock, it is clear that there may be some interactions not captured; the probability of testing may depend on the presence of ACT stock or the probability of prescribing may be related to anxiety regarding stockouts in the future. In addition, possible interactions between health-seeking behaviour and quality of care were not explored or included. Fears of stockouts may influence where patients choose to attend, and patient preference (including cost considerations) may also determine provider behaviour in prescribing ACTs or not. Further work is required to gain an understanding of patient and provider behaviour and the linkages between these factors. Any insights however are likely to be context specific and the linear approach adopted in this analysis may allow wider application of model results. There was insufficient evidence from literature review or the IMPACT 2 study to include staff training in the decision-tree to estimate quality of care.

This thesis has explicitly focused on the use of ACTs and has considered all other types of antimalarials as equivalent to ineffective treatment including the use of quinine in severe malaria. I also have not included the impact of co-administered antimalarials. My hypothesis was that poor access and treatment delivery reduced the effectiveness of efficacious treatments such as ACTs, and my intention was to predict the impact of addressing these barriers to effectiveness. However, it will be necessary in future work to include prescription of other antimalarials in order to more accurately assess impact on transmission and particularly on mortality, as well as interventions that may be required to include short course primaquine effectively (Littrell et al., 2011b).

6.2.2 Data limitations

The fitting of the original malaria transmission model was to data from 23 sites in sub-Saharan Africa. The authors admit that key parameters in the model were based on limited data and understanding especially of the natural history of malaria infection (and super-infection), and the complex evolution and manifestation of immunity (Griffin et al., 2010).

The model is further limited by its reliance on summary statistics of data collected through three different surveys, which were not powered to detect differences between the regions or controlled to reliably attribute any impact seen to particular health systems interventions. In particular, estimates of sector preference and the probability of being tested and/or receiving ACTs in the private sector were derived through patient recall. Patient recall is recognised to be unreliable (Eisele et al., 2013) and in this case may also be discordant with the findings of the outlet survey, e.g. complete stockouts on the day of the survey, despite patient reports of being treated with ACTs. The surveys did not control for the Hawthorne effect (McCambridge et al., 2014) and so provider behaviour may have been altered by the presence of a survey team. Data regarding hospitals and tertiary care was extremely limited.

Model parameterisation regarding the incidence of NMFI was estimated from an amalgamation of two surveys collecting demographic and clinical information during the rainy season in different regions of Tanzania to those of the IMPACT 2 study, as well as Tanzanian DHS data. It is unclear how applicable these estimates are to the different regions and across the dry season.

6.2.3 Interventions

This thesis has compared actual changes in selected health systems variables through the IMPACT 2 study as well as modelling a sequence of idealized scenarios. However, it is assumed that any changes are implemented at one time across the region, as though in a trial setting. In reality measures are taken over a period of time, which in itself may be related to the strength of the prevailing health system. In addition, I have assumed that these interventions are sustained successfully over time and long enough for them to

have an effect. Detailed data regarding the speed with which coverage of interventions is scaled up, heterogeneity in coverage levels achieved, and the degree of adherence to the interventions over time would allow more realistic predictions of the impact of health systems strengthening and the means by which it should optimally be achieved. This model has not considered dimensions of health systems strengthening related to health leadership and governance, which may be important in how interventions are implemented.

My analysis has not considered host-factors other than malaria infection and age-related immunity. The means by which individuals interact with health services and respond to treatment may be affected by other health-related factors, for example malnutrition or co-infection with HIV. The geographic distribution of HIV overlaps with malaria. It has been reported that HIV infection increases malaria susceptibility and reduces the efficacy of antimalarial drugs (Flateau et al., 2011, Gonzalez et al., 2012), and the interpretation of these interactions may depend on which source of healthcare is accessed. In addition, the analysis has assumed a stable setting, whereas in several malaria-endemic countries such as the Democratic Republic of Congo which are affected by ongoing conflict and unrest, alternative treatment delivery solutions may be more appropriate.

Finally I have considered the impact of introducing health systems interventions in isolation for this thesis; other concurrent malaria control programmes have not been included. Potential synergies between control measures such as LLINs, MDA or even malaria vaccination should be explored to see whether focusing interventions in specific population groups would influence transmission dynamics and treatment impact.

It would be ideal to validate the health systems model against data from a region that had scaled up health systems interventions in a systematic and controlled manner to compare predicted impact. The scope of data required would be immense, but may be possible in limited populations, for example control programmes on islands such as Zanzibar, to study which interventions were most critical.

6.3 IMPLICATIONS OF FINDINGS IN THE CURRENT MALARIA CONTROL CONTEXT

Roll Back Malaria and the World Health Assembly have set a goal of reducing malaria case incidence rates by 75% by 2015 and the fourth Millennium Development Goal is to reduce U5 mortality, to which malaria is a major contributor, by two thirds by the same year. An updated Global Malaria Action Plan has set an objective of reducing malaria deaths to near-zero levels by 2015 (WHO, 2013). The specified route to achieve these goals entails not only malaria prevention strategies but also includes targets of universal access to case management in the public and private sectors, and community case management of malaria (CCM) through community health workers. Health systems indicators for these targets relate to levels of treatment-seeking, use of testing, diagnostic-led prescription of ACTs and availability of inpatient care.

The model defined in this thesis enables policy-makers to consider which of these indicators should be addressed first and in which sector to promote transmission and mortality reductions locally. For example, reduced time to access care is a target in many malaria control plans, but the results presented here suggest that this may reduce mortality but have little impact on transmission. Hence the policy may have less significance in a low transmission setting in elimination planning but be an important consideration for higher transmission contexts. Similarly, hospital-based interventions are predicted to proportionally reduce mortality more than health systems improvements at a primary level in some medium-high prevalence contexts, and hence may be preferred if death rates are the main local concern. The model could also be used to evaluate the potential implications of policies in terms of overtreatment of NMFI and undertreatment of malaria cases. For example, it could be used to evaluate whether drug wastage was important or if allowing a more presumptive treatment approach would be better when prioritising the reduction of malaria deaths.

The findings of this theoretical model need to be considered in a practical context. Interventions to improve levels of diagnostic led treatment in the private sector, which were highly effective in the hierarchy of packages in Chapter 5, are also included in the Global Malaria Action Plan. 100% coverage of this target may not be feasible in a short timeframe and will undoubtedly require large investments (Hansen et al., 2013, Tougher et al., 2012). However the costs of harnessing the private sector in malaria control efforts should be evaluated against the costs of malaria disease. For example, the loss of potential future earnings due to premature child mortality in those under-12 months is estimated to be US$ 6,900 and US$ 8,100 in those under 5 years. The authors of the analysis estimated the annual cost of clinical malaria disease in Tanzania at US$131.9 million, including an average treatment cost per case of US$6.79 (Sicuri et al., 2013). It would be

important and informative to apply a cost-effectiveness framework to the outputs of this model to guide the focus on health systems strengthening measures to achieve the international objectives.

The role of improving ACT treatment programmes in transmission reduction may be compared to the predicted impact of the other control interventions in the Global Malaria Action Plan, such as LLINs, ITNs and IRS. A systematic review of 22 randomized control trials of ITNs estimated sustained use could reduce malaria incidence by 50% and mortality in children by one-fifth even in moderate transmission settings (Lengeler, 2004). More recent modelling suggests that in low prevalence settings, high (>80%) levels of coverage of LLINs may reduce parasite prevalence to less than 1% and that combinations of interventions may achieve similar reductions in moderate transmission settings (Chitnis et al., 2010, Agusto et al., 2013, Gatton and Cheng, 2010, Griffin et al., 2010).

The model outlined in this thesis estimated that at low transmission settings (i.e. Mbeya: approximately 6 clinical episodes per 1000 all-age persons per year, 3 episodes per 1000 U5s per year), some single health systems interventions such as 100% access or 100% ACT stock in public clinics or private outlets had the potential to reduce clinical incidence by 100% in all age groups. In contrast, in the medium-high Mwanza scenario (approximately 375 clinical episodes per 1000 all-age persons per year, 400 clinical episodes per 1000 U5s per year), the most effective package of interventions (namely 100% access to, use of and compliance with diagnostics and 100% ACT stock in the private sector) is predicted to reduce clinical incidence across all ages by 50% but by approximately 75% in U5s. It is important to also bear in mind that if aiming to interrupt transmission, then modest absolute benefits in the levels of severe disease or EIR may be sufficient to meet the programme's objective.

It would be important to model the impact of health systems improvements alongside other control measures to assess the consequences for local epidemiology, especially to explore targeting interventions to the age groups most likely to present with symptoms or with high asymptomatic parasite prevalence. Interventions may act synergistically through impact on vectors and human hosts to reduce parasite prevalence levels but may also overlap, for example the ACT-related prophylactic effect (whether through case management or MSAT) may be redundant in the context of high LLIN use.

6.4 FUTURE RESEARCH

Potential extensions to the structure of the model and the need for further data and understanding of health seeking and provider behaviour to improve parameterisation of the model have been described in Section 1.2. In particular further modelling work should focus on:

- Cost effectiveness analysis to estimate how the costs of addressing health systems barriers may be offset by morbidity and mortality averted
- Interactions of improving case management and access to care alongside other malaria control measures including potential synergies with malaria vaccine candidates
- Inclusion of appropriate treatment for NMFI to model a holistic approach to improving fever management
- Modelling interventions to enable case management to become more responsive to systems constraints i.e. communicating with communities to direct treatment seeking in case of stockouts
- Development of a user-friendly interface to aid planning at funding or local operational levels

6.5 CONCLUDING REMARKS

The research presented in this thesis has demonstrated that weak health systems and a poorly controlled diversity of antimalarial sources in malaria-endemic countries act as barriers to deploying ACTs effectively as both a first line treatment and a control measure. Addressing these constraints through specific planning may improve progress towards the targets set by Roll Back Malaria to decrease clinical disease and mortality, and in low transmission settings, to approach elimination.

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APPENDIX 1: MODEL EQUATIONS

Model 1: The aim in this first extension of the original transmission model is to incorporate the two main community sources of treatment - public sector health facilities and private sector informal outlets. I capture how access to healthcare and the quality of care received varies through three parameters:-

1. Following onset of symptoms, the probability of not seeking treatment (i.e. lack of access), the probability of attending a health facility and the probability of accessing a private drug shop (sector preference)
2. time taken to seek treatment at either a private outlet or a public facility, by those who do access care (i.e. delays to access)
3. probability of receiving an ACT for malaria infection in the public and private sectors (i.e. quality of care)

Model 1 Equations

$$\frac{\delta S}{\delta t}+\frac{\delta S}{\delta a}=r_P P+r_U U+\varepsilon_{SEV} r_D Sev-\Lambda S$$

$$\frac{\delta NT}{\delta t}+\frac{\delta NT}{\delta a}=\phi f_{NTX}\Lambda(S+A+U)-r_{NTX}NT$$

$$\frac{\delta Pr}{\delta t}+\frac{\delta Pr}{\delta a}=\phi f_{PR}\Lambda(S+A+U)-r_{PR}Pr$$

$$\frac{\delta CL}{\delta t}+\frac{\delta CLNT}{\delta a}=\phi f_{CL}\Lambda(S+A+U)-r_{CL}CL$$

$$\frac{\delta PrNT}{\delta t}+\frac{\delta PrNT}{\delta a}=(1-ftr_{PR})r_{PR}Pr-r_{NTXPR}PrNT$$

$$\frac{\delta CLNT}{\delta t}+\frac{\delta CLNT}{\delta a}=(1-ftr_{CL})r_{CL}CL-r_{NTXCL}CLNT$$

$$\frac{\delta Tx}{\delta t}+\frac{\delta Tx}{\delta a}=ftr_{PR}r_{PR}Pr+ftr_{CL}r_{CL}CL-r_{ACT}Tx$$

$$\frac{\delta D}{\delta t}+\frac{\delta D}{\delta a}=(1-\varepsilon)r_{NTX}NT+(1-\varepsilon_{CL})r_{NTXCL}CLNT+(1-\varepsilon_{PR})r_{NTX}PrNT+(1-\varepsilon)(1-f_{EFF})r_{ACT}Tx-r_D D$$

$$\frac{\delta Sev}{\delta t}+\frac{\delta Sev}{\delta a}=\varepsilon r_{NTX}NT+\varepsilon_{CL}r_{NTX}CLNT+\varepsilon_{PR}r_{NTX}PrNT+\varepsilon(1-f_{EFF})r_{ACT}Tx-r_D Sev$$

$$\frac{\delta A}{\delta t}+\frac{\delta A}{\delta a}=(1-\phi)\Lambda(S+U)+r_D D+(1-\varepsilon_{SEV})r_D Sev-\phi\Lambda A-r_A A$$

$$\frac{\delta U}{\delta t}+\frac{\delta U}{\delta a}=r_A A-r_U U-\Lambda U$$

$$\frac{\delta P}{\delta t}+\frac{\delta P}{\delta a}=f_{EFF}r_{ACT}Tx-r_P P$$

Key to model states: Model 1

State	Definition	Explanation
S	Susceptible	Susceptible: not infected
NT	Not Treated	Clinically Symptomatic but not treated
Pr	Private Sector outlet	Clinically Symptomatic case seeking care at private outlet
CL	Clinic/Health facility	Clinically Symptomatic case seeking care at health facility
PrNT	Private Not Treated	Clinically Symptomatic case not given ACTs at private outlet
CLNT	Clinic Not Treated	Clinically Symptomatic case not given ACTs at health facility
Tx	Treated	Clinically Symptomatic case given ACTs
D	Disease	Progression to Diseased state: if Untreated/Ineffectively treated
Sev	Severe Disease	Progression to Severe Malaria: if Untreated/Ineffectively treated
A	Asymptomatic	Asymptomatic (patent) malaria infection
U	Undetectable (Sub patent)	Subpatent malaria infection
P	Prophylaxed	Successfully treated malaria case in prophylaxed state

Key to model rates and parameters: Model 1

Parameter	Definition
Λ	Force of infection
ϕ	Probability of developing clinical symptomatic disease
f_{NTX}	Probability of not seeking or accessing early treatment if infected and symptomatic (1-f_{PR}– f_{CL})
f_{PR}	Probability of accessing care at a private trader/ informal outlet for a mild episode
f_{CL}	Probability of accessing care at a primary care clinic/public sector health facility for a mild episode
r_{PR}	Average rate of seeking treatment seeking at a private trader
r_{CL}	Average rate of seeking treatment seeking at a health facility
ftr_{PR}	Probability of receiving ACT treatment at private sector outlet for clinical malaria episode
ftr_{CL}	Probability of receiving ACTs at a public sector/government health clinic for clinical malaria episode
r_{NTX}	Average rate of developing disease (D) or Severe malaria if untreated
r_{NTXPR}	Average rate of developing disease (D) or Severe malaria if untreated with an ACT at a private trader
r_{NTXCL}	Average rate of developing disease (D) or Severe malaria if untreated with an ACT at a health facility
ε	Proportion of untreated infections that progress to severe disease
ε_{SEV}	Proportion of untreated severe infections that progress to death
r_{ACT}	Mean rate of reduction in gametocytaemia after treatment with ACT treatment

f_{EFF}	Probability that ACT treatment is efficacious
r_D	Average rate of recovery of an uncomplicated untreated symptomatic episode to asymptomatic state
r_A	Average rate of recovery from detectable asymptomatic state to undetectable (sub-patent) state
r_P	Average rate of reduction of prophylactic effect after ACT treatment
r_U	Average rate of clearance of sub-patent infection to return to susceptible state

Model 2: The aim of the second is capture the potential impact of overtreatment of non-malarial febrile illness (NMFI) with ACTs. I therefore extended Model 1 to investigate the clinical and transmission outcomes arising from policies of:-

1. Presumptive treatment in the private sector
2. Improved levels of diagnostic-led management (and hence quality of care) in private and public sectors.

I included the probability of febrile individuals (any cause) without malaria receiving ACTs at both private outlets and public health facilities. There are three main groups involved in the overtreatment of NMFI cases with ACTs:-

1. Febrile cases with no malaria infection
2. Febrile cases with subpatent malaria infection (i.e. undetectable by standard malaria testing)
3. Febrile cases with asymptomatic malaria infection (i.e. detectable by malaria testing).

Model 2 equations

$$\frac{\delta S}{\delta t}+\frac{\delta S}{\delta a}=r_P P+r_U U+(1-f_H)\varepsilon_{SEV} r_D Sev+(1-ftr_{NMFICL})r_{CL}SCL+(1-ftr_{NMFIPR})r_{PR}SPr+$$
$$(1-f_{EFF})r_{ACT}STx-\Lambda S-(1-f_{NTX})r_{NMFI}S$$

$$\frac{\delta NT}{\delta t}+\frac{\delta NT}{\delta a}=(1-\theta)\phi f_{NTX}\Lambda(S+A+U)-r_{NTX}NT$$

$$\frac{\delta Pr}{\delta t}+\frac{\delta Pr}{\delta a}=(1-\theta)\phi f_{PR}\Lambda(S+A+U)-r_{PR}Pr$$

$$\frac{\delta CL}{\delta t}+\frac{\delta CL}{\delta a}=(1-\theta)\phi f_{CL}\Lambda(S+A+U)-r_{CL}CL$$

$$\frac{\delta PrNT}{\delta t}+\frac{\delta PrNT}{\delta a}=(1-ftr_{PR})r_{PR}Pr-r_{NTXPR}PrNT$$

$$\frac{\delta CLNT}{\delta t}+\frac{\delta CLNT}{\delta a}=(1-ftr_{CL})r_{CL}CL-r_{NTXCL}CLNT$$

$$\frac{\delta Sev}{\delta t}+\frac{\delta Sev}{\delta a}=\varepsilon r_{NTX}NT+\varepsilon_{CL}r_{NTXCL}CLNT+\varepsilon_{PR}r_{NTXPR}PrNT+\varepsilon(1-f_{EFF})r_{ACT}Tx-r_D Sev$$

$$\frac{\delta D}{\delta t}+\frac{\delta D}{\delta a}=(1-\varepsilon)r_{NTX}NT+(1-\varepsilon_{CL})r_{NTXCL}CLNT+(1-\varepsilon)r_{NTX}PrNT+(1-\varepsilon)(1-f_{EFF})r_{ACT}Tx-r_D D$$

$$\frac{\delta Tx}{\delta t}+\frac{\delta Tx}{\delta a}=ftr_{PR}r_{PR}Pr+ftr_{CL}r_{CL}CL-r_{ACT}Tx$$

$$\frac{\delta A}{\delta t}+\frac{\delta A}{\delta a}=(1-\phi)\Lambda(S+U)+(1-f_{EFF})r_{ACT}ATrx+r_D D+(1-\varepsilon_{SEV})r_D Sev+(1-ftr_{PR})r_{PR}APr+$$
$$(1-ftr_{CL})r_{CL}ACL+(1-f_{EFF})r_{ACT}ATrx-\phi\Lambda A-(1-f_{NTX})r_{NMFI}A-r_A A$$

$$\frac{\delta U}{\delta t}+\frac{\delta U}{\delta a}=r_A A+(1-f_{EFF})r_{ACT}UTx+(1-ftr_{NMFIPR})r_{PR}UPr+(1-ftr_{NMFICL})r_{CL}UCL$$
$$-r_U U-\Lambda U-(1-f_{NTX})r_{NMFI}U$$

$$\frac{\delta UPr}{\delta t}+\frac{\delta UPr}{\delta a}=f_{PR}r_{NMFI}UPr-r_{PR}UPr$$

$$\frac{\delta UCL}{\delta t}+\frac{\delta UCL}{\delta a}=f_{CL}r_{NMFI}UCL-r_{CL}UCL$$

$$\frac{\delta UTx}{\delta t}+\frac{\delta UTx}{\delta a}=ftr_{NMFIPR}r_{PR}UPr+ftr_{NMFICL}r_{CL}UCL-r_{ACT}UTx$$

$$\frac{\delta APr}{\delta t}+\frac{\delta APr}{\delta a}=f_{PR}r_{NMFI}APr-r_{PR}APr$$

$$\frac{\delta ACL}{\delta t}+\frac{\delta ACL}{\delta a}=f_{CL}r_{NMFI}ACL-r_{CL}ACL$$

$$\frac{\delta ATrx}{\delta t}+\frac{\delta ATrx}{\delta a}=ftr_{PR}r_{PR}APr+ftr_{CL}r_{CL}ACL-(1-f_{EFF})r_{ACT}ATrx$$

$$\frac{\delta SPr}{\delta t}+\frac{\delta SPr}{\delta a}=f_{PR}r_{NMFI}SPr-r_{PR}SPr$$

$$\frac{\delta SCL}{\delta t}+\frac{\delta SCL}{\delta a}=f_{CL}r_{NMFI}SCL-r_{CL}SCL$$

$$\frac{\delta STx}{\delta t}+\frac{\delta STx}{\delta a}=ftr_{NMFIPR}r_{PR}SPr+ftr_{NMFICL}r_{CL}SCL-r_{ACT}STx$$

$$\frac{\delta P}{\delta t}+\frac{\delta P}{\delta a}=f_{EFF}r_{ACT}Tx+f_{EFF}r_{ACT}ATrx+f_{EFF}r_{ACT}UTx+f_{EFF}r_{ACT}STx-r_{P}P$$

Key to additional model states: Model 2

State	Definition	Explanation
SPr	Susceptible NMFI: Private	Uninfected case with NMFI seeking care at private outlet
SCL	Susceptible NMFI: Clinic	Uninfected case with NMFI seeking care at a clinic
UPr	Sub-Patent NMFI: Private	Undetectable infection with NMFI seeking care at private outlet
UCL	Sub-Patent: Clinic	Undetectable infection with NMFI seeking care at a clinic
UTx	Sub-Patent: Treated	Undetectable infection with NMFI treated with ACTs
APr	Asymptomatic NMFI: Private	Asymptomatic infection with NMFI seeking care at private outlet
ACL	Asymptomatic NMFI: Clinic	Asymptomatic infection with NMFI seeking care at a clinic
ATrx	Asymptomatic NMFI: Treated	Asymptomatic infection with NMFI treated with ACTs

Key to additional model rates and parameters: Model 2

Parameter	Definition
r_{NMFI}	Average rate of seeking treatment for a NMFI
ftr_{NMFICL}	Probability of receiving ACT treatment at a clinic for an NMFI episode
ftr_{NMFIPR}	Probability of receiving ACT treatment at a private outlet for an NMFI episode

Model 3: The initial two models consider management of uncomplicated malaria only at community level and do not include any management of severe malaria; which is modelled to as a result of ineffective, delayed or a lack of ACT treatment. Severe cases are assumed to either progress to death or recover to an asymptomatic state. In Model 3 is expanded to include a second pathway by which severe malaria may occur, namely acute severe malaria at presentation due to poor acquired immunity which can rapidly progress to severe fulminant state.

Three routes to potentially avert or treat severe disease are included:

1. Prevention of progression to fulminant severe disease in those at risk of early acute severe malaria by treatment with rectal artesunate and ACTs – which may occur at public facilities or private outlets
2. Referral of those at risk of early acute severe malaria to hospital/tertiary level facilities – which may occur from public facilities or private outlets
3. Treatment of severe malaria at a hospital/tertiary level facility with artesunate and ACTs – which may be early acute severe malaria or those uncomplicated symptomatic malaria cases that may not have sought treatment or were unsuccessfully treated either at a public facility or private outlets.

The aim of the extensions made to Model 3 is to investigate

1. The impact of health systems on the morbidity and mortality associated with malaria
2. The role of tertiary level health institutions e.g. district hospitals in the management of severe malaria and its consequences

Model 3 equations:

$$\frac{\delta S}{\delta t}+\frac{\delta S}{\delta a}=r_P P+r_U U+(1-f_H)\varepsilon_{SEV} r_D Sev+\varepsilon_{SEV} r_D HSev+(1-ftr_{NMFICL})r_{CL} SCL+(1-ftr_{NMFIPR})r_{PR} SPr+$$
$$(1-f_{EFF})r_{ACT} STx-\Lambda S-(1-f_{NTX})r_{NMFI} S$$
$$\frac{\delta NT}{\delta t}+\frac{\delta NT}{\delta a}=(1-\theta)\phi f_{NTX}\Lambda(S+A+U)-r_{NTX} NT$$
$$\frac{\delta Pr}{\delta t}+\frac{\delta Pr}{\delta a}=(1-\theta)\phi f_{PR}\Lambda(S+A+U)-r_{PR} Pr$$
$$\frac{\delta CL}{\delta t}+\frac{\delta CL}{\delta a}=(1-\theta)\phi f_{CL}\Lambda(S+A+U)-r_{CL} CL$$
$$\frac{\delta PrNT}{\delta t}+\frac{\delta PrNT}{\delta a}=(1-ftr_{PR})r_{PR} Pr-r_{NTXPR} PrNT$$
$$\frac{\delta CLNT}{\delta t}+\frac{\delta CLNT}{\delta a}=(1-ftr_{CL})r_{CL} CL-r_{NTXCL} CLNT$$
$$\frac{\delta D}{\delta t}+\frac{\delta D}{\delta a}=(1-\varepsilon)r_{NTX} NT+(1-\varepsilon_{CL})r_{NTXCL} CLNT+(1-\varepsilon)r_{NTX} PrNT+(1-\varepsilon)(1-f_{EFF})r_{ACT} Tx-r_D D$$
$$\frac{\delta Tx}{\delta t}+\frac{\delta Tx}{\delta a}=ftr_{PR} r_{PR} Pr+ftr_{CL} r_{CL} CL-r_{ACT} Tx$$

$$\frac{\delta U}{\delta t}+\frac{\delta U}{\delta a}=r_{A}A+(1-f_{EFF})r_{ACT}UTx+(1-ftr_{NMFIPR})r_{PR}UPr+(1-ftr_{NMFICL})r_{CL}UCL-r_{U}U-\Lambda U-(1-f_{NTX})r_{NMFI}U$$

$$\frac{\delta UPr}{\delta t}+\frac{\delta UPr}{\delta a}=f_{PR}r_{NMFI}UPr-r_{PR}UPr$$

$$\frac{\delta UCL}{\delta t}+\frac{\delta UCL}{\delta a}=f_{CL}r_{NMFI}UCL-r_{CL}UCL$$

$$\frac{\delta UTx}{\delta t}+\frac{\delta UTx}{\delta a}=ftr_{NMFIPR}r_{PR}UPr+ftr_{NMFICL}r_{CL}UCL-r_{ACT}UTx$$

$$\frac{\delta APr}{\delta t}+\frac{\delta APr}{\delta a}=f_{PR}r_{NMFI}APr-r_{PR}APr$$

$$\frac{\delta ACL}{\delta t}+\frac{\delta ACL}{\delta a}=f_{CL}r_{NMFI}ACL-r_{CL}ACL$$

$$\frac{\delta ATrx}{\delta t}+\frac{\delta ATrx}{\delta a}=ftr_{PR}r_{PR}APr+ftr_{CL}r_{CL}ACL-(1-f_{EFF})r_{ACT}ATrx$$

$$\frac{\delta SPr}{\delta t}+\frac{\delta SPr}{\delta a}=f_{PR}r_{NMFI}SPr-r_{PR}SPr$$

$$\frac{\delta SCL}{\delta t}+\frac{\delta SCL}{\delta a}=f_{CL}r_{NMFI}SCL-r_{CL}SCL$$

$$\frac{\delta STx}{\delta t}+\frac{\delta STx}{\delta a}=ftr_{NMFIPR}r_{PR}SPr+ftr_{NMFICL}r_{CL}SCL-r_{ACT}STx$$

$$\frac{\delta A}{\delta t}+\frac{\delta A}{\delta a}=(1-\phi)\Lambda(S+U)+(1-f_{EFF})r_{ACT}ATrx+r_{D}D+(1-\varepsilon_{SEV})r_{D}Sev+(1-ftr_{PR})r_{PR}APr-r_{A}A+$$
$$(1-ftr_{CL})r_{CL}ACL+(1-f_{EFF})r_{ACT}ATrx+(1-f_{H})(1-\varepsilon_{SEV})r_{D}Sev+(1-\varepsilon_{SEV})r_{D}HSev-\phi\Lambda A-(1-f_{NTX})r_{NMFI}A-r_{A}A$$

$$\frac{\delta WSev}{\delta t}+\frac{\delta WSev}{\delta a}=\theta\phi f_{PR}\Lambda(S+A+U)-w_{SEV}WSev$$

$$\frac{\delta Sev}{\delta t}+\frac{\delta Sev}{\delta a}=w_{SEV}WSev+r_{NTXPR}PrSevNT+r_{NTXCL}CLSevNT+\varepsilon(1-f_{EFF})r_{ACT}Tx+\varepsilon r_{NTX}NT+$$
$$\varepsilon_{CL}r_{NTXCL}CLNT+\varepsilon_{PR}r_{NTXPR}PrNT-(1-f_{H})r_{D}Sev-f_{H}r_{H}Sev$$

$$\frac{\delta PrSev}{\delta t}+\frac{\delta PrSev}{\delta a}=f_{PR}\phi\Lambda(S+A+U)-r_{PR}PrSev$$

$$\frac{\delta CLSev}{\delta t}+\frac{\delta CLSev}{\delta a}=f_{PR}\phi\Lambda(S+A+U)-r_{SEV}CLSev$$

$$\frac{\delta PrSevNT}{\delta t}+\frac{\delta PrSevNT}{\delta a}=(1-ftr_{SEVPR}-ftr_{REFPR})r_{PR}PrSev-r_{NTXPR}PrSevNT$$

$$\frac{\delta CLSevNT}{\delta t}+\frac{\delta CLSevNT}{\delta a}=(1-ftr_{SEVCL}-ftr_{REFCL})r_{CL}CLSev-r_{NTXCL}CLSevNT$$

$$\frac{\delta TxSev}{\delta t}+\frac{\delta TxSev}{\delta a}=ftr_{SEVPR}r_{PR}PrSev+ftr_{SEVCL}r_{CL}CLSev-r_{ACT}TxSev$$

$$\frac{\delta Href}{\delta t} + \frac{\delta Href}{\delta a} = ftr_{REFPR} r_{PR} PrSev + ftr_{REFCL} r_{CL} CLSev - r_H Href$$

$$\frac{\delta HTx}{\delta t} + \frac{\delta HTx}{\delta a} = ftr_H r_H Href + f_H ftr_H r_H Sev - r_{ACT} HTx$$

$$\frac{\delta HSev}{\delta t} + \frac{\delta HSev}{\delta a} = (1 - ftr_H) r_H Href + (1 - f_{EFF}) r_{ACT} HTx + f_H (1 - ftr_H) r_H Sev - r_D HSev$$

$$\frac{\delta P}{\delta t} + \frac{\delta P}{\delta a} = f_{EFF} r_{ACT} Tx + f_{EFF} r_{ACT} ATrx + f_{EFF} r_{ACT} UTx + f_{EFF} r_{ACT} STx + f_{EFF} r_{ACT} HTx + f_{EFF} r_{ACT} TxSev - r_P P$$

Key to additional model states: Model 3

State	Definition	Explanation
wSev	Waiting state: severe malaria	Susceptible: not infected
CLSev	Acute severe malaria: Clinic	Acute severe malaria seeking care at clinic
PrSev	Acute severe malaria: Private	Acute severe malaria not given ACTs and artesunate at private outlet
SevCLNT	Untreated Acute severe malaria: Clinic	Acute severe malaria not given ACTs and artesunate at clinic
SevPrNT	Untreated Acute severe malaria: Private	Acute severe malaria seeking care at private outlet
Href	Acute severe malaria referred to tertiary care	Acute severe malaria referred to tertiary care/hospital
HTx	Treated severe malaria: tertiary care	Severe malaria/Referred malaria given Artesunate and ACTs at tertiary care/hospital
HSev	Untreated severe malaria/Fulminant disease	Severe malaria/Referred malaria not or ineffectively treated:

Key to additional model rates and parameters: Model 3

Parameter	Definition
w_{SEV}	Force of infection
f_H	Probability of accessing care at a hospital/tertiary facility for a severe episode
ftr_{REFCL}	Probability of being referred to hospital for an acute severe malaria episode from a clinic
ftr_{REFPR}	Probability of being referred to hospital for an acute severe malaria episode from a private outlet
ftr_{SEVCL}	Probability of being treated with artesunate and ACTs for an acute severe malaria episode at a clinic
ftr_{SEVPR}	Probability of being treated with artesunate and ACTs for an acute severe malaria episode at a private outlet
r_H	Average rate of accessing care at a hospital/tertiary facility
ftr_H	Probability of being treated with artesunate and ACTs for severe malaria at a hospital

Review

Overcoming health systems barriers to successful malaria treatment

V. Bhargavi Rao[1], David Schellenberg[2], and Azra C. Ghani[1]

[1] MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, W2 1PG, UK
[2] Disease Control and Vector Biology Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK

The success of malaria control programmes is recognised to be handicapped by the capacity of the health system to deliver interventions such as first-line treatment at optimal coverage and quality. Traditional approaches to strengthening the health system such as staff training have had a less sustained impact than hoped. However, novel strategies including the use of mobile phones to ease stockouts, task-shifting to community health workers, and inclusion of the informal sector appear more promising. As global health funding slows, it is critical to better understand how to deliver a proven intervention most effectively through the existing system.

The conundrum of health systems

Over the past 10 years, rapid scale-up of preventative interventions against malaria have resulted in substantial declines in the burden of disease [1]. Although such trends are encouraging, the risks of malaria morbidity and mortality remain influenced by the performance of prevailing health systems [2,3]. The success of national malaria control programmes is increasingly recognised to be handicapped not only by resource constraints but also by the absorptive and technical capacities of the health systems to deliver interventions at the required levels of coverage and quality [1,3]. Given that international funding for such programmes is expected to plateau, it is critical to better understand how to implement a proven intervention most effectively through an existing system, and where the barriers are to an intervention, achieving its predicted potential [1,4].

The failure of previous 'vertical' (see Glossary) attempts to eradicate malaria (1955–1969) illustrates that sustained disease control requires integration into a functioning and efficient health system [2–4]. Although substantial progress has been made in understanding the strengthening of health systems, much of the evidence is context-specific, descriptive, or qualitative. High quality evidence on the effectiveness of strengthening interventions into health systems and their resulting impact on health outcomes remain limited.

There have been few approaches to address the delivery of case management. The 'systems effectiveness framework' [5] outlined by Tanner *et al.* describes how interventions decay in efficacy and are rendered less effective in practice through a cascade of interacting system barriers. This may be applied in the context of antimalarial delivery (Figure 1): first-line treatment for malaria, artemisinin combination therapies (ACTs) are highly efficacious, but issues such as the proximity of healthcare or availability of diagnostics may exert a sequential and cumulative impact leading to low ACT effectiveness, that is, less than 50% of febrile children being cured [1].

Using this framework of barriers to effectiveness, we summarise potential systems constraints into two main categories: (i) timely access to healthcare and (ii) quality of care at the source of treatment (including human resources, drug stocks, and the use of diagnostics), and review their impact on the implementation of ACT programmes considering both public and private sectors. Additionally, we present the first systematic summary of the effectiveness of interventions deployed to target the identified barriers in both private and public sectors.

Barriers to effectiveness

Impact of geographical access, treatment seeking, and delays

The geographical distance travelled to access care varies widely across different national and regional settings (e.g., a median of 8 km in Ethiopia [6] to 2 km in Kenya [7]), and this is also dependent on transport infrastructure; for example, in parts of rural Ethiopia over 90% of children live more than 1.5 h walk from a health centre [6]. Timely access (less than 24–48 h after symptom onset) to treatment, especially for the lowest two economic quintiles, is a Roll Back Malaria and Abuja Declaration target [8].

The impact of distance on seeking treatment for fever differs by country and context. Most studies reviewed show a clear reduction in accessing treatment with increasing distance to a health facility (13.9%/km [9] to 34%/km [7]) with access declining to low levels (<10%) once the health facility is more than 5 km from the home [7]. In addition, families that live further from primary care facilities wait longer to seek care for their febrile child than those living nearby, with a twofold increase in the odds of delay if the distance to healthcare was greater than approximately 3 km [10].

The impact of distance as a barrier to treating malaria becomes apparent given the narrow time limits for malaria infections to develop more serious complications [11].

Corresponding author: Rao, V.B. (bhargavi.rao@imperial.ac.uk).
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Glossary

Abuja Declaration on Roll Back Malaria: in April 2001, African Union countries meeting in Abuja, Nigeria, pledged to increase government funding for health to at least 15% and urged donor countries to scale-up support. The attendees resolved to halve the malaria mortality for Africa's people (by 2010). In addition, it was agreed that by 2005 at least 60% of those suffering from malaria should have access to correct, affordable, and appropriate treatment within 24 h of the onset of symptoms.

Accredited Drug Outlet (ADDO) scheme: a donor-supported initiative led by the Tanzanian Food and Drug Authority to train and license small, privately operated retail outlets in rural and poor areas to sell a set list of essential medicines, including selected prescription drugs.

ACT Watch: is a research project that aims to provide a comprehensive picture of the markets for antimalarials and diagnostic tests in order to inform national and international malaria case management policy decision making, through evidence from public and private sectors.

Affordable medicines facility: an innovative financing mechanism designed to expand access to the most effective treatment for malaria, artemisinin-based combination therapies (ACTs), hosted and managed by the Global Fund. It aims to enable countries to increase the provision of affordable ACTs through the public, private, and non-governmental organisation (NGO) sectors. To achieve this aim, the Global Fund has negotiated lower ACT prices with manufacturers and will pay a large proportion of this (a 'co-payment') directly to manufacturers on behalf of buyers across the public, private-for-profit, and not-for-profit sectors.

Antimalarial: any medicine recognised by the WHO for the treatment of malaria.

Antipyretics: any drugs or herbs that are used to reduce fever.

Artemisinin-based combination therapy (ACT): an antimalarial that combines artemisinin or one of its derivatives with an antimalarial or antimalarials of a different class.

Artemisinin monotherapy: an antimalarial medicine that has a single active compound, where this active compound is artemisinin or one of its derivatives.

Combination therapy: The use of two or more classes of antimalarial drugs/molecules in the treatment of malaria that have independent modes of action.

Dosing/treatment regimen: the timing and number of doses of an antimalarial used to treat malaria. This may vary by patient weight or age.

First-line treatment: the government-recommended treatment for uncomplicated malaria.

Informal outlet: an outlet that is not funded, licensed, or controlled by the government.

Minimum intervention training package (Kenya): a 2- to 3-day HCW training package developed by Population Services International (PSI) and the Kenyan Department of Malaria Control (DOMC) including workshops covering the epidemiology of malaria in Kenya, diagnosis-treatment-counselling–drug dispensing for uncomplicated malaria, basic techniques of stock management, principles of monitoring and evaluation, and practical sessions on diagnostic procedures using blood slides and RDTs. The target of the training was universal coverage of all front-line health workers providing outpatient services. The minimum package included the training above with either access to guidelines or the participants' training manual, and at least one of five job aids promoting the same case management recommendations in different formats.

Non-artemisinin therapy: an antimalarial medicine that does not contain artemisinin or any of its derivatives.

Non-malarial febrile illness (NMFI): infectious diseases in patients who present with undifferentiated fever and require malaria RDTs/microscopy – but in whom these tests are negative (i.e., other causes of malaria-like symptoms).

Non-recommended therapy: a treatment that is not endorsed by government guidelines for treatment of uncomplicated malaria.

Outlet: any point of sale or provision of a commodity to an individual. Outlets are not restricted to stationary points of sale and may include mobile units or individuals.

Paediatric formulation: antimalarial drug packaged specifically for children.

Plot model: a framework used to analyse case management, describing the different steps a person has to go through after becoming ill until finally being cured. The original paper was published in 1976 by M.A. Plot 'A simulation model for case finding and treatment in tuberculosis programme'.

Private sector facility: a treatment source that is not funded or controlled through the government.

Public sector facility: a primary healthcare facility funded through the government and under the authority of the district health department.

Quality-assured artemisinin-based combination therapies (QAACTs): are ACTs that comply with the AMFm and Global Fund to Fight AIDS, Tuberculosis, and Malaria's Quality Assurance Policy.

Rapid diagnostic test (RDT) for malaria: a test used to confirm the presence of malaria parasites in a patient's bloodstream.

Roll Back Malaria (RBM): is the global framework for coordinated action against malaria launched in 1998 under the auspices of the WHO.

Stockouts: occur when a pharmacy (in a medical store or health facility) temporarily has no medicine on the shelf available for distribution to patients. It may affect one medicine or many medicines, or in the worst case, all medicines. A stockout can be documented at one point in time or over a period of days, weeks, or months.

'Vertical' programmes: (also known as stand-alone programmes or the vertical approach) refer to disease control programmes focusing on a single given health problem or a specific demographic population, usually implemented in parallel to and in addition to other normal health activities.

Delays in seeking treatment can lead to disease progression requiring inpatient care. Individuals living in close proximity to primary healthcare services have reduced odds of malaria advancing from mild to severe disease [7,12,13]. O'Meara *et al.* found that the incidence of severe malaria more than doubled as travel time to the nearest primary care facility increased from 10 min to 2 h in Kenya [12]. In 2002, a Malaria Indicator Survey of Papua New Guinea [14] indicated that prevalence of infection was significantly lower in communities living within closer reach of a health facility (22.4% vs 35.6%). Similarly, in Côte D'Ivoire the presence of a healthcare facility was associated with protection against malaria infections [15].

Quality of care

Staffing and training Staff shortages are frequently highlighted as a concern. In Kenya, 10 of 34 public facilities had to close on the day surveyed due to staff absence [16]. A further Kenyan study of 36 government facilities in 2008 [17] identified inadequate staffing as a barrier to adherence to ACT prescription guidelines, due to additional time required for counselling, direct observation of the first dose, record keeping, and confirming the diagnosis, as well as poor supervision and inadequate quality of training. None of the healthcare workers (HCWs) had been exposed to full training in the use of first-line ACTs, and only half had experience of the minimum intervention training package in one Kenyan study [18]. Similar findings were reported in Uganda, Kenya, Angola, and Zambia [19–23]. Rural and poor areas where the malaria burden is disproportionately high suffer the most critical gaps in trained HCWs [1,2,24].

Stockouts Effective and sustained expansion of a treatment programme requires reliable and uninterrupted stocks. However, poor supply chain management is a common problem [24]. In Africa, availability of essential medicines in the public sector is 29.4% compared with 54% in the private sector, although with diversity by country [25].

Initially, the proportion of public facilities stocking at least one form of ACT, by weight or dosing schedule, on survey day ranged from 51% (2004) [26] to over 95% (2009) [22,23], with 20% of health centres having no ACT stock [27]. Up to 75% of facilities reported stockouts over the preceding 6 months with a median of 49 to 138 days with no stock [20,21,23,26]. More recent studies show some improvement [22,28–30], although in others the issue remains refractory [27,29,31]. Bottlenecks leading to stockouts at the point-of-service include delays to delivery at a facility (8–105 days since ordering) [21,32], poor forecasting at district and national levels, resource allocation, limited information systems, and lack of governance in national procurement [33,34].

In a systematic review of six studies comparing facilities with ACT stock to those without, ACT prescriptions increased, and non-recommended prescriptions decreased in the presence of stock; however, existence of stock did not ensure recommended treatment practice [34]. In a Ugandan study, only 60% of those needing an ACT were prescribed it despite adequate stock [20]. Interviews with

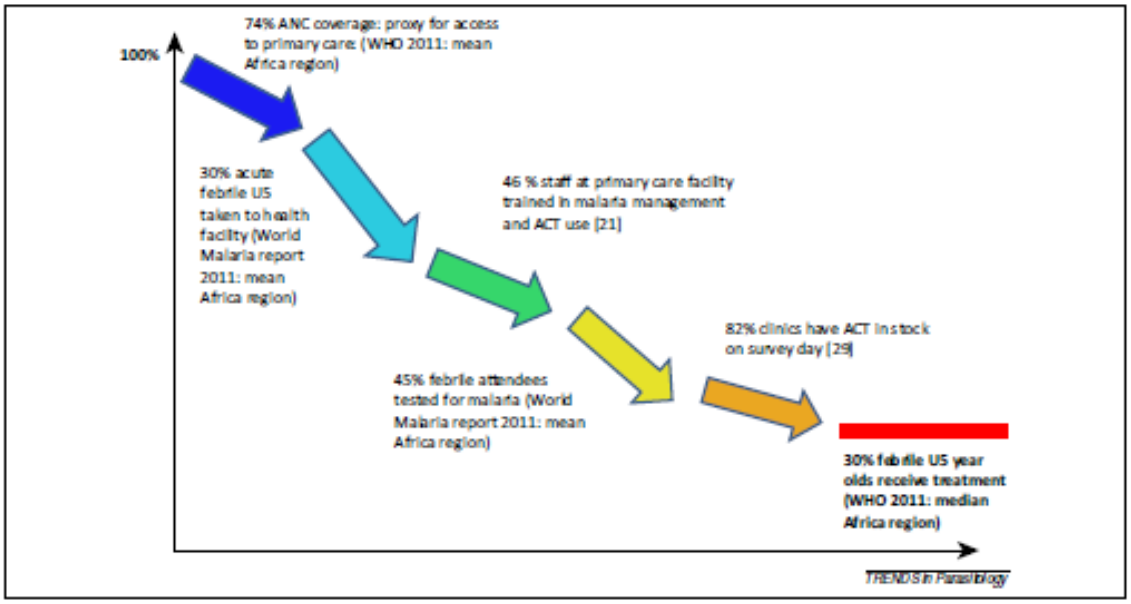

Figure 1. Systems barriers to effectiveness for treatment of fever [21,29]. The overall effectiveness of a highly efficacious treatment intervention, such as first-line treatment for malaria, artemisinin combination therapies (ACTs), may diminish through the sequential and cumulative impact of a cascade of interacting system barriers leading to less than 50% of febrile children under 5 (U5) years getting appropriate antimalarial treatment.

Kenyan rural HCWs revealed that nearly all rationed ACTs because of uncertainty in supply, with some admitting giving it to patients they felt were most 'deserving' of treatment [17]. In both Uganda and Kenya, despite ACT stock difficulties, there was usually an excess of non-recommended antimalarials such as chloroquine or amodiaquine [17,20].

Underdiagnosis and overtreatment Until recently, presumptive treatment and syndromic management was advocated in guidelines and national policies of the World Health Organisation (WHO). This approach resulted both in overtreatment, ranging from 47% to 95% of patients with non-malarial febrile illness (NMFI) being treated with antimalarials [19,22,28,35–40], and in some cases underdiagnosis of malaria of up to 30–40% [37,38,40]. Overtreatment is often with non-recommended antimalarials [31,36], but may also involve ACTs, with between 5.7% and 63.7% of those untested or with negative test results receiving first-line treatment [19,22,28,36,39]. Non-adherence to test results can be detrimental to those patients who are not parasitaemic. A Tanzanian study found the case fatality rate in test-negative patients to be significantly higher (12.1%) than for test-positive patients (6.9%), and over 60% of NMFI patients were not treated appropriately with antibiotics [35].

Diagnostic capacity has increased over time; in Zambia, 17% of public facilities surveyed in 2004 had access to diagnostic facilities for malaria, rising to 73% by 2006, mainly due to the introduction of rapid diagnostic tests (RDTs) [19,20]. In other countries, diagnostic capacity ranged from 25% to 100% of facilities surveyed [21,22,31,38]. However, testing of febrile patients before treatment has been limited [22,31,36,38–40] and varies widely between and within countries (e.g., 11% in one district of Tanzania to 99% in other districts) [40]. Nankabirwa *et al.* showed low utilisation of diagnostic tools and reliance on clinical symptoms in high transmission areas of Uganda led to almost 40% of children under 5 years (U5s) not being diagnosed or treated despite being parasitaemic [38].

The undertreatment of confirmed cases is recognised at low levels (0.7–3.8%) [20,22,28,36,37,40], but one Tanzanian study showed that up to 18.8% [37] of patients with a positive diagnostic test were not treated with any antimalarial medication.

Informal sources of treatment Informal sources for antimalarials, ranging from drug shops and pharmacies to general village stores and itinerant peddlers, are often geographically closer to home [41,42], less expensive to the individual [16,43,44], more likely to have drugs in stock [45], and can be perceived as being of better quality than public facilities [46–48]. The legal status of private retail outlets differs by country but most are not formally licensed to dispense malaria treatment [47,49]. Generally, drug retailers are unskilled workers with limited knowledge of the drugs, dosages, and how to store them appropriately [29,42,46,47], although in some cases government HCWs may work in drug shops [46,47]. As a result, antimalarials are often incorrectly prescribed or overprescribed presumptively for NMFI [30,31,41,43,50–52]. Sumba *et al.* found that the likelihood of full recovery following a febrile illness was significantly less for those who attended private outlets (37%) compared with public facilities (85%) [53].

Private outlets are run as businesses and hence have perverse incentives [50]. The patient is a client wanting an affordable product, even if potentially less effective. The seller wants a satisfied customer, but also needs to sell a product regardless of actual need. If appropriate diagnostics are deployed to confirm the diagnosis, sellers lose their profit margin from dispensing antimalarials [48,54]. Two related qualitative Ugandan studies found that although community acceptability of RDT use was high regarding improving access to effective treatment of malaria, there were fears that drug shops would compensate by overpricing RDTs and not adhere to the results [55,56].

There is good evidence of extensive distribution through the informal sector of antipyretics, substandard or counterfeit antimalarials, and artemisinin monotherapy or chloroquine as first-line treatments, although with substantial variation regionally [29,51,52,57–60]. A recent survey by ACT Watch (including DRC, Uganda, and Zambia) confirmed that availability of ACTs is particularly low in the private sector, whereas less effective drugs and artemisinin monotherapy are often readily available [29,51,52]. Quality-assured ACTs (QAACTs) represented less than 20% of the antimalarial market [29,43,50,60]. ACTs are also priced higher in the private sector compared with other antimalarials, despite this being the most common point of access. Recent studies report that older treatments such as chloroquine remain very cheap (under US$1), whereas ACTs were 4–22 times more expensive than the most commonly dispensed antimalarial in the private sector (a non-artemisinin based treatment in all countries surveyed) [29,60].

Interventions to improve quality of care

Reducing stockouts

Evidence of interventions at scale that lead to improved stock at the facility level is scarce (Table 1). A study in 24 Zambian districts demonstrated that the use of a commodity planner within the district logistics team coupled with direct central monthly ordering and prepacked drugs tailor-made for each facility increased the availability of paediatric ACTs to 88% compared with 51% in districts with no intervention. Similar improvements were seen for other essential medicines. Stockouts were almost eliminated in some cases, with scale-up of this supply chain model estimated to reduce child malaria deaths by 37% [61].

More recently, mobile phone technology has been applied to supply chain management, although limited to small studies. In Uganda, a short message service (SMS) reporting system deployed by the government resulted in over 85% of the facilities reporting weekly, although ACT stockouts remained at 54% [62]. Promisingly, a Tanzanian study using mobile phones to improve stock-counts showed a substantial reduction in the proportion of facilities without any antimalarials from 78% at baseline to 26% at follow-up, with stockouts eliminated by week 8 in one district [63]. Furthermore, a Kenyan study evaluating the use of SMS reporting for stocks of ACTs and RDTs found a reduction in the stockout of one or more ACT packs by 38% at the end of the 26-week period, and a decline in RDT stockouts by 24%. Importantly, district managers also responded to address to 44% of ACT and 73% of RDT stockout signals [64].

Indirect interventions may also improve supply. The introduction of subsidised ACTs in the private sector was associated with decreased public sector stockouts in Kenya, Madagascar, Niger, Nigeria, Tanzania, Uganda, and Zanzibar, with ACT stock present more than 80% of the time in all except Nigeria and Niger [41,45,65]. Improved stock levels in Tanzania was accompanied with a near fivefold increase in treatment seeking among adults [41,45].

Universal rational case management

The 2010 WHO guidelines on the treatment of malaria state that whenever possible 'prompt parasitological confirmation by microscopy or alternatively by RDTs is recommended in all patients suspected of malaria before treatment is started'. This policy change towards universal 'test and treat' acknowledged the widespread overtreatment of malaria and the risk of spreading drug resistance or tolerance, the need for improved disease surveillance and better quality of care, including for NMFI [66].

As outlined above, implementing rational (diagnostic-led) case management has proven difficult, especially at scale beyond trials under controlled conditions. Guidelines limiting treatment for children over 5 years to diagnosis-confirmed cases did not reduce unnecessary antimalarial use (Table 1), although ACT prescription for diagnostic-positive cases did improve (88–98.6%) [67–70]. However, recent studies have found increased emphasis on universal RDT use to be associated with reductions in unnecessary antimalarial treatments (up to 68% in several studies), although varying by transmission setting [28,40,71–75]. Undertreatment of test-positive cases at low levels was documented in a few studies [40,72,75].

Several studies demonstrated that withholding antimalarials in test-negative cases does not result in increased malaria-related deaths or severe morbidity, even in U5s [76–78]. Management of test-negative patients has also been shown to improve, with substantial decreases in antimalarial prescription and concomitant increases in prescription of antibiotics [odds ratio (OR) = 1.45–1.8] [40,71,72]. However, it is unclear if the latter reflects correct antibiotic treatment.

The cost implication of adding RDTs has been of concern, although several studies show little difference compared to clinical diagnosis [72,79–81].

Training

Delivering quality care depends on the capabilities and performance of HCWs. A 2009 review of 23 studies to improve HCW management of malaria confirmed that very little is known about which interventions work [82]. Aside from two studies of Integrated Management of Childhood Illness (IMCI) which showed significantly improved appropriate treatment [82], one public sector study demonstrated that training, mainly of limited duration and in didactic or workshop format, was significantly associated with recommended treatment of malaria when supplemented by additional inputs such as job aides or regular supervision.

Recent trials show that the link between levels of staff training and clinical performance is not straightforward (Table 1). In Uganda, patients were significantly less likely

Table 1. Interventions: improving quality of care in public health facilities[a]

Impact of improving supply chain management and reducing stockouts						
Author	**Year**	**Country**	**Setting**	**Intervention**	**Outcome**	**Impact**
World Bank, Zambian National Malaria Program and other agencies [61]	2010	Zambia	24 districts: 8 to each intervention and 8 control (3 arms)	• Both models: logistics commodity planner at district level • Model A: health facilities place orders to districts which transfer the order to the central level. Procured drug kits disaggregated at central level and distributed to the district store for assembly and delivery to facilities • Model B: direct ordering monthly to central level and the drugs are packed at the central level in sealed packages tailor-made for each individual facility. District only delivers to facilities	• Model A resulted in some improvement of drug availability in health facilities • Model B intervention dramatically improved the availability of essential medicines: e.g., availability of paediatric ACT was up to 88%, compared with 51% in control areas • Similar improvements were seen for other essential medicines, such as antibiotics	• Authors estimated that by 2015 scaling-up this supply chain model could reduce child malaria deaths by 37% • Scaling-up: estimated to treat an additional 110 000 children/year and avert 5400 child deaths/year • Considering improvements also in availability of other drugs – impact may be greater
Asiimwe *et al.* [62]	2011	Uganda	2 districts: Gulu, Kabale – 147 facilities Ministry of Health led	• SMS-based malaria monitoring platform • Training at facility and district level • Set-up cost of US$100/health facility, local technician support of US$400/month, and a cost of US$0.53/week/clinic	• ACT stockouts: 54% Kabale and 54% Gulu • RDT stockouts: 48% Kabale and 71% Gulu • >85% health facilities reported weekly and without monetary incentives or additional supervision	• Potential to improve timeliness in reporting of specific, time-sensitive metrics at modest cost and to manage stock data at district level
Alba *et al.* [41,45]	2010	Tanzania	Kilombero and Ulanga districts and Ifakara town – 10 facilities	• Subsidy for ACTs: free for U5s and pregnant women and subsidised price of TSH 300 (US$0.25) to others	• After subsidised ACT was introduced in 2007 – stocks were high for >80% months observed (90/108 in 2007; 88/108 in 2008)	• Treatment seeking among adults increased by 27% (unadjusted) • Treatment seeking adjusted for socioeconomic status: nearly fivefold increase (OR = 4.6 $P = 0.001$)
Barrington *et al.* [63]	2010	Tanzania	3 rural districts: Lindi, Kagama, Ulanga – 129 facilities (Novartis led)	• SMS management tool and a web-based reporting tool • Training at national, district, and facility levels • 21 week pilot study Involved two weight specific ACT packs and injectable quinine	• 95% mean facility response rate to SMS requests for stock data • 94% accuracy of stock reports • Decrease in facilities with stockout of one or more ACTs: 78% (baseline) to 26% (week 21) • In one rural district: stockouts virtually eliminated by week 8 • Overall: ACT stocks increased by 64% and quinine stock increased by 36%	• Use of simple SMS technology, via a public–private partnership model may be effective
Githinji *et al.* [64]	2013	Kenya	5 rural districts: Machakos, Mwamboweni, Ijara, Manga, Vihiga – 87 public health facilities	• SMS management tool and a web-based reporting tool • 26 week study • Training at facility and district levels • Involved four weight specific ACT packs and RDTs	• 97% mean facility response rate • 79% accuracy of stock reports but 93% accuracy of stockout reports • 38% decrease from baseline to 26 weeks in stockouts of one or more ACT packs • Total stockouts reduced by 5% • RDT stockouts reduced by 24% • District managers responded to 44% of ACT stockout and 73% of RDT stockout signals	• Incentives were used to encourage reporting: may introduce reporting bias • Web-based platform was regularly accessed by national and district level teams: possibility of better integration between levels and surveillance–response • Important impact on RDT stocks also
Impact of rational (diagnosis-led) case management						
Author	**Year**	**Country**	**Setting**	**Intervention**	**Outcome**	**Impact**
Testing of over 5 year olds whilst presumptive treatment of under 5 year olds						
Zurovac *et al.* [81]	2008	Kenya	3 districts: Bondo, Siaya, Kericho – 60 health facilities, 1540 patients (as below)	• Modelling implications of rational case management • Primary data from Skarbinski *et al.* [69] (below) • Policy: RDT use in all over 5 year olds and treatment with first-line ACTs	• High transmission: 61% less overtreatment and 21% lower costs but potential for 8% increase undertreatment • Low transmission: reduction in undertreatment errors (36% less – but low numbers) but increase in costs by 41%	• High transmission: a majority of patients would not be correctly treated with ACTs despite RDT use • High and low transmission: adherence to guidelines has potential to decrease treatment errors with acceptable costs

Table 1 (*Continued*)

Impact of rational (diagnosis-led) case management						
Author	**Year**	**Country**	**Setting**	**Intervention**	**Outcome**	**Impact**
Skarbinski *et al.* [69]	2009	Kenya	3 districts: Bondo, Siaya, Kericho – 60 health facilities, 1540 patients	• Cluster RCT: RDTs plus training, guidance, and supervision (TGS) or TGS alone • Policy: RDT use in all over 5 year olds and treatment with first-line ACTs • 100% RDT availability in intervention facilities	• 9% RDT negatives given ACT • Overtreatment low in both arms and not significantly reduced by RDT provision: 12% ($P = 0.3$) • Presumptive treatment reduced: 36% ($P = 0.03$) • 88% RDT positive treated with ACTs (vs 51% of smear positive treated with ACTs)	• RDTs could improve case management but more effective implementation strategies for guidelines are required
Masanja *et al.* [70]	2012	Tanzania	Rufiji district (14 facilities) pre-RDT implementation and Rufiji district (16 health facilities) post-RDT implementation	• Policy change: over 5 year olds to be treated after use of RDT if possible to guide decision making	• 12.6% increase in febrile patients tested ($P = 0.05$) • 7% of all test negatives treated with antimalarials (7.8% RDT negative): 7.6% reduction from pre-baseline (significant only for RDTs) • Overtreatment reduced: 39.1% to 24.7% ($P = 0.01$) • 83.2% RDT positives treated with ACT versus 41.7% microscopy positives	• High adherence to test result in rural settings is possible • Impact of RDTs is limited by overall low levels of appropriate testing • Greater impact during high transmission season
Juma *et al.* [67]	2011	Kenya	National cross-sectional cluster survey: 88 facilities with diagnostics (1096 patients) and 71 facilities no diagnostics (880 patients)	• Kenyan national guidelines change promoting ACTs and parasitological diagnosis in over 5 year olds • Presumptive treatment remained policy in USs • Only results in over 5 year old age group given	• At facilities with diagnostics: 53.7% tested (CI: 45.4–61.9) • 32.8% with negative test received ACTs (50.4% of negative test received some antimalarial treatment) • 58% untested received ACTs • 86.5% test positives received ACTs 1.2% RDT positives did not receive any antimalarial treatment	• ACT use prevailed in all age groups • Overtreatment remained despite test provision • Use of diagnostics remained limited
Ishengoma *et al.* [68]	2011	Tanzania	2 districts: Korogwe and Muheza. Longitudinal passive detection in 6 villages in Korogwe and cross-sectional survey in 6 villages in both districts	• Supply of RDTs – comparing performance of RDT use with microscopy with respect to treatment	• Sensitivity and specificity of RDTs in longitudinal study: 88.6 (87.5–89.7) and 88.2 (87.7–88.7) • Sensitivity and specificity of RDTs in cross-sectional surveys: 63.4 (59.8–67.1) and 94.3 (93.6–95.0) • Using RDTs reduced antimalarial dispensing in over 5 year olds from 98.9% to 32.1% • Post-RDT: 3.4% negative RDTs in over 5 year olds were treated • Pre-RDT period: 1.4% (79) cases not treated with antimalarials including 0.3% (19 – including 11 USs) that were slide positive • Post-RDTs: 0.8% (108) over 5 year olds not treated with ACTs	• Variation in sensitivity and specificity of RDTs depending on fever and parasite density • RDTs reduced overtreatment significantly
Universal testing and treatment: all ages						
Njama-Meya *et al.* [78]	2007	Uganda	601 children between 1 and 10 years recruited from census population and followed in study clinic	• Standard microscopy performed if fever – and treated only if smear positive	• 6 of 1608 smears falsely identified as negative – of which 4 went onto develop uncomplicated malaria and 2 cleared parasites without treatment • 13 of 1602 negative smears developed malaria within 7 days (0.8%) – all uncomplicated	• 32% febrile episodes were malaria • Withholding treatment on the basis of negative smear was safe • Saved >1600 treatments in 601 children over 18 months
Msellem *et al.* [72]	2009	Zanzibar	4 health facilities: 1187 patients	• Crossover validation trial • Comparing clinical diagnosis with RDT-aided treatment	• RDT use associated with lower ACT prescription than clinical diagnosis: OR: 0.04 (CI: 0.03–0.05; $P < 0.001$) • Prescription of antibiotics higher after RDT use: OR: 1.8 (CI: 1.5–2.2; $P < 0.001$) • Re-attendance due to perceived unsuccessful cure: lower after RDT consultation than clinical diagnosis: OR: 0.5 (CI: 0.3–0.9; $P = 0.005$) • 28 of 552 smear positive not treated (of which 26 due to false-negative RDTs)	• Total average cost per patient was similar: US$2.47 in RDT consultation versus US$2.37 for clinical diagnosis • Some risk of undertreatment if RDT is false negative

Table 1 (*Continued*)

Impact of rational (diagnosis-led) case management						
Author	**Year**	**Country**	**Setting**	**Intervention**	**Outcome**	**Impact**
Mosha *et al.* [79]	2010	Tanzania	2 districts: Same and Korogwe methods included – routine health information data, health facility cross-sectional RDT survey (8 facilities), and passive surveillance of cohort childhood morbidity	• Modelling cost implications of improving diagnosis in children • Primary data: RCT of different antimalarials for intermittent preventative treatment of malaria in infants (IPTi: [112]) • Comparison of routine care versus RDT-aided care	• Overdiagnosis of malaria with routine care compared with RDTs: highest in U5s in low transmission sites (RR: 17.9; CI: 5.8–55.3) than in over 5 year olds in low transmission site (RR: 14.0; CI: 8.2–24.2) • Less overdiagnosis risk in moderate transmission comparing routine versus RDT (RR: 2.2 in U5s and 4.2 in over 5 year olds) • Higher proportion diagnosed with respiratory infections in under 2 year old RDT cohort versus routine care (42% vs 26%, $P < 0.001$)	• In low transmission: proportion of morbidity attributed to malaria was lower in under 2 year olds RDT cohort compared with routine care: 0.08% versus 28.2% ($P < 0.001$) • Use of RDT reduced overall drug and diagnostic costs: 10% in moderate transmission and 15% in low transmission compared with routine care
d'Acremont *et al.* [77]	2010	Tanzania	Urban (Dar es Salam) and rural (Kilombero) – prospective 2 arm study: 2 facilities – 1000 children (603 negative RDT)	• No antimalarials if RDT was negative • Main outcome: occurrence of complications in untreated children	• 97% of children symptom-free by day 7 • 600 of 603 children were RDT negative when repeated after 7 days • 3 of 603 children with negative RDT later developed positive test within 7 days: no complications 4 children with negative RDT admitted to hospital (NMFI)	• Not treating RDT negative children with antimalarials is safe even in U5s
Kyabayinze *et al.* [74]	2010	Uganda	5 regions: Kapchorwa, Mubende, Iganga, Jinja, and Mbale; 58 low level health facilities – intervention deployed at 4/5 facilities (control: clinical diagnosis)	• Introduction of universal RDT testing for antimalarial treatment • Training of HCWs in policy Low level facilities had no diagnostic capability previously	• 90% uptake in tests • 30% overtreatment (25–35%) • Overtreatment more likely in U5s (OR: 2.6; $P < 0.001$) • Reduction of 38% in antimalarial prescription post-intervention (RR: 0.62; CI: 0.55–0.7; $P < 0.001$) • Compared with control arm: 35% reduction (RR: 0.68; CI: 0.57–0.69; $P = 0.005$) • 49% of HCWs believed that a negative RDT excluded malaria	• Use of RDTs to reduce overtreatment possible at low level facilities • HCW education needed to promote adherence to results
Ansah *et al.* [75]	2010	Ghana	Dangme West district – 4 health facilities, 7283 patients	• National policy of universal testing for treatment • Comparison of introduction of RDTs into one facility with access to microscopy (microscopy setting) to three facilities new to diagnostics (clinical setting)	• Microscopy setting: no significant difference between overtreatment in RDT arms or microscopy arms (51.6% vs 55%; $P = 0.16$) • Clinical diagnosis setting: reduction on overtreatment from 90.1% to 53.9% (OR: 0.12; 95% CI: 0.04–0.38; $P = 0.001$) • No deaths in U5s • Undertreatment in microscopy setting: 6.8% with RDTs versus 10.4% with microscopy • Undertreatment in clinical setting: 3.2% in RDT arm versus 2.7% in clinical arm	• Use of RDTs led to better targeting of antibiotics in clinical setting • If previous exposure to diagnostics – introduction of RDTs to aid rational case management is more limited than clinical diagnosis settings • Initial improvement in correct prescription of antimalarials after RDT introduction was not sustained after 3 months
Nyandigisi *et al.* [28]	2011	Kenya	National, cross-sectional surveys: 174 224 health workers and 2405 febrile patients; follow-up survey 1 year after baseline survey and policy implemented	• New malaria strategy: universal testing and treatment of test positives with ACT • Nationwide training of HCW	• Increased testing: 24–31% ($P = 0.09$) • Increased treatment by test result: 16–22% ($P = 0.048$) • If ACTs and diagnostics in stock: nonsignificant increase in testing and treatment by test • Poor availability of RDTs	• Highlights importance of availability of comprehensive package of case management interventions • Low levels of testing overall remain
Ssenwanga *et al.* [73]	2011	Uganda	6 districts: in each 1 sentinel site (all higher level health facilities): 166 278 patients tested	• Sentinel site surveillance: universal test and treat policy • Comparison of first 3 months with final 3 months: 3 years later	• Tests performed: 84% microscopy and 16% RDTs • Increase in testing those suspected of malaria: 58% (95% CI: 57–59%; $P < 0.001$) • Adherence to test: increased from 64% to 95% ($P < 0.001$) • Increase in appropriately given ACT: 20% (95% CI: 18–23%; $P < 0.001$) • Proportion of negative test not treated: 46% versus 91% ($P < 0.001$)	• Surveillance programme resulted in almost universal testing • Surveillance programme was less successful in promoting use of ACT in parasite positive patients than reducing overtreatment

Table 1 (*Continued*)

Impact of rational (diagnosis-led) case management						
Author	**Year**	**Country**	**Setting**	**Intervention**	**Outcome**	**Impact**
Bastiaens *et al.* [40]	2011	Tanzania	2 regions: Kagera and Mwanza region. Hospital-based survey febrile patients < 10 years pre- and post-policy change: 2 hospitals and 636 patients post-change, 610 pre-change	• National policy change to provision of RDTs and restriction of treatment to RDT positive	• Rubya: – Proportion of RDT positive treated: 100% (vs 100% pre) – Proportion of RDT negative treated: 10% (vs 76.9% pre) – Presumptive treatment: 2% (vs 67.5% pre) • Biharamulo – Proportion of RDT positive treated: 75% (vs 92% pre) – Proportion of RDT negative treated: 38.7% (vs 89.1% pre) – Presumptive treatment: 27% (vs 89% pre)	• Reduction in presumptive treatment and in overtreatment of negative tests where RDTs provided • All treatment was with ACTs • Undertreatment of 25% RDT positive patients (2/8) at Biharamulo not discussed by authors
d'Acremont *et al.* [71]	2011	Tanzania	Dar es Salaam: 3 hospitals and 6 health facilities surveyed before and after introduction of RDTs plus 3 matched control facilities with no RDTs	• Training and introduction of RDTs	• ACT use reduced in intervention group by 68% (CI: 57–80) and by 32% in control compared with baseline (CI: 9–54) • 7% of RDT negatives received an antimalarial post-intervention • Risk ratio overtreatment: post-intervention: 0.09 (0.06–0.13), i.e., reduction from 53% to 7% of test-negative patients treated • Risk ratio antibiotic treatment in all negative RDT patients: post-intervention = 1.45 (1.28–1.65) and control = 1.05 (0.91–1.26)	• Training and RDT implementation led to dramatic reduction in antimalarial overtreatment • Antibiotic prescription in test negatives increased: although unclear if this is rational treatment
Mtove *et al.* [76]	2011	Tanzania	Muheza district – 1 hospital, 985 children aged 3–59 months	• Treatment for URI on the basis of diagnostic result	• 16.4% RDT positive and treated with ACTs • 83.4% negative (807/985): no antimalarial treatment received • 6 children (0.6%) became RDT positive after enrolment (all were PCR negative at enrolment) • 12 (1.2%) hospitalised: 1 possible malaria: no deaths • Bacterial pathogen identified in 9/985 (0.9%): 8 in RDT negative and 1 in RDT positive	• RDTs had sensitivity of 97.8% (CI: 96.9–98.7%) and specificity of 96.3% (CI: 96.3–98.4%) • No missed diagnoses of malaria • New infections after consultation may undermine confidence in RDTs • Invasive bacterial disease was uncommon
Batwala *et al.* [80]	2011	Uganda	2 districts: Ishenyi and Iganga: 6 health facilities	• National guidelines: parasitological diagnosis before treatment • Facilities randomised to RDT, microscopy, or presumptive diagnosis	• Compared with microscopy – RDTs is most cost effective overall per case correctly diagnosed and treated in low and high transmission areas • Difference in cost effectiveness (ICER) was greater in high transmission (US$8.90) compared with low transmission (US$1.78) • Lowest cost presumptive diagnosis (US$0.62) but least effective	• At willingness-to-pay US$2.80, RDTs remain cost effective up to a value of cost of treatment of US$4.47 • As cost of ACTs reduce – presumptive treatment may become more attractive
Impact: training of healthcare workers						
Author	**Year**	**Country**	**Setting**	**Intervention**	**Outcome**	**Impact**
Ngasala *et al.* [83]	2008	Tanzania	2 districts: Kibaha and Bagamoyo: 16 health facilities – 3131 children	• RCT: staff training in clinical diagnosis and microscopy versus clinical training alone versus no training	• Antimalarial prescriptions did not significantly reduce in training alone arm (95.3% vs 99.5% untrained) • No difference in antibiotics prescriptions • No statistical significant difference in recovery rates or outcomes	• Additional training and supervision did not result in any significant impact on improving malaria case management compared with untrained workers
Skarbinski *et al.* [69]	2009	Kenya	3 districts: Bondo, Siaya, Kericho – 60 health facilities, 1540 patients	• Cluster RCT: training, guidance, and supervision (TGS) alone versus TGS and provision of RDTs • Baseline survey in both groups and follow-up • Results presented here for impact of TGS only in control group	• Increased ACT treatment of patients with uncomplicated malaria: 41% (P = 0.05) (compared with reduction of 22% in group with RDTs) • Reduction in treatment with non-recommended drugs: 46% (P = 0.003) • No significant increase in overtreatment with ACT • Significant increase in use of RDTs: 11% (P < 0.001) but no overall increase in diagnostic testing (any tool): 16% (P = 0.07)	• Overall: no significant impact of training, guidance, and supervision (TGS) alone on prescription of ACTs according to diagnostic result or by clinical diagnosis

Table 1 (*Continued*)

Impact: training of healthcare workers						
Author	**Year**	**Country**	**Setting**	**Intervention**	**Outcome**	**Impact**
Rowe *et al.* [84]	2009	Benin	Southeastern Benin: 1244 consultations – survey in 1999	• IMCI training plus additional study supports including supervision/non-financial incentives versus control group with only 'usual' IMCI supports (job aids/limited supervision) • Baseline survey in 1999 and follow-up in 2001–2004	• Performance increased in intervention and control groups: no significant overall difference (but diluted by persistence of untrained IMCI workers) • Per protocol analysis: IMCI training plus study support provided better care than those with 'usual' supports (27.3% improved; $P < 0.05$) • Both groups outperformed untrained workers • Only 29% of supervision visits occurred	• IMCI training is useful but insufficient for high levels of adherence • Additional supports can lead to additional improvements and are low cost
Wasunna *et al.* [18]	2010	Kenya	Bondo district: 22 public health facilities, 48 HCWs, 386 febrile children	• Enhanced in-service training programme of HCWs and provision of job aids re: new malaria management guidelines • No follow-up training or supervision	• 67% of staff received enhanced in-service training (none received full package training) • Trained HCWs: no significant improvement in reported case management tasks	• May need to consider inclusion of supervision and post-training follow-up

*Abbreviations: ACTs: artemisinin combination therapies; CI: confidence interval; HCW: healthcare worker; IMCI: integrated management of childhood illness; NMFI: non-malarial febrile illness; OR: odds ratio; PCR: polymerase chain reaction; RCT: randomised controlled trial; RDT: rapid diagnostic test; RR: relative risk; SMS: short message service; U5s: under 5 year olds.

to receive malaria treatment if seen by formally qualified HCWs [20]. In some studies, diagnosis-based management of malaria with ACTs did not improve with in-service training, increased access to national guidelines, or provision of malaria wall charts [20,28,83]; however, in other studies pre-service and in-service training increased the likelihood of ACT prescription [19]. In Kenya [21] and Uganda [20], supervision of HCWs was associated with improved adherence to guidelines. Multiple surveys [18,69,84] have found that uptake of training programmes is patchy and alone do not result in any significant improvements in case management, except a 46% reduction in the use of non-recommended drugs in one Kenyan study [69].

Outside malaria, a recent IMCI evaluation suggests that frequent supervision and other non-financial incentivisation (framed certificates and acknowledgement in local media) may improve care [84].

Interventions to increase access

Community case management and community health workers

Several countries are addressing the challenge of limited access to facilities in rural and poor areas by training local individuals to act as community health workers (CHWs), enabling integrated community case management of malaria (iCCMm) often with prepackaged drugs [85]. Implementation of CCM programmes across Malawi, Mali, and Zambia is estimated to improve effective access (i.e., access to a trained provider and to appropriate medicine) from 14% (9–17%) to 30–57% [86].

Two systematic reviews evaluating presumptive treatment of febrile children by CHWs have been published. Hopkins *et al.* [87] identified six studies, concluding that CHW schemes could improve treatment delivery and adherence, especially for groups located far from formal facilities. A second review considered evaluations of CHW programmes delivering multiple paediatric treatments and included several studies showing reduction in all-cause paediatric mortality up to 9 years after programme initiation [85]. Studies published since concur that CHWs in Africa can successfully provide presumptive ACT treatment along with packages of preventive services in both rural and urban settings [88–92].

More recent studies (Table 2) evaluating the performance of CHWs in delivering diagnostic-led management describe increased treatment seeking [93–96] and no increased progression to severe disease [97,98]. In addition, they document reduced overtreatment with ACTs (up to 96.8% adherence to RDT results seen in Tanzania [99]) and improved management of NMFI, including increased referral and appropriate treatment for pneumonia [93,98]. Two studies showed a reduction in malaria incidence and parasite prevalence in areas covered by CHW interventions, although it is not clear the extent to which this was causal [97,100].

Predictions of the cost effectiveness of CHW programmes using presumptive treatment vary. Only one study considered community level utilisation of RDTs, and found that in Zambia the cost per case diagnosed and correctly treated was less by iCCM rather than facility-level management [101].

Targeting the private sector

Training programmes targeting the performance of private sector drug outlets are included in two systematic reviews undertaken prior to RDT introduction [47,82]. In both, visual aids and on-site supervision aimed at informal providers were shown to improve performance. However, both reviews emphasise the difficulty in incorporating treatment sources operating outside traditional regulatory frameworks into treatment programmes, and sustaining behaviour change. Since then, studies have further shown that training can improve the performance of private retailers; in Kenya, trained retailers were more likely to sell the correct dose of antimalarial (OR 9.4 in one region

Table 2. Interventions: improving access through community case management of malaria (CCMm)[a]

Author	Year	Country	Setting	Intervention	Outcome	Impact
Elmardi *et al.* [95]	2009	Sudan	South Kordofan state: 20 villages	• Community volunteers trained in CCMm (RDT use plus ACT treatment) with supply from rural HC	• 30% CHW volunteers did not rely on negative RDT • Improved accessibility to ACTs: 25% to 64.7% • Improved treatment seeking behaviour: 83.3% to 100%	• Issue of overtreatment, i.e., test-negative patients treated • Community acceptance of programme
Yeboah-Antwi *et al.* [93]	2010	Zambia	Catchment area of Chikankata hospital: Siavonga and Mazabuka districts: 3215 children with fever	• Cluster RCT: CHWs with access to RDTs, ACTs and antibiotics (18) versus CHWs relying on clinical diagnosis (19 – control) with access to ACTs only in the management of matched febrile U5s	• 27.5% children in RDT arm received ACTs versus 99.1% in control arm (RR: 0.28; 95% CI: 0.14–0.38) • Non-severe pneumonia: 68.2% children in RDT arm received early and appropriate treatment versus 13.3% in control (RR: 5.32; 95% CI: 2.19–8.94) • 2 deaths in intervention arm versus 1 in control	• Promising result for reduction in overuse of ACTs and increase early and appropriate treatment for pneumonia and other NMFIs
Lemma *et al.* [97]	2010	Ethiopia	Tigray region: 2 districts	• 2 year pilot study: ACT at clinic and CHW level – 50% access to RDTs in year 2 versus control: ACTs and RDTs at clinic only	• Crude parasite prevalence at peak of transmission: 7.4% (CI: 6.1–8.9%) in intervention district versus 20.8% (CI: 18.7–23.0) in control • No difference in all-cause mortality (incidence RR: 1.03) • Risk of malaria specific mortality lower in intervention district (incidence RR: 0.6; 95% CI: 0.4–0.9; $P = 0.013$)	• Community based deployment of ACTs: reduced malaria transmission, lowered case burden for facilities and reduced malaria mortality and morbidity in study period
Chanda *et al.* [101]	2011	Zambia	2 districts: Chongwe (9 CHWs for 16 079 populations) and Kalomo (7 CHWs for 18 279 population)	• CHWs as delivery points for ACTs and RDTs for CCMm (adult and paediatric)	• 23–35.1% sought treatment at CHWs • 99.2–100% uncomplicated malaria treated with ACTs • All severe malaria cases and non-malaria fevers referred appropriately • Negative RDT cases not prescribed ACT: 99.4–100% • No progression to severe malaria or deaths • Cost per case correctly diagnosed: US$4.22 for CCMm versus US$6.12 for facility level • Utilisation of diagnostics and adherence to results and guidelines higher with CHWs than facility	• Good community reception • High levels adherence to test result • CCMm more efficient than health facility level management
Mubi *et al.* [99]	2011	Tanzania	Kibaha District: 5 villages, 22 CHWs, 2930 patients	• Alternating cluster RCT: CHWs trained in RDT use and clinical diagnosis – randomly assigned to one method on alternating weeks	• ACTs provided to 53.2% patients in RDT weeks versus 96.5% patients in clinical weeks (OR: 0.039; 95% CI: 0.029–0.053) • CHWs adhered to RDT results: 96.8% patients (CI: 95.8–97.6) • Referral: 10% in RDT weeks versus 1.6% clinical weeks • Perceived non-recovery more common after RDT diagnosis • No severe or fatal malaria in RDT negative patients (not treated with ACTs) • 4 deaths: 2 test positive and treated with ACT, 2 RDT negative)	• Opportunity for improved access, timely treatment and improved NMFI treatment
Tine *et al.* [100]	2011	Senegal	Bocconto health post: 8 villages, 12 CHWs, 1000 children	• RCT: CHWs trained in CCMm (oral for uncomplicated and pre-referral rectal for severe malaria) compared with this plus some CHWs able to administer monthly intermittent preventative therapy to children (IPTc)	• Incidence of malaria episodes: 7.1/100 child months at risk (95% CI: 3.7–13.7) in IPTc plus CCMm communities versus 35.6/100 child months at risk (95% CI: 26.7–47.4; OR: 0.2; 95% CI: 0.09–0.41; $P = 0.04$) • Parasitaemia prevalence lower in communities with IPTc plus CCMm (2.09% vs 4.6%; $P = 0.03$) • Adjusted OR shows protective effect of IPTc plus CCMm against anaemia (OR = 0.59; 95% CI: 0.42–0.82; $P = 0.02$)	• CHWs are able to deliver both CCMm and IPTc • Combining these interventions can provide significant additional benefits
Mukanga *et al.* [96]	2012	Uganda	Iganga district: 423 households from 7 villages with U5s	• Semi-structured questionnaire for caregivers • Acceptability survey following 1 year use of RDTs by CHWs in CCM programme	• 86% of households lived within 1 km of CHW home versus 25% within 1 km of health facility • Households further than 1 km from facility were more likely to use a CHW (OR: 1.72; 95% CI: 1.11–2.68) 89% acceptability of CHWs using RDTs	• CHW programmes increase access and were the first choice for more than 50% of caregivers sampled

Table 2 (*Continued*)

Author	Year	Country	Setting	Intervention	Outcome	Impact
Mukanga *et al.* [98]	2012	Burkina Faso, Uganda, Ghana	Multicentre: 12 villages in Burkina Faso, 16 villages in Ghana, and 14 in Uganda 4216 febrile children	• Open cluster RCT: two arm • Comparing CHW programmes with diagnostic tests, ACTs and antibiotics versus presumptive diagnosis and ACTs (plus antibiotics in Ghana)	• High compliance with RDT results • 4.9% RDT negative children given ACTs • Antibiotic overuse was common in Burkina Faso and Ghana for children who were RDT negative but also no increased respiratory rate	• RDT use by CHWs limits overuse of ACTs • Unclear re: impact of diagnostic tools by CHWs (respiratory rate) on antibiotic use • No increased fever persistence due to use of diagnostic tools
Seidenberg *et al.* [94]	2012	Zambia	Catchment area: Chikankata Mission Hospital: 440 women from 62 villages	•Cluster RCT: CHWs with (A) diagnostic tests and ACTs versus (B) presumptive diagnosis and ACTs • Household surveys of caregivers of U5s	• In both arms increase in care seeking from CHWs (RR: 1.39 in CHW A and 1.55 in CHW B) • Decrease in care seeking at health facility and traditional healers • For severe symptoms (i.e., difficult breathing): increase in CHW utilisation only seen in CHWs with diagnostics areas (A)	• CHW programmes can reduce burden on health facilities • Availability of diagnostics increases treatment seeking at CHWs for severe symptoms

*Abbreviations: ACTs: artemisinin combination therapies; CCMm: community case management of malaria; CHW: community health worker; CI: confidence interval; IMCI: integrated management of childhood illness; IPTc: intermittent preventative therapy for children; NMFI: non-malarial febrile illness; OR: odds ratio; PCR: polymerase chain reaction; RCT: randomised controlled trial; RDT: rapid diagnostic test; RR: relative risk; SMS; short message service; U5s: under 5 year olds.

and OR 53.5 in another) [54], and formally accredited training can reduce the numbers of unregulated drug shops, as shown by the Accredited Drug Outlet (ADDO) scheme in Tanzania (Table 3) [41,45].

The price and quality of ACTs has been a barrier to effectively expanding their use in the private sector. In 2009, the subsidy programme Affordable Medicines Facility for malaria (AMFm) was launched, seeking to reduce price through a co-payment facility, thereby increasing access to QAACTs and driving out ineffective drugs [60] (Table 3). The original AMFm pilot study in Tanzania showed significant increases in ACT market share (from 1% to 44.2% sales) [102], and a randomised controlled trial of subsidised ACTs in Kenya found an increased proportion of children receiving ACTs within 48 h of fever (14.6% to 40.2%), with significant reduction in the use of antimalarial monotherapy [43]. In both studies, the drug subsidy was passed to the end users. However, spatial analysis of the pilot showed that subsidised ACTs were more likely to be stocked in shops closer to towns, major roads, and with richer clientele, indicating that price reduction alone may not address inequities in access [103]. One early evaluation from Kenya showed that the subsidy was passed to customers, but only 11% of drug shops surveyed stocked the subsidised brand [104]. Two recent independent evaluations of AMFm (Phase 1) concluded that dramatic increases in QAACT availability (26.3–71.3% increase), market share (30–58.7% increase), and affordability had been seen in almost all pilot sites (except Niger and Madagascar) with reductions in availability of artemisinin monotherapy, although diagnostics stock remained low [60,65].

The Consortium for ACT Private Sector Subsidy (CAPSS) study in Uganda also piloted an AMFm subsidy approach to investigate whether access to QAACTs in the private sector could be improved. Evaluation at 2 years found increased market share with ACTs accounting for 69% of antimalarial purchases in pilot areas. The odds of purchasing an ACT within 24 h of symptom onset in an intervention region compared with control areas was 6.11 [95% confidence interval (CI): 4.32–8.62; $P < 0.0001$] [105].

Concluding remarks and future perspectives

The relationship between improving treatment delivery through health systems and resulting impact on health outcomes of infectious diseases is not straightforward [3]. Ethiopia, South Africa, Zambia, and Zanzibar [106,107] provide examples of how large-scale distribution of long-lasting insecticide treated nets (LLINs) and ACTs through formal health channels may be associated with reductions in malaria prevalence, admissions, and deaths.

From a public health perspective, the key to reducing malaria mortality is to ensure diagnosis-led, first-line treatment in a timely manner, before infections progress to severity. The INDEPTH Network Effectiveness and Safety Studies (INESS) group studied the decay in efficacy of ACTs in Ghana, and estimated the systems effectiveness of ACTs to be 13.5% (i.e., 865 of 1000 patients were not treated effectively), with the steepest decline due to lack of access to treatment within 24 h [108].

In this review, we have outlined the barriers posed by health systems factors limiting the potential success of malaria treatment programmes, and presented a review of interventions targeting these barriers. The population effects of improving individual dimensions of care are unknown and very difficult to predict or quantify in isolation; however, a few insights into potential strategies to alleviate delivery bottlenecks emerge (Figure 2).

CHWs have been successfully deployed in several settings to reduce delays in accessing care, increase treatment seeking, and provide diagnostic-led care of high quality including administration of pre-referral rectal artesunate to decrease the risk of severe malaria [109]. Although the cost effectiveness of a community-based strategy may vary with transmission intensity and local infrastructure, CHW schemes are especially valuable for communities that are traditionally hard to reach.

Interventions to improve the quality of care provided within the public sector present a mixed picture and are probably interdependent. The impact of stockouts on treatment delivery is evident, and the threat of stockouts appears to alter both provider and patient behaviour with

Table 3. Interventions: improving access and quality of care in the informal private sector[a]

Author	Year	Country	Setting	Intervention	Outcome	Impact
Training of private sector providers						
Abuya *et al.* [54]	2010	Kenya	2 districts: Kwale and Kisii	• 2 training initiatives for private sector retailers (PMRs): (i) Kwale: 2 day Ministry of Health training, per diems, no follow-up plus community education; (ii) Kisii: 3 day NGO training, per diems and follow-up visits but no community education	• Kwale: 18.8% trained PMRs sold correct dose versus 2.3% untrained (OR: 9.4; 95% CI: 1.1–83.7) • Kisii: 60.5% trained PMRs sold correct doses versus 2.8% untrained (OR: 53.5; 95% CI: 6.7–428.3) • Kwale: programme coverage: 25.3% outlets • Kisii: programme coverage: 69.7% outlets	• Kwale: potential utilisation of 48 000 U5s Kisii: potential utilisation of 30 000 U5s
Alba *et al.* [41,45]	2010	Tanzania	Kilombero and Ulanga DSS and Ifakara town	• National scheme: training ADDOs • Subsidised ACTs available at ADDO level	• Increased proportion of cases treated with an antimalarial: 31% (47/154) in 2004 to 43% (54/127) in 2008 (OR: 1.68; $P = 0.038$) ○ Confounded by SES (adjusted OR = 1.18; $P = 0.632$) and decreased in poorest quintile ○ Increase was found in patients over age 5 years (38% in 2004 to 52% in 2008) and not U5s (25% to 28%) • ACTs supply: 2% in 2006 (unsubsidised) to 29% in 2008 • ACT stock in urban area than rural: 38.1% in Ifakara versus 20–25.9% in rural drug shops • Reduction in market share of SP: 64% (2005) to 51% (2008); ACT 17% in 2008 • Reduction in artemisinin monotherapies found: urban: 20% outlets (2007) to 12% (2008)	• Availability of ACTs is needed for subsidy scheme to take effect
AMFm and ACT subsidies						
Sabot *et al.* [102]	2009	Tanzania	2 districts: Maswa and Kongwa plus Shinyanga district as control	• AMFm subsidy pilot: ACTs at 90% subsidy through private supply chain reviewed August 2007 up to August 2008	• Increased stocking of ACTs: 0% to 72% ($P < 0.001$) • % Customers purchasing ACTs rose from 1% baseline to 44.2% at 1 year ($P < 0.001$) • Increase in ACT purchase for U5s significantly higher than adults ($P = 0.005$) • No change in control districts • Consumers paid mean US$0.58 for ACT (similar to SP price) • Highly populated areas more likely to stock ACTs than remote ($P < 0.001$)	• Subsidy passed to consumers successfully • Price similar to other alternative antimalarials
Cohen *et al.* [103]	2010	Tanzania	2 districts: Maswa and Kongwa	• AMFm subsidy pilot: reviewed November 2007 up to November 2008	• Total ACT stocks rose: 55.8% to 72.9% (SP unchanged) • % Sales ACT: 31.5% to 39.3% (although total sales increased) • Geographical variation in stocking and sales: in shops closer to district town ($P < 0.01$), major roads ($P < 0.01$), and in those with higher SE clientele ($P < 0.01$)	• Overall increase in ACT availability • Similar geographical disparity patterns to other antimalarials need to be addressed
Kangwana *et al.* [43]	2011	Kenya	3 districts: Busia, Butere-Mumias, Teso	• RCT comparing subsidised ACTs through private sector retailers with training and community awareness. No interventions in control arm	• 96.3% of those in intervention who bought ACTs purchased it at subsidy price (US$0.25) • % Children receiving ACT within 48 h of fever increased by 14.6% in control group versus 40.2% in intervention (25% difference in mean: 95% CI: 14.1–35.9; $P = 0.0001$) • Significant difference between groups in % children receiving antimalarial monotherapy (reduction −10.4%; 95% CI: −3.9 to −16.9; $P = 0.0074$)	• Cost subsidy can increase ACT coverage • No significant difference in adequacy of dosing obtained or provided despite training in intervention arm

Table 3 (*Continued*)

Author	Year	Country	Setting	Intervention	Outcome	Impact
Smith *et al.* [104]	2011	Kenya	Webuye DSS area: 97 shops and 13 mission facilities	• National AMFm subsidy scheme: reviewed at 5 months	• ACT stocked by 44% retailers; • Quinine most stocked (61% shops), SP: 57% • 47% retailers regularly report stockouts of all antimalarials • 11% retailers stocked the subsidised brand ACT • Subsidised brands of ACT – mean cost US$1.60: 40% less than non-AMFm brands of ACT (mean cost US$2.86) • Artemisinin monotherapies cost more than twice as much as subsidy brands (US$5.40) • SP cost US$0.50 compared with mean cost ACT (US$2.70)	• Cost subsidy is apparent for AMFm brands of ACT • Large difference still between effective and ineffective therapies
AMFm Evaluation Team [60]	2012	Kenya, Niger, Ghana, Tanzania, Nigeria, Uganda, Madagascar, Zanzibar	Evaluation of AMFm pilots in 8 countries	• National AMFm subsidy scheme; Phase 1 evaluation	• Of the 8 pilots, success benchmarks met in 5 pilots for availability and QAACT price relative to most popular non-QAACT antimalarial and 4 pilots for QAACT market share • Large increases in QAACT availability, decreases in QAACT prices, and increases in QAACT market share (except Niger and Madagascar) • Response similar in rural and urban areas The price of co-paid QAACTs: variable across pilots, ranging from US$0.51 in Madagascar to US$1.96 in Uganda • In Nigeria and Zanzibar where artemisinin monotherapy was previously common, large and significant falls were observed with AMFm	• Subsidy schemes can result in increases in QAACT availability and affordability (seen in almost all pilot sites (except Niger and Madagascar) with reductions in availability of artemisinin monotherapy • However, diagnostics stock and use in the private sector remained low • Impact was limited in Madagascar and Niger: possibly due to lack of full-scale mass media campaigns and the structure of the private-for-profit antimalarial sector (higher proportion of general stores, and in Niger itinerant vendors)
Tallisuna *et al.* (QAPSS study) [105]	2012	Uganda	4 pilot districts: Kamuli, Kaliro, Pallisa, Budaka (104 public health facilities and >750 private outlets) and 1 control district: Soroti	• As per AMFm approach, i.e., subsidised ACTs with supporting interventions including provider training and demand generation	• QAACT accounted for 69% of market share in intervention districts • Purchase of ACT within 24 h of symptom onset for U5s increased from 0.8% at baseline to 26.2% (95% CI: 23.2–29.2%) • Odds of purchasing ACT within 24 h in intervention versus control district: 6.11 (95% CI: 4.32–8.62; $P < 0.0001$)	• Sixfold increase in all people (tenfold in U5s) purchasing effective malaria treatment within 24 h of symptom onset • 70% caregivers who purchased ACT complied with treatment schedule • Affordable treatment drives availability and uptake
Tougher *et al.* [65]	2012	Ghana, Kenya, Madagascar, Niger, Nigeria, Uganda, Tanzania, Zanzibar	Evaluation of AMFm pilots in 8 countries	• National AMFm subsidy scheme: 6–15 months after rollout	• In all pilots except Niger and Madagascar: large increases in QAACT availability (26.3–71.3%) and in market share (15.6–58.7%) in the private sector • Fall in median price for QAACTs per adult dose in private sector from US$1.28 to US$4.82 (in 6/8 pilots) • Decreased market share of oral artemisinin monotherapies in Nigeria and Zanzibar (where previously >5%) • Also found increases in QAACT availability in public sector facilities, especially Niger, Nigeria, and Madagascar	• Limited effect in Madagascar and Niger at this stage • Impact mainly observed in the private sector although some improvement in public sector stocks • Small-scale pilots can be replicated at scale

*Abbreviations: ACTs: artemisinin combination therapies; ADDOs: accredited drug dispensing outlets (ADDOs); AMFm: affordable medicines facility (Malaria); CCMm: community case management of malaria; CHW: community health worker; CI: confidence interval; IMCI: integrated management of childhood illness; IPTc: intermittent preventative therapy for children; NMFI: non-malarial febrile illness; PMR: private medical retailer; QAACT: quality-assured ACT; RCT: randomised controlled trial; RDT: rapid diagnostic test; SES: socioeconomic status; SP: sulfadoxine-pyrimethamine; SMS; short message service; U5s: under 5 year olds.

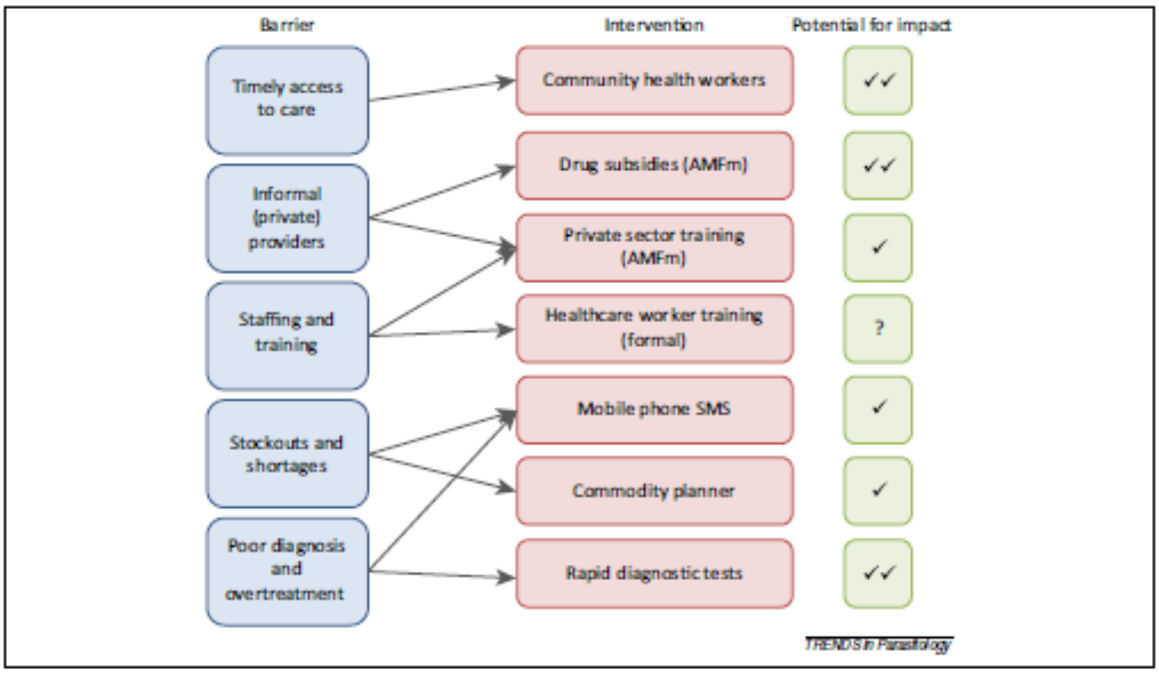

Figure 2. Summary of interventions to target health systems barriers. A summary of the barriers posed by health systems factors, rendering efficacious treatments such as artemisinin combination therapies (ACTs) less effective, and the health systems strengthening interventions aiming to overcome these barriers.

reports of stock-withholding, prescription of non-recommended drugs, and reluctance of patients to seek care at venues where they cannot be guaranteed treatment. Unfortunately, there is a paucity of published research on interventions to improve supply chains, although mobile phone technologies appear to offer hope with implications for other essential drugs. By contrast, there have been many evaluations of training in the public sector but few have shown sustained improvement in performance, although supervision may increase adherence to treatment guidelines and mobile phone technologies may also be used to improve performance [110].

The impact of increasing use of diagnostics is also complicated. There are individual benefits of ensuring that NMFI cases are correctly treated, but also community benefits of limiting potential emergence of ACT resistance. Conversely, overtreatment may potentially be associated with reduced risk of malaria transmission due to the prophylactic effect of ACTs [111], and thus a universal test-and-treat policy may in theory lead to increased transmission and altered demographics of infection.

The private informal sector may be seen as a barrier to national malaria strategies, or instead acknowledged as an important source of care and included in the spectrum of malaria control efforts. Schemes such as AMFm provide an innovative attempt to harness the private sector; however, challenges to success include ensuring a reliable supply chain and passing the subsidy to the patient. Lower prices encourage use of first-line drugs. Training interventions aimed at private outlets have been partially successful in Kenya and Tanzania, although long-term sustainability is unclear, and none of these studies address introducing diagnosis-led treatment.

The Research Agenda for Malaria Eradication (MalERA) collaboratively identified key knowledge gaps and strategies for health systems in reducing malaria transmission. They concluded that the overarching systems issue was the ability to rapidly assess bottlenecks to effective coverage of interventions, and the integration of interventions into health systems. In addition, the group defined specific research priorities; at facility level identifying HCW performance, at district level highlighting greater applications of existing strengthening tools, surveillance, and the importance of linking surveillance to actions (i.e., surveillance–response), and at national level using disease-specific programmes to strengthen health systems [4].

The barriers to successful malaria treatment identified in this review are consistent with the MalERA approach and equally applicable to other parasitic and infectious diseases managed at a primary care level. The review of interventions to address these barriers show that improving access and quality of care is a complex, interdependent process, often with unpredictable outcomes. Traditional strategies such as training appear to have less impact than hoped, whereas use of technologies to ease stockouts, task shifting to CHWs, and incorporation of informal points of care into planning appear more promising. As malaria control improves, such interventions may need to be tailored for surveillance as well as delivery, for example, using the SMS data on stockouts to improve disease

Box 1. Outstanding questions

- Is it possible to improve supply chain management of treatment and diagnostics on a national scale? Are any lessons applicable across countries?
- How can we best ensure that diagnostic testing is both used and adhered to in the public sector so that those who get ACTs actually need them?
- How do we keep community healthcare workers' standards high? Will financial incentives be required?
- How can we introduce diagnostic-led management into the informal and private sector?
- How best can we address the issue of counterfeit drugs and non-recommended antimalarials in the market?
- What is the impact of health system strengthening on malaria-related morbidity, mortality, and malaria transmission?

surveillance and linking this with appropriate control responses (surveillance–response). These interventions require further research extending beyond controlled small-scale trials (Box 1), but may be critical to the sustained success of malaria control strategies.

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The Potential Impact of Improving Appropriate Treatment for Fever on Malaria and Non-Malarial Febrile Illness Management in Under-5s: A Decision-Tree Modelling Approach

V. Bhargavi Rao[1]*, David Schellenberg[2], Azra C. Ghani[1]

1 Medical Research Council Centre for Outbreak Analysis & Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, United Kingdom, 2 Disease Control and Vector Biology Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

Abstract

Background: As international funding for malaria programmes plateaus, limited resources must be rationally managed for malaria and non-malarial febrile illnesses (NMFI). Given widespread unnecessary treatment of NMFI with first-line antimalarial Artemisinin Combination Therapies (ACTs), our aim was to estimate the effect of health-systems factors on rates of appropriate treatment for fever and on use of ACTs.

Methods: A decision-tree tool was developed to investigate the impact of improving aspects of the fever care-pathway and also evaluate the impact in Tanzania of the revised WHO malaria guidelines advocating diagnostic-led management

Results: Model outputs using baseline parameters suggest 49% malaria cases attending a clinic would receive ACTs (95% Uncertainty Interval:40.6–59.2%) but that 44% (95% UI:35–54.8%) NMFI cases would also receive ACTs. Provision of 100% ACT stock predicted a 28.9% increase in malaria cases treated with ACT, but also an increase in overtreatment of NMFI, with 70% NMFI cases (95% UI:56.4–79.2%) projected to receive ACTs, and thus an overall 13% reduction (95% UI:5–21.6%) in correct management of febrile cases. Modelling increased availability or use of diagnostics had little effect on malaria management outputs, but may significantly reduce NMFI overtreatment. The model predicts the early rollout of revised WHO guidelines in Tanzania may have led to a 35% decrease (95% UI:31.2–39.8%) in NMFI overtreatment, but also a 19.5% reduction (95% UI:11–27.2%), in malaria cases receiving ACTs, due to a potential fourfold decrease in cases that were untested or tested false-negative (42.5% vs.8.9%) and so untreated.

Discussion: Modelling multi-pronged intervention strategies proved most effective to improve malaria treatment without increasing NMFI overtreatment. As malaria transmission declines, health system interventions must be guided by whether the management priority is an increase in malaria cases receiving ACTs (reducing the treatment gap), reducing ACT waste through unnecessary treatment of NMFI or expanding appropriate treatment of all febrile illness.

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* E-mail: bhargavi.rao@imperial.ac.uk

Introduction

Malaria remains a major public health problem, with an estimated 216 million cases and 655,000 deaths in 2010 [1]. In endemic areas, a significant proportion of clinic visits and hospital admissions relate to malaria [1,2], with severe disease and mortality often ensuing from delayed or inadequate treatment [3–7]. Recent scaling-up of malaria control programmes has led to reductions in reported malaria cases, albeit slower than internationally agreed targets for 2010 [1]. However international funding for control programmes is expected to plateau, and fall to levels lower than required to meet such targets [1,8]. As such, it is essential that limited resources, including first-line treatments such as Artemisinin Combination Therapies (ACTs), are rationally managed.

Until recently presumptive treatment and syndromic management of all fevers as malaria was advocated in WHO guidelines and national policies, especially for children under 5 years (U5s). This has resulted in overtreatment (unnecessary prescription of antimalarials) with 47%–95% of patients with non-malarial febrile illness (NMFI) estimated to receive antimalarials [9–17]. Overtreatment is often with non-recommended antimalarials [11,18], but may also involve first-line ACTs [9,11,12,15,17]. The latest 2010 WHO guidelines revised protocols for the treatment of malaria and state that whenever possible *"prompt parasitological confirmation by microscopy or alternatively by rapid diagnostic test (RDT) is*

recommended in all patients suspected of malaria before treatment is started. Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible" [19]. This policy change was adopted to reduce routine overtreatment of malaria and the consequent risk of drug resistance, to expand disease surveillance and to improve quality of care for both malaria and NMFI, though its likely impact remains a subject of debate [20–24]. The WHO estimate expenditure on treatment may decrease as a result of testing before treatment and reduced prices for RDTs and ACTs [1], although any reduction in first-line drug costs could be complicated by a rise in anti-malarial resistance requiring alternative antimalarials [25–27]. However non-compliance with test results by healthcare workers (HCWs), i.e. treating with antimalarials despite a negative test for malaria, is common [28–30] and can be detrimental to those patients who are not parasitaemic. For example, a Tanzanian study found the case fatality rate in test-negative patients treated with antimalarials to be significantly higher (12.1%) than for test-positive patients (6.9%), and over 60% of NMFI were not treated with antibiotics [10].

The sustainability and efficiency of malaria control is limited by the capacity of impoverished health systems to deliver interventions at the required levels of coverage and quality, ensuring those who need treatment receive it, and that those who do not are not needlessly treated. There have been relatively few modelling approaches to address the delivery of treatment for case management. The "systems effectiveness framework" [31] illustrates how interacting health-systems barriers may sequentially reduce the in-field effectiveness of treatment interventions [32,33]. This has proved valuable as a means of analysing the steps to optimal case management. However outcomes such as the proportion of malaria cases that receive first-line treatment through all pathways (i.e. not solely via diagnostic-led management) and the levels of unnecessary treatment of NMFI with antimalarials are not addressed by this approach. Such outcomes are important given the limited budgets for the purchase and distribution of antimalarial treatment courses. Data from the INESS trial in Ghana, using this framework, estimates that just 13.5% of simple malaria fevers are treated effectively, with the greatest loss due to failure to access care within 24–48 hours [34]. Patient adherence was included in this analysis and constituted the second largest bottleneck [34]. However this differs from WHO estimates of cases of malaria treated with ACTs and other published studies [35,36] in some part because it does not include alternative non-recommended pathways to receiving treatment.

Here we extend the systems effectiveness framework into a decision-tree tool to estimate the effect of systems factors on rates of appropriate treatment for fever cases and appropriate use of ACTs. Decision-tree approaches have previously been used to consider the role of diagnostics in reducing the burden of childhood malaria in Africa [37,38]. Here we include considerations of treatment seeking, diagnostic availability, use and quality, as well as ACT stock in order to compare interventions to improve case management in a context specific manner. We also use this tool to undertake an early evaluation of the impact of the revised WHO guidelines on treatment outcomes for malarial and non-malarial fever.

Methods

Systems Effectiveness and Decision-Tree Model

We considered two approaches to evaluate the impact of improvements in case management on the appropriate treatment of fevers in U5 children in malaria endemic settings. The first follows the published stepwise systems effectiveness approach to case management [31,32,39], whilst the second is a decision-tree approach to malaria treatment in the public sector (Figure 1) extending previous similar decision-tree models for diagnostics [37,38]. The entry point to both scenarios is a febrile case seeking treatment. Treatment following clinical (i.e. non-diagnostic guided) diagnosis is included in the decision tree model, but not in the published systems effectiveness framework.

The outcome of the systems effectiveness approach is the proportion of malaria cases that receive correct diagnostic-led treatment with ACTs. In contrast, the decision-tree approach allows a wider spectrum of outcomes to be evaluated: i) correct treatment of malaria with ACTs (diagnostic-led or clinically diagnosed), ii) the under-treatment of malaria cases (i.e. those not given ACTs), iii) overtreatment of NMFI with ACTs, and iv) the overall number of febrile patients treated appropriately (i.e. both malaria cases given ACTs and NMFI not treated with ACTs).

Staff availability and training in malaria management were not included at this stage as, despite having potential impact, their effects can be difficult to quantify [40]. Stockouts of treatment for NMFI were not considered given the diversity of possible bacterial and non-bacterial causes, uncertainty regarding the need for antibiotics, and the high likelihood of basic antibiotics being available. In addition since the focus here is the impact of the health system, patient adherence to ACTs prescribed and drug failure were not included in either model.

Model Parameters

Model parameters for the moderate-high transmission setting analysis were derived from a previously published systematic literature review [40]. The parameters were restricted to data presented in studies published between January 2004 (following adoption of ACT as first-line treatment in most countries) and November 2012. The model parameters are shown in Table 1. For each health-systems parameter we extracted any relevant data from the papers restricting our analysis to medium-high transmission settings (as reported in the papers included), stratified by whether the study was conducted before or after the introduction of the WHO guidelines regarding universal rational (diagnostic-led) treatment in 2010 [19]. Parameters for diagnostic performance were derived from published values for the sensitivity and specificity of RDTs. We did not limit this to a specific type of RDT. We did not differentiate between the various types of RDTs or microscopy for parameters of diagnostic availability and use. Case management values for low prevalence scenarios were limited. We included studies published in regions outside Africa (including Afghanistan) and used the results to inform estimates of parameters for a density plot comparing medium-high to low prevalence settings.

For the baseline scenario we calculated the median of the extracted estimates for each parameter and the 25th and 75th percentiles for the parameter range. These ranges were chosen so as not to skew the results by sampling outliers. To generate uncertainty intervals we generated 1000 random parameter samples, drawing each parameter independently from a Uniform distribution between the 25th and 75th percentiles.

Case Management Scenarios

Parameters based on the literature prior to the publication of the new WHO guidelines were used as a baseline scenario representing current practice, since the rollout of guidance is in its early stage. We then investigated how improving case management at different points along the patient care-pathway impacted

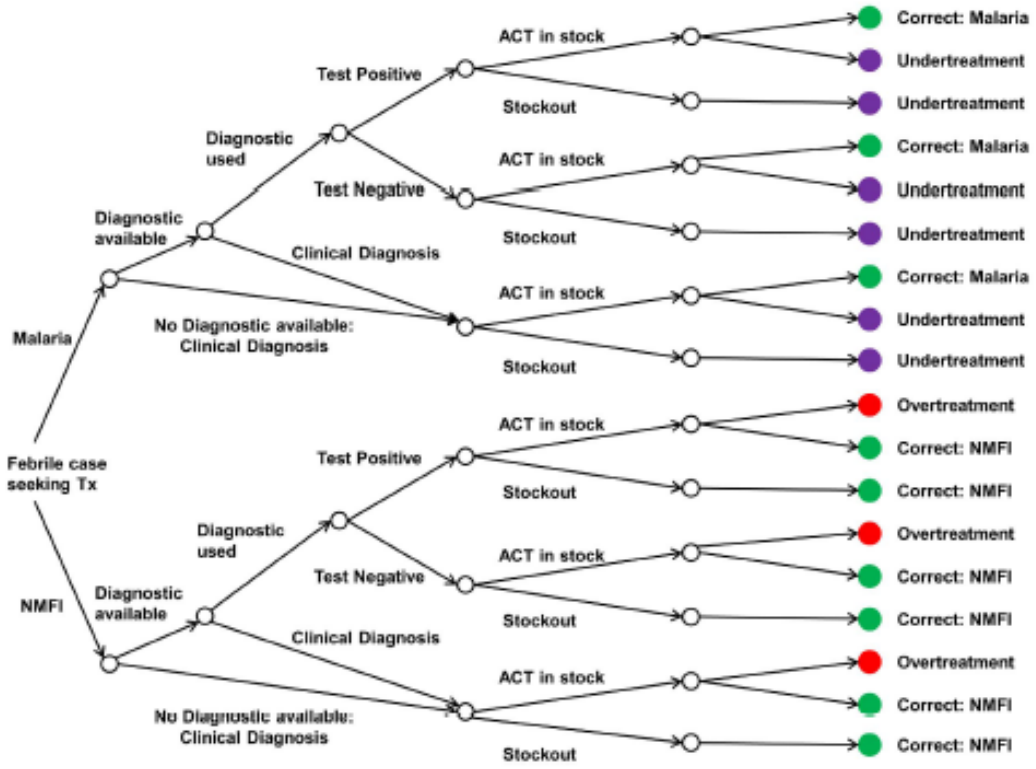

Figure 1. Decision tree modelling approach to malaria case management in the public sector. At the left-hand side the entry point is a febrile case seeking treatment. We next stratify on their true (unobserved) cause of fever as either malaria or non-malarial febrile illness (NMFI). The case management process then involves five steps – the availability of an RDT, whether the RDT is used, the outcome of the RDT given the true underlying cause of fever (based on the sensitivity and specificity of the diagnostic), whether an ACT is stock, and whether an ACT is prescribed given the RDT result or clinical diagnosis. This leads to four outcomes: correct treatment for malaria or for NMFI (shown as a green circle), under-treatment of malaria (shown as a purple circle), or overtreatment of an NMFI for malaria (shown as a red circle). In a perfect case management system there would be no under- or over-treatment.
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on the four outcomes in the decision-tree model. Table 2 summarises the set of scenarios considered.

We also performed the same scenarios using only data from Tanzania as a case-study, in order to compare published data from the early stages of the rollout of the new WHO guidance with modelled outcomes. Due to a paucity of published information, the values from all sub-Saharan Africa studies were used for the probability of seeking treatment at a public sector clinic. In addition, in the Tanzanian case-study, the probability of at least one dose of ACT being in stock was used rather than the probability of all doses of ACT being in stock due to limited data on the latter. Table 1 summarises the model parameters for the Tanzanian case-study.

Results

Figure 2 shows the outcomes from the systems effectiveness model. Using the baseline parameters obtained from studies undertaken prior to the 2010 WHO guidelines on rational case management, we estimate that 4.7% (95% uncertainty interval [UI]: 2.1–8.8%) of all malaria cases, and 14.7% (95% UI: 6.9–25.6%) of those malaria cases that attend the health facility will be treated correctly. In contrast, using the decision tree model to account for the correct outcome being possible despite imperfect case management (e.g. a case may receive an ACT despite not being tested) we estimate that 54% (95% UI: 48.9–59.3%) of all febrile attendees in the public sector will be correctly managed, and that 49% of malaria cases attending a public facility would receive first line ACTs (95% UI: 40.6–59.2%). This is similar to the WHO estimate of malaria cases being treated with ACTs at health facilities [1] and hence appears to represent a rational model for case management evaluation. We also estimate that 44% (95% UI: 35–54.8%) of NMFI cases attending the clinic would unnecessarily receive an ACT.

We next used the decision-tree model to estimate the effect of improving the various case management steps alone and in combination. Increased treatment-seeking was the single most effective step in increasing the proportion of all febrile cases that would be correctly managed and all malaria cases receiving an ACT. Modelling 100% attendance at the facility resulted in 49.6% all malaria cases (95% UI: 40.9–58.63%) receiving an ACT compared with 16.2% (95% UI: 11.8–20.8%) at baseline.

Table 1. Parameter estimates for each process in the cascade and decision-tree models.

	Pre universal rational treatment guidelines	Post universal rational treatment guidelines	Pre universal rational treatment guidelines	Post universal rational treatment guidelines	References
	All Studies		Tanzania		
Probability of seeking treatment at public sector clinic	0.28 (0.26–0.39)	0.29 (0.26–0.40)	0.28 (0.26–0.39)	0.29 (0.26–0.40)	[35,44–49]
Probability fever is due to malaria	0.22 (0.13–0.33)	0.22 (0.13–0.33)	0.18	0.1	[1,15,50–55]
Probability that a diagnostic is available	0.54 (0.36–0.97)	0.58 (0.50–0.83)	0.35 (0.34–0.36)	0.61 (0.55–0.68)	[9,11,12,14,17,18,35,43,44,55–60]
Probability that a diagnostic is used	0.39 (0.29–0.58)	0.46 (0.34–0.46)	0.69 (0.47–0.71)	0.71 (0.52–0.83)	[11,12,14–17,35,36,44,55–59,61–63]
Diagnostic sensitivity	0.90 (0.78–0.92)	0.86 (0.72– 0.92)	0.82 (0.63–0.92)	0.82 (0.62–0.86)	[59,64–68]
Diagnostic specificity	0.86 (0.8–0.92)	0.91 (0.82–0.98)	0.89 (0.83–0.95)	0.98 (0.91–0.98)	[55,59,64–68]
Probability that all doses of ACT are available	0.65 (0.54–0.73)	0.64 (0.62–0.68)	0.59 (0.51–0.67)	0.85 (0.81–0.90)	[11,12,17,18,35,43,57–61,69–75]
Probability that ACT is received if test positive	0.99 (0.91–1.0)	0.98 (0.76–0.99)	1.00 (0.99–1.00)	1.00 (0.87–1.00)	[11,12,16,17,35,36,56–59,61–63,65,76–78]
Probability that ACT is received if test negative	0.51 (0.39–0.71)	0.25 (0.11–0.53)	0.77 (0.53–0.81)	0.12 (0.08–0.20)	[11–17,35,36,55–59,61–63,65,76,77]
Probability that ACT received if untested	0.67 (0.65–0.84)	0.49 (0.23–0.71)	0.89 (0.79–0.95)	0.15 (0.08–0.21)	[11,15–17,35,55–59,61,63,74,76,77]

The values are stratified by whether the data were collected before or after the introduction of WHO diagnostic policy recommending universal diagnostic-led treatment for malaria. Values specific to a Tanzanian case study are also shown. The median and interquartile range from the published studies is presented. For the probability of seeking treatment at the public sector clinic, diagnostic sensitivity and diagnostic specificity, separate values for Tanzania were not available and so the general parameters were used. The probability of fever being due to malaria was assumed the same in the aggregated analysis but set to reflect the reduction in malaria incidence seen in Tanzania. In the Tanzanian case study, the probability of at least one dose of ACT being in stock was used rather than the probability of all doses of ACT being in stock due to limited data on the latter.

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However this would have little anticipated effect in improving case management of those patients attending the clinic. Perfecting a single step in the care pathway almost always resulted in an overall predicted increase in the proportion of fever cases attending clinic that are correctly treated. The one exception was a scenario of improving ACT stock alone (100% availability), under which our model predicted a 13% point reduction (95% UI: 5–21.6%) in correct management of all febrile cases.

The breakdown of correct fever management into the proportion of malaria cases receiving an ACT and the risk of NMFI being over-treated with an ACT is shown in Figure 3, depicting the absolute percentage point and relative percentage change in these two outcomes predicted under a range of scenarios for improving case management steps. Provision of 100% stock of ACTs predicted a 28.9% point (95% UI: 20.5–36.1%) increase in the proportion of malaria cases given an ACT, which corresponds to a 59% increase relative to baseline. However, this was also accompanied by a 26% point (95% UI: 17.0–34.7%) anticipated increase in the overtreatment of NMFI, potentially resulting in 70% NMFI cases (95% UI: 56.4–79.2%) receiving an ACT. Thus the modelled decrease in correct management of all febrile cases in a scenario of 100% ACT stock is due to a larger proportion of NMFI cases predicted to receive ACTs since there is no limitation by drug stock.

Single interventions aimed at increasing availability or use of diagnostic tools were forecast to have little effect on improving the management of malaria cases or reducing NMFI overtreatment. Modelling perfect compliance with diagnostic results without any increase in diagnostic stock or use (i.e. positive tests treated with ACTs and negative tests not treated with ACTs) led to very little projected change in the proportion of malaria cases receiving an ACT but anticipated an 8.9% point reduction (95% UI: 2.6–19%) in NMFI overtreatment with ACTs (18% relative reduction). Improved diagnostic quality, (100% sensitivity and specificity) also led to small predicted improvements in malaria treatment and a decrease in NMFI overtreatment even when all other conditions were maintained at baseline. Combinations of improvements to diagnostics deployment however, may show an effect on NMFI management, for example, increasing the availability and use of diagnostics is predicted to reduce overtreatment of NMFI with ACTs to 38% (95% UI: 27.3–50.7%), constituting a 14% point reduction from baseline. This scenario also projected improved overall management of malaria cases, with 57% (95% UI: 47.7–65.8%) of malaria cases receiving ACTs, i.e. a 7% point increase (95% UI: −1.4–16.8%).

Using Tanzania as a case-study, we compared predicted case management outcomes using published before and after the 2010 WHO guidelines. The Tanzanian Malaria Indicator Study reported that malaria prevalence amongst U5s had dropped from 18% in 2007 to 10% in 2011 [41]. The data collected from studies published in the year following the guidelines rollout is summarised in Table 1, and indicates stock levels of any dose of ACTs had increased (from 59% to 85%) as well as availability of any diagnostic tools (from 35% to 61%). At this stage, levels of diagnostic usage were not seen to have substantially increased (69% compared to 71%), although compliance to test results had improved (the probability of receiving an ACT with a negative test result reduced from 67% to 14%) and treatment of untested cases

Table 2. Scenarios for improved malaria case management.

Scenario	Modified Parameters
Baseline	
100% diagnostic availability	Probability that a diagnostic is available = 1
100% diagnostic use	Probability that a diagnostic is used = 1
100% ACT stock	Probability that all doses of ACT are available = 1
100% compliance with test results (i.e. treatment of test-positive only)	Probability that ACT is received if test positive = 1
	Probability that ACT is received if test negative = 0
Perfect diagnostic	Diagnostic sensitivity = 1
	Diagnostic specificity = 1
100% diagnostic availability & use	Probability that a diagnostic is available = 1
	Probability that a diagnostic is used = 1
100% diagnostic availability & ACT stock	Probability that a diagnostic is available = 1
	Probability that all doses of ACT are available = 1
100% diagnostic use and compliance with results	Probability that a diagnostic is used = 1
	Probability that ACT is received if test positive = 1
	Probability that ACT is received if test negative = 0
100% diagnostic availability, use & compliance	Probability that a diagnostic is available = 1
	Probability that a diagnostic is used = 1
	Probability that ACT is received if test positive = 1
	Probability that ACT is received if test negative = 0
100% diagnostic availability, use & compliance & ACT stock	Probability that a diagnostic is available = 1
	Probability that a diagnostic is used = 1
	Probability that all doses of ACT are available = 1
	Probability that ACT is received if test positive = 1
	Probability that ACT is received if test negative = 0
100% perfect diagnostic availability, use & compliance & ACT stock	Probability that a diagnostic is available = 1
	Probability that a diagnostic is used = 1
	Diagnostic sensitivity and specificity = 1
	Probability that all doses of ACT are available = 1
	Probability that ACT is received if test positive = 1
	Probability that ACT is received if test negative = 0

Table 2 describes the scenarios used in the model to investigate the impact of improving case management at different points along the patient care-pathway. Scenarios of individual interventions e.g. 100% ACT stock were first considered and then combinations of interventions were studied. The health system parameters that are perfected in each scenario are defined here. The results from the decision tree model for each of these scenarios are shown in Figures 3, 4, 5.

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had also decreased (86% untested febrile cases to 15%). Using these parameters in the decision-tree, Figure 4 depicts the predicted percentage change in the overall proportion of cases (both malaria and NMFI) correctly treated, the proportion of malaria cases correctly treated and the proportion of NMFI overtreated. The model estimates a 30% point increase (95% UI: 26.5–33.6%) in the proportion of all attending cases correctly treated would have occurred in the early stages of the implementation of the guidelines, i.e. a 52% relative increase compared with the pre-WHO guidance baseline. Contributing to this overall predicted improvement is a 35% point reduction (95% UI: 31.2–39.8%) in the proportion of NMFI treated inappropriately with ACTs, resulting in potentially only 13% of NMFI patients being overtreated following the guidance rollout. However we also predict a 19.5% point reduction (95% UI: 11 to 27.2%) may have ensued following rollout of the new WHO guidelines in the proportion of malaria cases receiving an ACT if they attend a clinic, i.e. 37.5% of attending malaria cases are given ACTs. Overall, on the basis of published health facility data from Tanzania, the percentage of all malaria cases in the community treated with ACTs is modelled to have reduced from 16.8% to 10.6%. Thus despite improved access to diagnostics, improved ACT stock and compliance to test results (but no increase in the overall proportion tested), the model outputs suggest a reduction in the proportion of malaria cases given ACT as treatment could have occurred. This does not mean that these malaria cases were not treated at all since we have not included other antimalarials aside from ACTs in our analysis. Exploration of the different pathways by which a malaria case may receive ACTs reveals a greater than twofold increase in the modelled probability of a malaria case being tested and receiving treatment on the basis of a positive test result (9.4% vs. 24%). However there is greater than fourfold reduction in the predicted probability of malaria cases receiving ACTs through other pathways (42.5% vs. 8.9%), i.e. in

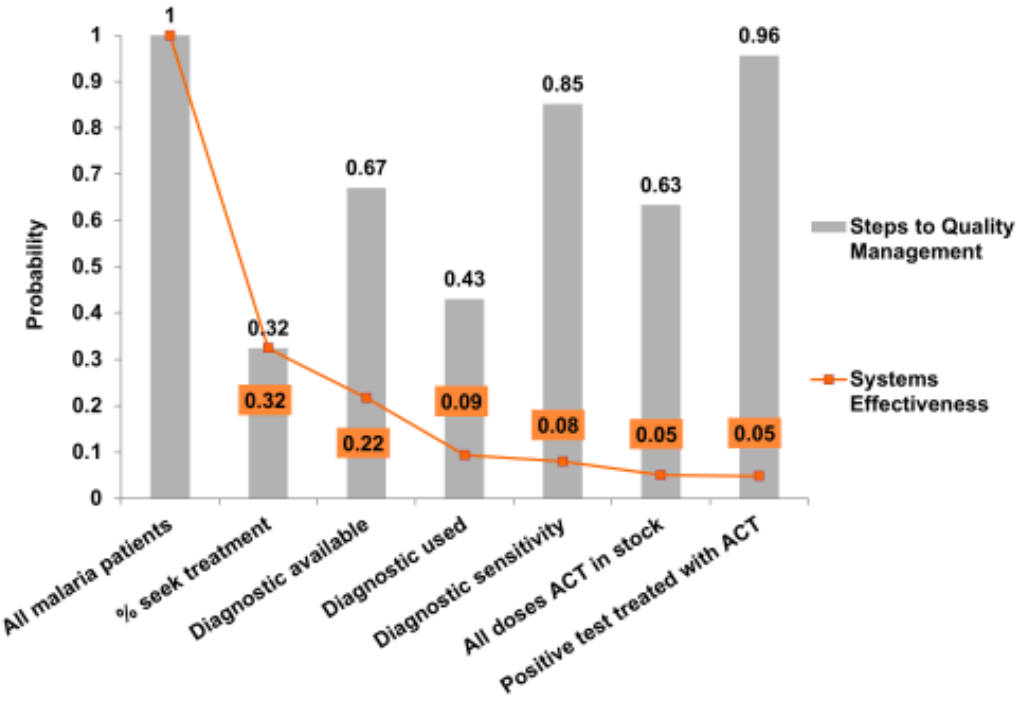

Figure 2. Estimated proportion of malaria cases at each case management point in the systems effectiveness pathway. The grey bars show the probabilities for each step for malaria case management whilst the orange line and values show the cumulative probability along this pathway. Data here is taken from studies published across sub-Saharan Africa prior to the rollout of the WHO guidelines on universal national management.
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those untested or in those who falsely test negative and are hence untreated. Similar outputs are seen when comparing the combined dataset from all countries.

Figure 5, using Tanzania data as a baseline case-study, shows the predicted gap between cases needing treatment and cases receiving treatment for the idealised scenarios investigated. At baseline we predict that there is a high degree of overtreatment, with less than a quarter of patients modelled to receive ACTs actually needing antimalarials, whilst there is a substantial treatment gap (i.e. malaria cases not given ACTs) with only half of patients needing antimalarial treatment forecast to actually receive ACTs. Overtreatment can be reduced by improving compliance with diagnostic results, as well as diagnostic availability; although a treatment gap may remain. In contrast high levels of ACT stock alongside high availability, use and compliance to diagnostic tests are predicted to reduce the treatment gap, i.e. increase the likelihood that those in need of treatment receive ACTs. However, this may also increase over treatment (i.e. NMFI given ACTs unnecessarily). If additionally the performance of the diagnostic test is improved (here we assume 100% specificity and sensitivity), the model output predicts no further treatment gap or treatment excess. Figure 5 illustrates the potential policy trade-off between increasing diagnostic use and compliance versus increasing ACT stock with respect to reducing the treatment gap and limiting treatment excess at medium-high transmission settings.

Discussion

Our simple decision-tree model can provide insight into aspects of delivering care most likely to impact on care quality and programme efficiency, and can quantify the intuitive qualitative effects of refining different steps of the care pathway in order to help to inform decisions and guide investments in improving fever management.

Our model suggests that the single most important intervention to increase the overall percentage of all febrile cases managed correctly and all malaria cases in the community treated with ACTs would be to improve attendance within 24 hours at a health facility. Considering only those who attend a primary health facility, increased ACT stock levels was the most critical intervention in potentially improving in the proportion of febrile malaria cases receiving treatment with ACTs. In contrast, the greatest predicted reduction in NMFI cases being overtreated following a single health system intervention was following improved compliance with diagnostic results; although this was anticipated to be associated with a reduction in the proportion of malaria cases receiving ACTs. Multi-pronged intervention strategies were most effective in balancing possible improvements in malaria treatment with the risks of NMFI overtreatment. However substantial improvements in malaria case treatment were not achieved as model outputs without increasing ACT stock levels. Interventions targeted at diagnostic tool availability, use and

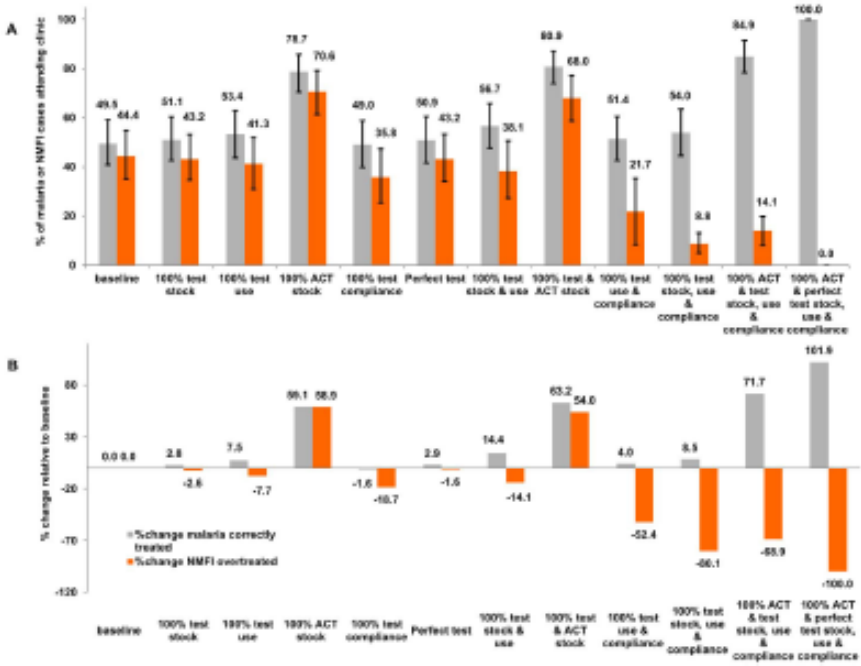

Figure 3. Results from the decision tree model for cases attending the health facility. A) % of malaria cases correctly treated with an ACT (grey bars) and % of non-malarial febrile illness (NMFI) overtreated with an ACT (orange bars) in a variety of scenarios as defined in Table 2 B) % change from baseline of malaria cases correctly treated with an ACT (grey bars) and % of non-malarial febrile illness (NMFI) overtreated with an ACT (orange bars) in each of the scenarios depicted in Figure 3A and defined in Table 2.
doi:10.1371/journal.pone.0069654.g003

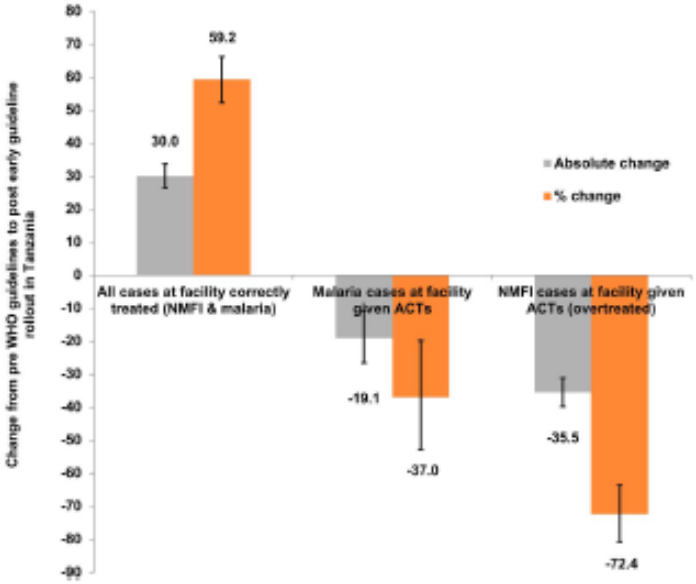

Figure 4. Change in case management outcomes after early rollout of WHO 2010 guidelines in Tanzania. The absolute percentage point change (grey bar) and percentage change relative to the baseline scenario (orange bar) following the introduction of the WHO 2010 case management guidelines advocating diagnostic-led treatment for all ages in Tanzania in 1) estimated proportion of attending cases correctly treated (both malaria and NMFI); 2) proportion of malaria cases correctly treated and 3) proportion of NMFI cases given an ACT. Data used were collected during the early period of the rollout of the new guidance and thus may not reflect more recent improvements in case management.
doi:10.1371/journal.pone.0069654.g004

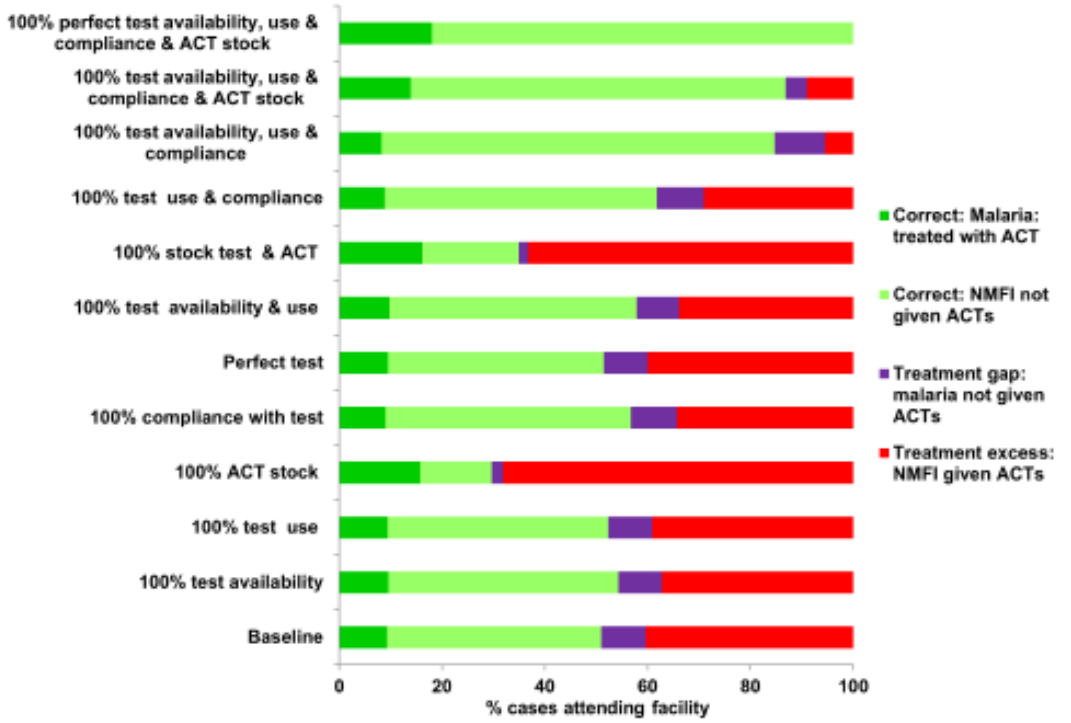

Figure 5. Modelled impact on treatment gap and treatment excess in Tanzania. Figure depicting the % treatment gap and % overtreatment (treatment excess) of all febrile patients attending health facilities using Tanzania as a case study, in the scenarios defined in Table 2. Desirable outcomes, namely malaria cases receiving ACTs and NMFI cases not being treated with ACTs are depicted in green. The % treatment gap, i.e. cases that need ACTs but that do not receive ACTs are depicted in purple. The % treatment excess i.e. cases that do not need antimalarials but are given ACTs unnecessarily are depicted in red.
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compliance may improve NMFI management rather than significantly impacting on malaria treatment.

In Tanzania despite reported improved access to diagnostics and compliance with their results as well as expanded ACT stocks, the proportion of malaria cases treated with ACTs is predicted by the model to have reduced following rollout of new WHO guidelines, whilst levels of NMFI overtreatment are predicted to have decreased. This is due to an anticipated large reduction in the numbers of malaria cases that receive ACTs despite being untested or who test falsely negative. Our model did not differentiate between the likelihood in receiving ACTs if untested due to healthcare choice or lack of diagnostic availability. However, this model output highlights the need for improved quality of testing, and also proper communication of the new WHO guidance to HCWs to prevent any malaria under-treatment if diagnostics are unavailable. Of note our analysis did not include patients receiving antimalarials other than ACTs.

Health system interventions for case management of malaria must be guided by whether the priority is improvement in malaria cases receiving ACTs, i.e. reducing the treatment gap, reducing ACT waste through unnecessary treatment of NMFI, i.e. treatment excess, increasing appropriate treatment of all febrile illness or expanding the most cost-effective solution for that particular epidemiological environment. This has implications for the recent emphasis on rollout of RDTs and the WHO guidance, but also highlights the need to focus on stock-management and improving HCW training in diagnostics. These priorities and the most cost-effective way to manage fevers may vary by transmission setting. Lubell et al, used a decision-tree cost modelling approach to suggest that use of diagnostics at moderate and low levels of transmission was more cost-beneficial than presumptive treatment (providing compliance to test results was high), but that this was less clear in high transmission settings [38]. We found a paucity of data on case management indicators in low malaria prevalence settings, but our results mirror intuitive assumptions that the high levels of diagnostic use and compliance with results may have an important role to play here in reducing levels of overtreatment with ACTs in NMFI cases.

A limitation of our decision-tree approach is the assumption that the parameters are independent of each other. It would seem likely that the availability and use of diagnostics are related to each other, and stock levels of ACTs may also influence whether testing occurs, but there is little data to parameterise such an association. We did not include staff training in this analysis at this stage, as there is much uncertainty about the impact of training on HCW performance [28,30,42]. In addition we used the same probability of receiving ACTs when untested irrespective of the presence of diagnostics which may not reflect reality and will need further

study of HCW behaviour. From a published systematic review [40], we used aggregated data from several countries from across Africa (and outside Africa for a low prevalence scenario), but these are unlikely to be comparable, and fail to provide specific guidance to nuanced health systems setting. Data from Tanzania alone gave a similar pattern of results; however the majority of the aggregated data was also from East Africa. There was substantial variation in data collection methods, sample sizes and the nature of the data collected. Despite these limitations, our results demonstrate the feasibility of such a decision-tree approach to quantify the effects of investing in changing health systems parameters, which could be made site-specific if such data were available.

Further work is required to explore the most cost-effective targets to expand the delivery of antimalarials and reduce ACT waste, given limited malaria control budgets and the potential rise of ACT resistance. In addition, this approach could be extended to delivery through other sectors including community HCWs and the private drug shops. This would be a useful tool with which to reflect on the impact of private sector subsidy schemes such as the Affordable Medicines Facility for malaria (AMFm) [43]. It will also be critical to investigate if improving access to and the performance of health systems may allow reductions in malaria transmission intensity and disease mortality and morbidity. As malaria transmission declines and appropriate treatment for NMFI becomes of increasing importance, it will become necessary to adopt a holistic approach to investing in improving fever management, both malaria and NMFI, taking into consideration the particular characteristics of the health systems, including the contributions of public, private and community delivery.

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Author Contributions

Conceived and designed the experiments: VBR DS AG. Performed the experiments: VBR. Analyzed the data: VBR. Wrote the paper: VBR DS AG.

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