Predicting the Cost-effectiveness of Strategies for Case Management of *Plasmodium falciparum* Malaria in Sub-Saharan Africa

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Prof. Dr. M. Spiess
Dekan

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ACT	Artemisinin-based combination therapy
AL	Artemether-lumefantrine
AMFm	Affordable Medicines Facility–malaria
AQ	Amodiaquine
AS	Artesunate
CHOICE	CHOosing Interventions that are Cost-Effective
CHW	Community health worker
CMC	Case management coverage
CMH	Commission on Macroeconomics and Health
CQ	Chloroquine
DHS	Demographic and Health Survey
EIR	Entomological inoculation rate
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GBD	Global Burden of Disease
HMIS	Health Management Information System
HMM	Home-based Management of Malaria
IBPAPA	Infectious bites per adult per annum
ICER	Incremental Cost-effectiveness Ratio
IIR	Infection importation rate
IM	Intramuscular
IPT	Intermittent preventive treatment
IRS	Indoor residual spraying
ITN	Insecticide-treated net
IV	Intravenous
LF	Lymphatic filariasis
MDA	Mass drug administration
MDG	Millennium Development Goal
MICS	Multiple Indicator Cluster Survey
MIS	Malaria Indicator Survey
MSAT	Mass screening and treatment
NC	Net cost
NE	Net effects
NMF	Non-malarial fever
NTD	Neglected tropical disease
PCD	Passive case detection
*Pf*HRP2	*Plasmodium falciparum* Histidine Rich Protein 2
PQ	Primaquine
RBM	Roll Back Malaria
RDT	Rapid diagnostic test
SP	Sulfadoxine-pyrimethamine

WHO   World Health Organization
UNICEF   United Nations Children's Fund
U.S. PMI   United States President's Malaria Initative

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Summary

Malaria is an important cause of death and illness in children and adults, particularly in the tropics. The World Health Organization (WHO) estimated that, worldwide, there were 655,000 malaria deaths in 2010, of which 91% were in Africa, and 216 million cases, of which 91% were due to *Plasmodium falciparum (P.falciparum)*. However, case estimates are particularly uncertain, due to the ambiguous definition of a malaria case and methods used for their quantification.

Efficacious interventions against malaria exist, but it is not clear what their full impact will be or how they could be most efficiently implemented. A cornerstone of malaria strategies is case management, which consists primarily of administering drug treatment to cure the disease, and was the focus of this thesis. Currently, the aim of most countries in sub-Saharan Africa is to control malaria and reduce the disease burden by increasing coverage of effective preventive and curative interventions. However, in some places successes in reducing disease burden have lead countries to consider whether and how local interruption of malaria transmission could be achieved and maintained. In these settings, improved surveillance is critical, but it is not clear what it should consist of. It is important to consider the long-term effects of intervention and intervention combinations, such as the dynamic effects on population immunity, which are not captured within the time frame of intervention trials, and their impact in real health systems. Mathematical models can offer guidance in these situations.

In 2006, Smith and colleagues presented individual-based stochastic simulation models of the biology and epidemiology of *P. falciparum* malaria. As part of this project, a model for the case management of malaria was developed which permitted simulation of the dynamic effects of treatment on transmission. For this

thesis, these models were extended to low-transmission settings and used to predict the levels of passive case detection and treatment that would be needed to prevent local re-establishment of transmission in different settings. We assessed the uncertainties in model predictions resulting from stochastic variation and from the assumptions in our model formulations. We found that, even at rather low levels of receptivity, case management alone could not reliably prevent re-establishment of *P. falciparum* malaria transmission in the face of medium to high importation rates. Model assumptions regarding rates of decay of natural immunity resulted in significantly different odds of transmission re-establishment, highlighting the urgent need for research in this area.

We also developed a literature-based estimate of the per-person cost of screening an entire population for *P.falciparum* infection using diagnostic tests. We used this cost estimate along with simulation model outputs to analyse the cost-effectiveness of mass screening and treatment (MSAT) as a burden-reducing intervention, relative to the cost-effectiveness of scaling up case management or insecticide-treated net (ITN) coverage. We found that MSAT may be a cost-effective strategy at medium to high transmission levels and at moderate ITN coverage. This finding is in contrast to the current focus on MSAT as an intervention for low or near-elimination settings. Future analyses comparing the cost-effectiveness of case management with that of preventive interventions should include both disability and deaths averted (expressed in DALYs) as an outcome measure. The analysis also highlighted the need for alternative measures of uncomplicated malaria burden to capture the impact of case management in simulation models of its cost-effectiveness. An approach to do this, using data available in community surveys, is presented in this thesis.

Finally, the previous case management model was extended to allow a finer-grained simulation of health systems and a drug action model was integrated to

allow simulation of the effects of case management on parasite densities. The development and parameterization of the new case management model, and its potential future uses and limitations, are presented in the last sections of this thesis.

1. **Introduction**

1.1. Epidemiology of malaria

Malaria results from infection with a protozoan parasite transmitted by species of the mosquito genus *Anopheles*. Five species of the *Plasmodium* parasite can infect humans. The most serious form of the disease, and that which most affects Sub-Saharan Africa, is caused by *Plasmodium falciparum*. *P. vivax, ovale*, and *malariae* cause milder forms of the disease. A fifth species, *P. knowlesi*, primarily affects monkeys but infection in humans has been reported [1].

Malaria parasites, which at this stage are called sporozoites, are inoculated into the human host by a feeding female mosquito. After several stages of development within the human, sexual-stage parasites, called gametocytes, are taken up by a mosquito feeding on an infective person, and the malaria transmission cycle is complete. These parasites develop within the mosquito and are injected into another person at a subsequent feed.

After a period spent in the liver, the inoculated parasites start to multiply in red blood cells of the infected host, often leading to symptoms which include headache, fatigue, and muscle and joint aches, usually followed by fever, chills, vomiting and worsening malaise. In general, uncomplicated malaria is a curable disease if diagnosed and treated promptly and effectively. If left untreated, parasite burden continues to increase and may lead to severe malaria, particularly in the case of *P.falciparum*. Severe malaria usually manifests with one or more of the following: coma (cerebral malaria), metabolic acidosis, severe anaemia, hypoglycaemia, acute renal failure or acute pulmonary oedema. If untreated, severe malaria is usually fatal [1].

The geographical distribution of malaria has been reduced significantly since 1900, due both to concerted control efforts and to broader socio-economic development. The estimated area of human malaria risk was reduced by around half, from 53% to 27% of the Earth's land surface [2]. An estimated 3.3 billion people were at risk of malaria in 2010, with populations in sub-Saharan Africa having the highest risk of acquiring malaria. During 2010, there were 106 countries in which malaria was considered endemic [3].

Malaria is an important cause of death and illness in children and adults, particularly in the tropics. The clinical consequences of malaria infection depend to a great extent on the level of the individual's acquired immunity to malaria. In areas of stable transmission, clinical malaria affects primarily children under five years of age and pregnant women, as immunity acquired through previous exposure renders infections largely asymptomatic in older children and adults. In areas of low or unstable transmission, the risk of clinical malaria is high across all age groups [1].

Determination of morbidity and mortality from malaria is fraught with difficulty, due in part to low health facility use and deficient systems for collection of vital statistics. The World Health Organization (WHO) estimated that, worldwide, there were 655,000 malaria deaths in 2010, of which 91% were in Africa, and 216 million cases, of which 91% were due to *P. falciparum* [3]. Case estimates are particularly uncertain, due to the ambiguous definition of a malaria case and methods used for their quantification. Using alternative methods, Hay *et al* concluded that there were 451 million cases of *P.falciparum* malaria globally in 2007; their distribution is shown in Figure 1.1 below [4].
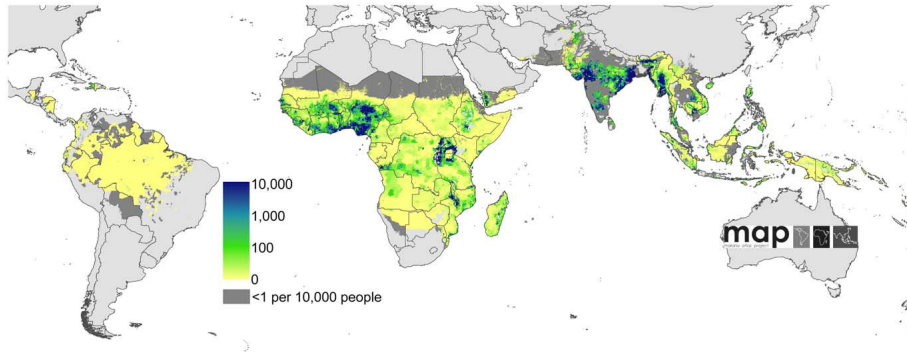
Figure 1.1 Global clinical burden of *P.falciparum* in 2007
(Source:[4])

Malaria disproportionately affects poor people, who are the least able to afford prevention and treatment, and places enormous strain on national resources, those of both government and households. There is evidence that it reduces productivity and impairs the cognitive development of children, negatively impacting economic growth [5].

1.2. Case management and integrated malaria control

Effective malaria control requires an integrated approach. Preventive measures against malaria include preventive chemotherapy (e.g. intermittent preventive treatment (IPT) in pregnancy), prevention of mosquito bites (e.g. distribution of insecticide-treated nets (ITNs)), or interventions to reduce the vector population (e.g. indoor residual spraying (IRS) of insecticides and ITNs). A malaria vaccine has shown promise in Phase 3 clinical trials [6] and could be available as early as 2015. Curative interventions consist primarily of administering drug treatment with the objective of completely eliminating from the body the parasites that caused the symptoms. Effective treatment can also curtail malaria transmission by reducing the parasite reservoir in the population.

Most symptomatic malaria is diagnosed and treated in communities, peripheral health facilities, and in informal health structures. Malaria can be diagnosed in one of several ways. Historically, most diagnosis of malaria in Africa has been based on symptoms, primarily fever. However, the accuracy of malaria diagnosis based on clinical symptoms is quite low. Microscopy is an alternative which involves collection and staining of a blood smear and examination of the red blood cells under a microscope for malarial parasites. Diagnosis using microscopy requires laboratory equipment, and its accuracy depends to a great extent on the quality of the blood smear and experience of laboratory personnel; therefore, it is only available in limited locations in sub-Saharan Africa. The advent of rapid diagnostic tests (RDTs) offers the possibility to extend parasite-based diagnosis to areas where microscopy is not available. RDTs are immunochromatographic tests, often dipsticks, which detect circulating parasite antigens in a finger-prick blood sample; they require no electricity or additional equipment and can be performed with limited training [7].

In 2010, WHO recommended that all suspected malaria cases receive parasitological confirmation where possible [1]. The advantages of confirmatory diagnosis are improved management of febrile disease, both parasite-positive and parasite-negative, as the correct drugs can be prescribed for the illness; reduction of side effects, selection pressure for drug resistance and costs of antimalarial drugs; and better public trust in the case management system. The risks of such a strategy are primarily that some true malaria cases may be missed due to false-negative test results and thus antimalarial treatment withheld when it is indicated; however, several recent studies suggest that restricting antimalarial treatment to parasitologically confirmed cases of malaria is safe, as morbidity and mortality did not increase in patients who were not treated with an antimalarial drug following a negative RDT result [8;9]. Another concern is whether satisfactory adherence to the test result by health workers can be achieved [10]. The use of RDTs also adds

costs to case management which may outweigh cost savings from reduced antimalarial consumption; these cost savings depend to a large extent on prevalence of parasitaemia in the clinical population and adherence of clinicians to the test result [11].

A variety of antimalarial medications are available. Two drugs, chloroquine (CQ) and sulfadoxine pyremethamine (SP), were until recently the mainstay of treatment for uncomplicated *P.falciparum* malaria. These drugs, given orally, were affordable and widely available [12]. However, resistance to these compounds has developed, rendering them ineffective. Fortunately, an alternative exists – artemisinin-based combination therapies (ACTs). ACTs are the most effective treatments currently available for uncomplicated *P.falciparum* malaria and in 2006, the WHO recommended ACTs as the first-line treatment for *P.falciparum* malaria worldwide [13]. ACTs are given orally, and must be taken daily, usually for three days. Five ACTs are currently recommended for use by the WHO: artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, and dihydroartemisinin plus piperaquine. Artemisinin and its derivatives should not be used as oral monotherapies for the treatment of uncomplicated malaria due to their potential to foster emergence and spread of drug resistance [1].

Young children and pregnant women are particularly vulnerable to severe malaria. Severe malaria requires treatment with parenteral quinine, artesunate or artemether, followed by a complete course of an effective ACT as soon as the patient is able to take oral medications. Intravenous (IV) artesunate is currently preferred to quinine for the treatment of severe malaria in adults and children. If complete treatment of severe malaria is not available, WHO recommends that patients be given pre-referral treatment with rectal artesunate, quinine intramuscular (IM), artesunate IM, or artemether IM and referred immediately to

an appropriate facility for further treatment. Intensive nursing care and supportive interventions as indicated (such as fluid replacement and blood transfusion) are strategies to reduce mortality from severe malaria [1].

1.3. Case management in elimination and pre-elimination settings

Successes in reducing malaria disease burden in some places have placed the prospect of eventual malaria eradication back on the international agenda [14] and have prompted a consultative process to identify of a set of research and development priorities for worldwide eradication of malaria [15]. An estimated 1 billion people live in areas of low *P.falciparum* malaria risk, where elimination could be epidemiologically feasible [16].

WHO defines malaria elimination as the interruption of local mosquito-borne malaria transmission, or zero incidence of locally contracted cases, and eradication as the permanent reduction to zero of the worldwide incidence of infection. However, the definition of elimination is still shifting, given the recognition that a small number of secondary cases will be inevitable as long as eradication has not been achieved, since infections will continue to be imported [17]. Malaria elimination should also include *P.vivax* and other strains [15;18], which will be more challenging due to the ability of *P.vivax* to relapse [19].
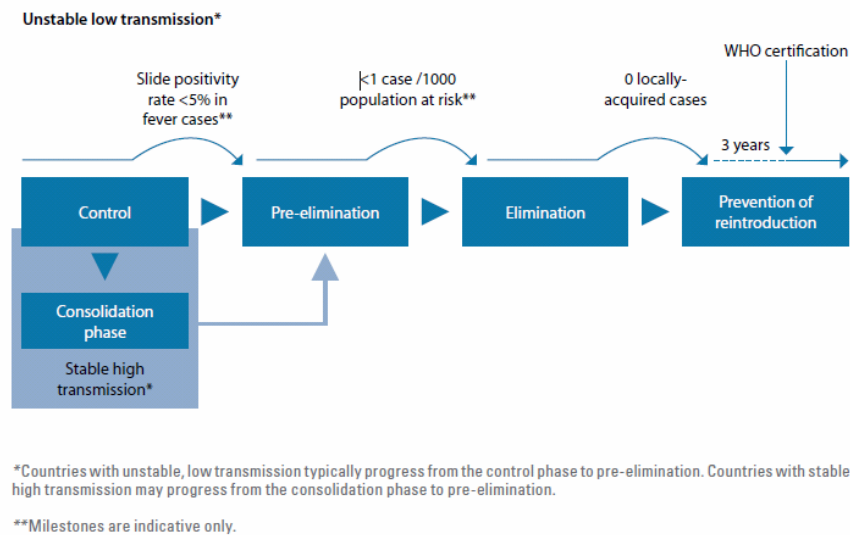
Figure 1.2 Phases of malaria control through prevention of reintroduction (Source: [20])

WHO has established programme phases and milestones on the path to malaria elimination, moving from control, to elimination, to prevention of reintroduction (Figure 1.2). The transition from each phase to the next requires a programme re-orientation and different interventions. In the control phase, the goal is to reduce the malaria disease burden to a level at which it is no longer a public health problem, through achieving high coverage with current interventions. In the pre-elimination stage, it is critical to perfect the quality and targeting of case management and vector control operations, and to reduce the onward transmission from existing cases in residual and new active foci. Establishment of a strong surveillance system is essential at this stage. Finally, once elimination is achieved, the focus is on preventing onward transmission of imported cases [20].

In programmes which aim at reducing transmission, the WHO recommends that a single dose of primaquine (PQ), a drug which kills gametocytes, be added to ACT treatment. In addition, PQ is one of few drugs which are effective against hypnozoites, or liver-stage parasites, that cause relapse in *P.vivax*. However, in individuals that have glucose-6-phosphate dehydrogenase (G6PD) deficiency,

primaquine can cause haemolysis. These risks need to be considered when giving PQ; they also make PQ an imperfect tool for mass administration in elimination programmes [1].

Where the aim is to interrupt local transmission or prevent its re-establishment, prompt and effective diagnosis and treatment of all malaria cases is critical. Therefore, in pre-elimination and elimination settings, surveillance is an intervention in and of itself which involves detection of infections and includes a timely and effective health system response. Although there is consensus around the need for improved surveillance for elimination, it is not clear what this intervention should consist of.

Individuals can be infected with malaria, and capable of transmitting the disease, without showing clinical symptoms. Programmes transitioning to low transmission conditions need advice on when and under which conditions it would be optimal for them to add active case and infection detection to their response strategies, and the effects of combining it with vector control interventions [21;22]. One option that is being considered, but has not yet been empirically tested, is mass screening and treatment (MSAT), which involves screening the whole population of interest and only treating those who test positive, regardless of symptoms. This approach could be useful to reduce the parasite reservoir in the targeted area [1].

Prior to embarking on malaria elimination, countries need to assess the technical, operational and financial feasibility of achieving and maintaining interruption of malaria transmission. Such an exercise was recently carried out in Zanzibar [14]. An understanding of malaria resurgence risks and the interventions that will be needed to prevent re-establishment once malaria transmission has been locally interrupted, is of critical importance to malaria control programmes when setting objectives and planning malaria strategies.

1.4.   Global malaria targets and intervention coverage levels

The Roll Back Malaria (RBM) Partnership comprises hundreds of partners, including malaria endemic countries, their bilateral and multilateral development partners, the private sector, nongovernmental and community-based organizations, foundations, and research and academic institutions. Its overall aim is to provide a coordinated global response to the disease. Current RBM Partnership goals and targets call for reducing global malaria deaths to near-zero by the end of 2015; reducing global malaria cases by 75% from 2000 levels by the end of 2015; and eliminating malaria by the end of 2015 in 10 new countries since 2008. These targets will be met by achieving and sustaining universal coverage for all populations at risk of malaria using locally appropriate interventions for prevention and case management, and accelerating the development of surveillance systems [23].

In recent years, disbursements for malaria control have increased dramatically, from an estimated US$ 200 million in 2004 to approximately US$ 2 billion in 2010, much of it from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the U.S. President's Malaria Initiative (PMI) and the World Bank [3]. This is a great improvement, although it still falls short of the approximately US$ 6 billion estimated to be needed in 2010 [23]. Concerns about stagnating donor aid for malaria have led to calls to donors to sustain funding and to countries to find alternative financing strategies to reduce reliance on donor aid [24]. This situation also calls for more efficient use of scarce resources [3].

Funding increases have made possible remarkable decreases in morbidity and mortality due to *P. falciparum* malaria in a range of settings across Sub-Saharan Africa. These decreases have been achieved primarily by the application of IRS and ITNs and the introduction of ACTs [25-27]. Coverage of preventive

interventions, primarily ITNs, has increased dramatically in the last decade. It is estimated that 50% of all households in sub-Saharan Africa owned at least one net in 2011, compared to 3% in 2000 [3]. However, increases in malaria prevalence and incidence have been recorded of late, despite increasing intervention coverage, in some sub-Saharan African countries ([28],A.Bennett, personal communication). This Red Queen phenomenon, in which malaria interventions need to improve over time just to maintain the effect on prevalence or incidence they had when first introduced, is due to the interaction between transmission and immunity [29]. This reality must be considered when planning interventions and predicting their impact. Also, in such a situation, increasing access to effective medicines to avert severe illness and mortality becomes ever more imperative.

By 2010, ACTs had been adopted as national policy for first-line treatment in 42 out of 43 malaria-endemic countries in Africa [3]. However, although public sector procurement of ACTs has increased greatly in recent years, data suggest that case management coverage with effective medicines is still low in many countries. The mean proportion of children under five years of age with fever that were treated with an antimalarial drug was 32%, and less than 15% received an ACT, in 11 of 13 countries for which survey data were available in 2007-2008 [30].

In 2010, 37 of 43 malaria-endemic countries in the WHO African Region reported having adopted a policy of providing parasitological confirmation for all age groups. The percentage of reported suspected malaria cases in the public sector receiving a parasitological test has increased from 20% in 2005 to 45% in 2010, but overall is still low in most African countries. In 2010, the number of ACTs distributed by national malaria control programmes in Africa was more than double the number of tests carried out, indicating that a large proportion of the suspected malaria cases are treated with ACTs without confirmatory diagnosis [3].

Little data is available about the extent of parasitological testing outside the public sector, but in a recent study from six countries, it was found to be less widespread in the private than in the public sector [31].

Limited availability, acceptability and affordability of ACTs are major reasons why, following change of national policies to ACTs, use of these drugs remains low in many high-burden countries [32]. Problems include high use of the informal sector, where first-line drugs, if available, are often unaffordable and product quality is low [31;33]; breakdowns in supply chains [34] and poor diagnostic and prescribing practices in public health facilities [35;36]; and sub-optimal patient compliance to treatment regimens [37].

Strategies to improve the quality of malaria case management and increase coverage include engaging and training community members and informal providers. The Affordable Medicines Facility– malaria (AMFm) is an initiative to make subsidized ACTs available in the private sector. Others have focused on improving care-seeking and quality of care in the public sector. A systematic review of current evidence to identify those provider and user behavior interventions that are most effective in improving prompt and effective treatment of malaria was published in 2009. It concluded that very little is known about what interventions work [38].

1.5.   Integrated models of malaria case management

As noted above, many efficacious interventions against malaria exist, but it is not clear what their full impact will be. Intensifying resource constraints make increasing the efficient use of resources and demonstration of intervention cost-effectiveness ever more important. Policy-makers require guidance as they make

choices on which interventions to implement in different settings. It is important to consider the long-term effects of intervention and intervention combinations, such as the dynamic effects on population immunity, which are not captured within the time frame of intervention trials, and their impact in real health systems. It is not financially or operationally feasible to conduct field studies of a large number of interventions and intervention combinations in every possible location, and mathematical models can offer guidance in these situations.

For accurate predictions, models of the impact of malaria interventions should consider the prevailing level of case management. Effective case management modifies disease burden (uncomplicated, severe and death) as well as influencing transmission by decreasing host infectivity. In addition, interventions modify the demands on the health system, resulting in cost savings from reduced health system use that need to be accounted for in cost-effectiveness analysis. Moreover, case management is an intervention in its own right and the health and economic implications of scaling up coverage are critical questions.

Malaria models in the last few decades of the 20th century focused in large part on morbidity and mortality, rather than transmission. These models used empirical estimates of the effectiveness of interventions, studies on disease burden, and unit costs to quantify morbidity and mortality and likely cost-effectiveness of interventions. Impact estimates generally came from field trial results, which assess only short-term effects under well-controlled conditions, with no explicit consideration of the dynamics of transmission and immunity [39].

To address this gap, in 2006, Smith and colleagues presented individual-based stochastic simulation models of the biology and epidemiology of *P. falciparum* malaria, which were developed to study long-term impacts and cost-effectiveness of intervention strategies [40] (Figure 1.3). These models simultaneously capture

the dynamics of infection, acquired immunity, parasite densities, the consequences of infections (morbidity, mortality and infectivity to mosquitoes), the health system and economics. The integrated models were formally fitted to numerous datasets from different ecologic and epidemiologic settings. As part of this project, a model for the case management of malaria was developed which permitted simulation of the dynamic effects of treatment on transmission [41].
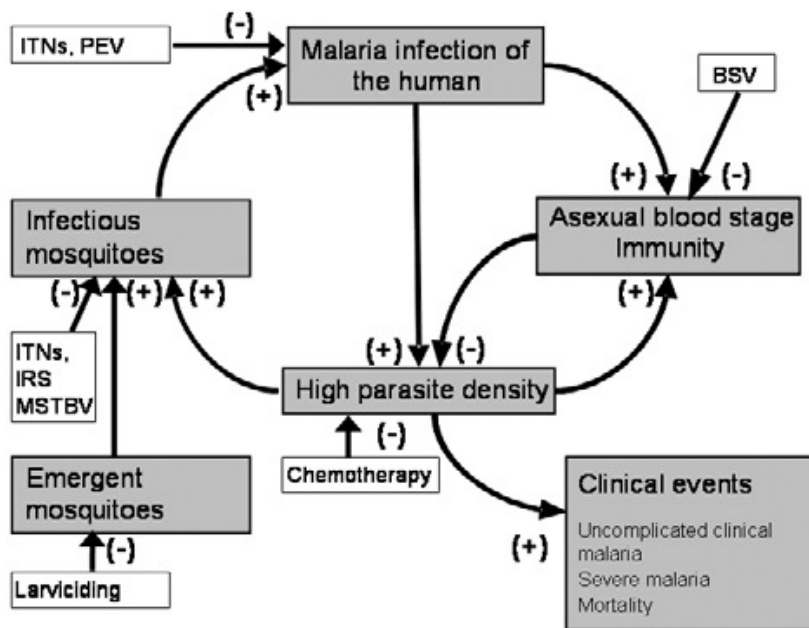
Figure 1.3 Key causal factors and outcomes in the models of malaria epidemiology and interventions.

Abbreviations: BSV: blood stage vaccine; MSTBV: mosquito stage transmission blocking vaccine; PEV: pre-erythrocytic vaccine; ITNs: insecticide treated nets; IRS: indoor residual spraying.
(Source: [39])

The case management model was appropriate for the purpose of that study, which was to predict the impact and cost-effectiveness of a pre-erythrocytic malaria vaccine. Case management coverage level was varied resulting in different parasitological cure rates, and a model for the costs of case management, based on data from Tanzania, was developed. These models, applied to low-transmission settings, were also suitable for simulating the effect of varying levels of passive

case detection (PCD) on local re-establishment of transmission and were extended to enable simulation of MSAT. The results of these studies are described in this thesis.

Evaluation of intervention effects requires quantification of the malaria burden in the absence and presence of the intervention. Current estimates of uncomplicated *P.falciparum* malaria burden are problematic as a result of imprecise terminology and estimation techniques that do not allow for the complexity of the natural history of the disease. In practice, and in our models, the definition of a malaria episode attempts to capture the illness caused by a single *P.falciparum* malaria infection. However, this definition is deficient as a measure of disease burden because the amount of illness that an infection causes depends to a great degree on the timing and effectiveness of treatment. The effectiveness of improved case management is thus likely to be underestimated if malaria burden is reported in this way, and estimates of malaria burden will be biased. Therefore, this thesis presents an alternative measure and estimation method for quantifying uncomplicated malaria burden using recalls of illness from cross-sectional surveys carried out in the community.

Additionally, the Tediosi *et al* case management model [41] was extended to allow a finer-grained simulation of health systems and their impact on coverage for predicting the cost-effectiveness of case management interventions, such as improved diagnosis. Also, a drug action model was integrated as an additional model component to allow simulation of the effects of case management on parasite densities, which is needed to simulate sub-curative treatment.
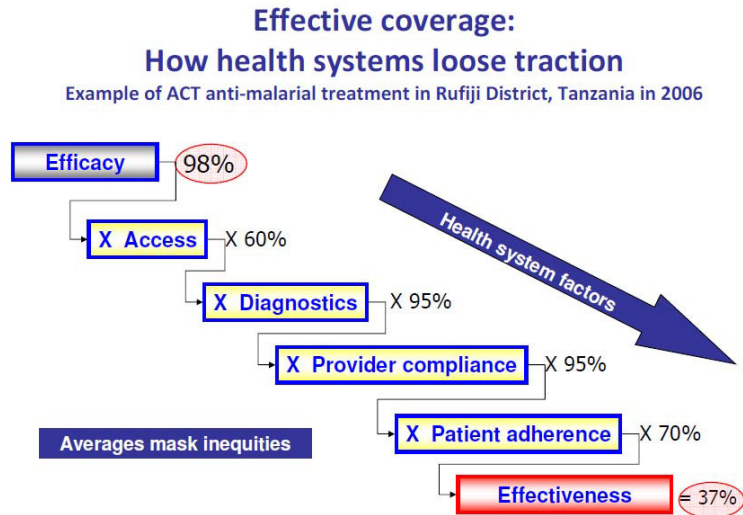
Figure 1.4 How interventions lose traction in health systems
(Source: D. de Savigny)

A number of factors affect the level of case management. Taking the example of ACTs in Rufiji, Tanzania, Figure 1.4 shows how apparently very efficacious interventions can lose their effectiveness under real-life conditions due to a variety of health system factors. Sub-optimal access, targeting accuracy, provider compliance and consumer adherence can all reduce the impact of an intervention. Evidence suggests that these health system factors are major obstacles to progress in a number of malaria endemic countries (unpublished data, INDEPTH Effectiveness and Safety Studies of Antimalarials in Africa). Human behaviour is shaped by the particular social, economic, cultural and health systems context, which can help explain the burden of malaria and inform the design and planning of case management interventions [42]. Furthermore, health systems are dynamic, and feedback effects of changes to one part of the system can be substantial [43]. A *P. falciparum* malaria case management model, integrated with pharmacodynamics, was developed to enable inclusion of these factors.

1.6.   Objectives of this thesis

- Use an existing set of models of *P.falciparum* malaria case management and transmission to predict the impact of passive case detection (PCD) and treatment (Chapter 2) and cost-effectiveness of mass screening and treatment (MSAT) (Chapter 3) in varying transmission and health system settings.
- Present an alternative method for estimation of uncomplicated *P.falciparum* malaria burden (Chapter 4).
- Develop a model for *P.falciparum* malaria case management that, when integrated with dynamic models of the natural history and transmission of the disease, permits simulation of the impact of health system factors on treatment coverage, the effects of drug treatment on parasite densities and the impact of changes in the case management system (Chapter 5) on human behavior and health outcomes. Parameterize this model with data on current case management and the costs and effects of alternative delivery strategies (Chapter 6).

2. Can we depend on case management to prevent re-establishment of *P. falciparum* malaria, after local interruption of transmission?

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2.1. Abstract

Recent declines in malaria burden in many parts of the world have prompted consideration of how interruption of *Plasmodium falciparum* transmission could be maintained, if achieved, and notably whether large-scale vector control could be replaced with surveillance. This information is essential for elimination feasibility assessments and planning. The risk of re-establishment of transmission depends mainly on vectorial capacity (receptivity), likely to rebound once vector control is removed, the rate of importation of infections (vulnerability), the capacity to detect and treat infections and the level of immunity in infected individuals. Timely detection and removal of new infections is likely to be critical to prevent re-establishment of transmission. We assess, through mathematical modeling and simulation, which levels of case detection and treatment (case management) are required to prevent re-establishment of transmission of *P. falciparum* after local interruption of transmission has been achieved, in settings with varying receptivity and vulnerability. We find that, even at rather low levels of receptivity, case management alone cannot reliably prevent re-establishment of *P. falciparum* malaria transmission in the face of medium to high importation rates. Thus, if vector control is to be discontinued, preventing the importations by controlling transmission in source areas will generally be necessary for preventing reintroduction in such settings, and cannot be substituted by very high levels of case management coverage.

2.2.   Background

Recent years have seen remarkable decreases in morbidity and mortality due to *Plasmodium falciparum* malaria in a range of settings across Sub-Saharan Africa. These decreases have been achieved primarily by the application of effective vector control tools, such as indoor residual spraying (IRS) and insecticide-treated nets (ITNs), and the introduction of artemisinin combination therapies (ACTs) [25-27]. Such successes, which have been made possible by increased donor commitment to malaria control, have prompted national health policy-makers and their partners to consider how interruption of transmission could be maintained, if achieved [14].

Evidence suggests that in some areas with a relatively low endemicity, local transmission could be [44], or may already have been [45], interrupted. In such places, for example the Kenyan highlands and Zanzibar, vector control was critical to bringing about substantial decreases in transmission and continues to be widely applied. However, it is likely to be difficult to sustain the will to maintain high levels of these interventions, particularly after malaria has ceased to be a public health problem [46]. Policy makers will need guidance on when it is safe to scale down large-scale vector control operations aimed at achieving interruption of transmission and on when to proceed with a policy that relies mostly on surveillance. Maintenance of transmission interruption without large-scale vector control has been possible in several areas with moderate vectorial capacity, such as Reunion Island [47] and Singapore [48]. In other places, such as Mayotte in the Comoros Islands, interruption of *P. falciparum* transmission has proved elusive even when it seemed imminent, despite intensive control efforts, and it seems that vector control will need to be maintained to prevent resurgence of malaria [49].

Understanding malaria resurgence risks is of critical importance to malaria control programmes when setting objectives and planning malaria strategies.

In closed systems, interruption of transmission would be maintained automatically once achieved. However, in reality, human populations are connected to each other, and as long as local vectors have sufficient capacity to transmit malaria, local transmission can be reintroduced through immigration of infected people or infective mosquitoes. The greater the magnitude of this immigration, the more likely malaria transmission will resurge, all else equal. Evidence indicates that current control strategies, even applied at very high coverage, will be insufficient to interrupt transmission in much of Sub-Saharan Africa [50], so importation of infections will remain a major challenge for the foreseeable future for countries in the region which seek to maintain local interruption of transmission.

Health systems which deploy methods for timely detection and removal of imported infections can prevent re-establishment of transmission. For instance, Singapore, which reported elimination of malaria in 1982, saw a large cluster of imported *P. falciparum* malaria infections in 2005, but local onward transmission was prevented through early diagnosis, treatment and screening [51]. Likewise, in the United States of America, outbreaks of locally transmitted malaria have been detected and contained on several occasions since certification of the country's malaria-free status [52].

Individuals can be infected with malaria, and capable of transmitting the disease, without showing clinical symptoms. Intervention strategies based on case detection and treatment target individuals with clinical disease, whereas others, such as mass drug administration or screening and treatment, include individuals without signs of illness. Although the latter types of approaches may identify a larger proportion of infections, screening or diagnosis with methods appropriate

for use in the field, notably rapid diagnostic tests or microscopy, may still miss a significant number of infections with low or sub-patent parasite densities [53;54]. These types of approaches may also be less sustainable long-term, because of their costs and organizational requirements, potential to accelerate development of drug resistance, and refusal of healthy individuals to participate in repeated screenings [55-57].

After interruption of transmission, individuals' naturally-acquired immunity will decay in the absence of exposure to malaria. Although the mechanisms involved are poorly understood, this decay in immunity could be expected to influence re-establishment of transmission in two ways. First, an infected individual with a lower anti-parasite immunity is more likely to be infective to mosquitoes. Second, an infected individual with a lowered immunity is more likely to show clinical symptoms and thus, given access to appropriate care, to be treated promptly, reducing the parasite reservoir. Both these effects need to be considered in assessing the likely outcomes of different strategies.

The vectorial capacity is the capacity of the combined vector populations present in an area to transmit disease agents, expressed as the potential number of inoculations per time unit originating from an infective person with no prior immunity. In the absence of major structural environmental or socio-economic changes, it is probable that, after withdrawal of large-scale vector control operations, the vectorial capacity will revert quickly to the same level as prior to control. As the vectorial capacity is difficult to measure, the pre-intervention entomological inoculation rate (EIR) may be a good proxy measure for the receptivity.

The risk that transmission will re-establish in an area thus depends mainly on the local receptivity, or vectorial capacity, the local vulnerability, or infection

importation rate (IIR), the capacity to detect and treat infections, and the level of immunity in infected individuals. The purpose of this paper is to assess, through mathematical modeling and simulation, which levels of case detection and treatment (case management) are required to prevent re-establishment of transmission of *P. falciparum* after local interruption of transmission has been achieved, in settings with varying receptivity and vulnerability.

2.3. Methods

Individual-based stochastic simulation models of the biology and epidemiology of *P. falciparum* malaria were developed to study long-term impacts and cost-effectiveness of intervention strategies, and have been described elsewhere [39;40]. Briefly, there is a simulated population of humans who are updated at each five-day time step via model components representing new infections, parasite densities, acquired immunity, uncomplicated and severe episodes, direct and indirect malaria mortality, infectiousness to mosquitoes, and case management. Simulated immunity to asexual parasites, derived from cumulative exposure to both inoculations and parasite densities and maternal immunity, acts mainly by controlling parasite densities [58]. The probability of a clinical attack of malaria depends on the current parasite density and a pyrogenic threshold [59]. Severe malaria comprises two categories of episodes: those that occur as a result of overwhelming parasite densities, and those that arise when an uncomplicated malaria episode coincides with non-malaria co-morbidity. Mortality can be either direct (following severe malaria) or indirect (uncomplicated malaria in conjunction with co-morbidity, or during the neonatal period as a result of maternal infection) [60]. There is also a model of the dynamics of malaria in mosquitoes [61].

Infectivity of hosts to mosquitoes at a given time point is modeled as a function of asexual parasite densities 10, 15 and 20 days previously, allowing for the delay resulting from the time course of gametocytemia [62]. Effective treatment completely clears parasites by the next time step, ending the infection, while ineffective treatment has no impact on asexual parasite densities. By clearing asexual parasites, case management renders individuals uninfectious to vectors at later time points. Given sufficiently high case management coverage, this lowered infectivity translates into a future reduction in EIR. We do not model the effects of drug treatment on gametocytemia.

Previous studies using these models [63;64] focused on settings of medium to high transmission intensity, for which the model outcomes could be presumed to be insensitive to importation of infections. We have now extended these models to include importation of infections, and applied them to low and medium transmission settings.

We used three different pre-intervention EIRs of two, 20, and 50 infectious bites per adult per annum (ibpapa), with a pattern of seasonality as observed in Namawala, Tanzania [65]. The infection status and immune status at the start of the simulation are determined by exposing the simulated population to the same annually recurring pattern of inoculations for a lifetime-long burn-in at the start. The level of case management coverage was set at zero during the burn-in period in all simulations in order to ensure that the simulated vectorial capacity was the same across all scenarios. Case management coverage was changed to the appropriate level at the beginning of the main simulation.

We used a population size of 1,000, with underlying demography based on East African life tables [66]. In our simulations, to interrupt transmission, we applied mass drug administration at 100% coverage and cleared all infections from vector

mosquitoes over a period of 30 days at the beginning of year 2. These interventions are not intended to be realistic, but were a convenient way to locally eliminate malaria in our simulations. Achievement of such high coverage of mass drug administration would be nearly impossible in a real-life setting, nor do we consider the mechanism by which all infections could be simultaneously cleared from vector mosquitoes.

The case management component [41] models a health system using ACT. Individuals with uncomplicated malaria were assigned a probability of accessing treatment over the next five-day period, expressed as percent coverage, which was varied between 0% and 100% at 10% intervals. These probabilities were constant over the entire time period of the simulation. We considered only case detection and treatment based on clinical symptoms. Compliance to the drug was set at 90% [67], and the drug was assumed to be 98% effective. In patients who did not comply, the drug was assumed to have an effectiveness of 20%. All severe cases were assigned a probability of receiving treatment as an inpatient of 48%, and parasites were cleared in all hospitalized cases who survived [41].

Imported infections were simulated by assigning infections to individuals in the population stochastically every 30 days at a constant average rate throughout the simulation period. No infected mosquitoes entered the local system. The rate of imported infections was Poisson distributed with mean of 0, 0.02, 0.2, 2, or 20 imported infections per 1,000 persons per annum. These rates compare to estimates of infection importation rates in Zanzibar ranging from 2 to 8 infections per 1,000 inhabitants per annum in 2008 [14;68] and cases reported as imported in South Africa from 1981 to 1999 ranging from about 0.02 to about 0.17 per 1,000 population [69]. The IIR of 0 was included as a reference scenario to check that transmission had indeed been interrupted by mass drug administration and clearing infections from vectors.

We evaluated the impact of all possible combinations of these scenarios on the number of malaria episodes expected over the last 14.75 years of the simulations. For each IIR, we chose a threshold number of cases over the 14.75-year period after interruption of transmission, above which we considered transmission to have re-established. This threshold was calculated by taking the 97.5 percentile of the Poisson distribution of the number of imported cases that would be expected over the period, and multiplying this by 3, thus allowing each imported infection to give rise to a maximum of 2 secondary infections before classifying the simulation as one where transmission was re-established. The reason for using the 97.5 percentile was to establish a very generous threshold for re-establishment. If malaria is considered to have re-established under these conditions, it is not likely to be kept out under more strict definitions.

We assessed the uncertainties in model predictions resulting from stochastic variation and from the assumptions in our model formulations by using 100 different seeds for the random number generator and an ensemble of 14 model variants as described in Table 2.1. The ensemble consists of a base model, used in previous publications [63;64], and thirteen variants on that model, with each one representing a different set of assumptions about malaria transmission and epidemiology. The motivation for using model ensembles is to assess how our understanding of a particular phenomenon is affected by uncertainty in model assumptions. Our ensemble of stochastic simulation models of malaria epidemiology incorporates different assumptions about decay of immunity and about heterogeneities in exposure, co-morbidity and access to treatment [70].

While the base model assumes that, in a given transmission setting, entomological exposure depends only on age, the model variants for heterogeneities in exposure include random variation in the availability of the human host to mosquitoes.

Thus, the expected number of entomological inoculations is additionally a function both of the individual and of log-normal noise. Three different parameterisations were considered - *R0063* assigns most variation to be inter-host, *R0068* assigns the variation predominantly to within host variation, and *R0065* is intermediate.

The model for natural immunity used in the base model, developed primarily for simulating the epidemiology of malaria in endemic settings, does not allow for any decay of immunity in the absence of exposure. To allow for such decay, the base model was extended by two alternative algorithms. In both cases, the model variants were parameterised so that in the absence of new exposure, the decayed value is some fixed proportion of that at the previous five-day time step. The half life of the decay is either fixed at 10 or 1,000 years or estimated during the model fitting process.

Finally, the model variants for heterogeneities in co-morbidity and access to treatment assign each simulated individual a status for each of the two kinds of heterogeneity at birth, which they carry throughout their life, structured in each case so that 50% of the population are assigned to each of the high and low status categories, with the values in the base model multiplied by either 1.8 or 0.2. Two of the model variants simulate these heterogeneities singly, while the third simulates both, where they are assigned to individuals independently of each other.

Analyses were conducted using R statistical software version 2.11.1 [71].

2.4. Results

Figure 2.1 illustrates the use of model ensembles to simulate clinical episodes over time, in a setting with a pre-intervention EIR of 2 ibpapa. Model variant medians

for simulated incidence post-intervention were higher at 20% (a) case management coverage than at 80% (b), indicating the effect of higher case management coverage in reducing transmission. In these scenarios, where IIR=2 per 1,000 persons per annum, the higher case management coverage level seems to prevent the resumption of transmission in most simulations, in contrast to the lower case management coverage level. There was a much larger variation among model variant outcomes post-intervention at the lower case management coverage level.
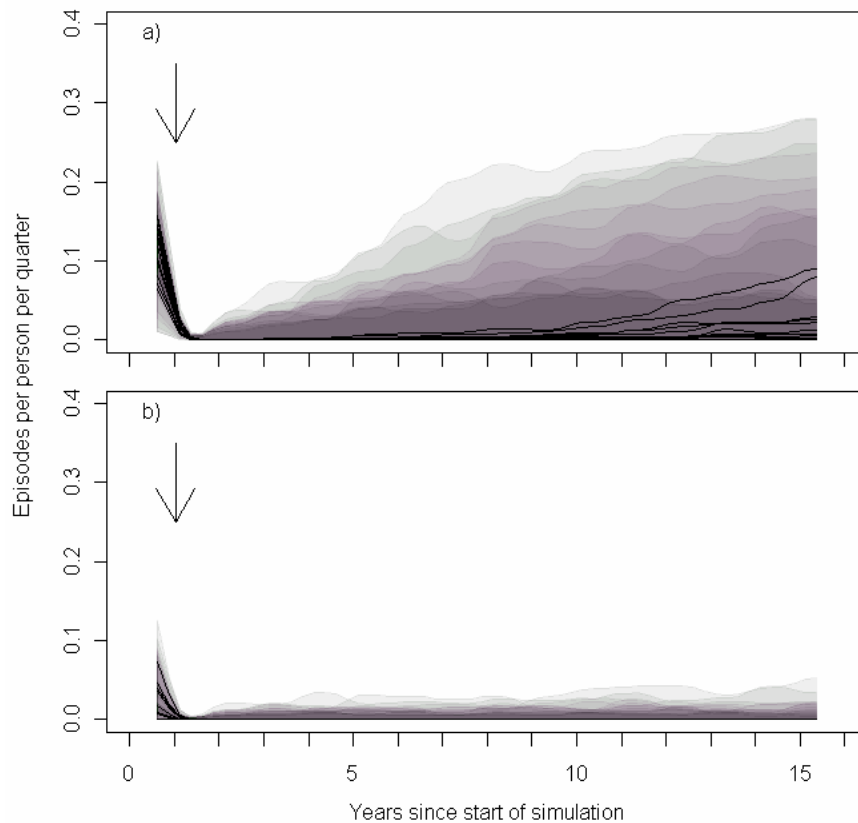
Figure 2.1 Simulated clinical incidence by model variant with 20% (a) and 80% (b) case management coverage

IIR=2 per 1,000 persons per annum, and pre-intervention EIR=2 ibpapa.
Black lines: model variant medians; gray shading: 95% probability interval around each median. Results are smoothed to remove the effect of seasonality. The arrow indicates the time point where transmission is interrupted with mass drug administration and clearing infections from vectors.

Figure 2.2 depicts the proportion of model variant simulations in which transmission remained interrupted as a function of case management coverage at different IIRs. In the lowest transmission setting with a pre-intervention EIR of 2 ibpapa (Figure 2.2a), there was a positive relationship between case management coverage and the proportion of simulations in which transmission remained interrupted for all IIR levels except at 0.02 imported infections per 1,000 persons per annum. At IIR=0.2 per 1,000 persons per annum, 60% case management coverage resulted in maintenance of interruption of transmission in 86% of simulations of the median model variant. At IIR=2 and 20 per 1,000 persons per annum, predicted success was much lower; at IIR=2, at 60% case management coverage, transmission remained interrupted in only 66% of simulations of the median model variant, while at IIR=20, transmission remained interrupted in only 15% of simulations of the median model variant at 60% case management coverage. At IIR=0.2 and 2 per 1,000 persons per annum, most of the benefits from increasing case management coverage seem to be gained at lower coverage levels; at 70% case management coverage, the imaginary curve through the median model variant results flattens off . As seen from the boxplot, variation in probability of success over the model variants was relatively large at the IIR levels 2.0 and 20. At the lowest IIR, 0.02 per 1,000 persons per annum, case management coverage level had little effect on the probability of success; however, at this low IIR level, the probability that no infections were imported during the observation period in a simulation was 74%. At IIR=0.2 per 1,000 population per annum, this probability was approximately 5%.

In the higher transmission settings (Figures 2.2b and 2.2c), at IIR= 0.2 per 1,000 persons per annum, higher case management coverage slightly increased the proportion success in preventing re-establishment, but even with perfect passive case detection, transmission returned in at least half of simulations of the median

model variant. In these settings, at IIR= 2 or 20 per 1,000 persons per annum, interruption of transmission was never, or almost never, maintained.
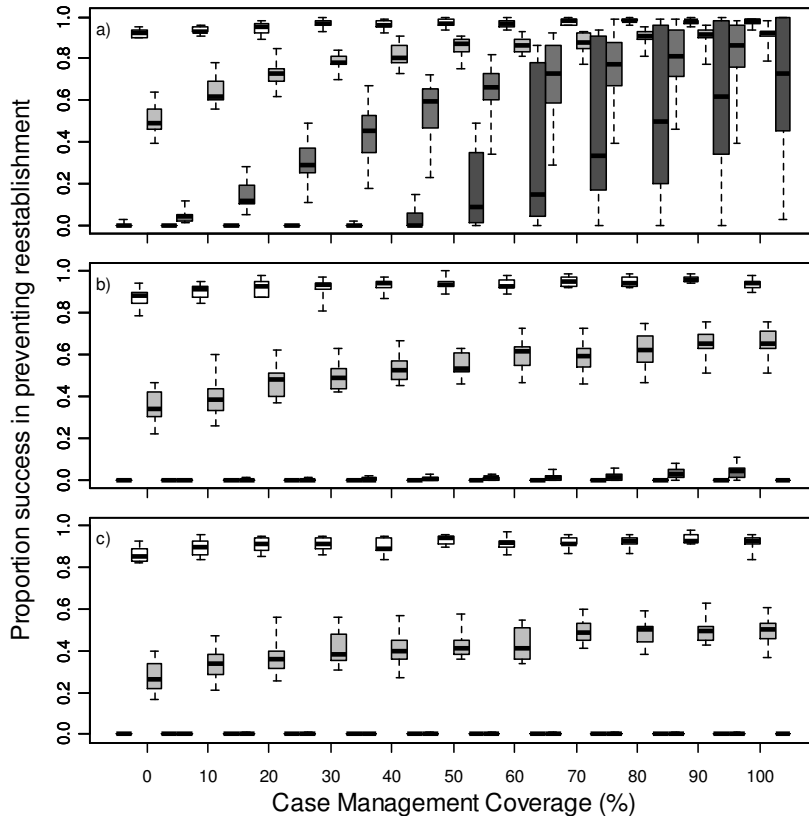
Figure 2.2 Boxplot of the proportion of simulations in which transmission remains interrupted by model variant at a pre-intervention EIR of 2 ibpapa (a), 20 ibpapa (b) and 50 ibpapa (c).

Fill colours: white: Infection importation rate (IIR) = 0.02, light gray: IIR = 0.2, medium gray: IIR = 2, dark gray: IIR = 20
Boxplot shows the median, maximum, minimum, and interquartile ranges.

Figure 2.2 primarily serves to show the trends among case management coverage, IIR, and the proportion of simulations in which transmission remains interrupted, and where most model variants agree and where there is a wider range in predictions. The median proportion of simulations in which transmission remains interrupted may be biased and should not be over-interpreted, as it is unclear how

to weight the fourteen model variants to allow for plausibility, goodness of fit and correlations both in structure and parameter values.

In general, at low case management coverage, the model variants for heterogeneities in exposure resulted in a higher proportion of simulations in which transmission remained interrupted. At medium to high case management coverage, it was the decay of immunity model variants which resulted in a higher proportion. The model variants with heterogeneities in access to treatment usually resulted in a lower proportion of simulations in which transmission remained interrupted.

For each pre-intervention EIR, we fitted a logistic regression model to the probability of success in preventing re-establishment of transmission, with covariates in case management coverage, the natural logarithm of the infection importation rate, and each of the fourteen model variants as categorical variables. Backward stepwise regression showed that removing any of the independent variables from the model was found to significantly decrease the model's goodness of fit at the 95% confidence level, so all covariates were kept. We then tested for interaction between case management coverage and the natural logarithm of the infection importation rate. From the likelihood ratio test, the interaction term was found to be significant ($p<0.001$), although it has only a slight effect.

The fitted relationships between case management coverage and the probability that transmission remains interrupted, for the base model and at different IIRs, are shown in Figure 2.3 (EIR = 2 ibpapa) and Figure 2.4 (EIR = 20 ibpapa). The figure at EIR = 50 ibpapa looks very similar to that at EIR = 20 ibpapa and is not shown. At EIR = 2 ibpapa, the odds ratio that transmission remains interrupted associated with a tenfold decrease in IIR is 16.6 (95% ci: 15.6, 17.6). At EIR = 20 ibpapa, the corresponding odds ratio is 23.7 (95% ci: 21.5, 26.3).
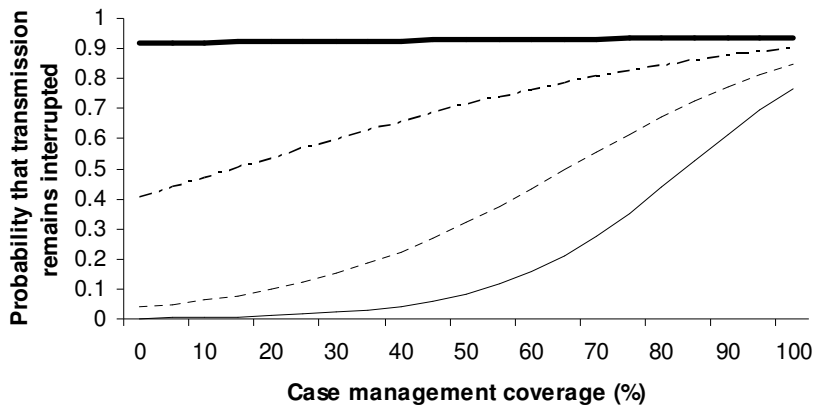
Figure 2.3 Best-fitting regression model predictions for the probability that transmission remains interrupted, as a function of case management coverage and infection importation rate, at pre-intervention EIR of 2, using the base model

Thin line: IIR=20, Dotted line: IIR= 2, Dashed line: IIR= 0.2, Thick line: IIR=0.02 imported infections per 1,000 per annum.
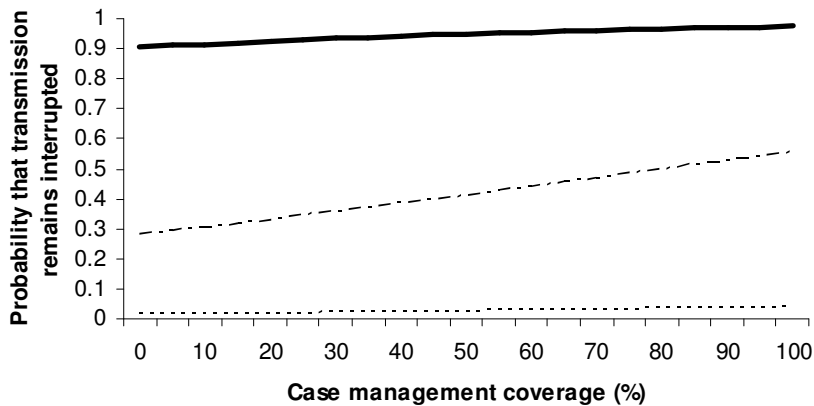
Figure 2.4 Best-fitting regression model predictions for the probability that transmission remains interrupted, as a function of case management coverage and infection importation rate, at pre-intervention EIR of 20, using the base model

Thin line: IIR=20, Dotted line: IIR= 2, Dashed line: IIR= 0.2, Thick line: IIR=0.02 imported infections per 1,000 per annum.

Table 2.1 shows that, at a pre-intervention EIR of 2 ibpapa, the model variants

which included decay of immunity with a shorter half-life were found to have a

relatively large positive effect on the odds that transmission remained interrupted relative to the base model. By contrast, model variants *R0674,* which assumes uncorrelated heterogeneity in co-morbidity and access to treatment, and *R0678*, which assumes heterogeneity in access to treatment, were found to have a relatively large negative effect on the odds that transmission remained interrupted relative to the base model.

At the higher pre-intervention EIRs of 20 ibpapa and 50 ibpapa (not shown), the model variants had much smaller effects on the odds that transmission remained interrupted relative to the base model. This is evidenced by the much narrower range in the odds ratios. Moreover, in these transmission settings, it was the model variants that assumed heterogeneity in entomological exposure that had the largest positive effects on the odds that transmission remained interrupted.

Table 2.1 Descriptions of model variants and predicted odds ratio that transmission remains interrupted for each model variant relative to the base model, at pre-intervention EIR of 2 and 20 ibpapa.

Model identifier	Description	Half-life of decay (years) $t_{1/2} = \dfrac{-\ln(2)}{\alpha_b}$	$t_{1/2} = \dfrac{-\ln(2)}{\alpha_c}$	odds ratio, EIR=2	95% confidence interval		odds ratio, EIR= 20	95% confidence interval	
R0125	Fixed decay in immune proxies	∞	10 [a]	4.57	4.02	5.21	1.47	1.27	1.71
R0132	Estimation of decay in immune proxies	∞	14	4.31	3.79	4.90	1.29	1.11	1.49
R0115	Fixed decay in effective cumulative exposure	10 [a]	∞	4.17	3.67	4.74	1.29	1.11	1.50
R0133	Estimation of both decay parameters	250	19	3.89	3.42	4.42	1.37	1.18	1.59
R0131	Estimation of decay in effective cumulative exposure	1187	∞	2.42	2.14	2.74	1.36	1.17	1.58
R0065	Mass action: $E_a(i,t)$ varies between and within hosts	∞	∞	2.18	1.93	2.47	1.89	1.63	2.20
R0670	Heterogeneity in susceptibility to comorbidity	∞	∞	2.03	1.80	2.30	1.22	1.05	1.41
R0063	Mass action: $E_a(i,t)$ varies mainly between hosts	∞	∞	1.86	1.64	2.10	2.04	1.75	2.37
R0121	Fixed decay in immune proxies	∞	1000 [a]	1.63	1.45	1.84	1.18	1.02	1.37
R0068	Mass action: $E_a(i,t)$ varies mainly within hosts	∞	∞	1.44	1.27	1.62	1.53	1.32	1.78
R0111	Fixed decay in effective cumulative exposure	1000 [a]	∞	1.30	1.15	1.46	1.14	0.98	1.33
R0674	Uncorrelated heterogeneities in access to treatment and susceptibility to comorbidity	∞	∞	0.63	0.56	0.71	1.04	0.89	1.21
R0678	Heterogeneity in access to treatment	∞	∞	0.56	0.50	0.63	0.87	0.75	1.02

$E_a(i,t)$: the expected number of entomological inoculations, adjusted for age and individual factors .

α_b : decay applied to the two measures of the effective cumulative exposure.

α_c : decay applied to the function representing the immune status.

[a] These parameters were fixed, in other models the decay parameters were estimated. Decays shorter than the shortest fixed values gave unacceptable fits to the data.

2.5. Discussion

Although maintaining interruption of malaria transmission would bring benefits, it would also require reorientation of programmatic strategies, significant long term financial commitments, and major operational preparations. Therefore, the decision to pursue transmission interruption and prevention of re-establishment of transmission is not trivial. Prior to embarking on such a course a thorough evaluation of the likelihood of success, and what will be required to maintain it, is desirable.

Early detection and treatment of infections is critical to prevent onward transmission in the face of renewed vectorial capacity. However, our findings also suggest that, even where vectorial capacity is low, maintaining interruption of transmission is likely to require continued vector control at or above moderate levels of vulnerability (IIRs on the order of 0.2 per 1,000 population per annum or higher). Even perfect passive case detection will fail to identify imported asymptomatic infections, which under these circumstances will be sufficiently numerous to result in a considerable probability of resumption of transmission. The chances that an imported infection is asymptomatic will depend on the immunity profile of the immigrant/visitor, which in these analyses was assumed to match that of the simulated population.

Statistical analysis revealed that modeled outcomes were sensitive to several of the model assumptions. At low pre-intervention EIR levels, decay of natural immunity is an important driver of whether or not interruption of *P.falciparum* malaria transmission can be maintained. This is because, as immunity decays, more infections are likely to be symptomatic, and therefore detectable and treatable by the passive case management system. Also, in the base model, individuals are

assumed to have homogenous access to treatment and to be at similar risk of co-morbidity. In this analysis, introducing heterogeneities in these factors increased the risk of re-establishment. These findings suggest that areas with these kinds of differentials among population sub-groups may face specific challenges in maintaining transmission interruption.

In higher transmission settings, variations in these assumptions did not have as large an effect on the odds that transmission remained interrupted. At higher pre-intervention EIRs, the vectorial capacity is the dominant determinant of re-establishment. In these settings, immunity was much higher post-interruption than in the low-transmission setting, and thus even with decay, a large number of infections remain asymptomatic.

The perhaps counter-intuitive finding that the models assuming heterogeneity in force of infection had positive effects on the odds that transmission remained interrupted could be explained in several ways. First, if infections are concentrated in the same people, a given level of case management coverage will result in a higher proportion of infections being treated than if infections are spread more evenly across the population (because a single treatment will terminate all co-infections in that host). Second, this finding may be due to the way we have constructed our outcome variable. Where certain individuals have higher availability to mosquitoes than others, this may result in a lower number of episodes (as multiple infections can give rise to only one episode at a time).

There are several factors that are likely to affect the probability of success in preventing re-establishment which were not considered here. Characteristics of the population under consideration, for example the size of the population and the degree of interaction between individuals, were not studied. Interruption of transmission is easier to achieve and maintain in smaller populations than in large

ones, *ceteris paribus*, as re-introduction of transmission is an infrequent, and hence highly stochastic, event. Our results, using a population of 1,000, therefore, offer an optimistic estimate of the probability for prevention of re-establishment, and make predictions at very low IIRs problematic. Also, our models assume perfect mixing within each mosquito population across all humans. Patch models may offer a way forward to more accurately capture the phenomena of heterogeneity in interactions, as well as spatial heterogeneity in transmission.

The probability that transmission remains interrupted or conversely, re-establishes, is also likely a function of geographical and temporal heterogeneities in importation of infections. We assume that imported infections mix uniformly with the simulated population and enter at a constant rate; however, in reality, individuals bringing malaria infections into an area may concentrate in a particular place. If this effect is important, we expect transmission to spread more slowly, and to be easier to arrest, provided that such foci can be located. Also, rates of case importation may not be constant over time. Our models could incorporate this, but refining these assumptions would require temporal data on human migration patterns. This is an important area of further research [49;72].

Our rapid method of interrupting transmission likely had an effect on chances of maintaining interruption, as even with the model variants which capture immunity decay, immunity levels remained relatively high in the population for a certain time. In reality, interruption of transmission would take longer and immunity would be lower upon its achievement, resulting in a higher proportion of secondary (locally transmitted) infections manifesting clinically. The level of immunity in the population at the time of interruption, which drives the proportion of infections in the population which are asymptomatic, is an important determinant of the probability of success in preventing re-establishment. This may

lead our models to overestimate the probability of re-establishment of transmission.

On the other hand, our method of importing infections may have led us to underestimate the probability of re-establishment of transmission. We assign imported infections randomly to individuals in the simulated population, who are exposed to the same transmission and therefore have the same immunity profile. However, it is likely that transmission in source areas is substantially higher than in the simulated population, and thus individuals importing infections would be expected to have higher immunity. Our current models do not offer the possibility to simulate this immunity differential readily; however, if this were the case we could expect a lower probability that imported infections are symptomatic and therefore detectable by the case management system.

There is a need to extend these models to capture other features of real health systems [73-75]. It would be important to assess the importance of the capacity of the system to react to outbreaks by temporarily improving case management coverage or by implementing emergency vector control operations when outbreaks occur. In countries which succeed in actively interrupting transmission, the health system will likely have strong surveillance and epidemic response capacity, which could contain outbreaks and reduce local transmission again to zero. Screening of potential asymptomatic carriers would likely be a part of this response and was not modeled here. It is also possible that, following interruption of transmission, the case management system would be strengthened to enable more intensive routine detection of cases. Under these conditions, interruption of transmission would be more likely to be maintained, but probability of success would, again, depend to a great degree on the immunity profile of the population concerned.

The case management model offers a very simple description of the health system and does not consider diagnosis, provider practices or patient behaviour which could alter coverage. For a better understanding of the role of case management in achievement and maintenance of transmission interruption, a more realistic case management model is needed.

Thus, there remains a significant unfinished research agenda to increase the understanding of the relationship between case management coverage, vulnerability, receptivity and prevention of re-establishment of *P. falciparum* malaria transmission. Nevertheless, we believe that the results described here provide important input into the discussions surrounding the feasibility of maintaining interruption of malaria transmission in various contexts.

2.6. Conclusion

Even at rather low levels of receptivity, case management alone cannot reliably prevent re-establishment of *P. falciparum* malaria transmission in the face of medium to high importation rates, even if all clinical cases are treated. Thus, if vector control is to be discontinued, preventing the importations by controlling transmission in areas from which imported cases originate is a precondition for preventing reintroduction in such settings. Achieving very high levels of case management coverage does not appear to substitute for this. Alternatively, a system of active surveillance to prevent importation, including screening of all potential carriers at points of entry, could be considered, but in most areas this strategy is not likely to be feasible.

Model variants assuming decay of natural immunity resulted in lower odds of transmission re-establishment, relative to the base model that assumed no such

decay. These findings highlight the urgent need for research into the mechanisms and rate at which naturally- acquired immunity to *P.falciparum* malaria decays in the absence of exposure, to inform current and future malaria elimination efforts. Certain characteristics of the population, in particular heterogeneities in co-morbidity and access to treatment, also appeared to influence simulated probability of success. There is a need for further analysis of effects of different population sizes and patterns of within-population interaction and of geographical and temporal heterogeneity of imported infection rates.

A key issue that has not been addressed here is the related economic analysis. Interruption of transmission and prevention of re-establishment, whether through increased case management coverage or other strategies, will carry significant costs, which need to be evaluated together with appropriate outcome measures and compared to other possible uses of funds to optimize resource use. A recent study found that malaria elimination is unlikely to be cost-saving in most cases, even over a time frame of 50 years, but may bring additional benefits that would make it a worthy investment [76].

The costs and effects of screening asymptomatic individuals, either in response to a detected case or indiscriminately in at-risk populations, will likely need to be considered in addition to case management. Data from field studies are needed to determine the most cost-effective surveillance and response models in different settings and to inform future modeling efforts [22]. Importantly, the costs of surveillance are unlikely to increase linearly with coverage; isolated or marginalized populations are usually the last to be reached and the most expensive to serve, resulting in significant diseconomies of scale at the higher coverage levels. In addition, the appropriate outcome measure to use in settings where malaria burden is already very low, as would be the case in places which are close to or have recently achieved elimination, is unclear. Further methodological

developments to quantify the benefits of transmission interruption are needed to apply economic evaluation usefully.

The results of these analyses need to be taken into account in global and national discourse and in feasibility assessments of and planning for elimination of malaria [14]. Failure to plan for prevention of re-establishment could result in loss of the last decade's tremendous gains towards rolling back malaria.

2.7. Acknowledgements

3. Modeling the cost-effectiveness of mass screening and treatment for reducing *Plasmodium falciparum* malaria burden

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3.1. Abstract

Background

Past experience and modelling suggest that, in most cases, mass treatment strategies are not likely to succeed in interrupting *Plasmodium falciparum* malaria transmission. However, this does not preclude their use to reduce disease burden. Mass screening and treatment (MSAT) is preferred to mass drug administration (MDA), as the latter involves massive over-use of drugs. This paper reports simulations of the incremental cost-effectiveness of well-conducted MSAT campaigns as a strategy for *P. falciparum* malaria disease-burden reduction in settings with varying receptivity (ability of the combined vector population in a setting to transmit disease) and access to case management.

Methods

MSAT incremental cost-effectiveness ratios (ICERs) were estimated in different sub-Saharan African settings using simulation models of the dynamics of malaria and a literature-based MSAT cost estimate. Imported infections were simulated at a rate of two per 1,000 population per annum. These estimates were compared to the ICERs of scaling up case management or insecticide-treated net (ITN) coverage in each baseline health system, in the absence of MSAT.

Results

MSAT averted most episodes, and resulted in the lowest ICERs, in settings with a moderate level of disease burden. At a low pre-intervention entomological inoculation rate (EIR) of two infectious bites per adult per annum (IBPAPA) MSAT was never more cost-effective than scaling up ITNs or case management coverage. However, at pre-intervention entomological inoculation rates (EIRs) of

20 and 50 IBPAPA and ITN coverage levels of 40 or 60%, respectively, the ICER of MSAT was similar to that of scaling up ITN coverage further.

Conclusions

In all the transmission settings considered, achieving a minimal level of ITN coverage is a "best buy". At low transmission, MSAT probably is not worth considering. Instead, MSAT may be suitable at medium to high levels of transmission and at moderate ITN coverage. If undertaken as a burden-reducing intervention, MSAT should be continued indefinitely and should complement, not replace, case management and vector control interventions.

3.2. Background

Mass drug administration (MDA), where the entire population is treated with anti-malarial drugs, was tried on a number of occasions during the malaria eradication efforts of the last century, and sporadically since then. Mass screening and treatment (MSAT), which involves screening the whole population of interest and only treating those who test positive, has not been empirically tested, although an upcoming clinical trial in Burkina Faso aims to evaluate it [77]. Another variant proposed is "focal screening and treatment", which involves screening all people living in a defined geographical area [78]. This approach is now being used in an attempt to contain emerging artemisinin-resistant falciparum malaria in western Cambodia [79].

Unfortunately, MDA has proved disappointing in most instances for the objective of interrupting transmission. A review of experiences with anti-malarial drug mass administrations was carried out in 2003; these projects undertook MDA with varying frequencies and numbers of rounds [80]. The authors found that MDA has almost always failed to interrupt transmission, although it often led to a marked reduction in parasite prevalence and probably a transient effect on malaria-related morbidity and mortality. The authors concluded that direct MDA with a full therapeutic drug dose might have a role to play in circumstances such as the control of epidemics, or in relatively low transmission areas or in those with a short transmission season. However, it is not likely to have a sustained effect in most malaria-endemic areas.

These discouraging findings are echoed by several recent model-based investigations of MDA and MSAT. Mathematical malaria transmission models are useful tools to synthesize data and make predictions about intervention impact

where trials are not feasible. One study found that only in areas with low transmission of less than 10 infectious bites per adult per annum (IBPAPA) could parasite prevalence be reduced to less than one percent with annual MSAT and insecticide-treated nets (ITNs) at 80% coverage [81]. Additional investigations of the impact of MDA and MSAT using different drugs, at different timings, and with correlation in probability of participating in successive rounds, in varying initial endemicity settings, were undertaken using a similar model [82]. Transmission was found to rebound to previous levels within about two years after one round of the intervention in a low-endemicity setting. However, repeating the intervention or combining it with vector control enhanced and extended the impact.

Even if it could be achieved, a major challenge to maintaining local transmission interruption would be the importation of *Plasmodium falciparum* infections. Human populations are connected to each other, and as long as local vectors have sufficient capacity to transmit malaria, local transmission can be sustained or re-introduced through immigration of infected people or infective mosquitoes. A recent modelling study [83] found that, even at relatively low receptivity levels, case management alone could not reliably prevent *P. falciparum* transmission re-establishment in the face of medium to high importation rates. These findings suggest that achieving and maintaining local transmission interruption without large-scale vector control across most of sub-Saharan Africa will be difficult for the foreseeable future.

Although MDA or MSAT rounds can be expected to have only an ephemeral effect on prevalence, it may be a viable strategy to reduce malaria disease burden if carried out regularly. Intermittent preventive treatment in pregnant women, children and infants are targeted, continuous MDA forms that have been found to reduce burden in specific population groups [84;85]. To evaluate the potential role

of MDA or MSAT for burden reduction, it is important to consider both the expected effectiveness and intervention cost.

The effectiveness of both MDA and MSAT strategies may be compromised by the difficulty of achieving sufficient coverage due to refusal of populations to participate in repeated screenings and/or treatments and population movements. A further disadvantage of MSAT is that sub-patent parasitaemia will be missed, and if this contributes significantly to the infectious reservoir, the intervention effect will be limited. Experience indicates that the success of these approaches is predicated on the ability to deploy them multiple times at high coverage levels and together with vector control measures [78]. Mass treatment is thought likely to be more effective if introduced following reductions in transmission due to other interventions, such as distribution of ITNs and indoor residual spraying (IRS) [86].

Due to concerns about the potential for MDA to contribute to the spread of drug resistance [80], MSAT is currently preferred to MDA, as it avoids the massive over-use of drugs [57]. However, it is bound to be more difficult and costly to organize and implement than MDA. There is no known evaluation to date of the possible cost-effectiveness of MSAT for reducing malaria disease burden.

This paper's objective is to predict the incremental cost-effectiveness of well-conducted MSAT campaigns as a strategy for *P. falciparum* malaria disease-burden reduction in sub-Saharan African settings with varying receptivity (ability of the combined vector population in a setting to transmit disease) and access to case management, compared to the same setting in the absence of MSAT.

3.3. Methods

Simulation model

A dynamic, individual-based, stochastic model of malaria biology and epidemiology was used. The model corresponds to the base model in an ensemble of stochastic simulation models that has been developed recently [70]. Briefly, a simulated human population was updated at each five-day time step via model components representing new infections, parasite densities, acquired immunity, uncomplicated and severe episodes, direct and indirect malaria mortality, infectiousness to mosquitoes, and case management. Simulated immunity to asexual parasites, derived from cumulative exposure to both inoculations and blood stage parasites and transferred maternal immunity, acted mainly by controlling parasite densities [58]. The probability of a clinical malaria attack in a simulated individual depended on the current parasite density and a pyrogenic threshold [59]. Severe malaria comprised two episode categories: those that occurred as a result of overwhelming parasite densities, and those that arose when an uncomplicated malaria episode coincided with non-malaria co-morbidity. Mortality could be either direct (following severe malaria) or indirect (uncomplicated malaria in conjunction with co-morbidity, or during the neonatal period as a result of maternal infection) [87]. Malaria dynamics in mosquitoes was also modelled [61;88].

Transmission settings

The vectorial capacity, or receptivity, is the ability of the combined vector population in a setting to transmit disease, expressed as the potential number of inoculations per time unit originating from one infective person with no prior immunity. A setting has a baseline vectorial capacity, which can be altered by interventions undertaken by the health system, such as vector control. The

effectiveness of MDA and MSAT in terms of burden reduction is likely related to the actual vectorial capacity (the baseline modified by interventions), which co-determines, together with immunity, the parasitaemia prevalence in the population and the proportion of asymptomatic infections. An infected individual with lower immunity is more likely to show clinical symptoms and thus, given access to appropriate care, to be treated promptly by the health system, reducing the parasite reservoir to be addressed by MSAT.

The pre-intervention entomological inoculation rate (EIR) was used as a good proxy for the baseline receptivity. Three pre-intervention EIRs of two, 20 and 50 IBPAPA were simulated, with a seasonality pattern as observed in Namawala, Tanzania [65]. These EIRs correspond to parasite prevalence in children under five years of age of approximately 16%, 50%, and 62% [58]. The infection status and immune status at the start of the simulation were determined by exposing the simulated population to the same annually recurring pattern of inoculations for a lifetime-long burn-in at the start. The case management coverage level was set at zero during the burn-in period in all simulations in order to ensure that the fitted vectorial capacity was the same across all scenarios. Case management coverage was changed to the appropriate level at the beginning of the main simulation.

ITNs were distributed at 40%, 60% or 80% population coverage at the beginning of years 1, 4, 7 and 10. Imported infections were assigned to individuals in the population via a Poisson process every 30 days at a constant average rate of two imported infections per 1,000 population per year throughout the simulation period. This rate was chosen because it is on the lower end of the infection importation rate range (two to eight infections per 1,000 inhabitants per annum in 2008) estimated in Zanzibar, one of the few places from which preliminary data are available [14;68]. No infected mosquitoes were imported.

Case management models

The effectiveness of MSAT is probably related to case management coverage, which determines the proportion of symptomatic infections that gets treated. The case management component [41] models a health system using artemether-lumefantrine (AL), an artemisinin-based combination therapy (ACT), as treatment for uncomplicated malaria. Individuals with uncomplicated malaria fevers were assigned a probability of accessing treatment over the next five-day period of 20, 35 or 55%. These probabilities were constant over the entire simulation period. They represent the fever treatment-seeking behaviour range recorded in children under five years of age, using 14-day recall, in nationally representative surveys conducted in malaria endemic countries in sub-Saharan Africa [89;90], converted to five-day probabilities for use in the model. Compliance to the treatment regimen was set at 90% [67], and the drug was assumed to be 85% effective [91]. In patients who did not comply with the full regimen, the drug was assumed to have 20% effectiveness [92]. All severe cases were assigned a 48% probability of receiving treatment as an in-patient [93], and parasites were cleared in all hospitalized cases who survived.

Infectivity of hosts to mosquitoes at a given time point was modelled as a function of asexual parasite densities 10, 15 and 20 days previously, allowing for a delay resulting from the time course of gametocytaemia [62]. Effective treatment completely cleared parasites by the next time step, ending the infection, while ineffective treatment had no impact on asexual parasite densities. By clearing asexual parasites, treatment rendered individuals un-infectious to vectors at later time points. Given sufficiently high treatment coverage, this lowered infectivity translated into a reduction in EIR. Neither drug treatment effects on gametocytaemia nor prophylactic drug effects were modelled, but as AL has a

relatively short half-life, and few treatments were given after the first MSAT round, this is likely to be of limited consequence.

MSAT timing, coverage and compliance

Five different timings for MSAT were simulated, according to the seasonal transmission pattern – at the month before the peak of EIR, at the peak of EIR, at the month before the trough of EIR, at the trough of EIR, and at the month after the trough of EIR. The intervention was conducted annually in years 5 to 12, for a total of eight rounds. In the base case, MSAT was applied at 85% coverage, which is the level that was achieved in a well-conducted mass drug administration for malaria in the Gambia [56]. ACT was given simultaneously to all individuals with a level of parasitaemia at or above 40 parasites/µl. A detection limit of 40 parasites per µl corresponds to the nominal value for standard microscope procedures that count parasites against 200 leukocytes, assuming a white cell count of 8,000 leukocytes per µl. Therefore, rapid diagnostic tests (RDTs) were assumed to have about the same level of detection as microscopy. All those who were screened and tested positive by RDT took the drug and complied fully with the regimen, while none of those who tested negative took the drug. Correlation among individuals in participation in different MSAT rounds was not considered.

The optimal day of the calendar year to conduct an MSAT campaign was defined as the one, among the days considered, which minimized the number of episodes from the beginning of the intervention year to the end of the simulation period. This occurred one month before the trough in transmission, defined as the lowest EIR, consistent with other modelling studies [81]. This timing was used to evaluate the MSAT cost-effectiveness in settings of varying baseline receptivity, ITN and case management coverage.

All scenarios had a population size of 100,000, with underlying demography based on East African life tables [66], and were run 10 times, each time with a different seed for the random number generator.

Estimating the cost of MSAT

Methods used to estimate the costs per person screened are described in detail in supplementary information (see Additional file 1).

For costing purposes, MSAT was assumed to be conducted through house-to-house visits by village volunteers or community health workers (CHWs). Two situations were considered: 1) a village of 1,000 inhabitants where a cadre of CHWs, trained to manage fever presumptively, existed and 2) a similar village where volunteers were newly selected from the local population and had no previous training or experience with managing illness. In situation 2, the MSAT-attributable costs of selecting and training village volunteers for the MSAT intervention may be lower if the volunteers proceed to take on roles beyond that of the MSAT intervention; however, this was not considered

The marginal cost consists of the additional costs that would be incurred when undertaking an MSAT campaign, based on new resources that would need to be used to deliver the intervention. When spare capacity in the health system exists, the use of that spare capacity is not included in the marginal analysis. By contrast, the average cost includes all those costs involved in delivering a health intervention, whether resources are shifted away from other activities, or whether spare capacity is used. In a generalized costing, an average cost analysis is problematic, as countries differ in their level of infrastructure, structure of the health system and capacity use. Therefore, other than the two starting points

considered (with (situation 1) and without (situation 2) an existing network of CHWs), only the marginal intervention cost was estimated.

Based on a literature review of similar interventions, costs included in the estimate were household enumeration, social mobilization, delivery (comprising volunteer or CHW remuneration and supplies), training and supervision of village volunteers or CHWs. For the delivery, training and supervision costs, an ingredients approach was used, which involved building up a cost estimate by considering the quantity and value of each resource used. For the other costs, per-person costs were borrowed from similar interventions described in the literature.

Systems costs from the district level upwards and in health facilities were not included. A functioning health system was assumed to be able to accommodate an annual MSAT intervention without hiring additional staff or making further investments at these levels. Clearly, if the health system were poor, further investments might be needed in order for MSAT to be successful, and this could greatly increase the costs.

In this analysis, costing was conducted from a provider perspective. It was assumed that there were no direct costs to individuals and that indirect costs were negligible, since the intervention was infrequent and conducted at individuals' homes.

Some of the costs presented here are relatively fixed and thus sensitive to the scale at which the intervention is conducted. For example, the average costs of a sensitization campaign would likely decrease as more people are included in the target population. However, for the MSAT intervention, most of the costs are variable and significant economies of scale are unlikely. Therefore, economies and diseconomies of scale were not explicitly considered in this analysis.

The intervention was undertaken over a period of six days, with the first five days for initial visits and one additional day for return visits to cover those not found at the first visit. During initial visits, each team, which consisted of three volunteers or CHWs, could complete on average one household visit per hour, at an average household size of five people [94]. This included time for administering a questionnaire, conducting RDTs, waiting for the results, and prescribing ACT to any who tested positive. At this rate, eight household visits could be done in a day during initial visits (assumption 1), allowing five teams to cover a population of 1,000 in a five-day period if every member of the population were present during the first (and only) visits. The first drug dose was assumed to be taken under supervision by the CHW, and the remaining doses were left with the households to be taken without supervision.

In the absence of data relating coverage to number of follow-up visits, 40% of target households were assumed to have at least one member absent on the first visit, with 20% having all members missing and 20% having one member missing. A repeat visit was thus required to 40% of the households. Fifty percent of members missing on the first visit were assumed to be found on the second visit. Return visits were assumed to take half the time, as some of the houses would already have been screened and there would be fewer people to screen and treat. Thus, five teams would be needed for the second visits to achieve approximately 85% population coverage.

N_v, the number of volunteers or CHWs needed, is dependent upon factors like the population density, infrastructure, and the time it takes for a household visit. Therefore, an alternative, assumption 2, was considered, where only five household visits could be accomplished in a day during initial visits. In this case, eight teams would be required for the first and second visits.

Per diems were assumed to be given to volunteers or CHWs as incentives and to cover transport. The role of incentives in improving performance and encouraging sustainability of interventions is a subject of debate; in a number of settings, interventions relying on community volunteers have suffered from a lack of financial and non-financial support [95]. Salaries that may be paid to CHWs for performing their roles were not included as this was not considered an incremental cost incurred by the MSAT intervention.

Each supervisor was assumed to be able to supervise three volunteer or CHW teams and received per diems according to the length of the intervention. Training costs in situation 1 comprised only the cost of an additional training on using and interpreting RDTs, while in situation 2, volunteers needed to be recruited and trained in all aspects of the intervention.

All costs were converted to 2007 US$, using the US$ average market exchange rate in the study year and the US$ GDP deflator for the appropriate year [96].

The total cost per person screened per MSAT campaign was approximately 2007 US$5–11, depending on different health system scenarios and assumptions about the number of houses that could be visited per day. These costs were added to the age-dependent ACT presented in Table 3.1.

Table 3.1 Estimated costs per person screened by cost category and ACT costs by age group

Screening cost category	Costs per person screened (2007 US$)
Household enumeration (E_p)	0.29
Social mobilization (M_p)	0.27
Delivery (D_p)	
Remuneration (W_p)	
Assumption 1	1.06
Assumption 2	1.70
Supplies (U_p)	1.78
Supervision (I_p)	
Assumption 1	0.48
Assumption 2	0.76
Training (T_p)	
Situation 1, Assumption 1	1.20
Situation 1, Assumption 2	1.92
Situation 2, Assumption 1	3.92
Situation 2, Assumption 2	6.28
Total costs (S_p)	
Situation 1, Assumption 1	5.08
Situation 1, Assumption 2	6.72
Situation 2, Assumption 1	7.80
Situation 2, Assumption 2	11.08
ACT costs	**Cost per course + 25% wastage (US$)**
Age	
<3 years	1.260
3−9 years	1.960
10−14 years	2.660
15+ years	3.360

The model for the cost of MSAT is separate from the epidemiological and case management models. Case management coverage may be higher where a network of trained CHWs exists. However, in this analysis the MSAT cost model was used to develop a plausible range for MSAT cost, and these costs were applied to all the health system scenarios. Clinical cases were costed as treated in health facilities using the case management model [41], and the proportion of episodes treated in facilities was presumed unaffected.

Incremental cost effectiveness ratio

The health care costs for malaria episodes were calculated for each intervention scenario and its comparator, where MSAT was omitted. The case management cost inputs are described in detail elsewhere [41], and were updated with the costs of an ACT, artemether-lumefantrine (AL), as first line treatment for uncomplicated malaria [97]. Case management costs included direct costs for patient care, but not patient indirect costs (notably loss of productive time due to illness) since inclusion of these in cost-effectiveness analysis remains controversial and methods for valuing them vary widely [98]. The cost savings to the case management system associated with adding MSAT to the comparator scenario were computed as $DC_{cmnoMSAT}$ - DC_{cmMSAT}, where $DC_{cmnoMSAT}$ are the direct costs of case management in the scenario without MSAT and DC_{cmMSAT} are the direct costs of case management in the case of MSAT. These cost savings were subtracted from the direct MSAT intervention cost, DC_{MSAT}, to give a net MSAT intervention cost, NC_{MSAT}, computed as follows: $NC_{MSAT}=DC_{MSAT} - (DC_{cmnoMSAT} - DC_{cmMSAT})$. The savings to the case management system constituted only the marginal cost of averted cases, and fixed costs remained constant.

Table 3.2 Determinants of intervention costs

Intervention cost category	Determinant of cost			
	ITN coverage	MSAT	Case management coverage	Vectorial capacity
ITN	**X**			
MSAT	**X**	**X**	**X**	**X**
Case management	**X**	**X**	**X**	**X**

Table 3.2 shows the determinants of total health system costs in each scenario. . ITN costs were fixed per person costs, assuming single occupancy, and therefore

were determined only by the ITN coverage level in the population. MSAT costs constituted primarily the fixed cost of screening individuals, but also depended on patent parasitaemia prevalence in the population, which in turn was driven by the vectorial capacity and ITN and case management coverage levels. Case management costs were a function of the health system use by the population (case management coverage) as well as the disease burden, which was determined by the vectorial capacity, ITN coverage, MSAT coverage and case management coverage itself (through its effect on recurrences and transmission).

The net intervention effects were expressed as the number of episodes averted, *i.e.* the difference in the number of episodes between intervention and comparator scenarios. An incremental cost-effectiveness ratio (ICER), expressed as dollars per case averted, was calculated for each scenario with MSAT compared to the same scenario without MSAT, as the net cost (NC) of the intervention divided by the net effects (NE) of the intervention: $ICER_{MSAT} = NC_{MSAT}/ NE_{MSAT}$. If the ICER is lower, the intervention is more attractive.

The ICER value is sensitive to the time horizon over which it is calculated [99]. Therefore, to investigate how the ICER changed over the time period of the intervention, an annual ICER was calculated for each year of the intervention as $ICER_{MSATn} = NC_{MSATn}/NE_{MSATn}$, where n is the year of intervention, beginning from the time the intervention starts.

The cost-effectiveness of scaling up case management coverage or ITN coverage from a given level to one level higher was assessed in each health system, in the absence of MSAT. The objective of this analysis was to compare, roughly, the relative cost-effectiveness of undertaking one or another intervention, in different settings. Cost per ITN distributed was set as US$7, which is similar to the US$7.03 median financial cost per ITN distributed reported in a recent cost and

cost-effectiveness review of malaria control interventions [100]. Case management costs were as previously described; fixed infrastructure costs remained constant and scale-up costs included only the marginal costs of treating additional cases.

Costs and effects were both discounted at an annual rate of 3% in the analysis [101]. The practice of discounting adjusts the value of future costs and effects to a present value, according to the timing at which they are incurred or occur. This is done to reflect the individual and societal preference to have resources and money now rather than in the future [102].

3.4. Results

Figure 3.1 illustrates how all-age parasite prevalence evolved in a selected scenario. In this scenario, the pre-intervention EIR was 20 IBPAPA, case management coverage was 20% and ITN coverage was 40% at each distribution round. Prevalence began to decrease after the first ITN distribution, dropped considerably after the first MSAT round, and reached near zero by the fifth MSAT round. However, it returned to and exceeded pre-intervention levels about three years after all interventions were discontinued; the higher post-intervention prevalence is due to reduced immunity in the population. Prevalence never reached zero in any of the simulations, even during the time when MSAT was conducted. An analysis of the probability of interruption of transmission is outside the scope of this paper.
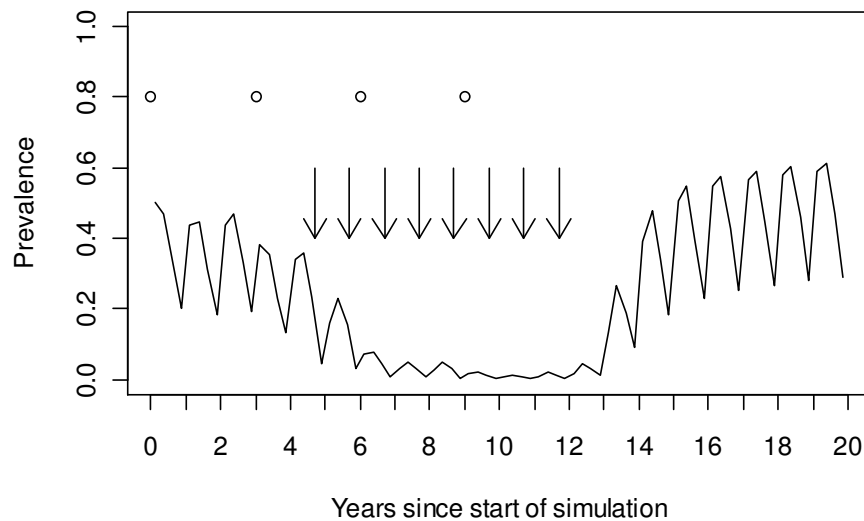
Figure 3.1 Median all-age parasite prevalence over the simulation period

MSAT was conducted annually one month before the trough of transmission in years 5–12, at a pre-intervention EIR of 20 ibpapa, case management coverage of 20%, two imported infections per 1,000 population per annum, and ITN coverage of 40%. Circles indicate ITN distributions and arrows indicate MSAT campaigns.

In Figure 3.2, the average number of episodes averted by MSAT is plotted against the average number of episodes per 1,000 population per year in the comparator scenario, for each factorial combination over the intervention time period. The number of episodes in the all age population in the comparator scenario with no ITNs or case management was greatest at the intermediate transmission level (EIR of 20 IBPAPA). Although infection prevalence increased with increasing transmission over almost all of the age range, the incidence of acute malaria attacks in older children and adults was substantially greater at lower transmission levels than at higher ones. This is because immunity levels rise with increasing transmission, so a smaller proportion of infections are symptomatic than at lower transmission levels. Therefore, reductions in transmission may actually lead to an increased incidence of disease due to *P.falciparum* [59].

The three panels combined show a bell-shaped curve; MSAT averted the most episodes where the number of episodes in the comparator was intermediate. This level was reached with different combinations of interventions at each pre-intervention EIR. At a pre-intervention EIR of two IBPAPA, MSAT averted the most episodes when the coverage of the other interventions, ITN and case management, was zero. As case management coverage increased, MSAT averted fewer episodes since transmission was lower and some episodes had already been averted by case management. With any non-zero level of ITN coverage, transmission was so low that there was essentially no disease for MSAT to avert. At pre-intervention EIRs of 20 and 50 IBPAPA, the number of episodes averted by MSAT was maximized at ITN coverage of 40% and 80% in each distribution round, respectively, without case management. These levels of ITN coverage reduced transmission sufficiently to allow MSAT to have a sustained effect. MSAT was more effective if this optimal transmission level was reached via ITNs rather than case management because MSAT and ITNs have different modes of action and thus complement rather than duplicate each other. Without ITNs, vectorial capacity remained high and individuals became re-infected very soon after treatment with MSAT, limiting the intervention's effectiveness.
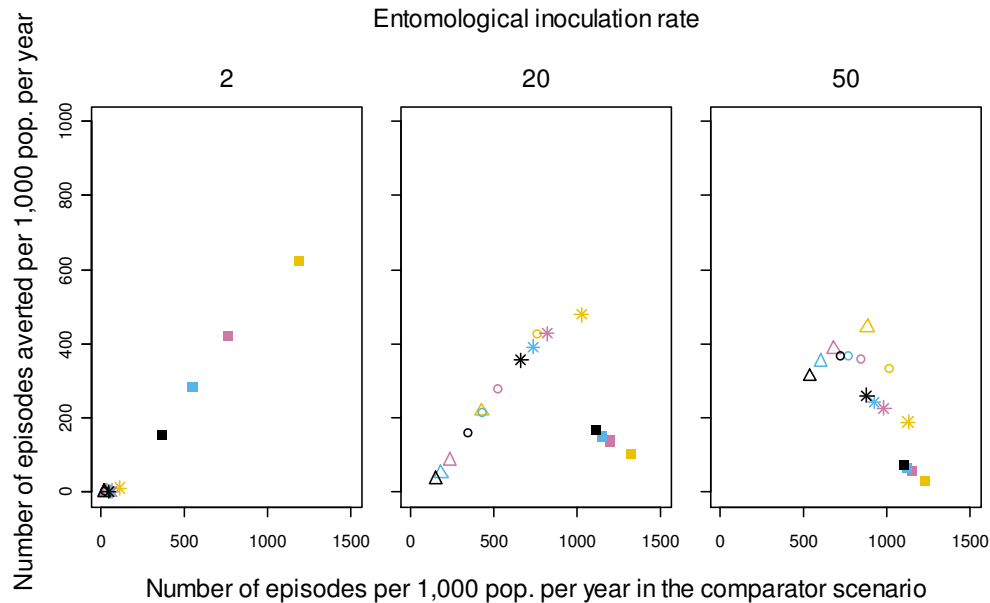
Figure 3.2 Number of episodes averted as a function of number of episodes in the comparator scenario

Number of episodes averted per 1,000 population per year over the 12.75 years from the beginning of the simulation period until one year after the last MSAT campaign are plotted against the number of episodes in the comparator scenario over the same time period, for each factorial combination averaged over 10 unique seeds. Colors indicate levels of case management coverage: Yellow: 0%, Pink: 20%, Blue: 35%, Black: 55%. Plotting characters indicate levels of ITN coverage: Squares: 0%, Stars: 40%, Circles: 60%, Triangles: 80%.

The natural logarithm of the ICER for adding MSAT to scenarios with varying levels of case management and ITN coverage at different pre-intervention EIRs is shown in Figure 3.3. The average ICER over the 10 seeds for each factorial combination is plotted against the average number of episodes in the comparator scenario over the same time period. This figure suggests that MSAT was most cost-effective in settings with a moderate disease burden. At a pre-intervention EIR of two IBPAPA, this level of disease burden was achieved without case management and ITNs. MSAT was least cost-effective where case management and ITN coverage were at their highest levels. The lowest (best) ICER at pre-intervention EIR of 20 IBPAPA occurred where ITN coverage was 40% at each distribution round, and the number of episodes was approximately 700 per 1,000

population per year. At the highest pre-intervention EIR, 50 IBPAPA, the lowest (best) ICER was achieved where case management and ITN coverage levels were at or near their maximum, and the disease burden level was similar to that of the best-ICER scenarios in the other pre-intervention transmission settings. MSAT was never cost-saving in any of these scenarios.
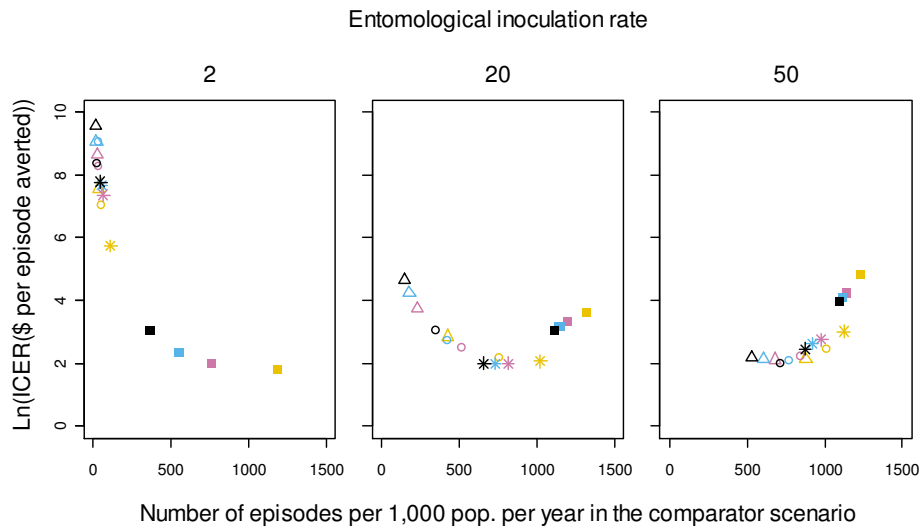
Figure 3.3 Logarithm of MSAT ICER as a function of number of episodes in the comparator scenario

Costs and effects were aggregated over the 12.75 years from the beginning of the simulation period until one year after the last MSAT campaign, using the high MSAT cost estimate. The natural logarithm of the MSAT ICER was plotted against the number of episodes in the comparator scenario over the same time period, for each factorial combination averaged over 10 unique seeds. Colors indicate levels of case management coverage: Yellow: 0%, Pink: 20%, Blue: 35%, Black: 55%. Plotting characters indicate levels of ITN coverage: Squares: 0%, Stars: 40%, Circles: 60%, Triangles: 80%.

Figure 3.3 is a close, inverted, reflection of Figure 3.2, demonstrating that the variation in ICER was driven in large part by the net effects of the intervention. However, the ICER considers, in addition to the net effects, its net costs, or the difference between the MSAT intervention costs and the case management savings due to the intervention. In some scenarios, particularly at the lowest pre-intervention EIR, increased case management reduced the net effects of MSAT but also its net costs, so the difference in ICERs was smaller than the difference in net

effects. Thus, the curves of ICERs in Figure 3.3 are less linear than those representing numbers of episodes averted in Figure 3.2.

Figure 3.4 illustrates the average ICER in each year from the start to the end of the intervention, for each health system and transmission setting. At a pre-intervention EIR of two IBPAPA, with no ITNs and the lowest three case management coverage levels, the ICER showed a decreasing trend, indicating that the intervention became more cost-effective over time. The same was true at a pre-intervention EIR of 20 IBPAPA and ITN coverage of 40 to 80%, and at a pre-intervention EIR of 50 IBPAPA with ITN coverage of 80%. The opposite was observed in the other scenarios; at an EIR of 50 IBPAPA and without ITNs and case management, there were actually more episodes in scenarios with MSAT than in the comparator scenarios in later years. This resulted in a negative ICER (not plotted), and suggests that under these circumstances, doing MSAT would be more costly and less effective than not doing it. This is probably because MSAT interfered with acquired immunity in this fairly high transmission setting. The bumps in the curves observed in scenarios with ITNs are due to reductions in the number of episodes averted by MSAT in years 3 and 6 of the intervention, with ITNs distributed several months before. As in Figure 3.3, the net effects of the intervention were the main driver of the year to year variation in the ICER, including through their effects on case management costs.
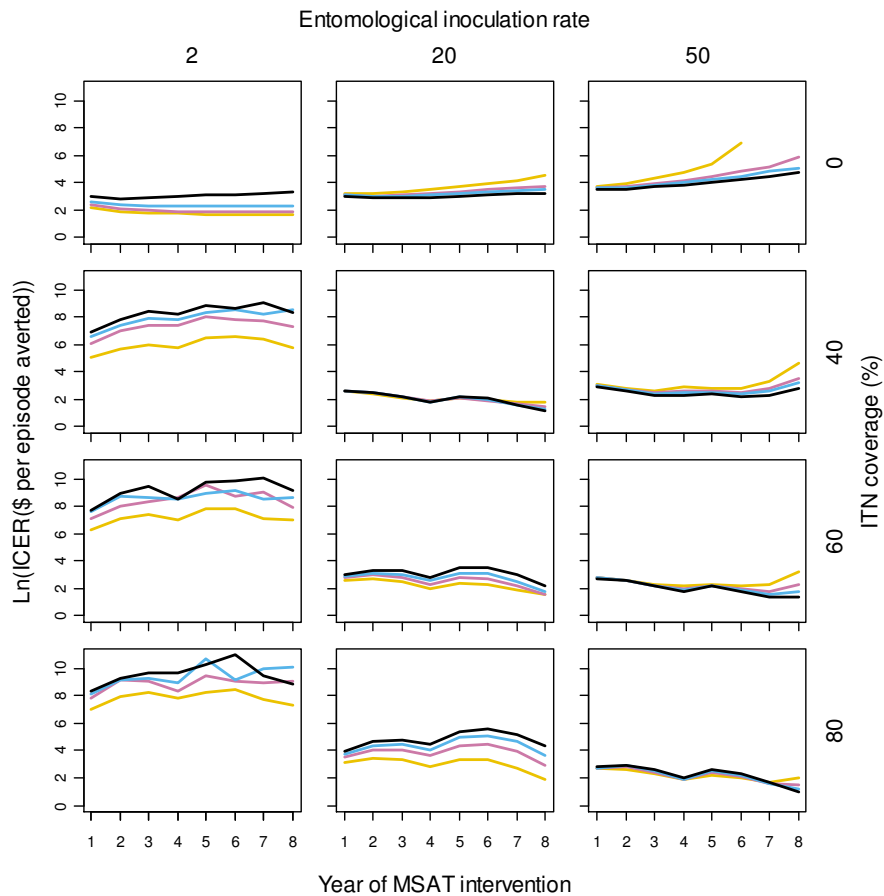
Figure 3.4 Logarithm of MSAT ICER in each year of the intervention

The natural logarithm of the annual MSAT ICER was calculated using the high MSAT cost estimate and averaged over 10 unique seeds, in different transmission and health system settings. Lines indicate levels of case management coverage: Yellow: 0%, Pink: 20%, Blue: 35%, Black: 55%.

Table 3.3 Incremental cost-effectiveness ratio (ICER) for different interventions

Baseline interventions		Annual EIR in the absence of interventions											
		2				20				50			
CM coverage (%)	ITN coverage (%)	MSAT 11$	MSAT 5$	CM	ITN	MSAT 11$	MSAT 5$	CM	ITN	MSAT 11$	MSAT 5$	CM	ITN
0	0	9.5	4.3	2.9	0.9	56.3	26.6	11.2	2.8	177.1	84.1	14.9	7.0
20	0	12.4	4.7	1.0	-0.3	42.0	19.2	15.3	1.3	105.2	49.3	22.1	4.1
35	0	18.0	6.7	-0.6	-0.8	37.3	16.5	22.2	0.4	91.0	42.1	39.2	2.9
55	0	34.4	13.6	–	-0.8	33.1	13.9	–	-0.6	78.4	35.6	–	1.7
0	40	523.6	238.0	2.3	22.8	**12.5**	**5.7**	**5.0**	**5.1**	**30.9**	**14.4**	**7.6**	**11.7**
20	40	1932.3	877.4	2.4	41.3	**12.5**	**4.9**	**5.8**	**3.6**	**25.0**	**10.9**	**10.0**	**8.8**
35	40	3276.3	1487.8	2.8	51.2	**12.9**	**4.6**	**5.9**	**2.8**	**22.5**	**9.3**	**13.5**	**7.5**
55	40	4668.5	2120.1	–	61.6	**13.6**	**4.4**	–	**1.9**	**19.9**	**7.6**	–	**6.2**
0	60	1817.6	826.3	2.9	76.7	**14.1**	**6.4**	**3.0**	**6.0**	**17.7**	**8.1**	**5.7**	**12.3**
20	60	5496.8	2497.7	2.9	120.8	**20.0**	**8.2**	**2.6**	**6.2**	**15.4**	**6.3**	**6.9**	**9.8**
35	60	7654.3	3477.7	3.8	153.7	25.4	10.2	2.2	6.8	**14.2**	**5.3**	**8.4**	**8.8**
55	60	11003.4	4999.7	–	178.4	34.2	13.8	–	7.8	**13.3**	**4.4**	–	**7.4**
0	80	3565.8	1620.9	3.1	–	27.7	12.6	2.0	–	**13.4**	**6.1**	**4.1**	–
20	80	9669.7	4394.5	4.0	–	68.3	30.2	2.1	–	**14.1**	**5.6**	**4.6**	–
35	80	14505.9	6592.2	4.6	–	111.7	49.5	2.9	–	**14.8**	**5.5**	**4.2**	–
55	80	17126.3	7782.7	–	–	165.6	73.5	–	–	**16.0**	**5.5**	–	–

Comparison of ICERs of conducting MSAT with ICERs of increasing case management or ITN coverage in different baseline health system settings (two leftmost columns), at different pre-intervention EIRs. ICERs for case management and ITNs refer to scaling up coverage from the baseline to the next highest coverage level, holding coverage of the other intervention constant. Negative ICERs indicate that the intervention is cost-saving due to reductions in case management costs. Bold figures represent settings where MSAT may have comparable or lower ICERs to either scaling up ITNs or case management coverage to the next level.

Table 3.3 compares the ICERs for the three interventions undertaken separately in each baseline health system setting, using high and low estimates for the per-person cost of the MSAT screening component (see Additional file 1). At a pre-intervention EIR of two IBPAPA MSAT was never the most cost-effective intervention. Increasing ITN coverage from 0 to 40% appeared to be the most cost-effective intervention and in fact, was cost saving where a health system was in place (hence the negative ICER). From a baseline of 40% ITN coverage and above, scaling up case management coverage was the most cost-effective option and, as expected, the MSAT ICERs became very large.

At a pre-intervention EIR of 20 IBPAPA, scaling up ITN coverage to the next level was the most cost-effective intervention in settings of 0 and 40% ITN coverage. At 60% ITN coverage, scaling up case management coverage became the most cost-effective intervention. However, at 40% ITN coverage, the MSAT ICER was in a similar range to that of scaling up ITN and case management coverage. At a pre-intervention EIR of 50 IBPAPA, the ICERs of scaling up ITN coverage from 0 or 40% were the lowest. Interestingly, at an ITN coverage of 60%, MSAT was similarly cost-effective to scaling up ITN coverage further.

3.5. Discussion

To date, MSAT for malaria has been considered almost exclusively as an intervention to interrupt local transmission of the parasite, or as a response to an epidemic in a previously malaria-free area. Even if MSAT does not result in sustained interruption of transmission, it may be a cost-effective strategy to reduce the malaria burden in some areas that are pursuing disease control. If used in this way, MSAT should be continued indefinitely, similar to ITN distribution.

Where prevalence is very low, infections are more likely to be symptomatic and thus detected by the passive case management system. The addition of mass treatment, therefore, will probably not have a large effect on the incidence of disease, particularly where case management coverage is high. Where prevalence is high, a greater population proportion will harbour asymptomatic infections, increasing the effectiveness of mass treatment relative to passive case detection. However, under these circumstances, individuals may become re-infected very soon after treatment through MDA or MSAT, limiting the intervention impact in averting disease. Of course, the effectiveness will also depend on characteristics of the intervention itself, such as the frequency with which it is carried out, population coverage and compliance to diagnostic tests and treatment regimens.

These results suggest that, in all the transmission settings considered, achieving a minimal level of ITN coverage is always a "best buy", and in low transmission settings, MSAT is probably never worth considering for burden reduction from a cost-effectiveness perspective. This finding is in contrast to the current focus on MSAT as an intervention for low transmission or near-elimination settings. Instead, MSAT may be more suitable at medium to high transmission levels and at moderate ITN coverage. In these settings, the cost-effectiveness of MSAT may be comparable to that of scaling up case management and ITN coverage.

An interesting finding from this preliminary analysis, and one that merits further investigation, is that achieving 80% ITN coverage across all settings, as per current global malaria strategies [23], may not be an efficient use of resources, particularly in low-transmission settings. Given stagnating donor funding for malaria, and the fact that ITNs account for the largest share of most malaria programme expenditure [3], this finding may be important for malaria programme managers' decisions.

The judgment as to whether or not an intervention is cost-effective rests upon the decision maker's valuation of a unit of health gain, or the ceiling ratio. Values used in practice are usually quoted per disability-adjusted life-year (DALY) averted, and are based on affordability expectations (such as $US150 per DALY), some multiple of gross national income or gross domestic product, or preference-elicitation methods [103]. This study's results, presented in 2007 $US per episode averted, do not refer to a ceiling ratio and thus do not allow assessment of whether MSAT is cost-effective or not. Rather, they provide an initial indication of the conditions under which this strategy may be worth pursuing.

The effects of correlations in intervention coverage, either between repeat distributions of the same intervention or between receiving MSAT, ITNs and case management, have not been analysed. In principle such correlations may result in either under- or overestimation of the effects of the interventions. Positive correlation between interventions is similar to adding new interventions preferentially into population subgroups with relatively high pre-existing coverage. This may be efficient when effectiveness is greater at low transmission, but in general might be expected to make the intervention package overall less cost-effective.

The estimate of the cost-effectiveness of MSAT relies on the per-person cost of the intervention, which was estimated from secondary data on costs for similar interventions. To account for this uncertainty, a high and a low cost estimate were used. All campaign costs incurred were attributed to the MSAT intervention. However, MSAT could be more cost-effective if delivered jointly with other interventions, since household visits constitute most of the intervention costs. Notably, the MDA costs for neglected tropical diseases have been shown to be reduced where programmes are integrated in places where diseases co-exist [104] and evidence suggests this integration can be effective [105]. An ITN distribution

programme was successfully integrated with MDA for lymphatic filariasis and onchocerciasis in Central Nigeria [106]. Also, costs per person screened were assumed constant and incentives to community health workers were included; this cost might vary depending on the implementation stage, the use of volunteers, or the programme scale [107]

On the other hand, achieving good MSAT implementation may incur costs that were not considered in the cost estimate and presupposes a fairly strong health system capable of organizing such an endeavour; otherwise, control programmes for other diseases may suffer. In this analysis, MSAT population coverage in each round was assumed to be 85% and compliance to be perfect. A well-conducted MSAT campaign will require careful planning, social mobilization, community involvement, and improvement of health care infrastructure, as was documented in Vanuatu [108]. This is not trivial; for example, the difficulties of maintaining an effective census record in a past MDA campaign in Tanzania have been described [109]. While achieving these high levels of MSAT compliance and coverage may be challenging, the aim of this study was to predict the cost-effectiveness of the intervention under optimal conditions; future analyses could explore the sensitivity of ICERs to reduced coverage and compliance.

The estimate of cost savings from averted case management due to MSAT comprised only the marginal costs, assuming that the fixed costs remained unchanged. However, a much lower malaria burden may free up capacity for other interventions, boosting the cost-effectiveness of MSAT. If this spare capacity can be used, it could have significant benefits for the control of other diseases.

In these simulations, MSAT was conducted using existing diagnostic and pharmaceutical tools. Microscopy and the current generation of RDTs fail to detect many low-density infections, thus a number of sub-patent infections is

missed. More sensitive diagnostic tools appropriate for use in the field are a target for future development [110], and if these become available, the MSAT impact could be enhanced. There could be benefits of other drug regimens, for example adding primaquine (PQ) to ACT regimens, which would make MDA/MSAT more effective in reducing transmission [22], although a recent study found that addition of PQ to ACT did not improve elimination of parasitaemia and prevention of gametocyte carriage in carriers with low-density parasitaemia in the dry season in Sudan [111].

As in the case of MSAT, economies or dis-economies of scale were not considered in the costs of scaling up case management and ITN coverage. The model for the costs of scaling up case management coverage does not account for investments in infrastructure that would need to be made when increasing coverage. In reality, scaling up case management may be more costly than it appears in this analysis. Moreover, a single estimate of distribution cost per ITN (with single occupancy) was used; these vary depending on scale, mode of distribution and other factors [112]. This analysis could be extended by varying unit costs at different coverage levels and assessing the sensitivity of results. Also, if each ITN were assumed to cover more than one person, the cost-effectiveness of ITNs would increase.

In addition, the model used for ITNs, where the killing effect of the net decayed exponentially with a half-life of 2.64 years, is quite simple. Estimating the cost-effectiveness of ITNs and case management was not this paper's focus, and it aimed only to compare ICERs in orders of magnitude. Understanding of the cost-effectiveness of ITNs and case management relative to each other and to other interventions could be improved using more complex models; one such model for ITNs is currently being developed [113].

The comparison of MSAT ICERs with those of scaling up ITN and case management coverage should not be construed as pitting the interventions against one another, as combinations of the interventions may well be an appropriate strategy. Improvements in case management, in particular, represent investments in the wider health system; they are valuable on that basis alone and cannot be directly compared with preventive interventions such as ITNs and MSAT. Furthermore, the use of episodes as the measure of effects resulted in a biased ICER for case management relative to the other two interventions. Case management's impact was considered only in terms of reduced host infectivity (and thus reductions in future transmission) and decreased recurrences of illness due to one infection. However, as a curative intervention, the most important effect of case management is to reduce severe disease and mortality, and this was not captured in the ICER denominator presented here. Scaling up case management is thus likely to appear much less cost-effective in this analysis than it would be in reality. Future analyses comparing the cost-effectiveness of case management with that of preventive interventions should include both disability and deaths averted (expressed in DALYs) as an outcome measure.

3.6. Conclusion

Mass screening and treatment (MSAT) for malaria may be worth considering as a burden-reducing intervention in certain areas that possess adequate resources and health system capacity to implement it well. If undertaken, it should be as a complement, and not a replacement, for case management and vector control interventions, like insecticide-treated nets (ITNs). Also, policy-makers and planners should be prepared to continue it indefinitely, until new interventions become available or other developments make local transmission interruption a real possibility.

MSAT is at the high end of a case management continuum that goes from passive case detection, to screening only febrile or clinically suspected malaria in a small radius around a confirmed case, to screening all individuals at a large radius around a confirmed case, to MSAT and mass drug administration (MDA). One or another of these options may ultimately be a better use of resources than MSAT. More data is needed to determine the most cost-effective surveillance and response strategies in different settings.

3.7. Authors' Contributions

VC conceived the study, performed the analyses and wrote the manuscript. OJTB advised on analyses and contributed to the manuscript. DH wrote the code for the simulations and helped with preliminary analyses. NC helped develop the study design and contributed to the manuscript. NM and ADP helped with the analysis of the simulations. TAS advised on study design and analyses and contributed to the manuscript. All authors read and approved the final manuscript.

3.8. Acknowledgements

3.9. Additional file 1. Estimating the cost of MSAT

This Additional file presents a literature-based costing of MSAT campaigns for malaria, delivered through house-to-house visits via a community-based approach. Intervention delivery through house-to-house visits by village volunteers or community health workers (CHW) is likely to achieve high coverage rates. This is how mass drug administration (MDA) for malaria was usually done during the historic eradication campaigns [109],

In Vanuatu, communities were enlisted to conduct MDA and community-based surveillance and self-monitoring [114]. In Zanzibar, the success of the MDA campaign against lymphatic filariasis (LF) has been attributed to the drug distributors, or "filarial prevention assistants", who were selected based on their experience, residence in and acceptance by the communities where they worked [115].

Literature on operations and cost of similar interventions was reviewed to identify major cost items, variables, and assumptions needed, and to get an idea of the order of magnitude of per-person cost that has been estimated for these interventions. Total cost per person screened was built and its range explored in a sensitivity analysis. Limitations of the methodology were explored as well.

Previous studies on the costs of community-based interventions

Home-based management of malaria

Delivery of treatment for suspected malaria through home-based management of malaria (HMM) has been applied in sub-Saharan Africa [116]. The average net intervention cost to promote HMM in rural Burkina Faso, including training,

purchase of the first drug stock, bags, labels and packing of drugs, incentives to CHWs, and supervision and drug distribution, was 1994 US$ 0.06 per resident child [117]. The cost of HMM in a trial in urban Ugandan children, including the cost of artemether-lumefantrine, was estimated at about US$ 34 per child per year [118]. In a study in Nigeria, the cost of design and implementation of a strategy on use of CHWs for HMM of malaria, including consumer and provider costs, was between US$ 1.40 and US$ 1.70 per villager. Recruitment and training of CHWs contributed the highest proportion of these costs [119]. Unfortunately, these studies are not directly comparable due to differences in the intervention design, collection and inclusion of cost data, and size and composition of the study population. Furthermore, HMM is quite different from MSAT in that it does not involve household visits; instead, individuals generally visit the CHW when they are ill.

Recently, interest in whether CHWs can use RDTs prior to prescribing antimalarial treatment has increased. Since parasitological testing with RDTs would be an integral MSAT component, literature on this topic was reviewed. A cluster randomized trial in Zambia found that CHWs were able to successfully use RDTs, ACTs and amoxicillin to manage both malaria and pneumonia in the community [120]. A study of a 3-hour training course for CHWs in Zambia on how to use and interpret RDTs estimated that the course cost approximately 2006 US$ 175 per CHW, including supplies (job aids), transportation, lodging, salaries, and per diems for CHWs, trainers, observers and MOH personnel. If only supplies, transportation, and lodging for CHWs were included, the cost was 2006 US$ 66 per CHW trained. Significantly more trained CHWs conducted and read the test results correctly compared to CHWs who had received only the manufacturer's instructions or job aids [121].

Neglected tropical diseases

Preventive chemotherapy is used as a key approach in control and elimination programmes for neglected tropical diseases (NTDs), notably LF, schistosomiasis, onchocerciasis, soil-transmitted helminths and trachoma [122]. These diseases are often found in areas which are co-endemic for malaria. Many components of MDA programmes against these diseases could be quite similar to those of MSAT programmes against malaria. Therefore, the costing literature for MDA for these NTDs were reviewed, with a focus on African settings. A major difference between the costs of MDA for NTDs and malaria is that drugs for MDA are often donated, and thus incur zero financial costs to the control programme. In addition, distribution often relies on unpaid volunteers, which are also not included in estimates of financial costs.

LF is currently targeted for elimination by the World Health Organization (WHO), and the principal strategy relies on concurrent administration of a drug combination, albendazole with diethylcarbamazine or albendazole with ivermectin, once-yearly for four to six years. A multi-country cost analysis of MDA for LF published in 2007 revealed that financial costs per person treated per round (not including drugs or volunteer time) in the sub-Saharan African programmes ranged 2002 US$ 0.06 – 0.54, with coverage rates ranging 65% – 91%. However, when the cost of donated materials, notably drugs, was included, cost per person treated was around US$ 5 [107].

All of these programmes involved house-to-house visits by volunteers, with or without additional distribution through distribution posts. Cost categories were: training, mapping, mobilization and education, drug distribution, adverse reaction monitoring, surveillance/laboratory (e.g. tracking of community members in MDA area, laboratory work for case identification, testing, etc.), and administration.

Input categories were: medications and laboratory supplies, personnel, transport, general supplies, and recurrent and capital costs for facilities and equipment. The analysis was conducted from a national program perspective and, as many inputs were shared among multiple programmes, costs were apportioned accordingly. Drug distribution generally represented the largest proportion of financial expenditures. The principal determinants underlying variability in the lymphatic filiariasis costing appeared to be the number of years that the programme had been running; the use of volunteers; and the size of the population treated [107].

Mean financial cost of the African Programme for Onchocerciasis Control was 2008 US$ 0.58 per person treated, not including volunteer time, which was valued at 2008 US$ 0.16. Again, drugs were donated so are not included in the cost. The scale and stage of the program made a large difference to unit costs [104].

MDA for malaria

Only one article with information on the cost of MDA for malaria was found in a literature search. A weekly MDA in Vanuatu, conducted by trained village volunteers for nine weeks (together with ITN distribution and implementation of larvivorous fish), cost US$ 9 per person: US$ 5.6 for the impregnated bednets, US$0.7 for antimalarials, US$0.4 for materials for microscopical diagnosis, and US$2.3 for transportation and travel allowances for the staff and volunteers. About 90% coverage was achieved in the first three rounds [108]. This MDA was conducted on a small island at short intervals, which is quite different from annual MSAT scenarios in mainland Africa.

Some other studies contained useful information about the operational considerations when undertaking MDA for malaria, such as on how the intervention was carried out, on the number of households that could be visited in

a day, and on realistic coverage levels. For example, a report from an MDA in Tanganyika (present-day Tanzania) described the detailed individual census system that was drawn up before the trial and continually updated, and noted the need for repeated household visits and community participation to achieve high population coverage [109]. One study gave an indication of the time that would be needed to cover a particular population with MDA in an area of north Nigeria with reasonably good accessibility [123]. A report on the Garki project in northern Nigeria stated that in compact villages, each two-person team covered between 150 – 180 people per day, whereas in scattered villages, they covered around 90 – 100 persons per day [124]. Of course, these interventions did not involve screening prior to treatment.

Although these costs give a useful indication of what could be expected with MSAT for malaria, the interventions are so different that they cannot be applied directly to MSAT for malaria; screening prior to treatment, as in the case of MSAT for malaria, is a more complex and time-intensive intervention than mass treatment alone and will require additional training of volunteers or CHWs.

Algorithm

The screening cost per person screened (S_p) in an MSAT campaign round was estimated according to the formula:

$$S_p = E_p + M_P + D_p + I_p + T_p$$

where E_p is the household enumeration cost per person screened, M_P is the social mobilization cost per person screened, D_p is the delivery cost per person screened, I_p is the volunteer or CHW supervision cost per person screened, and T_p is the volunteer or CHW training cost per person screened.

For those that test positive and receive a drug, the drug cost needs to be added. These costs will depend on the total prevalence level in the population and the relationship of prevalence to age.

Household enumeration

Costs of surveying and conducting a census of the target population were assumed to be borne every time that a mass treatment campaign was planned. In reality, costs in subsequent years might be lower if only updating of an existing census were required.

Household enumeration costs were borrowed from a study which estimated the per-person cost of conducting a national census in Tanzania [125] (Table 3.4).

Social mobilization

Costs for social mobilization are programme costs which are relatively fixed irrespective of the covered population size; as such the per-person costs are quite sensitive to the intervention scale. Social mobilization costs were borrowed from a cost study of introducing ACTs [126] (Table 3.4). This study reported the costs of development and production of information, education and communication materials and communication and publicity in a rural Tanzanian district of approximately 200,000 population over three years. While the ACT introduction study assumes that the cost of these activities declines in subsequent years, for the MSAT programme, a constant per person cost per round (as in year 1) was assumed, given the more intense communication efforts that would be required with a MSAT programme (owing to the need to achieve high coverage and the fact that the target population is not ill).

Delivery costs

Delivery costs per person screened per round was estimated as the sum of the volunteer or CHW per diem per person screened per round, W_p, plus the cost of supplies per person screened per round, U_p. The cost of transport of volunteers or CHWs was assumed to be negligible, as they would be based in the community and would travel only short distances, and in any case this could be covered by the per-diem remuneration.

$$D_p = W_p + U_p$$

Remuneration

Remuneration per person screened per round, W_p, was estimated as:

$$W_p = \frac{W_{dv} \cdot N_{vt} \cdot \sum_1^r N_{d,r} \cdot N_{t,r}}{N_p}$$

Where W_{dv} is the daily per diem for the volunteers or CHWs, N_{vt} is the number of volunteers or CHWs in each team, N_p is the number of people screened, $N_{d,r}$ is the number of days for visit r of the MSAT campaign, and $N_{t,r}$ is the number of teams participating in visit r, with

$$N_{t,r} = \frac{P \cdot p_{a,r-1}}{S_h \cdot N_{d,r} \cdot N_{h,r}}$$

Where P is the total population targeted for the intervention, S_h is the average household size, $N_{h,r}$ is the number of households that a team of volunteers or CHWs can visit per day in visit r, and $p_{a,r}$ is the proportion of households with at least one member (still) absent on visit r, with $p_{a,0} = 1$.

Assumptions made in the calculation of remuneration costs are summarized in Table 3.5 and per-person costs under assumptions 1 and 2 are presented in Table 3.1.

Supplies

The cost of supplies per person screened per round, U_p, is estimated as

$$U_p = R_p + L_p + G_p + A_p + Y_p$$

where R_p is the cost of an RDT, L_p is the cost of a lancet, G_p is the cost of a pair of gloves, A_p is the cost of an alcohol swab, and Y_p is the cost of paper and printing per person. Sources for these prices are given in Table 3.4.

RDT costs were calculated with an additional 12% added for transport, insurance and delivery [97] and another 25% for wastage [127]. For the other supplies, we did not cost delivery but did assume the 25% wastage rate.

Per-person cost of supplies is presented in Table 3.1.

Supervision

Cost of supervision per person screened per round, I_p, was estimated as

$$I_p = \frac{W_{ds} \cdot \sum_{1}^{r} N_{d,r} \cdot N_{t,r}}{N_p \cdot N_{ts}}$$

where W_{ds} is the daily remuneration of the supervisor, N_p is the number of people screened, N_{ts} is the number of teams per supervisor, here taken to be three, $N_{d,r}$ is

the number of days for the visit r of the MSAT campaign, and $N_{t,r}$ is the number of teams participating in the visit, as given under delivery costs, remuneration.

Per-person cost of supervision under assumptions 1 and 2 is presented in Table 3.1.

Training

Training of volunteers or CHWs is needed before each round. In situation 1, the CHWs have already been trained in presumptive management of febrile illness. However, they need to be instructed in the MSAT intervention and trained in conducting and interpreting RDTs and record-keeping. RDT training costs were borrowed from a study in Zambia [121].

In situation 2, where no network of community health workers yet exists, volunteers need to be recruited and trained in all aspects of the intervention (RDT, ACT administration, etc). Recruitment and training costs were borrowed from a study of a community health worker strategy in Nigeria [119].

Training costs per person screened per MSAT round for situation 1 are thus estimated as

$$T_p = \frac{N_v \cdot C_p}{N_p}$$

where N_v is the total number of CHWs participating in the campaign, C_p is the cost of the RDT training course per CHW, and N_p is the number of people screened.

Training costs per person screened per MSAT round for situation 2 are estimated as

$$T_{p2} = \frac{N_v \cdot C_{pt}}{N_p} + T_{p1}.$$

where N_v is the total number of CHWs participating in the campaign, C_{pt} is the cost of recruiting and training per CHW, and N_p is the number of people screened.

Training costs per CHW or volunteer are sensitive to the scale of the training programme. Costs for recruiting and training in situation 2 were modified in an attempt to adjust for this (see Table 3.4), but this remains a source of uncertainty in our costing estimate.

Sources for training costs are presented in Table 3.4 and per-person cost of training in situations 1 and 2 and under assumptions 1 and 2 is presented in Table 3.1.

Artemisinin-based combination therapy

Prices for ACTs were as described in a previous publication [97]. Costs were calculated with an additional 12% added for transport, insurance and delivery [97] and another 25% for wastage [127]. ACT costs are presented in Table 3.1.

Calculation of total costs

The cost estimates are summarized in Table 3.1. In situation 1, cost per person screened per round is estimated as US$ 5.08 under assumption 1, and US$ 6.72 under assumption 2. In situation 2, cost per person screened per round is estimated as US$ 7.80 under assumption 1, and US$ 11.08 under assumption 2.

Discussion

To date, MSAT has not been implemented anywhere, so there were no actual costs that could be used for this analysis. However, it is encouraging that the estimate of roughly US$5–11 per person screened (including RDT costs but excluding drug cost) is in a similar range to the cost per person treated in a once-yearly MDA for LF (US$5, including drug cost, no screening) [107]. This analysis suffers from the inevitable limitations of a generic costing based on secondary data. First, the cost of non-tradable inputs (e.g. personnel) could be expected to vary significantly among countries, for example according to level of income [128], which was not considered. Second, this cost estimate included primarily the marginal costs of MSAT, assuming that the health system could accommodate the intervention without, for example, hiring additional staff in health facilities or expanding the drug supply system. The validity of that assumption will depend very much on whether there is spare capacity in the health system. Two situations were considered; one where CHWs were already managing febrile illnesses and another where a system of village volunteers needed to be set up. Since training costs for volunteers or CHWs constitute about a quarter of the total costs of the intervention, this is likely to be a major component of the costs of investing into the health system. As mentioned above, efficiencies of scale or scope that could be achieved by expanding MSAT or integrating MSAT with other disease control programmes were not considered. However, as the majority of costs are variable, this is unlikely to change the estimate significantly.

It is not clear how the costs of an intervention involving household visits would vary with population density: e.g. the difference between rural and urban settings. Distances between households are shorter in cities so transport and time costs will likely be lower, but it may also be harder to find people at home in large cities than in villages [129] and thus more repeat visits may be necessary in cities. Two

different assumptions about the number of household visits that could be accomplished in a day were made in an attempt to account for this. Transport for the village volunteers or CHWs was assumed to be negligible, since they live within the community, but for very spread-out villages these could be more substantial.

More data is needed on the operations and costs of interventions involving household visits in sub-Saharan Africa, as these may be necessary to reach the high levels of intervention coverage called for in global malaria control targets. It is hoped that the work described here contributes to discussions about the costs, feasibility and efficiency of these types of interventions.

Table 3.4 Cost parameters, values and sources

Cost Parameter	Symbol	Cost (2007 US$)	Source
Household enumeration			
Household enumeration cost per person	E_p	0.29	[125]
Social mobilization			
Social mobilization cost per person	M_p	0.27	[126]
Remuneration	W_p		
Daily remuneration of volunteers or CHWs	W_{dv}	10	[130]; G. Ferrari, personal communication
Supplies	U_p		
Price of 1 pair of sterile gloves	G_p	0.23	G. Ferrari, personal communication
Price per lancet	L_p	0.03	G. Ferrari, personal communication
Price of 1 alcohol swab	A_p	0.19	G. Ferrari, personal communication
Price of black ink printer cartridge		115	G. Ferrari, personal communication
Price per ream of paper		2.39	http://eetd.lbl.gov/paper/counting/html/purchasing.htm
Price of Paracheck RDT per test	R_p	0.61	[131]
Supervision			
Daily remuneration of supervisors	W_{ds}	40	G. Ferrari, personal communication
Training	T_p		
Situations 1 and 2: Cost of RDT training course per volunteer or CHW	C_{pr}	68	[121]
Situation 1: Cost of recruiting and training village volunteers per volunteer	C_{pt}	154	[119]; estimate is half of the cost due to assumed economies of scale

Table 3.5 Input parameters, values and sources

Input Parameter	Symbol	Assumption 1	Assumption 2	Source
Total population targeted for MSAT	P	1000		Assumption
Number of people screened	N_p	850		[56]
Average household size	S_h	5		[94]
CHWs or volunteers per team	N_{vt}	3		G. Ferrari, personal communication
Number of CHWs or volunteers - first and second round	$N_{v,1}$ $N_{v,2}$	15	24	Calculation
Number of households visited per team per day - first round	$N_{h,1}$	8	5	Assumption
Number of houses visited per team per day - second round	$N_{h,2}$	16	10	Assumption
Number of days per MSAT campaign	N_d	6		Assumption
Number of days - first round	$N_{d,1}$	5		Assumption
Number of days - second round	$N_{d,2}$	1		Assumption
Proportion of households with at least one member missing on first visit	$p_{a,1}$	0.4		Assumption
Proportion of households with all members missing on first visit		0.2		Assumption
Proportion of households with only one member missing on first visit		0.2		Assumption
Proportion of members missing on first visit that are found on second visit		0.5		Assumption
Number of teams per supervisor	N_{ts}	3		Assumption
Number of printer cartridges used per MSAT campaign		2		Assumption
Number of reams of paper per MSAT campaign		5		Assumption
Distribution costs as percentage of the RDT price		12%		[97]
Wastage rate of drugs and supplies		25%		[128]

4. Measuring the burden of uncomplicated *P.falciparum* malaria

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4.1. Summary

Malaria disease burden is modified by treatment. While this is the primary reason for treating malaria, the dynamic effects of treatment are generally ignored in estimates of burden of disease, which is usually presented in terms of numbers of clinical cases or episodes [3] with the main sources of data being reporting of clinical cases from health facilities and parasite prevalence surveys. The failure to include the dynamic effects of treatment in estimates of burden leads to misunderstanding of measures of burden. It also leads to bias in both empirical estimates of the impact of changes in case management, and in simulation models of cost-effectiveness of malaria interventions.

This paper examines these challenges in detail, and considers how they can be overcome.
It proposes an approach for measuring burden of disease that recognizes the distinction between burden and counts of episodes. This technique makes use of data available from standard designs of community surveys, together with analyses of patterns of fever in malaria therapy patients and data on recall bias from Asembo, Kenya. Application of this approach to data from Zambia for 2010 gave an estimate of 2.6 (1.5, 3.8) malaria attributable fever days per child-year. To obtain valid estimates of the overall malaria burden using these methods, there remains a need for surveys to include the whole range of ages of hosts in the population and for patterns of seasonality in confirmed cases to be available.

4.2. Introduction

Malaria continues to be a major cause of disability and death in countries where it is endemic. Accurately estimating the burden of morbidity due to the disease[1] is critical for guiding programmatic strategies and resource allocation, and evaluating the impact of malaria control measures. However, commonly-used approaches for estimating malaria burden are problematic as a result of imprecise terminology and estimation techniques that do not allow for the complexity of the natural history of the disease.

When promptly and effectively treated, malaria illness is of short duration, but if untreated a single *P.falciparum* malaria infection can last for many months, causing recurring clinical attacks interspersed with asymptomatic periods [132] during which parasitaemia is often sub-patent. This can be clearly seen in the time courses of parasitaemia and fever observed when malaria was used for treating neurosyphilis (Figure 4.1).

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[1] Here we consider only the morbidity burden, though most of the malaria burden, measured in terms of disability-adjusted life years (DALYs) or quality adjusted life years (QALYs) is contributed by mortality [41]
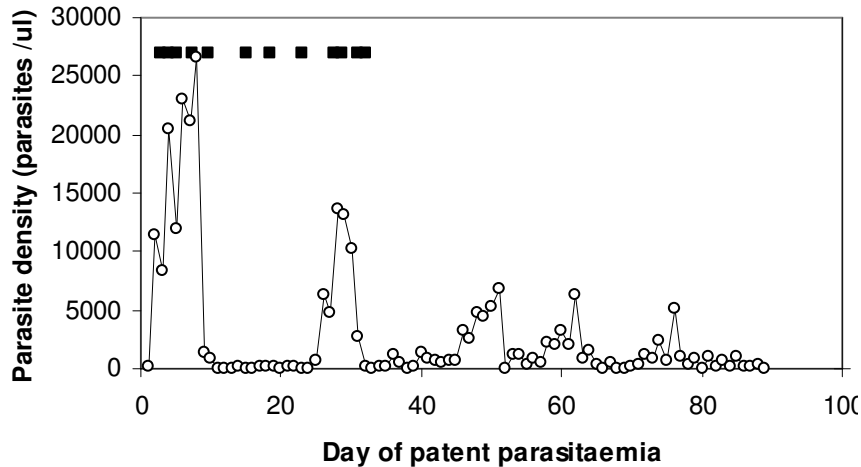
Figure 4.1 Pattern of parasitaemia and febrile illness in a malaria-therapy patient (Patient S-519)

○—○: Parasite densities; ■indicates a day on which fever (core temperature >=103. °F) was recorded.

The full histories of many untreated malaria infections were recorded when artificial inoculations of malaria parasites were used for treating neurosyphilis [133]. Figure 4.1 shows the time pattern of parasitemia and fever in a neurosyphilis patient treated with *P.falciparum*. In this figure, this single (untreated) infection gives rise to five periods of high parasitaemia. The first two of these are each associated with several bouts of fever indicated by the black bars at the top (see definitions in Table 4.1).

This sporadic pattern of clinical symptoms of untreated disease complicates the definition of clinical incidence. For many infectious diseases, for instance influenza, each incident infection leads to one and only one period of illness, or episode. Burden can thus be estimated from the incidence of disease and the duration of episodes, with an appropriate weighting used to convert numbers of episodes into DALYs or QALYs. By contrast, with malaria, one incident infection may lead to multiple periods of illness (or may be asymptomatic throughout, though this may be infrequent [134]). Malaria burden is often expressed as numbers of episodes, but it is not clear whether one episode is intended to refer to

(i) all illness resulting from a single infection event; (ii) one uninterrupted period of illness; or (iii) all malaria illness within a given period. Infections that are treated promptly and effectively when they first lead to symptoms unambiguously contribute one episode to this total, but when treatment is delayed, or if the infection remains untreated, it is unclear how many periods of illness can result from a single infection event. This matters because the disability caused by the disease (and the risk of life-threatening complications) are clearly less when it is treated promptly, but these benefits may be invisible, depending on how incidence is calculated. The term episode clearly refers to some of set of bouts, but just how many and which bouts make up an episode is not clear. In Table 4.1 we propose a definition that captures this ambiguity.

Statements about incidence of malaria disease are consequently often vague or misunderstood. For instance, the World Health Organization (WHO) estimate of 225 million cases in 2009 [135] is widely interpreted as the number of people infected although it is intended to refer to the total number of clinical episodes. Confusion is not limited to lay interpretations, for the relationship between a malaria infection and the amount of illness it causes is far from straightforward.

In many countries, mostly outside Africa, burden is reported using passive case detection data, and in WHO statistics, estimates of morbidity rates for these countries are corrected for reporting completeness, diagnostic error, and attendance rates [3;136]. In most of sub-Saharan Africa, presumptive treatment has been the norm, so that reporting of the numbers of treatments has not been used to estimate disease burden. Instead, maps of *P.falciparum* prevalence determined from surveys have been combined with information on climate suitability for malaria transmission and population density in order to classify populations into different endemicity levels. Estimates of clinical incidence for different endemicity levels have been derived primarily from longitudinal surveys

of febrile malaria episodes in children, detected either actively or passively [30;137;138]. The estimates of populations at risk and endemicity-specific estimates of disease rates have together been used to produce national and continent-wide estimates of the number of clinical malaria episodes [4].

Longitudinal studies of malaria must always involve treating the acute episodes that are discovered, and thus all the burden of disease subsequent to effective treatment of an infection is averted[2]. In several longitudinal studies [65;139], dramatic decreases in fever rates over time have been observed, presumably for this reason. Intensive research studies are therefore likely to substantially underestimate clinical attack rates in the general population.

An alternative to these approaches is to use recalls of illness from cross-sectional surveys carried out in the community. An increasing body of data is available from Demographic and Health Surveys (DHS), Multiple Indicator Cluster Surveys (MICS), and Malaria Indicator Surveys (MIS), which include ask respondents to provide a recall of illness during the previous two weeks for each of their children. We show here how these data can be used to estimate the burden of malaria disease, and suggest how improved estimates might be obtained.

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[2] Treatment also reduces onward transmission to mosquitoes, but this effect is not relevant to the present discussion.

Table 4.1 Definitions used in this paper

Term	Meaning in this paper
Malaria infection	Those parasites descended from a single inoculation of sporozoites[3]
Incidence of infection	The number of new infection events in a population in unit time
Bout of illness	An uninterrupted set of days during which a patient is considered, or considers themselves, to be ill for at least part of each day
Malaria episode	A set of bouts of malaria illness considered by the patient or carer to be of common malaria aetiology*
Incidence of clinical malaria	The number of malaria episodes in a population in unit time
(Point) prevalence of clinical malaria	The proportion of the population suffering from symptoms of malaria aetiology at any one time
Malaria burden	The morbidity or disability associated with malaria (ideally measured by days of illness, DALYs, or QALYs)

*This definition is intended to capture the way in which the word episode is used, whereby intermittent fever bouts, within a period of continual high parasitaemia characteristically lasting a few weeks (Figure 1), are likely to be thought of as part of a single episode.

4.3. Methods

Data sources

The method involves using four distinct sources of data for different quantities required in the overall estimate of burden.

1. Incidence of disease in the community: Malaria Indicator Survey data from Zambia

Data on history of fever in the last fourteen days from the 2010 Malaria Indicator Survey from Zambia [140] were used. Just over 34% of children under five

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[3] It is debatable whether co-inoculated but genetically distinct parasites should be considered part of the same infection.

reported a fever in the last two weeks. This is period prevalence of fever, biased by recall. Of these 34% took an antimalarial drug.

2. *Recall bias in community surveys of incidence: daily prevalence of fever, Asembo, Western Kenya*

For analysis of recall bias in recalls of fever, data of Feikin et al [141] for children from Asembo, Kenya were used. These comprise recalls of fever, elicited separately for each day in a 14-day recall period, in a survey of approximately 25,000 people in Asembo, Bondo District, Kenya (Figure 4.2). (We found a similar pattern in the data of Genton *et al* [142] from Papua New Guinea.)
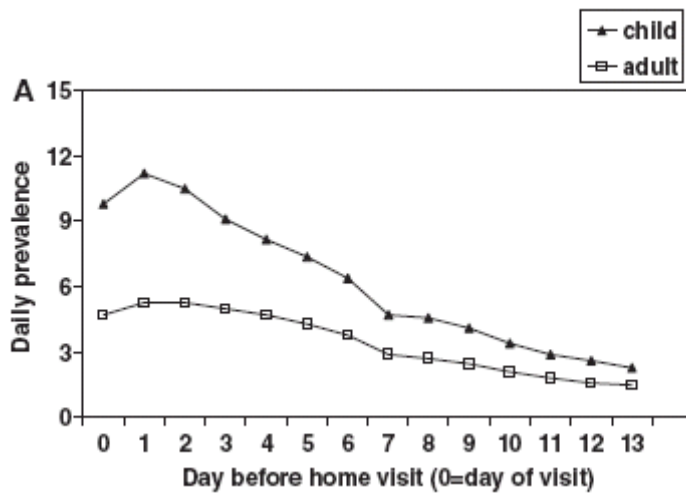
Figure 4.2 Daily prevalence of fever calculated as percentage of persons reporting symptoms on each day in the 2 weeks prior to home visit, Asembo, Western Kenya

Source: [141]

3. *Seasonality of fever: Health Management Information System (HMIS) records of Malaria Indicator Survey data from Zambia*

4. Patterns of fever in untreated hosts: malaria-therapy data

Patterns of fever in untreated and inadequately treated malaria patients were analysed using the data of 330 neurosyphilis patients treated with *P. falciparum* in the National Institutes of Health laboratories in Columbia, South Carolina and Milledgeville, Georgia in the United States of America [132]. For each of these patients, the days on which fever (core temperature >=103. °F) occurred was recorded.

Estimation of recall bias as a function of recall period

Two-week morbidity recalls do not elicit complete information about illness during the reference period, and the usual survey procedures do not directly provide any information about recall bias. However recall bias can be estimated when respondents are asked individually about illness on each distinct day during the recall period. This is because independence of the timing of the survey and the illness justifies the presumption that variations in fever rates by recall period reflect recall bias.

The relative frequencies of fever reports by day of recall in the Asembo data provide a direct estimate of the recall bias associated with a specific period of recall. Assuming that a fever on the previous day is reported with 100% sensitivity, an estimate of the recall probability for a fever i days prior to interview is $\hat{r}_i = F_i/F_1$ where F_i is the fever prevalence recorded in the survey for the single day, i days prior to interview. ($\hat{r}_0 = F_0/F_1 < 1$ because surveys are usually carried out early in the day, before all fevers are yet evident.)

Estimation of recall bias in two-week morbidity recalls

The probability that a survey respondent reports fever, conditional on fever having occurred during a two week recall period, differs from $\hat{r}_i$ because fever bouts extend over multiple days (Figure 4.4a), and there may be multiple bouts during a single recall period (Figure 4.1). The overall recall probability for a two week period, allowing for these effects, was estimated by applying the estimates of $\hat{r}_i$ obtained from the Asembo study to simulated interviews of malariatherapy patients.

The recorded follow-up periods were divided into fourteen-day intervals during which there was daily monitoring, leading to a total of 3715 fourteen-day intervals, during 755 of which there was one or more day of fever. Data were discarded for days that could not be included in these intervals because of gaps in or termination of the monitoring of the patients.

For the analysis of recall in the absence of treatment, each day of follow-up (j=1,2..14) in each of these intervals was evaluated as though the patient had been interviewed at j=14. Each day of fever was assumed recalled with probability $\hat{r}_{14-j}$ so that the probability that any fever was recalled in the simulation was

$$\tilde{r} = 1 - \prod_{j=1}^{14}\left(1 - I_j\hat{r}_{14-j}\right)$$ where $I_j = 1$ if there was fever on day j and $I_j = 0$ if there was no fever on day j.

The true treatments administered to the malaria-therapy patients (predominantly sub-therapeutic doses) were ignored in this analysis. To estimate the effects of treatment on survey recalls, simulated treatments were assigned stochastically to each day of fever with probability t_0 corresponding to the probability of prompt and effective treatment. Where treatment was assigned, it was assumed that this

would be reported, so that intervals with treatment were always reported in the simulated surveys as including fever days. To estimate the values of t_0 in Zambia, the simulations were repeated with different values of t_0. The proportion of recalls reporting treatment, among those reporting illness, $\tilde{t}$, was plotted as a function of t_0 and the value of t_0 corresponding to the observed proportion in the Zambian MIS, was read off the graph, thus providing an estimate of the daily treatment rate in Zambia.

Estimation of period prevalence of clinical malaria from survey data

MIS use two week recalls to elicit histories of both illness and of treatment. The signs and symptoms of malaria are common to those of other diseases, so interviews alone perform poorly in assigning malaria as the cause of illness. To determine the proportion of recalled illness that is due to malaria, parasitological testing is needed. Using 14-day recalls, individuals with reported fever may not be parasitaemic at the time of the survey, however Rapid Diagnostic Tests (RDTs) based on the presence of the *P.falciparum* Histidine Rich Protein 2 (*Pf*HRP2) to determine the prevalence of malaria infections. As *Pf*HRP2 persists in the bloodstream for up to a month following parasite clearance [143;144], *Pf*HRP2 positivity (unlike blood slide positivity) can be used to estimate the malaria-attributable fraction of the recalled fevers and hence the period prevalence of clinical malaria.

The processes determining both questionnaire and RDT outcomes can be represented by the branching process shown in Figure 4.3, where the columns RDT, Fever, Treated indicate the outcomes recorded at the survey, and the branches correspond to a classification of respondents according to whether they are parasite positive by RDT, whether they suffered a malaria or non-malaria fever

in the reporting period, whether they received treatment, and whether the fever was reported at the survey.
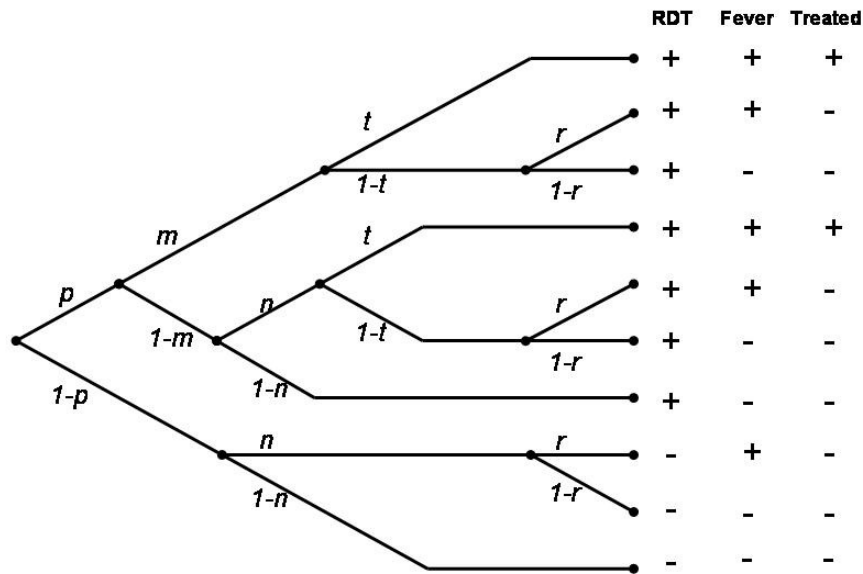
Figure 4.3 Events underlying cross-sectionally recorded outcomes

p is the RDT positivity; *m* is the probability of clinical malaria during any two week period, conditional on infection; *n* is the probability of non-malaria fever during any two week period; *t* is the probability of treatment with an antimalarial conditional on being both infected and febrile during the two-week period; and *r* is the probability that an untreated fever is reported.

Malaria fevers and non-malaria fevers are not distinguishable at the individual level in field data, so the ten branches shown in Figure 4.3 correspond to five observable categories of outcomes, with probabilities $P = \{P_1, P_2, P_3, P_4, P_5\}$ as in Table 4.2. We use a Bayesian approach to estimate the parameters *p*; *m*; *n*; *t* by fitting these probabilities to the data from Luangwa, Zambia (Table 4.2). *t* is slightly lower than $\tilde{t}$, the reported proportion of RDT positive febrile children who had been treated, because of the under-reporting of untreated fevers. Because the available data from Luangwa did not provide a precise estimate of $\tilde{t}$ we use data from the national MIS survey to estimate the distribution of this variable, and incorporate this distribution into the Bayesian model, noting that the expected value of $\tilde{t}$ is:

$$\frac{mt+(1-m)nt}{mt+(1-m)nt+m(1-t)r+(1-m)n(1-t)r}$$

The reporting probability, r, is not identifiable from the field data. By making a series of assumptions we can use the distribution of $\tilde{r}$ estimated from the malariatherapy data, as a prior distribution for r in the Bayesian analysis. This makes all the parameters in the decision-tree identifiable. In addition to assuming the same duration and frequency of bouts of fever in untreated individuals in the two datasets, we also consider treatment with anti-malarial drugs only in parasite positive individuals, assume that treatment never occurs in the absence of illness, and that respondents who fail to report illness are otherwise indistinguishable from those that report. We further assume that recall bias in treatment is negligible, but that untreated fevers are recalled with some probability, $r<1$.

To complete the specification of the Bayesian model we use uninformative ($Uniform(0,1)$) priors for p, m, n, and t. A Markov chain Monte Carlo method was then used to estimate these parameters assuming the probabilities $P = \{P_1, P_2, P_3, P_4, P_5\}$ to follow a multinomial distribution.

Estimation of numbers of days of illness

The same analyses of malaria-therapy patients, with simulation of surveys and treatments, were used to estimate the numbers of days of illness associated with each recall of fever, conditional on the proportion of recalled fevers reporting treatment, $\tilde{t}$. For this analysis, days of fever in the true malaria-therapy dataset, subsequent to the simulated treatments, were not counted in the total days of illness, thus simulating effective therapy that truncated the illness on the date of treatment. Since the MIS surveys were conducted only at one time of the year, the incidence estimates needed to be adjusted for the effect of seasonal variation in

clinical incidence. This was achieved by scaling the estimate of the clinical incidence recorded in the HMIS data during the survey period to the annual average incidence.

Table 4.2 Outcomes at survey and their probabilities

RDT positive	Reports fever	Reports treatment	Probability	Frequency in district survey	Frequency in national MIS*
No	No	No	$P_1 = (1-p)\big((1-n)+n(1-r)\big)$	355	
No	Yes	No	$P_2 = (1-p)nr$	131	
Yes	No	No	$P_3 = p\big(m(1-t)(1-r)+(1-m)\big((1-n)+n(1-t)(1-r)\big)\big)$	35	
Yes*	Yes	No	$P_4 = p\big(m(1-t)r+(1-m)\big(n(1-t)r\big)\big)$	46	686
Yes*	Yes	Yes	$P_5 = p\big(mt+(1-m)nt\big)$		353

*The report of the national MIS does not distinguish antimalarial drug used by RDT positive children from use by RDT negative children. Since only 16.7% of children with fever reported use of a diagnostic test, we assume for the present analysis that antimalarial drug use was independent of RDT positivity.

4.4. Results

Duration of bouts and recall bias

The daily prevalences of fever reported by Feikin et al [141] clearly indicate the fevers a few days prior to survey are much less likely to be recalled than those the previous day. If each recalled period with illness only entailed only day of fever, then a simple mean of the recall-day specific probabilities, $\hat{r}_{14-j}$, could be used to estimate the overall recall bias, which would be substantial. However, bouts of fever in malaria-therapy patients (as defined in Table 4.1) frequently last several days (Figure 4.4a), and if these are not treated, there may be several bouts in one recall period, so that, while the proportion of days with fever is 5.4%, only 17.8% of two week periods include one or more days of fever (Figure 4.4b).
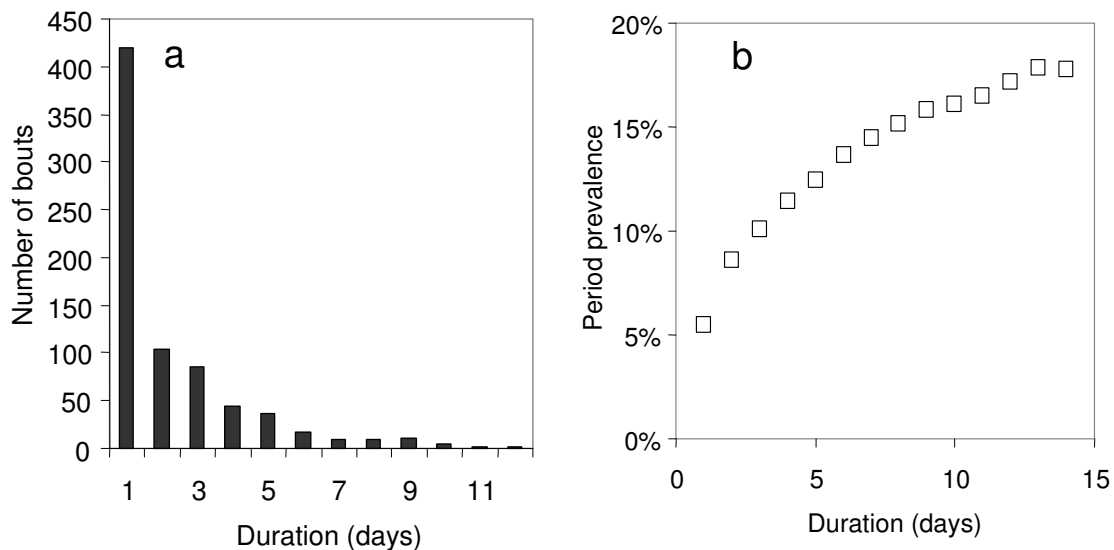
Figure 4.4 Effect of bout length on period prevalence in the malaria-therapy data

a: distribution of durations of bouts of fever in the malaria-therapy data; b: period prevalence of fever in the malaria-therapy data, as a function of the duration of the period.

Each additional day of fever adds to the probability that the illness will be recalled, leading to a recall probability that is much higher than the daily recall

probabilities reported in the Asembo study, so that when we apply the recall probabilities from the Asembo study to the patterns of fever occurrence in the malaria-therapy data, we estimate that 612 out of 755 (81%) of 14-day intervals with fever days would have been recalled, corresponding to 19% underreporting and a value of $\tilde{r}=0.81$ (Figure 4.3).We use this as the value of r in the estimation of $\tilde{t}$ (see above).

The probability that fever will be recalled is further complicated by the effects of treatment. While Figure 4.4 provides a description of the actual malaria-therapy data, simulation of treatments under the assumption that a treated fever will always be recalled increases the simulated probability that morbidity will be recalled, while decreasing the corresponding number of days of fever (Figure 4.5).
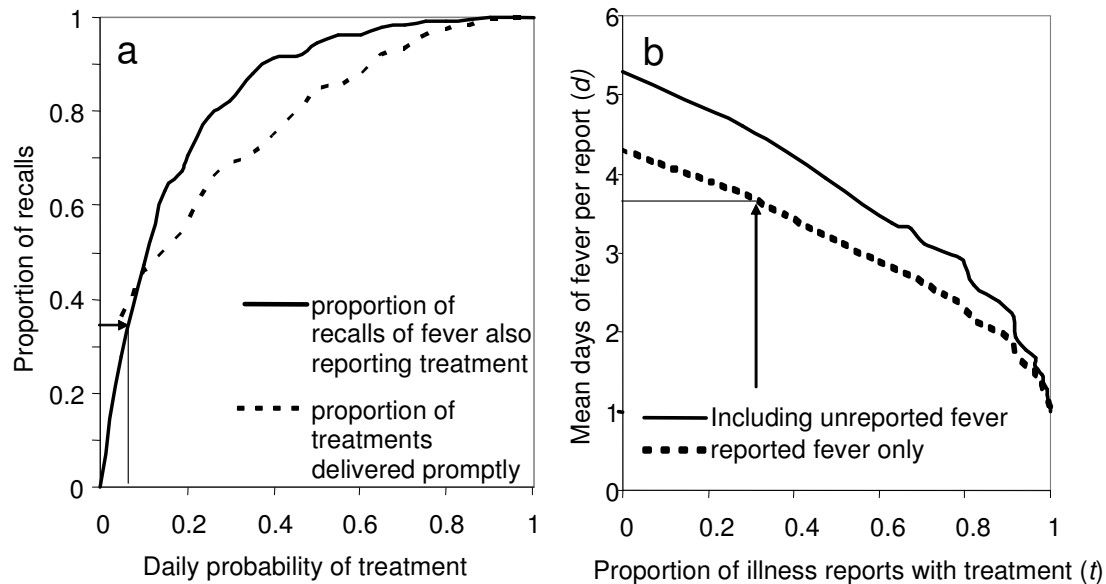
Figure 4.5 Proportion of recalls of fever also reporting treatment

The plots were constructed by simulating effective treatments applied to malaria therapy data (see Methods) with 14 day morbidity recalls, with recall bias based on the Asembo data. The arrows correspond to the observed proportion of morbidity recalls reporting treatment in the Zambian MIS survey.

The proportion of recalls mentioning treatment has a non-linear relationship with the daily probability of treatment, because recurrent fevers provide multiple

opportunities to treat, so even a modest rate of prompt treatment will result in a very high proportion of recalled fevers being treated. The 34% of recalls in the Zambian MIS data that reported treatment (Table 4.3) thus corresponds to only about 7% treatment per day of fever (Figure 4.5a). The proportion of treatments delivered promptly on the same day is also not the same as the daily probability of treatment because prompt treatment (as defined in the MIS questionnaire) may occur on either the same day, or the day after onset of fever. A 7% daily probability that a fever will be treated consequently corresponds to a probability almost twice as high as this that treatment will occur in the first two days, which is comparable with, though somewhat lower than, the 18.7% of fever reports that indicated receipt of prompt anti-malarial treatment in the survey, t_e.

Numbers of days of fever associated with each recall

As the treatment rate increases, the number of fever days corresponding to each report decreases (Figure 4.5b). In the absence of treatment, the 755 two-week periods of malaria-therapy with at least one day of fever averaged 4.3 days of fever each. Allowing for the estimate of 19% underreporting of two-week periods with untreated fever in the model of ascertainment, each report of fever corresponds to 5.3 days of fever in this model. As treatment rates increase, the number of days of fever corresponding to each report decrease, since an increasing proportion is averted by the treatments, until in the limiting case of 100% prompt and effective treatment, each report corresponds to exactly one day with fever (Figure 4.5b).

Estimation of total burden of uncomplicated malaria

Table 4.2 gives the numbers of respondents in the Luangwa district malariological survey in each of the four classes categorized by RDT positivity and reports of fevers. The recalled treatment rate by RDT positivity is estimated from the

national level data (right hand column of Table 4.2). The Bayesian estimation

procedure provides interval estimates for p, m, and n, conditional on the

distribution for $\tilde{r}$ assembled from the Asembo and malaria-therapy data (Table

4.3).

Table 4.3 Parameter estimates and their origins

	Name	Source of estimate	Estimate (95% credible interval)*
p	Period prevalence of malaria infection	Bayesian model	0.14 (0.12, 0.17)
m	Probability of malaria fever conditional on infection	Bayesian model	0.48 (0.29, 0.67)
pm	Period prevalence of malaria fever	Bayesian model	0.07 (0.04, 0.10)
n	Period prevalence of non-malaria fever	Bayesian model	0.33 (0.29, 0.39)
$\tilde{r}$	Probability that fever is recalled	Asembo and malaria therapy data	0.81 (0.78, 0.84)
t	Proportion of periods with malaria fever that were treated	Bayesian model	0.29 (0.27, 0.32)
$\tilde{t}$	Proportion of malaria positive recalls where treatment was received	MIS data	0.340 (0.31, 0.37)
t_0	Daily probability of treatment	Asembo and malaria therapy data and MIS data	0.07
t_e	Probability of prompt and effective treatment	MIS data	0.187
d	Days of malaria fever during recall period among those who report malaria fever	Read from Figure 4.5b as a function of t	3.7
$\bar{I}$	Annual average incidence of confirmed clinical malaria at health facility (cases per month)	HMIS data from Luangwa District (Figure 4.6)	102.3
I	Incidence of confirmed clinical malaria at health facility (cases per month) during period of MIS survey	HMIS data from Luangwa District (Figure 4.6)	258.0
b	Days of malaria fever per person-year at risk	$b = \dfrac{365}{14} dpm \dfrac{\bar{I}}{I}$	2.6 (1.5, 3.8)

*Bayesian credible intervals for data derived quantities were computed assuming *Uniform*(0,1) priors for proportions. For derived quantities, the credible intervals were computed by sampling from the joint posterior densities of the individual parameters. Where no interval estimates are shown, fixed values were included in the calculations, so the uncertainty in these variables is not included in the final estimate.

Of the 14% of children with evidence of malaria parasites, half of them (7%) are estimated to have suffered malaria fevers during the interval. Only 29% of children with fever were treated at some point in the interval. This is lower (because of recall bias in the fever data) than the observed proportion of recalls mentioning treatment (34%) among those who mentioned fevers.

Figure 4.6 Average number of confirmed cases by month in Luangwa District Zambia 2009-2010
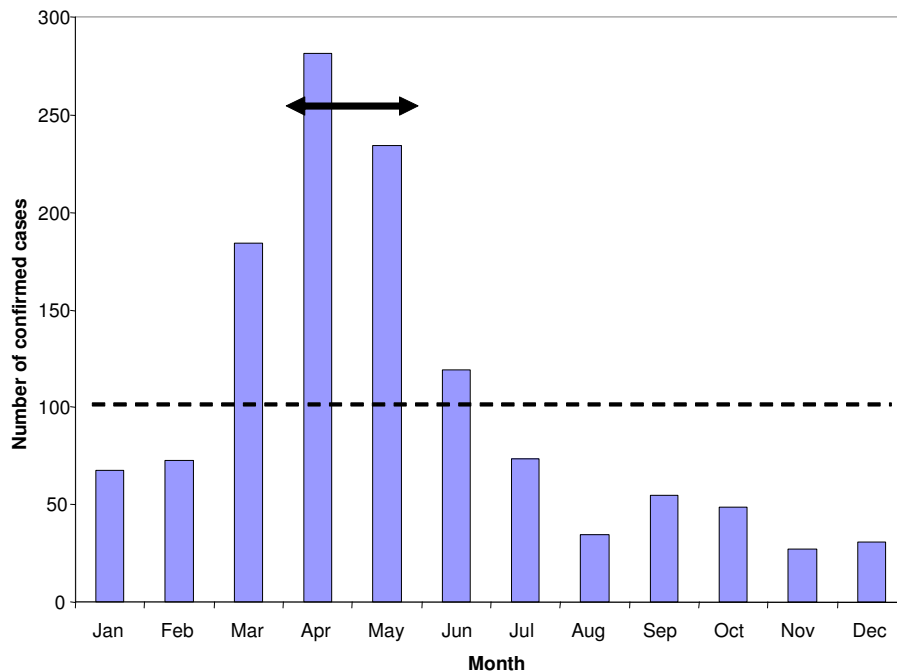
The dashed line corresponds to the annual average incidence and the double headed arrow to the survey period and the corresponding average incidence.

Figure 4.6 shows the seasonality in confirmed malaria cases at all health facilities in Luangwa district, Zambia. The MIS surveys in Luangwa were typically conducted during peak transmission season (April-May) and thus the annual burden estimate needs to be scaled by the ratio of malaria fever incidence over the whole year, relative to the incidence during this period (Table 4.3). It is assumed that this district is representative in terms of the degree of seasonality, and the targeting of the MIS surveys to the peak season of incidence. This provides an

estimate of the average days of malaria fever per person-year in Zambian children of 2.6 (1.5, 3.8) days of malarial fever per person at risk per year.

This estimate seem plausible, though the credible intervals (which capture most of the uncertainties in the data) do not capture the full level of uncertainty implied by the assumption that patterns of fever in Zambian children may be similar to those in malaria-therapy patients, or that recall patterns in Kenya can be applied to Zambia.

4.5. Discussion

Definitions and methods for estimating rates of uncomplicated malaria morbidity depend on the purposes for which the information is needed. Thus, WHO estimates of malaria burden refer in principle to the amount of disease that is eligible for anti-malarial treatment[4]. This is different from the level of transmission (which is addressed in a companion paper)[5], and from the amount of disease that would be averted by eradicating the infection. The economic burden of the disease includes the costs of diagnosing malaria negative patients, of preventive measures in visitors, and of investments lost because of concerns about the disease. These considerations lead to the conclusion that proliferation of measures is unavoidable. This paper focuses specifically on measures of health burden, defined in terms of the experience of the sick individual.

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[4] Under this definition, all febrile illness with incidental parasitaemia should be included in the burden calculations. This, however, leads to double-counting in overall disease burden statistics, since much of this illness should also be recorded as respiratory infections

[5] A variety of methods are being developed for measuring transmission, in particular serological approaches [145] and model-based approaches combining parasitological and clinical data [146]. MIS provide data relevant to many of these approaches and may well prove key to measuring transmission as well as disease burden, but the two objectives should be clearly distinguished.

Unfortunately, current practice in measuring burden in this sense is not satisfactory. From the clinical perspective, it is good enough to identify an "episode" or "case" when an individual presents to a health facility with febrile illness and detectable parasitaemia. This is also useful for commodity forecasting and managing clinical workloads. It may also be suitable for use in intervention trials where the goal is simply to detect a difference between two or more arms. It is suboptimal as a measure of health burden, because it ignores what is going on in the infected people who are not reporting to the health facility or reporting late. When such data are used for managing resource allocation between interventions they can be seriously misleading because: (i) they can give a quite false idea of the importance of malaria relative to other illnesses, and (ii) they substantially understate the impact on health burden of improvements in case management practice. Strikingly, the roll-out of ACT as first-line therapy across Africa barely impacts official estimates of burden, which show only a modest improvement over time, driven by scaling up of vector control.

The proxy indicators generally used to indicate trends over time in disease rates can be fundamentally misleading. The Global Fund to fight AIDS, TB and Malaria (GFATM), in its Monitoring and Evaluation (M&E) toolkit for countries, recommends parasite prevalence and anaemia prevalence as morbidity indicators for national malaria control programs [147]. These indicators are frequently collected in Malaria Indicator Surveys (MIS) and a recent study from Zambia used them as evidence of health impact of interventions [148]. However, they are not direct measures of malaria morbidity, they are multifactorial [149] and they may change at different rates from clinical malaria incidence [150].

Reported histories of fever in the previous two weeks collected through community-based surveys provide a more direct measure of morbidity, and at least in some situations have been validated as comparative morbidity measures [151].

However, to obtain health burden estimates, corrections must be made for the benefits of treatment on duration of illness, for recall bias, and for diagnostic error. Correction for levels of incidental parasitaemia is critically important when the malaria situation is changing, since the diagnostic performance depends on the level of asymptomatic parasitaemia and may also change over time.

In this paper, we have incorporated all these considerations into an approach for estimating the number of days of illness due to malaria as a percentage of all days of observation and applied this to a specific set of surveys in Zambia. The approach uses outcomes assessed in MIS surveys, recall data from Kenya, and data on the natural history of malaria fever from malaria-therapy patients. Clearly the appropriateness of combining these datasets can be questioned, especially the assumption that the patterns of fever in African children parallel those in malaria therapy patients. However the approach does lead to parameter estimates (Table 4.3) with at least face validity, and unfortunately these are the only datasets we have available that provide all this information. Estimates of burden, based on this approach, would be a substantial improvement on current practice in cost-effectiveness analysis. The Appendix discusses the implications of this for simulation modeling of case management, and how this relates to previous practice.

Some of the data limitations could be addressed by improvements in survey design. First, cross-sectional surveys of malaria illness and treatment-seeking need to include questions on history of fever and measure parasitaemia in all age groups, not just children under five. As malaria control efforts are scaled-up and transmission falls, malaria illness shifts into older age groups [28] due to slower acquisition of immunity. Burden will thus fall harder on older children and adults, and monitoring systems need to allow for this reality in order to capture the full burden of malaria illness. Second, there is a need for more data like those from

Asembo to estimate recall bias. Ideally, 24-hour recalls would be used but this would reduce the size of available databases. Finally, the current practice of carrying out MIS surveys at approximately the same time across whole countries means that there are limited data available on seasonality in either parasitological or clinical indices. Data for each period of the year are essential for unbiased estimates of annual burden, and could in principle be obtained by carrying out rolling surveys visiting different clusters in a random order throughout the year.

4.6. Conclusion

Measurement of malaria burden is fraught with complexity mainly due to the natural history of the disease and to sub-optimal health facility utilization which means that treatment is often delayed or not sought. Definitions of malaria episodes are either ambiguous or difficult to use because we rarely have good information about patterns of infection, recurrence of fever or asymptomatic infection.

This paper suggests that the point prevalence of malaria attributable disease, or equivalently, the days of malaria fever in unit time, should be used as a measure of burden. This avoids the problem of defining a malaria episode, and we contend that it can in principle be estimated in an unbiased way from data that is already collected in national MIS combined with data on seasonality. Estimates of recall bias and duration of bouts that we use in this paper could be applied more generally.

It is hoped that this work will stimulate a dialogue on how to improve measurement of the burden of uncomplicated malaria, for the benefit of all those who are suffering from or are involved in the fight against the disease.

4.7. Acknowledgements

4.8. Appendix: Burden of uncomplicated malaria in simulation models

Studies of likely long-term impacts and cost-effectiveness of novel intervention strategies are often best carried out by simulation modeling. Measures of disease burden in such studies need to be aligned with the data that can be obtained from field studies, and should use the same terminology and definitions. Simulation modeling disciplines the practitioner into using explicit definitions.

We previously developed individual-based stochastic simulation models of the biology and epidemiology of *P. falciparum* malaria [39] and applied these to estimating the cost-effectiveness of scaling up case management [41]. These models went beyond previous static models (such as those published by the Global Forum for Health Research [92]) by including the effect of treatment in truncating an infection and the dynamic effects of treatment on transmission. However in modeling scaling up effective case management the model of Tediosi *et al* [41] assumed a constant duration of illness for episodes of clinical malaria. This was taken from the Global Burden of Disease (GBD) study [152] without critically evaluating the GBD meaning of a malaria episode.

A further criticism of the Tediosi *et al* [41] case-management model was that assumed treatment rates were very low in relation to clinical incidence. The clinical incidence rates were fitted to data from the villages of Ndiop and Dielmo in Senegal [59;153]. These data were from daily surveillance carried out with the explicit intention of detecting and treating every clinical malaria attack, and reported higher rates than other studies.

The Tediosi *et al* [41] model is an individual-based discrete time representation of the dynamics of malaria using five-day timesteps. Bouts of illness (see Table 1)

are represented by classifying each time step according to whether it included any days of malaria fever. In publications based on these models [41;63;64], numbers of episodes are calculated by grouping together bouts occurring within 30 days of each other in the same individual, following an approach used in some field studies [154]. This period can be justified by reference to prophylactic periods associated with treatment and the duration of standard *in vivo* tests for drug resistance. It can be thought of as the period over which the patient or health care system considers the bouts of illness to be part of the same illness (Table 4.1).

Treatment coverage in such models, defined as the proportion of sick intervals where treatment is applied, maps non-linearly onto the data available from 14-day recalls in MIS, MICS, or DHS surveys. This is because if treatment coverage is perfect and treatment completely effective, each episode is treated, and the infection causing it removed, during the first bout. There is therefore one bout per episode. As treatment coverage decreases, the number of bouts per episode increases. The amount by which bouts and episodes diverge across settings with different treatment coverage will depend on how many bouts each new infection is expected to generate in the absence of treatment and on their severity.

Coverage values for input to the models can however be inferred from the mapping of model predictions of 14 day treatment rates as a function of the time-step specific treatment rate. The relationship depends on the details of the epidemiological model. Figure 4.7 provides calibration results for a family of 14 different models with 5-day time steps, all variants on the original model used by Tediosi *et al* [41], and applied in recent simulations of the likely impact of malaria vaccines on clinical incidence [70] .

That can be used to estimate the amount of under-reporting of bouts if surveys are undertaken with different recall periods. For example, to estimate this with a

fifteen-day recall period (approximating , we set the health system memory to 15 days and surveyed the population every 15 days, recording the number of treatments given and the number of episodes). Figure 4.7 shows that in our model, the probability of seeking treatment in any 5 day period is lower than the corresponding 15-day probability, because individuals can be sick multiple times in a 15-day period, and some fevers go untreated. Figure 4.7 also shows how this relationship is model-dependent.

5- vs 15-day treatment-seeking probabilities
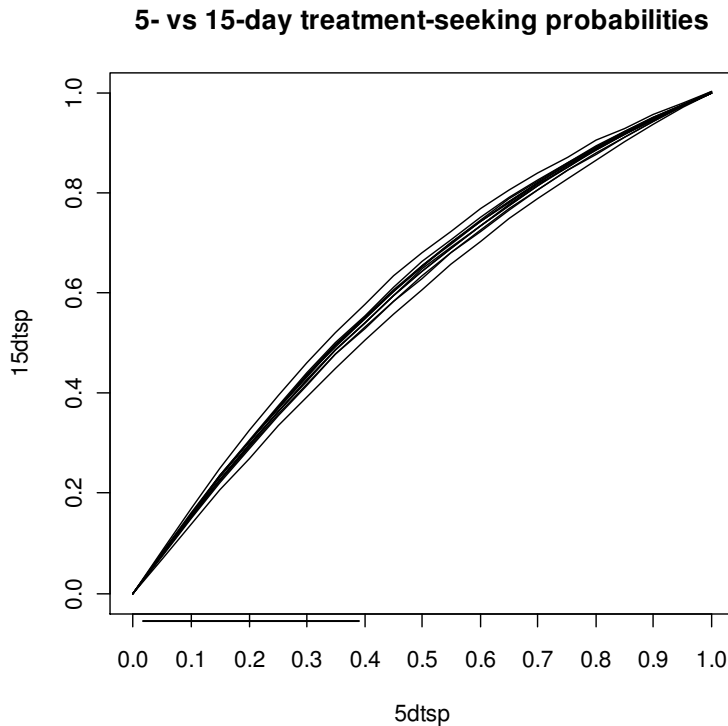
Figure 4.7 Five- vs 15-day treatment-seeking probabilities

Simulation of a setting where EIR=20, with a population size=2000. Lines are sub-model medians.

We used an ensemble of 1 4 model variants. The ensemble consists of a base model, used in previous publications [63;64], and thirteen variants on that model, with each one representing a different set of assumptions about malaria transmission and epidemiology. Our ensemble of stochastic simulation models of malaria epidemiology incorporates different assumptions about decay of immunity and about heterogeneities in exposure, co-morbidity and access to treatment [70].

R0674 (uncorrelated heterogeneities in access to treatment and susceptibility to comorbidity) and *R0678* (heterogeneity in access to treatment) are not shown since at high treatment coverage levels, there is a limit to the amount of heterogeneity possible. Above about 55%, heterogeneity in treatment-seeking starts to decrease, since the upper half cannot go above 100% probability of accessing treatment. The ratio of upper to lower treatment-seeking probability thus starts to change. Overall 15-day treatment-seeking probabilities of above that level cannot be simulated with the *R0674* and *R0678* sub-models.

5. Development of a *P. falciparum* malaria case management model integrated with pharmacodynamics

5.1. Background

In 2006, Smith and colleagues presented individual-based stochastic simulation models of the biology and epidemiology of *P. falciparum* malaria, which were developed to study long-term impacts and cost-effectiveness of intervention strategies [40]. Models of health system effectiveness in intervention delivery are an important part of the simulation of any preventive and curative intervention, as the prevailing health system modifies the disease burden and thus the gains expected from an intervention. Therefore, as part of this project, a decision tree model for the case management of malaria was developed, based on data from Tanzania [41]. This model was novel for its consideration of the effect of treatment on malaria transmission. In addition to averting severe morbidity and mortality, treatment reduced burden by reducing recurrent clinical attacks due to one infection and by reducing infectivity of the population. In simulations using this model, the reduced burden on the health system resulting from preventive interventions and case management were considered.

The Tediosi *et al* [41] model for case management of uncomplicated malaria consisted of three parameters – treatment-seeking (from the formal sector, self-treatment, or no treatment-seeking), patient compliance to the drug regimen, and treatment cure rate in the presence and absence of compliance. An uncomplicated malaria case that was treated in the last 30 days was assumed to either seek treatment in the formal sector or not seek treatment. The model for severe malaria assumed that it could either be treated as an in-patient or not treated, and there

were three possible outcomes – death, full recovery, or recovery with neurological sequelae. In-patient case fatality rates were taken from a study in Tanzania while corresponding community case fatality rates were estimated. Algorithms were also developed to estimate the cost of case management [41].

This model was adequate for predictions of the cost-effectiveness of other interventions in the presence of different levels of treatment coverage. However, it did not allow simulation of the multiple factors which determine the treatments given in real health systems. In particular, alternatives to the public sector or self-medication as sources of treatment were not considered, and neither was the response to diagnostic tests, imperfect provider compliance with treatment guidelines, or sub-optimal drug quality. The model also failed to consider the impact of malaria case management on management of non-malarial febrile disease. Increased use of confirmatory diagnosis offers the potential to improve treatment and therefore reduce morbidity and mortality from other causes, and should be considered in estimations of the cost-effectiveness of case management interventions. Second, there was no drug model, so clinical and parasitological outcomes were predicted within the case management model, and treatment either completely cleared parasites or had no effect. In reality, drug treatment should act to reduce parasite densities, and the outcome is not dichotomous. Drug treatment may cure clinical symptoms but not eliminate parasites, with implications for recurrences of illness, infectivity, and development of drug resistance; this could not be simulated with the previous model.

There was agreement that the Tediosi *et al* model needed to be revised to incorporate improved simulations of the contribution of the informal sector, diagnosis, referral and drug action. This motivated the development of a case management model integrated with a model for malaria pharmacodynamics.

Alongside development of the model, potential interventions to be simulated were identified (see Table 5.1). Criteria for selecting interventions were primarily 1) potentially high impact and 2) broad applicability. Intermittive preventive treatment in infants, children and pregnant women was explored separately.

Table 5.1 Interventions to simulate using the case management model integrated with pharmacodynamics

(Source: A. Schapira, 2009)

Intervention	Strategic variants		Secondary questions
	Technical	**Operational including targeting**	
		CHEMOTHERAPY	
Case management uncomplicated: treatment	Schizonticidal ▪ ACTs ▪ Mono-artemisinins ▪ SP *P.falciparum* gametocytocidal (primaquine)	Integrated Management of Childhood Illness Differentiation by risk group, e.g.: <5 Public ➢Facility-based free or paid ➢Community (home) -based) Formal private paid/SM ➢Franchises Informal private paid/SM ➢Improved drug vendors Global subsidy	Secondary questions: Sequential ACTs vs multiple 1st line ACTs Higher than standard dose of drugs like chloroquine AIDS interactions Pregnancy specific protocols
Case management uncomplicated: diagnosis	Presumptive (clinical) Microscopy *P.falciparum* RDTs	Differentiation according to risk group, e.g. presumptive diagnosis in <5s and confirmatory in others in high transmission settings	
Active case detection (screening fever cases)	Schizonticidal ▪ ACTs *P.falciparum* gametocytocidal	For elimination In epidemic To compensate case management	
Mass screening		For elimination	
Mass treatment		In epidemics	
Case management severe malaria	Artemisinin suppositories as stand-by or complete Parenteral artemisinin or quinine	Children/All Community/facility-based standby/ Only hospital-based parenteral	

5.2. Overview of new simulator and fitting to data

As previously, the new case management model works in conjunction with other model components to predict impact and cost-effectiveness of interventions. Briefly, there is a simulated population of humans who are updated at each time step via model components representing new infections, parasite densities, acquired immunity, uncomplicated and severe episodes, direct and indirect malaria mortality, infectiousness to mosquitoes, and case management. Simulated immunity to asexual parasites, derived from cumulative exposure to both inoculations and parasite densities and maternal immunity, acts mainly by controlling parasite densities [58]. The probability of a clinical attack of malaria depends on the current parasite density and a pyrogenic threshold [59]. Severe malaria comprises two categories of episodes: those that occur as a result of overwhelming parasite densities, and those that arise when an uncomplicated malaria episode coincides with non-malaria co-morbidity. Mortality can be either direct (following severe malaria) or indirect (uncomplicated malaria in conjunction with co-morbidity, or during the neonatal period as a result of maternal infection) [155]. The models which simulate the clinical consequences of malaria infection are collectively termed "pathogenesis" model.

While the previous models used five-day time steps, the new simulator works on a one-day time step. The previous within-host model, which used a statistical description of parasite densities, was replaced with a mass action model of *P. falciparum* asexual parasite densities fitted to malariatherapy data [156]. The published model used a discrete time-step of two days. Our implementation adapted this to a one-day time-step by interpolating the parasite multiplication rate. Drug effects and natural immune effects of previous exposure were represented by further modifying the parasite multiplication rates. The models for

pharmacodynamics [157] and for case management were also implemented on a one-day time step. The ability to predict parasite densities each day allows a finer-grained simulation of the action of drug treatment that people receive, since potent antimalarial drugs generally act to significantly reduce parasite densities within hours of being administered. It also allows a more realistic simulation of people's response to illness and treatment.

An overview of the new simulator and its components is presented in Figure 5.1. The pathogenesis models determine if an individual becomes sick, and whether the sickness is uncomplicated or severe. The case management model, which comprises the clinical scheduler and clinical decisions modules, determines whether, when and how the sickness is treated and how long it lasts. The case management model works together with the models for drug action, severe outcomes, and within-host dynamics to predict clinical and parasitological outcomes. The other components are as described in previous publications [40], with the addition of a model for the dynamics of malaria in mosquitoes [61]. The code for these models can be downloaded on openmalaria (http://code.google.com/p/openmalaria/).
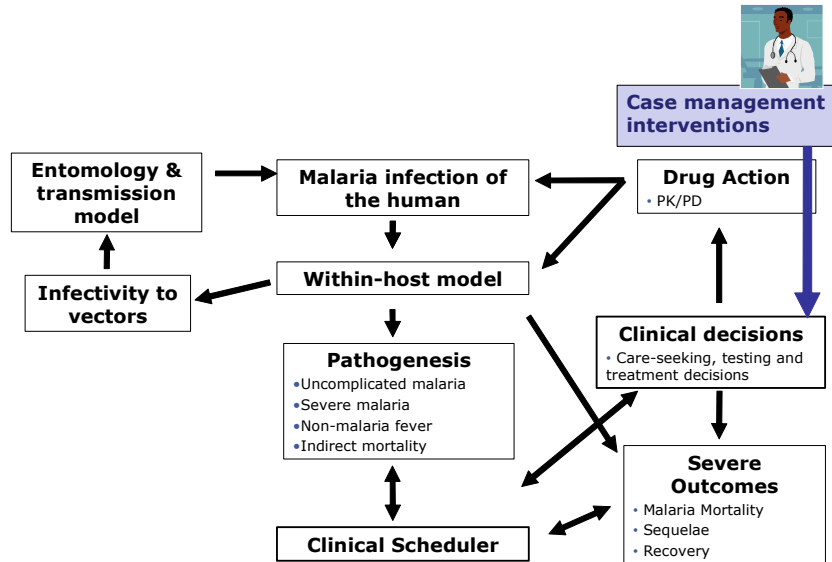
Figure 5.1 Module overview of new simulator

The parameter values for each of the components of the one-day time step model were estimated by fitting to data from a total of 61 malaria field studies of different aspects of malaria epidemiology [39]. However, efforts so far to validate this model by comparing results from the five-day and the one-day models lead to the conclusion that the predictions of the force of infection model for incidence in older age groups were far too high. The force of infection model was thus replaced with an alternative [158] and the whole model is currently being re-fitted.

5.3. Presentation of case management model

Each day, the within-host model generates a parasite density, *Y(t),* which is a function of the parasite density at the previous time point and a drug factor, if relevant. For each individual, the pathogenesis model is then called to determine the individual's new state. Given *Y(t)* and the patient's history, the pathogenesis model calculates the individual's pyrogenic threshold and the probability that an

event occurs [59] and the event type [155]. The pathogenesis model also generates indirect deaths and non-malarial fevers according to age-specific functions.

To avoid confusion of terms while adapting the clinical model for a one-day time step, we developed the following notation (see Chapter 4):

- Bout: a "bout of sickness" describes a fever, malarial or otherwise, or period of severe illness, usually lasting no more than five days. This is the main unit of interest for the purposes of the case management model.
- Episode: the health-system's reporting unit; each bout is either considered the start of a new episode, or, if occurring within the health system memory (currently 30 days) of the start of the last episode, considered part of that episode.

Thus, at least in low transmission settings, an episode should roughly correspond to one malaria infection (which can cause multiple bouts). An episode's severity is considered to be that of its worst bout.

Each individual is assigned a clinical state which lasts until the next event. At any given time point, there are five possible states: healthy (including asymptomatic infections), uncomplicated malarial fever with or without a recent history of treatment, severe malaria, and dead. The corresponding events are start of an uncomplicated malarial fever from a healthy state, start of severe malaria (from healthy or uncomplicated malaria states), direct death (from a severe malaria state) and recovery (from uncomplicated malaria or severe malaria states). Transitions from severe malaria to uncomplicated fever, or from uncomplicated malaria to direct death, are not allowed. If the non-malarial fever option is enabled, an additional state of uncomplicated non-malarial fever is also possible.

Since state changes are not possible at every time-step, the clinical scheduler component of the case management model (see Figure 5.2) decides and tracks the clinical state of the individual and allocates individuals to the clinical decision and severe outcomes models, based on the state as determined by the pathogenesis model and recent illness and treatment history.
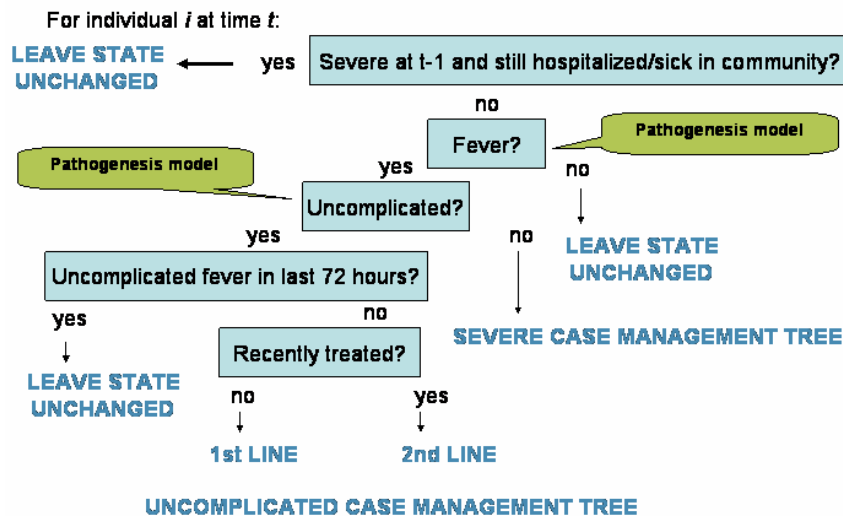
Figure 5.2 Clinical scheduler module

A *bout* commences with a morbidity *event* and concludes with a recovery or mortality *event* (stressing terminology used). When the bout first occurs, the clinical scheduler calls the clinical decision model. At the start of an uncomplicated fever, a potential treatment-seeking delay is modeled. The bout duration of uncomplicated malarial fevers and non-malarial fevers is fixed at three days from the time of seeking treatment, or from the start of illness (if treatment is not sought). If an individual delays seeking treatment for one or two days, bout duration becomes four or five days, respectively. During this time, the clinical scheduler maintains the individual in the same state, unless the pathogenesis models indicate that the illness has progressed to severe or the individual has died

from a non-malarial illness. After this time period, it is assumed that parasite densities have been reduced by treatment or immunity, or that the individual has recovered from the non-malarial illness, and the individual is returned to the healthy state.

While healthy or during an uncomplicated bout, a severe bout may commence. In this case, the clinical scheduler calls the clinical decision model, cancels any recent drug treatment, and allocates the individual to the severe case management decision tree. The severe bout is fixed at six days long when the patient enters hospital immediately or not at all; a one-day delay to hospital entry is also considered possible which increases the bout length to seven days.

Mortality due to malaria is possible during severe malaria bouts, and considered as a stochastic function of the proportional reduction in parasite density each day of the case (Hardy *et al,* unpublished). Each day during the severe illness, the clinical scheduler calls the severe outcomes model, which applies the appropriate case fatality rate to determine whether or not the individual died that day. For delayed hospital entry, the community death rate takes effect on the first day. Mortality events are always modeled as happening at the end of the associated severe episode.

The clinical decision component of the model consists of stochastic decision trees concerned with determining the treatments given (including the actual schedule followed and dose sizes taken), along with whether the patient was hospitalized and whether treatment or hospitalization delays occurred. The decision trees also provide information necessary for calculating costs, derived from treatment-seeking behaviour, drugs administered, and diagnostic tests used.

The decision tree for uncomplicated fever is shown in Figure 5.3. The simulated individual has a fixed chance of seeking treatment immediately, or, if yet to do so, on the following two days. Delays to treatment-seeking are modeled by starting the drug curve (of parasite density versus time) on the second or third day after the occurrence of the episode. If treatment is not sought on all three occasions, the individual reverts to the healthy state.
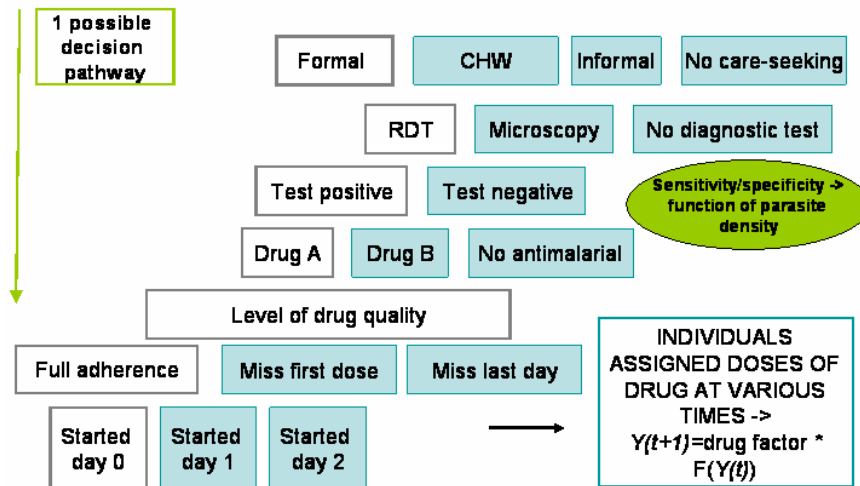
Figure 5.3 Uncomplicated fever decision tree

The first decision branch is whether and where to seek care. In health facilities, patients can be tested with a rapid diagnostic test, by microscopy, or not be tested at all; at community health workers, we assume that only RDTs are possible, which may or may not be used. Each test has a sensitivity and specificity which are functions of parasite density. To model this, we looked for a function to relate parasite densities to the probability of a positive outcome. Methods for doing so are described below.

Based on the results of the test, the simulated individual can receive one of several antimalarial drug regimens, or no antimalarial treatment. Providers may respond to a given test result by prescribing or not prescribing antimalarials. The drugs can be given at various levels of quality. We also consider three possible adherence

options: good adherence, missing the first dose of the drug (common when patients vomit upon taking the drug), or missing the last day (as when treatment is stopped before the end of the recommended regimen). The individual is deemed to recover three days from the time of treatment-seeking (or, from the onset of illness, if treatment is not sought).

If a bout of uncomplicated malarial fever occurs in an individual who has been treated with antimalarials within the last 14 days, it is assumed this would be considered as a treatment failure [13] which should be treated with the second-line drug. The decision tree is identical but the values of treatment-seeking, quality of care and compliance parameters are modified.

In the case of severe malaria, the path through the case management decision tree is determined at the start of the episode. The tree may determine that a one-day travel-time delay occurs, in which case in-hospital decisions are not determined until the next day.

The decision tree for severe malaria is shown in Figure 5.4. Individuals can initially either seek treatment from a lower-level source, in hospital, or not at all. There is a possibility of pre-referral treatment with referral to hospital on the same or next day; pre-referral treatment reduces parasite densities on the first day of illness. Diagnostic testing is considered for costing purposes but is assumed not to affect treatment received. The treatment schedule is found and applied in the same way as with an uncomplicated case. Entry to hospital temporarily removes the individual from the transmission cycle.
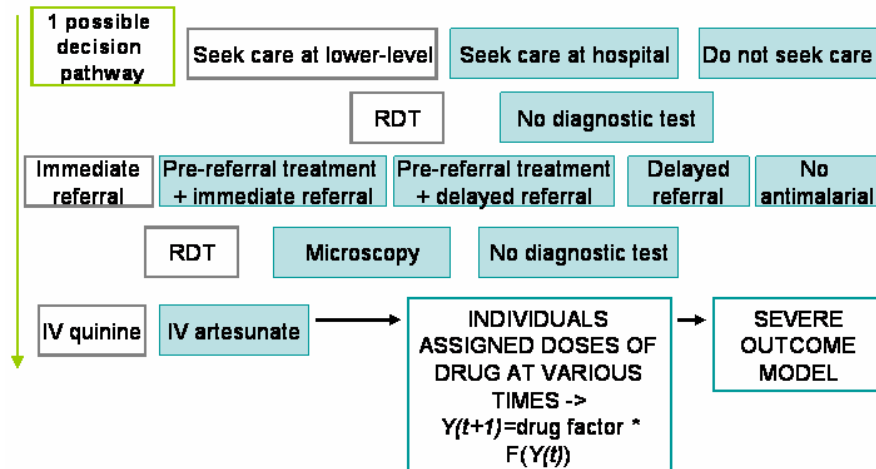
Figure 5.4 Severe malaria decision tree

In both severe and uncomplicated cases, the relevant case management decision tree determines treatments given. For each drug and age group, the standard regimen is specified– dose size (in milligrams), and times given (in hours), and then modified, based on the decision tree outputs, by reduced drug quality, adherence and delays to taking treatment.

The treatment schedule is applied to the individual as a list of pending medications that are given over the next time points. Any previously pending medications are cancelled when new treatments are prescribed, and drugs are only costed when taken, so that if an individual progresses to severe after receiving treatments for an uncomplicated case, remained unconsumed medications are not costed.

Parasite diagnostics

Data from [159] were used to model the outcome of RDTs for *P. falciparum*, which show the percent sensitivity (and the 95% confidence interval) found for the RDT BinaxNOW Malaria in a rigorous field trial, at different levels of parasitaemia. This assay is based on detection of the antigens HRP-2 for *P.*

falciparum and aldolase for generic *Plasmodium*. The sensitivities listed for *P. falciparum* were associated with the mid-points of the parasite density ranges listed, and one minus the specificity for a density of 0 parasites.

To model microscopy, the data shown in Table 5.2 were assumed. This was sourced from expert opinion (personal communication, A. Schapira), backed by the observation that microscopy diagnostic errors are noted more commonly for low-density parasitemias of 10 to 100 parasites/µl [160].

Table 5.2 Sensitivity and specificity of microscopy (P.falciparum) by parasite density

(Source: A. Schapira, 2009)

Parasite density (parasites / µl)	Sensitivity of microscopy (*P. falciparum*)
>100	90%
0–100	75%
Specificity	75%

A sigmoidal function was found to be a good match for this data. Since the probability of obtaining a positive outcome when testing a sample with no parasites is non-zero, the sigmoidal had to be scaled. With a parasite density of Y, probability of a positive outcome with zero parasites α, and parameter β, this gives us the probability of a positive test outcome as a function of parasite density:

$$f(Y) = (1-\alpha) + \alpha \frac{Y}{Y+\beta}$$

and thus the diagnostic test's output can be modelled as Bernoulli (f(Y)).

The parameters in Table 5.3 were used to model RDT and microscopy diagnostics.

Table 5.3 Parameters used to model diagnostic sensitivity and specificity

Parameter	Description	RDT	Microscopy
α	Specificity	0.942	0.75
β	density at which sensitivity is half given $\alpha = 1$	50	

5.4. Model of incidence and management of non-malarial fevers

Clinical decisions on management of fevers affect health outcomes and costs for both malarial and non-malarial illnesses. Correct targeting of antimalarials to malarial fevers and antibiotics to those non-malarial fevers (NMF) that need them is desirable. The use of malaria diagnostic tests to confirm the presence or absence of malaria parasites could help to achieve this; where fever is often treated presumptively as malaria, they might be expected to result in reduced mortality from non-malarial illnesses, as well as lowering malaria treatment costs and slowing the spread of antimalarial drug resistance. This is because a negative malaria diagnostic test result would likely prompt consideration and treatment of alternative causes of fever, while a positive test would increase the certainty that the symptoms are indeed due to malaria. These benefits and costs should be included when evaluating the cost-effectiveness of varying levels of parasitological diagnosis. We therefore present a model for the management and clinical outcomes of NMF.

Non-malarial fever (NMF) incidence and severity

Table 5.4 Estimated incidence of non-malarial fevers

(Source: A. Schapira, 2009)

Age-group	All fever pppy		RR	Estimated non-malarial fevers pppy
0-11 mo.	9.1	9.66	1	6.08
12-59 mos	9.8			
5-9 vrs.	6.06	6.06	0.63	3.81
10-14 yrs.	4.16	4.16	0.43	2.62
15-59 yrs.	6.43	6.43	0.67	4.05
60 yrs +	8.6	8.6	0.89	5.41

To model age-based incidence of non-malarial fever, the data shown in Table 5.4 were used. In order to transform this into a continuous function for frequency given age, we interpolated linearly on the data-points generated as follows:

- For each age group, we added a data point centred on the age axis with frequency as given in the age group.
- We added data points at ages 0 and infinity, taking frequency from that of the youngest and oldest age groups.

The incidence of NMF was modeled as an interpolated linear function. NMFs can only start at a given time point if it has been determined that a malarial fever is not starting at that time point. If both a NMF and a malarial fever occur within the health system memory, only the malaria episode is reported.

Each NMF has a certain age-based probability of needing antibiotic treatment, which was assumed to be independent of parasitological status.

Model for the probability of antibiotic administration

We assumed that each individual has a probability of antibiotic administration, $P(AB)$, which varies according to treatment-seeking location. For NMF seeking treatment in a health facility, $P(AB)$ is a function of the average probability of being prescribed an antibiotic in the absence of a malaria test; whether the individual had a negative or a positive malaria diagnostic test result; and whether the individual needs or does not need an antibiotic (this latter captures signs and symptoms that would indicate to a health worker need for antibiotics, in the absence of knowledge of malaria parasitological status).

Thus:

$$\text{logit}(P(AB)) = \beta_0 + \beta_1 * I(MD-) + \beta_2 * I(MD+) + \beta_3 * (need)$$

and

$$\beta_0 = \text{logit}(P_0) - \beta_3 * P(N_n)$$

where β_0 is the log odds of receiving an antibiotic in the absence of need and of a malaria test; β_1 and β_2 are the effect of a negative and positive test, respectively, on the log odds of receiving an antibiotic; and β_3 is the effect of needing an antibiotic on the log odds of receiving it. $I(X)$ is 1 when event X is true and 0 otherwise; event "need" is the event that death may occur without treatment, and "MD-" and "MD+" are the events that a malaria parasite diagnostic was used and indicated no parasites and parasites respectively. P_0 is the average probability of being prescribed an antibiotic in the absence of a malaria test, and $P(N_n)$ is the probability that a NMF needs an antibiotic.

For a NMF seeking treatment in the informal sector,

$$\text{logit}(P(AB)) = \beta_0 + \beta_4$$

where $\exp(\beta_4)$ is the effect of seeking treatment in the informal sector on the odds of getting antibiotics. In general, it is not known how the chance of getting an antibiotic depends on health facility attendance. Therefore, for the purposes of this model, β_4 was set to 0, assuming that the overall probability of getting an antibiotic is not affected by seeking in the informal sector but targeting of antibiotics to those in need is improved in health facilities both by malaria diagnosis and additional diagnostic procedures (e.g. measuring respiratory rates, examining for symptoms of viral infection, etc).

For NMF seeking treatment from community health workers (CHWs) who are trained in malaria diagnostic testing and management of non-malarial fevers, $P(AB)$ is assumed to be the same as in formal sector. If treatment is sought from community health workers (CHWs) trained to administer only presumptive treatment for malaria, or if no treatment is sought, $P(AB) = 0$.

For malaria fevers,

$$\text{logit}(P(AB)) = \beta_0 + \beta_1 * I(MD-) + \beta_2 * I(MD+) + \beta_3 * (need)$$

and

$$\beta_0 = \text{logit}(P_0) - \beta_3 * P(N_m)$$

where $P(N_m)$ is the probability that a malarial fever needs antibiotics. This is assumed to be zero, as NMF are only assumed to occur in the absence of malaria fevers.

NMF case fatality rates

The case fatality rate of fevers that do not need antibiotics is assumed to be 0.

$$CFR_a \mid need = \gamma_{0a} (1 - \varepsilon_{AB} * I(AB))$$

where $CFR_a \mid need$ is the age-based case fatality rate given need for antibiotics, γ_{0a} is the age-based case fatality rate in the absence of antibiotics, given need, and ε_{AB} is the efficacy of the antibiotic on the case fatality rate. $I(AB)$ takes the value 1 if the individual receives an antibiotic and 0 if s(he) does not.

6. **Parameterization of a *P. falciparum* case management model integrated with pharmacodynamics**

6.1. Background

To parameterize the one-day time step case management model integrated with pharmacodynamics, we collected and analysed evidence on patient and provider behaviour that influences the level of effective case management coverage. This was divided into two sets of data: 1) levels of treatment-seeking for fever or malaria, quality of care and patient use of medicines under usual practice; and 2) the impact and cost of interventions to improve treatment-seeking, quality of care and use of antimalarial drugs. Usual practice was defined as ACTs policy but with limited interventions above and beyond what was available under previous first-line antimalarial drug policies. We also aimed to gain an understanding of the relative importance of determinants of these variables.

Health system classification

Successful ACTs-based malaria case management requires considerable health system capacity, which includes human resources, infrastructure, health commodities, logistics, tracking progress and effective financing. In order to provide general cost-effectiveness results for different health system settings, we planned to group countries by health system type and assign each group a common set of parameters in the case management model that determine baseline case management coverage. In simulations of intervention effectiveness, we would also match estimates of cost and impact from intervention studies to health system groups.

Recently, there is increased global recognition of the need to invest in health systems while working towards disease-specific targets [161;162]. WHO-CHOICE (Choosing interventions that are cost-effective) has undertaken to improve costing of health systems interventions [163] and through the Alliance for Health Policy and Systems Research, WHO is promoting the generation and use of health policy and systems research as a means to improve health and health systems in developing countries.

In 2000, the Commission on Macroeconomics and Health (CMH) classified countries by the need for additional health systems investments [164]. Following a review of work on classifying health systems, we found that, more than 10 years on, the CMH remains the reference for this type of work. A recent analysis on the intervention and health system costs of scaling up to reach the health Millennium Development Goals (MDGs) used the CMH classification, adjusting it to take account of specific constraints related to maternal health [165]. A 2009 attempt to create a health system typology for the 41 countries and 5 Indian states estimated to have the highest child mortality was unable to find variables upon which countries grouped. Scarce data for comparison of health systems in low-income countries was identified as a major problem [166].

Our work ran into a similar problem, as we found that countries did not cluster easily according to all of the variables in our case management model – access, provider compliance, and patient adherence. The complexity of health systems and the state of malaria case management therein lead us to conclude that the results of simulating case management in generic health systems using our model would have limited utility. Instead, data on case management from a particular place can be input into the model for geographically-specific predictions of cost-effectiveness; alternatively, it makes more sense to define several levels for each

parameter and investigate what effect varying each has on the results, without referring to particular health system types.

6.2. Methods

We undertook a review of published literature using the keywords in Table 6.1.

Table 6.1 Literature review search strategy

Key words used in search:	Location	Disease/conditions
Treatment Diagnosis Case Management Treatment-seeking Care-seeking Demand Access Equity Coverage of poor Health services performance Quality of care/of health services Prescribe Adherence Compliance Use of drugs/medicines Cost Cost-effectiveness Health services efficiency Community health Performance improvement Informal sector Shopkeepers/Drug vendors Global ACTs subsidy Affordable Medicines Facility for Malaria Franchising/accreditation	Africa	Malaria Fever

We considered primarily material published from 2001 onwards, as this is the year that South Africa changed its first-line treatment policy to ACTs and WHO recommended them as first line treatment for uncomplicated malaria. The last database search was conducted in late 2009, although efforts were made to update this with key additions to the literature thereafter. Searches were limited to material published in the English language.

The electronic databases used were PubMed and African Journal Online, and manual search for relevant references. We also attempted to include gray literature by searching the sites of World Bank, WHO, the UK Department for International Development, Partnerships for Health Report project, Quality Assurance Project, Health Systems Resource Centre, Population Services International, Management Science for Health, Malaria Consortium, DHS, MICS, GFATM, MIS, and BASICS.

Criteria for inclusion as data for the parameter estimates were as follows:

1. Studies with original quantitative data on actual treatment-seeking for fever/malaria, quality of care for fever/malaria, or use of antimalarial drugs where the sample is representative of the population under study.
2. Studies of interventions specifically undertaken to improve these variables, where there is a quantifiable change in patient or provider behaviour from the introduction of an intervention.
3. Both types of studies had to present both numerator and denominator information for outcomes.
4. In the case of intervention studies, they had to be either RCTs, time series measurement, pre-post design with or without a control, and post design with a control.

When assessing the strength of the study, we considered whether it was a peer-reviewed study, the sample size, and whether the study reported statistical significance of results.

Providers were defined as anyone responsible for dispensing antimalarials and were categorized as formal/informal, public/private and community-based. Self-treatment was defined as not consulting a provider.

We excluded studies conducted in populations where malaria is not endemic; studies on chemoprophylaxis or mass treatment; studies which were not representative of the underlying variable to be estimated (for example, studies of treatment-seeking behaviour conducted at health facilities, or studies of adherence in a supervised population); studies of knowledge and perceptions with no data on actual patient or provider behaviour for recent illness episodes experienced or treated; and general reviews with no original data.

6.3. Main findings

Care-seeking

There is a large body of literature on care-seeking for febrile illness across sub-Saharan Africa, particularly among children under five in rural areas. Many of the studies use household survey methodology, interviewing caretakers about actions taken for recent childhood fevers (usually the last two weeks). The majority of these found high treatment rates (most over 90%), and that multiple treatments were common (most over 40%). Self-treatment was the first response to fever in about half of all cases, often with inappropriate drugs and dosages. Often, febrile children were given an antipyretic only. In most studies around half of fever cases

received some treatment in the official health sector, and this was higher in urban areas and for cases of higher perceived severity [93;167-171].

Varying definitions of treatment sources are used, particularly for self-treatment. For example, studies differ in their definitions of "self" and "home" treatment, and in whether they consider treatment-seeking from a shop or pharmacy to be self-treatment [172]. Definitions seem to be shifting to differentiating between the public/ not-for-profit sector, which includes public health facilities, community health workers, and non-profit health facilities, and the private sector, which encompasses outlets with or without qualified health workers [31].

Whereas earlier studies focused more on describing treatment-seeking behaviour, more recent work seeks to understand why people make the choices they do [173]. Baume et al found that mothers seem to be very aware of start of fever and its course, suggesting that caretaker recognition of fever is not a major impediment to care-seeking [174]. Several studies have assessed the accuracy of mothers' diagnoses of malaria in their children, often finding quite a low sensitivity [175]. The availability of drugs, perceived quality of provider, distance from health center, perceived severity of illness, duration of sickness, and costs/ability to pay have all been found to influence choice of provider [174;176;177]. Some evidence indicates that smaller children are more likely to be taken to a health centre, suggesting that mothers recognize the advantages of seeking care in the public sector and are deterred by other factors such as cost or convenience [178].

Recent work in medical anthropology seeks to place access to health care within the broader context of livelihood insecurity to better understand the many dimensions that influence access. This work highlights the importance of understanding how people mobilize household and community assets to access care [179].

Findings indicate that delays in treatment seeking from the formal sector are substantial, even where physical access to care is relatively good [180]. A study in Ghana conducted in 2002-2004 found that only 11% and 33% of children consulted a trained provider within 24 and 48 hours, respectively [181]. A study from Kenya reported a median waiting time of 2 days to any treatment, and that only <3% of fevers were treated within 24 hours using the nationally-recommended 1st line drug, sulfadoxine-pyremethamine (SP), obtained largely through the public formal sector [182]. In a study of children presenting to health facilities and drug shops in Uganda, the mean duration of illness was 3.6 days; for those with no prior treatment it was 2.16 days [183].

Previous work suggested that convulsions, a symptom of severe malaria, were associated with supernatural causes and prompted treatment-seeking from traditional healers [174;184-186]. However, more recent research indicates that this seems to be no longer the case. 57% of respondents in a rural Tanzanian community said that malaria was a cause of convulsions [187]. De Savigny *et al* found that of malaria-attributable deaths in Tanzania, nearly 79% used modern biomedical care as first resort [188] This suggests that in this population, something broke down in the transaction to obtain that care or in the quality of care at the point of contact.

Treatment-seeking for adult febrile illness has been a relatively neglected area of research. Guyatt and Snow attempt to fill this gap, extending their household survey to treatment-seeking in three age groups (under 5, 5-14, 15+). Surprisingly, the study found that, in a rural, low-transmission area of Kenya, there were no significant differences in prevalence of reported fever or treatment-seeking for recent fever by age. Overall, only 33% of all fevers were treated with an anti-malarial drug, due to the large proportion of visits to the informal sector where

anti-malarials were infrequently prescribed, with no significant difference by age [189].

Rapid urbanization across much of sub-Saharan Africa has prompted inquiries into the differences between malaria/fever care-seeking patterns of rural and urban populations. A study in coastal Kenya found that urban care-seeking for malaria was surprisingly similar to rural care-seeking; 52% of lifelong rural resident mothers and 47% of urban resident mothers used only shop-bought drugs for recent (2 week recall) episodes of childhood febrile illness. Urban mothers were more likely to contact a private clinic (24% vs. 15%) and less than half as likely to consult a government service (22% vs. 10%). Urban mothers had better access to prescription-only drugs such as SP or amodiaquine (AQ), which were stocked more frequently in shops [178]. A study in Kenya found that, for adults and children with acute illness, in a rural area 80% received some treatment (of which 55% was self-treatment), while in an urban area 91% received some treatment (of which 50% was self-treatment) [190]. The high prevalence of self-treatment in urban areas begs the question of whether community-based initiatives would be cost-effective in these settings. Time before action taken was significantly shorter in urban (1.05+- 1-67 days) than rural (2.32 +- 0.82 days) areas in a study in Nigeria [191]

Are national policy changes from chloroquine to newer, more effective antimalarials having an impact on treatment-seeking and access? Several studies suggest that treatment-seeking patterns are relatively consistent [192-194], and that access to ACTs remains very low in settings from Tanzania and Kenya to Burkina Faso [195;195;195-197]

Recently-conducted household surveys investigating treatment-seeking for febrile children in six Africa countries highlighted the continuing dominance of the

private sector as a source of fever treatment for children [31]. Coverage with an ACT was found to be low although variable across countries, with Uganda and Zambia having relatively higher rates.

By contrast, in another study from Tanzania, self-treatment seems to have decreased following the policy change from chloroquine (CQ) to SP [198]; this may be because CQ was no longer available in shops and was not replaced with SP [199]. In North A district, Zanzibar, care-seeking for fever by children at public health facilities increased by two-fold following the introduction of free ACTs. The authors hypothesize that these two are related, but note that there were no stock-outs of ACTs during this period, and that physical access to health facilities is quite good in the area [26].

For nationally representative estimates of treatment-seeking for febrile illness, the Demographic and Health Surveys (DHS) and the Malaria Indicator Cluster Surveys (MICS) represent the most geographically complete and directly comparable source. Indicators are the percentage of children under five with fever in the two weeks preceding the survey and of those, the percentage who took antimalarial drugs the same or next day. These are disaggregated by background characteristics. There is also data on the percentage of children who took specific antimalarial drugs, and the percentage who took them the same or the next day. Given the large variation among countries in treatment-seeking patterns [3], it would be advisable to use household survey data to simulate specific settings.

Quality of care

Quality of care is multidimensional. For our purposes, adequate care can be defined as performing a diagnostic test on a febrile patient and prescribing an

antimalarial to a test positive patient with sufficient active ingredient, in the appropriate dosage, and not prescribing an antimalarial to a test-negative patient.

With regard to diagnostic testing, recent developments to ensure RDT quality [200;201] and evidence that restricting antimalarial treatment to parasitologically confirmed cases of malaria is safe [8] have allayed some of the early concerns that RDTs were not sufficiently accurate to justify withholding life-saving drugs. Studies have shown that increased use of parasitological diagnosis can improve the management of febrile disease [202]. However, concerns with moving to a test-based strategy for young children include doubts about the sensitivity of the test under field conditions and satisfactory adherence to the test by health workers [10]. This issue is not completely resolved and some have called for additional and larger studies that include severe outcomes. This would include studies on etiologies of non-malarial fevers, antibiotic prescribing and thus clinical benefits of improved treatment of alternative fever causes [203].

Availability and affordability of drugs and diagnostics in places where people access treatment are prerequisites for adequate quality of care. Outlet surveys conducted in six countries in the frame of the *ACT Watch* project found that availability of quality-assured ACTs, at affordable prices, is very low, particularly in the private sector where most antimalarials are distributed. Availability of diagnostic tests also varied considerably by country but in general was quite low, particularly in the private sector [204]. Stock-outs in public health facilities are a major problem [34;205]. However, treatment guidelines often are not followed even when the first-line drug is in stock [206].

Quality of care in the public sector has been found to be higher, in general, than in the informal sector. In a study in Tanzania, care-seeking from a government health facility was the main predictor increasing the likelihood of prompt access to ACT

[195]. However, recent household surveys suggest that case management practices in the public sector are far from ideal – fewer than half of children managed in the public sector received a blood test for malaria, and between 7 and 47% received an ACT [31]. The high use of the informal sector for fever treatment in Africa is in part a response to perceived poor quality of services offered in the public sector [177].

Prescription of the correct drug in the appropriate dose is often sub-optimal. Hetzel *et al* found that, despite high health facility usage rates in rural Tanzania, only 23% of children and 11% of adults received timely treatment with an appropriate and correctly dosed antimalarial; inappropriate dosing of antimalarials, including in public health facilities, was documented as a problem [207]. In four Kenyan districts three years after SP replaced CQ as first-line treatment, SP was only prescribed in the correct dosage in 34% of pediatric prescriptions. Counseling and observation of taking treatment were also poor [208]. Another study, with a small sample size, found that children were never prescribed second line treatment (SP) even if it was a repeat treatment-seeking visit [174]. Nine months after introduction of artesunate-amodiaquine (AS-AQ) in public facilities in Burundi, AS-AQ prescription was only 14.1% [194] Zurovac *et al* examined prescribing practices in health facilities 4 to 6 months after the policy change from SP to artemether-lumefantrine (AL). The study found that only three-quarters of children with fever (and a positive test or no test) were prescribed an antimalarial, and only 28% got AL. Many were prescribed the second line drug (AQ). The presence of a positive test did made a child more likely to get AL [209]. It seems that health workers may prescribe AL for cases perceived as "more urgent" while using other antimalarials for other cases [210]

Two additional problems are low diagnostic testing rates, and prescription of antimalarials to test-negative patients. Even when available, diagnostic tests are

often not used or their results ignored [211;212], even in areas of low-
.transmission [213]. Hamer *et al* found that only 28% of febrile patients were
tested in facilities where diagnostics were available, and many who tested negative
(58% by blood slide, 36% by RDT) still got antimalarials. 72.6% had no test
performed and 66% were prescribed antimalarials anyway [214]. Overdiagnosis
may lead health workers to miss other serious causes of febrile illness, as found in
Tanzania, where 66% of slide-negative patients were not treated with antiobiotics,
of which 7.6% died [215]. In 2009, Kenya initiated a new policy of universal
parasitological diagnosis and targeted treatment with AL. Nation-wide surveys in
Kenya found that, in health facilities where AL and malaria diagnostics were
available, about half of patients with fever were tested, and about half of test-
negative patients were treated with an antimalarial, even following exposure to
implementation activities to promote the new policies [205].

Zurovac *et al* reported that in four districts in Kenya, actual treatment practices
differed dramatically from the national guidelines, which stated that febrile
children under five should be treated presumptively for malaria but that over-fives
should be tested before treatment. About a half a year after the new first-line drug,
AL, was delivered to health facilities, only 43% of febrile patients over five years
were given a diagnostic test, compared to 26% of children under five. Prescribing
differed little across age groups, however; antimalarials were prescribed for the
majority of adults and children with negative test results and those without tests
performed. AL prescriptions usually followed a positive test result. The authors
conclude that different age-specific recommendations for diagnosis may be
difficult to implement [216]

Other studies, however, have shown more positive results. A dramatic reduction in
the use of antimalarials following implementation of RDTs was documented in
urban Tanzania [217]. In Senegal, where the public health sector is quite strong

and in the presence of a small financial incentive to the consumer (who have to pay for first-line antimalarial drugs), parasite-based diagnosis increased to 86% over the three-year period following the policy change, resulting in a drop in ACT prescriptions to roughly the same number as confirmed malaria. This suggests that high adherence to an RDTs-based policy is achievable on a national scale [218].

Why do health workers fail to follow recommended treatment practices? An increasing number of studies have explored this question. In the Zurovac *et al* study above, only 28% of children had AL prescribed, even when it was in stock, with health workers preferring to prescribe AQ. Factors associated with higher likelihood of AL prescription were health worker's pre-service training, in-service training including AL use, presence of a positive malaria test, main complaint of fever and temperature greater than or equal to 37.5 degrees Celsius. Stock-outs and lack of training of health workers continued to be a challenge. Most (92%) of children received AL in the correct weight-specific dosage [209]. Interestingly, in a study from Zambia, in-service training and provision of job aids did not seem to influence AL prescribing [219]. Chandler found that 33% of slide-negative patients in a hospital OPD were prescribed antimalarials. The variation among hospitals was not apparently related to the transmission level, and patient demand was not seen to be a factor driving over-prescription [220]

A qualitative study published in 2008 looked specifically at the issue of why health workers do not prescribe ACT when it is indicated. The reasons found related either to specific failings in introduction of policy (1) mixed/unclear and incorrect messages delivered during training and (2) availability/continued supply of AQ; and 2) more general health systems issues (workload of staff and erratic nature of drug supply) [221].

Treatment in the informal sector is well-documented as often inappropriate [182;222] . Following the change to SP as first-line policy, Kachur *et al* found that, in rural Tanzania, only 17% of clients who visited drug stores to obtain medicine for a patient with fever or malaria actually purchased an antimalarial drug, while 77% purchased anti-pyretic medications. Of those that did purchase antimalarials, education of household head was significantly correlated, suggesting the importance of cost. The same study found that patients seeking treatment from drug stores for febrile illness were as likely to have malaria parasitemia as those seeking treatment in the formal sector, which confirms that the role of the informal sector in malaria case management cannot be ignored [193].

Poor drug dispensing practices in the informal sector are being compounded by a large market for counterfeit antimalarial medicines in Africa [223]. A nationwide survey in 2001-2002 of CQ, quinine and antifolates sold in the informal sector in Cameroon found 12-74% of the samples to be of poor quality or containing no active ingredient [224]. A recent analysis of drugs sourced from urban or peri-urban pharmacies in six African countries found that 35% of all samples failed quality tests, including 19% of artemether-lumefantrine fixed dose combination and 42% of artemisinin monotherapies [33]

Patient use of antimalarial drugs

Definitions of adherence and methodological differences among studies complicate the comparison of adherence studies. Some rely on self-reported adherence [225], while others combine this with pill counts/bottle inspections [226;227] and/or biological methods [228] . To be considered completely adherent, most studies considered both number and timing of doses. Studies differ in how they treat vomiting of doses in measurement of adherence [229].

It is generally believed that the simpler the dosing schedule, the higher the adherence. Abuya *et al*'s study bears this out, with SP used more appropriately than AQ although "adequate use" is not well-defined. One of the few studies to examine adherence in the informal sector, this paper found adherence to AQ of 2-12%, and to SP of 46-84% [222]. In rural Senegal, less than a year after the policy change to AQ+SP as first-line treatment, 38% were considered strictly adherent [230] . Adherence to tablets was better than syrup (45% vs. 28%), which echoed previous findings [231].

In research studies, adherence to AL has been found to be high [232;233]. Fogg *et al* found 90% probable adherence to Coartem in a study in a Uganda outpatient department. However, this was quite a controlled study and subjects were given careful instructions explanations by health workers [67]. In less controlled studies, adherence was still found to be quite high: 88% reported adherence to AL was found in rural Tanzania, and most non-adherence was due to untimely dosing rather than missing doses [225]. In another study from Tanzania, the full dose was taken at a satisfactory time in about 90% of cases [227]. However in Malawi, only 65% of patients were completely adherent according to pill count and dose-recall interviews [226] and in Kenya, only 64% were [234].

Adherence to co-packaged or co-blistered ACTs has been found to be lower in general. 77% adherence to AS+AQ, assessed by self report and pill count, was documented in children under five in Zanzibar [229]. Adherence of 48% to AS+AQ was found in a remote rural area of Sierra Leone, where patients had relatively little education and the treatment had been implemented for some time [235]. Another study found 75% complete adherence to AS+SP (based on self-report and tablet counts), but with counseling and packaging interventions [236].

Several studies assessed adherence in atypical settings, with contrasting findings. In a refugee settlement where SP-AS was given at a clinic, without clear marks of timing or dosage on the packaging, only 39% probable adherence was found [237]. Among internally displaced persons in Uganda, Kolaczinski *et al* found that overall adherence to blister-packed CQ plus SP distributed through community health workers was 96%. However, this measure relied heavily on self-reports, even when the blister pack was not presented, sampling bias may be a problem, and the patient population may not be representative of non-conflict areas in Africa [238].

Education level in the patient or caregiver, lack of supervised intake of the first dose   [229], poverty level [225], and unclear instructions from prescribers [237] are some of the main factors associated with non-adherence. In one study, children were found less likely to be adherent [226]. Conversely, improved packaging [231] and pictorial inserts and verbal instructions [239;240] increased adherence.

Drawing on the literature review, a set of baseline model parameters is proposed in Table 6.2. A database has been compiled with quantitative results of the literature search.

Table 6.2 Proposed baseline parameters for case management model

Input variable	High or best estimate (Source)	Alternative estimate (Source)
% that seek treatment in formal sector	50 [3]	20 [3]
% that seek treatment in informal sector	80 [3]	30 [3]
% not treated	20 [3]	0 [3]
% that seek treatment on the same or next day	30 [140]	
Formal sector		
% tested	35 [31;241]	
Of those tested ,% tested by microscopy	20 (Assumption)	
Of those tested, % tested by RDT	80 (Assumption)	
Of those that test positive, % that get antimalarial treatment	95 [213;214]	
Of those that test negative, % that get antimalarial treatment	50 [205]	
Of those not tested, % that get antimalarial treatment	60 [214]	
% of facilities that have ACT in stock	90 [209]	60 [209]
Of those that test positive, % that get ACT (where ACT in stock)	70 [214]	
Of those that test negative, % that get ACT (where ACT in stock)	30 [214]	
% of AL that is good quality	95 (Assumption)	
% of SP that is good quality	90 (Assumption)	
% AL prescribed correctly	90 [242;243]	
% SP prescribed correctly	34 [208]	
% good adherence to ACT	90 [67]	39 [237]
% good adherence to SP	95 (Assumption)	
Informal sector		
% tested	0 [31]	
% that get antimalarial treatment	30 [182]	
% that get ACT	6 [31]	
% of ACT that is bad quality	19 [33]	
% of SP that is bad quality	50 [33]	
% that get correct dose of ACT	70 [244]	
% that get correct dose of SP	46 [222]	
% good adherence to ACT	50 (Assumption)	

Interventions and strategies to improve case management

We reviewed the literature on interventions to improve access to malaria treatment by modifying patient and provider behaviour. We did not include wider health system interventions, for example removal of user fees in public health facilities or improvements in drug and diagnostic quality control or supply chains.

Given the large and persistent share of the informal sector in providing anti-malarial treatment across Africa, and the inappropriate care they offer, several approaches to improve their practices have been piloted. These interventions require first identifying retailers and characterizing their practices [245]. One approach has involved training shopkeepers to recognize malaria and improve dispensing [246;247]. In rural Kenya, the proportion of shop-treated childhood fevers receiving an adequate dose of a recommended antimalarial drug (CQ or later, SP) within 24 hours rose from 1% to 28%, following training for drug retails and community education [248] The estimated annual cost for implementation of this programme on district scale was US$ 45,489, or US$ .10 per capita, or a cost per DALY averted of US$ 3.85 [249]. Cost-effectiveness was modeled based on data from the early implementation phase, assuming that the same level of effectiveness would be maintained on a larger scale. This may be plausible, as the programme showed a higher effectiveness when it was scaled up [248]. The analysis is dependent on assumptions of a district population of about 473,000, annual fever incidence of 4.8 per child, that 56% of children visit a shop first for fever, and that the programme would have an eight-year life span. Larger-scale studies are needed to show whether this type of programme can be cost-effective on a large scale, with combination therapies, and whether it is sustainable.

Due to the high cost and difficulty of reaching numerous retail outlets, an alternative approach involved training drug wholesalers to educate retailers dosing

and distribute job aids/posters. The study design was limited, in part because shops were not randomized. Following the intervention, 32% of shops receiving job aids (assumed to have been "informed") prescribed to mystery shoppers the approved first line drug (SP), against 3% of those that were assumed not to have been informed. The cost of intervention in the first six months was US$ 8300, for a district of 900,000 or US$9-11 per retail outlet reached [250]. Many of these costs were fixed (such as development of shopkeeper job aids and posters) that could be spread over additional districts and annualized, making the average yearly costs much lower.

One study was found that evaluated a relatively large scale Ministry of Health program to train retail sector providers in Kenya. It found that the program led to significant improvements in provider knowledge and practices. About 31% of intervention providers sold AQ with correct advice on use to surrogate clients, compared to about 5% of control retailers [251].

In Tanzania, a new class of outlets known as Accredited Drug Dispensing Outlets (ADDOs) was created to improve access to treatment in the private retail sector. The intervention involved a combination of private drug shop dispenser training, incentives, accreditation and regulation. Subsidized AL was made available in both health facilities and ADDOs in 2007. ADDOs were found to greatly improve availability and accessibility of drug shops, and the quality of advice and dispensing in these outlets, and the use of the private retail sector increased despite much higher prices than in health facilities. However, the low affordability of AL restricted its availability, and SP and amodiaquine were still the most dispensed drugs. This study highlighted the importance of the private retail sector in provision of antimalarial treatment, but concluded that affordability of ACTs must be improved if they are to be widely dispensed [252]. A companion study in the same area found that contemporaneous health education campaigns aimed at

increasing people's knowledge of appropriate malaria treatment seemed to improve care-seeking [253]

To address the problem of limited affordability and accessibility of ACTs, particularly in the private sector, a subsidy scheme entitled the Affordable Medicines Facility - malaria (AMFm) was recently launched. Hosted by GFATM, it negotiates with drug manufacturers to reduce the price of ACTs to both public and private sector first-line buyers, who are expected to pass on the highest possible proportion of this price benefit. Countries participating in AMFm must also implement "supporting interventions" to ensure the increased availability and safe use of ACTs. AMFm Phase 1 is being implemented through pilots in eight countries, and data is available from initial pilot projects in Tanzania and Uganda. In Tanzania, the proportion of consumers in the intervention districts purchasing ACTs rose from 1% at baseline to about 44% one year later, while no change was observed in the control district [254]. However, caution should be exercised when applying the findings of this small-scale study to the envisaged AMFm.

Only one published study was found with data on the impact of private sector ACT subsidies on coverage of prompt effective treatment. The intervention, a cluster-randomized trial in Kenya, involved provision of subsidized packs of pediatric ACT to retail outlets, training of retail outlet staff, and community awareness activities. While there was no significant difference in treatment-seeking behaviour between the control and intervention arms, at follow-up the percentage of children receiving AL on the day of fever or the following day was 25% greater in the intervention arm. This suggests that the increase in coverage was indeed due to a change in the type of drugs dispensed in the private retail sector. Furthermore, most caregivers paid the recommended retail price for the subsidized ACT [244].

There is virtually no evidence on the feasibility or impact of introducing RDTs in the private retail sector in Africa, although a randomized trial is upcoming in Uganda [255].

An alternative distribution mechanism to public health facilities and the private retail sector is community, or home- based, case management. Delivery of treatment for suspected malaria through home-based management of malaria (HMM) has been discussed and applied in sub-Saharan African countries, with various degrees of implementation, for some years [256-259]. These experiences resulted in WHO's development of the *Roll Back Malaria strategy for improving access to treatment through home management of malaria* [116]. This strategy consists of four major components: an effective communication strategy, training of community-based providers, availability of medicines, and supervision and monitoring.

The average net cost of an intervention to promote home management of malaria in rural Burkina Faso, including training, purchase of the first stock of drugs, bags, labels and packing of drugs, incentives to community health workers (CHWs), and supervision and drug distribution, was 1994 US$ 0.06 per resident child [117]. The cost per villager, including consumer and provider costs, of design and implementation of a strategy based on use of CHWs for near and appropriate treatment of malaria was between US$ 1.40 and US$ 1.70 [119]. Both interventions seemingly resulted in improved management of febrile illness.

There is some evidence of the effectiveness of HMM, although evidence of its cost-effectiveness, particularly with ACTs, is limited [260]. A study at sites in four African countries examined the feasibility, acceptability and utilization of ACT provided at community level. Results from a post-intervention household survey of recent treatment- seeking for febrile illness showed high coverage (52-75%

treated with ACTs from a CHW) and adherence (71-87% treated promptly (receiving first dose on first or next day) and correctly (dose and duration)). 98% of all children were correctly dosed. However, this was a very controlled research setting and monitored over a short time period; community health workers were not paid but were given other incentives [261] The cost of delivering home management of malaria in a trial in urban Ugandan children, including the cost of AL was estimated at US$ 33.83 per child per year. Home Management of Malaria greatly increased the proportion of febrile children receiving prompt and effective treatment with antimalarial drugs. However, the health effects were modest, suggesting that most antimalarials were given for non-malarial febrile illness [118].

Some studies suggest that CHWs can be trained to effectively use RDTs to better target malaria treatment and that adherence to test results is high [262;263]. Harvey *et al* reported on a 3-hour training course together with provision of job aids for CHWs in Zambia on how to use and interpret RDTs. The course cost approximately 2006US$ 175 per CHW, including supplies, transportation, lodging for CHWs and salaries, per diems, and transportation costs for the trainers, observers and Ministry of Health personnel. When only supplies, transportation, and lodging for CHWs costs were included, the total cost per CHW was 2006US$ 66 per CHW trained. Following the course, significantly more CHWs conducted and read the test results correctly than those who had received only the manufacturer's instructions or job aids [121].

There is now increased interest in exploring whether CHWs can be trained to manage both malaria and pneumonia using RDTs, or integrated community case management (ICCM). The WHO and UNICEF now recommend ICCM where malaria and pneumonia are major killers. A cluster randomized control trial in Zambia found that training CHWs to prescribe amoxicillin to children with

nonsevere pneumonia and AL for malaria after use of RDTs results resulted in a five-fold increase in the proportion of children with non-severe pneumonia who received early and appropriate treatment. Furthermore, use of AL dropped dramatically; CHWs adhered well to RDT results [120]. Preliminary evidence from Uganda suggests that CHWs can be trained to assess manage malaria and pneumonia in children, but this study only assessed performance immediately following training and these findings need validation in a real-life setting [264]

The evidence on impact of interventions to improve provider practices in public health facilities is mixed. Agyepong *et al* found improvements in prescribing practices in clinics where a training for dispensers was held [240], but it is not clear whether this translates into better adherence, and if so, whether these results can be sustained over time. One study found that gains in knowledge following in-service training for medical assistants on malaria treatment had deteriorated within a year [265]. It appears that knowledge does not always result in improved practice. Eriksen *et al*'s study suggests that staff with less training did not perform worse than others [198], leading her to suggest, as others have, that factors such as motivation, job satisfaction, cultural factors and financial incentives are probably more important. In a study of clinical practice in a health facility in Malawi, only 71% of ill children that should have gotten an antimalarial according to gold standard clinician actually did, and neither in-service training nor supervision were associated with fewer treatment errors [266]. These findings are similar to those of Rowe *et al*, who reported that 50% of children were correctly treated. In this study, neither in-service fever training nor supervision was significantly associated with correct treatment [267]. More recent evidence from Kenya indicated that in-service training and job aids were not sufficient to improve provider case management practices following the policy change to ACTs as first-line treatment

Given these results, it is unclear how providers can be convinced to adhere better to current malaria treatment guidelines involving RDTs and ACTs. Mobile phone text message reminders are an innovative intervention that was shown to improve health worker adherence to case management guidelines in Kenya [268]

In the case of severe malaria, some evidence indicates that improved provider practices can reduce in-hospital mortality. Biai *et al* found that paediatric in-hospital malaria mortality was reduced from 10% in the control group to 5% in the intervention group by providing a financial incentive to staff and better supervision [269]. Recently, evidence has emerged that rectal artemisinins as pre-referral treatment can reduce mortality where patients cannot take medicines orally and access to injections will take several hours [270].

6.4. Conclusions

Treatment-seeking for febrile illness from the informal sector remains high, and the influence of the implementation of new treatment policies on these patterns is only beginning to be understood. Care-seeking for severe illness remains a neglected area of research, although recent studies have shown that, in some settings, resorting to traditional healers first is no longer a significant reason for delay. The multiple factors influencing treatment-seeking for fever in Africa, both on the supply and demand side, are well-recognized. There is a need for a greater understanding of the key bottlenecks in different settings, as well as documentation of best practices of countries that seem to be performing better than most, like Uganda and Zambia.

In addition, descriptive evidence indicates that quality of care is sub-optimal, including under ACTs policy. However, a clearer understanding of the multiple

factors that lead health workers to treat inappropriately, and convincing evidence from well-designed, large-scale intervention studies to address these issues, is needed. In addition, more data is needed on the etiology and management of non–malarial fevers. Another area where information seems to be scarce is on referral, and its relation to malaria mortality in severe cases. Finally, more information on diagnostic and treatment practices in the formal and informal private sector would also be very useful.

Adherence to ACT seems to be relatively high, even under routine conditions. However, particularly where education levels are low and patient provider communication is poor, adherence has been found to be sub-optimal. The impact of the introduction of RDTs on adherence is unclear; studies where patients were only treated after receiving a positive RDT test showed both relatively high [225] and low [235] adherence. There is still room to improve adherence, for example through better communication between providers and patients/caretakers and more attention to groups that are thought to be less adherent, in particular children.

There are a number of difficulties which arise when comparing studies on human behaviour related to malaria treatment, including methods, sample, types of questions asked, and the way the data are presented [172]. In addition, there are numerous drivers for the results which are unique to the social, economic, cultural and health systems context in which the studies were undertaken. For example, epidemiology of febrile illness, level of infrastructure, stage of implementation of new policies, and health worker remuneration and incentives are just some of the factors that influence patient and provider behaviour. Thus, it is debatable how much descriptive or intervention data can be applied across settings. Notably, there is a lack of data from vast swathes of Africa where malaria burden is high; studies are needed to fill those gaps.

7. **Discussion and Conclusion**

The overall aim of this thesis was to predict the impact and cost-effectiveness of *P.falciparum* malaria case management interventions in different transmission and health system settings. In low-transmission settings where policy-makers are considering pursuing elimination, as well as in settings of higher endemicity where the immediate goal is reduction of disease burden, case management is a critical component of integrated strategies against malaria.

An existing integrated set of models was applied to examine the effect of passive case detection (PCD) in the aftermath of local transmission interruption, and was extended to simulate the cost-effectiveness of another chemotherapy-based intervention, mass screening and treatment (MSAT). This work also contributes a revised method for estimation of uncomplicated malaria burden and a new case management model, integrated with a model of pharmacodynamics, which will enable a more precise, finer-grained analysis of the effects of scaling up case management and improving diagnosis and treatment practices on health outcomes and drug resistance.

This discussion places the case management models in context. It then discusses the implications of the studies undertaken and summarizes the strengths and limitations of the new case management model and the outlook for future modeling.

7.1. Context of case management models

Models of the impact and cost-effectiveness of malaria case management can be divided into two broad categories. The first includes models where case

management (and economics) is considered separately from the biology of the disease. The second category comprises models which bring together case management, biology and, in the case of cost-effectiveness, economics.

A number of models have investigated case management interventions to reduce malaria burden. Some of these are very simple models which use data on baseline case management parameters and estimates of intervention impact to predict treatment effectiveness [271-273]. Others use estimates of disease burden, intervention effectiveness, and unit costs to predict cost-effectiveness of interventions or combinations of interventions in different settings [11;128;274-276]. There is no within-host or transmission model, and the main effect of case management is to reduce mortality from the treated bout. There is no explicit consideration of the dynamics of transmission and immunity, the loss of which results from reduced exposure.

A few modeling studies consider changes in immunity levels and the dynamic effects of case management on transmission [277-279]. To date, the application of population dynamic transmission modeling of infectious diseases together with methods for economic evaluation has been extremely limited [280]. Several previous models bring together aspects of malaria biology, case management and economics [281;282]. The Yeung *et al* model, developed primarily to study the spread of antimalarial drug resistance, used variable antimalarial and ACT coverage rates and adherence and the simulated level of resistance at each time step as the determinants of cure rate. Costs to the provider and patient were combined with predicted numbers of cases, cures and failures to estimate cost-effectiveness of different case management strategies. The predecessor to the case management model presented in this thesis [41] was integrated into a set of models which combined parasitology, burden of disease, health systems, transmission and economics. It modeled care-seeking and costs in the formal

sector and self-treatment, based on real data from Tanzania. The work presented in this thesis adds a pharmacodynamic model, integrated with a more complex case management component, to this already quite comprehensive set of models.

7.2.   Implications of studies on passive case detection and MSAT

The passive case detection study was the first to apply the integrated models to answer questions regarding local elimination of malaria transmission. The models are well-suited for this purpose for several reasons. First, interruption or re-establishment of malaria transmission is a stochastic process and is likely to depend greatly on random variation in risk, human movement, treatment-seeking, and other factors. The stochastic models capture this variation, allowing predictions of the probability of re-establishment based on multiple simulations with different random number seeds. Second, the use of model assumptions allows investigation of the effect of model uncertainty on predictions. The findings highlight the urgent need for research into the mechanisms and rate at which naturally- acquired immunity to *P.falciparum* malaria decays in the absence of exposure. Many people in sub-Saharan Africa could be in this position in the future if current efforts to control malaria lead to reductions in malaria transmission without eliminating the parasite, and this is likely to be a key driver of intervention impact in the longer-term.

However, our analysis ignores several sources of heterogeneity which may be critical in low-transmission settings. Notably, it does not include spatial heterogeneity in interactions among people and mosquitoes, or in transmission. This may lead to overestimation of the probability of local interruption of transmission, as residual transmission is likely to be concentrated in geographically-defined foci. A transmission dynamic spatial model with multiple

interacting populations would be required to capture this heterogeneity. In addition, the models were fit to data from medium or high transmission intensities, and have not been validated with data from low-transmission settings. Finally, it was not readily possible to simulate immunity differentials between individuals importing infections and the simulated population; this may bias the estimated probability of transmission re-establishment.

One methodological issue which arises in studies of malaria elimination is the difficulty of defining such a concept. WHO currently defines malaria elimination as zero incidence of locally-contracted cases [20]. However, until eradication is achieved, importation of infection and some degree of onward transmission is almost inevitable in most places; under the WHO definition, a number of countries currently certified as malaria-free would not qualify [51;283]. Our study established a threshold allowing each imported infection to give rise to a maximum of 2 secondary infections before classifying the simulation as one where transmission was re-established, but this was somewhat arbitrary.

The costs of interrupting transmission and preventing re-establishment must be considered alongside the expected benefits in terms of disease burden, potential health care savings to caretakers and providers, and other benefits using an appropriate time horizon and discount rate, to inform the decision. Cost-effectiveness analysis is likely to be insufficient to inform decision-making for elimination, as many of the benefits of elimination go beyond health outcomes. A recent analysis found that pursuing elimination is unlikely to be cost-saving because of the high upfront costs need to find and eliminate the last infections, as well as the ongoing costs for preventing re-introduction [76] . However, non-health benefits to achieving and maintaining elimination may be substantial and need to be taken into account in making investment cases for interruption of malaria transmission. These additional benefits are currently very uncertain. There

is a need for further research and methodological developments for economic evaluation of malaria elimination.

Surveillance in near-elimination or elimination settings will likely require interventions based on active case detection, either indiscriminately or in response to a detected case. There is a need for more data from field studies on the costs and effectiveness of different surveillance strategies. The impact of such approaches will likely be determined to a great degree by rates of decay of natural immunity in the absence of exposure. This information could be combined and used with the model to help predict the most cost-effective surveillance and response models in different settings.

The MSAT study reported here was a first attempt to quantify the effects, in terms of burden reduction, and costs of one variant of active case detection. These findings suggest that MSAT may be most cost-effective in settings of moderate transmission intensity, and not low transmission, as has often been assumed. The appendix presents a methodology for estimating costs which could be generalized to other interventions involving household visits. An area of uncertainty is the investments in the health system that would need to accompany such an intervention to ensure its successful implementation.

The study highlights the scope for extending the analysis of the cost-effectiveness of scaling up combinations of interventions. In future studies, DALYs should be used as the outcome measure in the cost-effectiveness equation. In addition, an alternative method for estimating malaria burden which does not assume a fixed three-day duration of uncomplicated malaria episodes could improve the accuracy of the cost-effectiveness estimate. Finally, future analyses should consider a sensitivity analysis varying the unit cost of interventions, particularly case management, at different coverage levels. The current case management costing

model does not take account of investments in infrastructure or activities that would be needed to scale-up malaria treatment, which are likely to be substantial.

7.3. Case management model integrated with pharmacodynamics: strengths, limitations, and outlook

The case management model developed as part of this thesis will enable more accurate simulations of case management, including the activities involved in changing treatment practices, and the effect of drug treatment. It will also permit investigation of the development and spread of drug resistance, which is one of the most pressing questions in malaria control today [284;285].

The added complexity of the one-day time step models comes at a cost. Enormous computational power is required to fit the model parameters to data; this is achieved through the use of volunteer computing through the internet [39]. It was difficult to predict how long this would take, and ultimately it was beyond the time frame allocated for this thesis. In addition, the models are quite time-consuming and computationally intensive to run.

Adding additional detail to an already-complex set of models also makes it more difficult to understand the key drivers of results and risks increasing users' reluctance to engage with and trust model outputs. The community of potential users for such models is still being defined, and for the time being, may need to be limited to those who have considerable experience using and interpreting simulation results. For this reason, the current utility of standard tools and interfaces for analyzing model outputs is questionable – those with data analysis skills and knowledge of the models will want more flexibility to analyse and present results.

Developing the integrated case management model required harmonizing the workflow of a large multidisciplinary team. The core program is now entirely written in the general purpose programming language C++; the project therefore required interacting not only with developers of other models components (in this case, the within-host and drug action models), but also with those developing the code. While a complex code base increases the functionality and versatility of the simulation platform, it is quite obtuse to non-programmers. This remoteness of modelers from the code can inhibit interaction with the models and result in mutual dependency of modelers and coders, which can slow down model development. Efforts to develop user interfaces for experiment creation are challenged by the ever-changing code base.

One of the objectives of the literature search presented in this thesis was to add geographical specificity to the case management model by defining parameters for particular places. However, data was found to be limited in geographical coverage and by study methodology. Also, case management variables are very dependent on local context, change over time and can vary substantially within a country [173]. This leads to considerable uncertainty in case management parameters, arguing for the use of sensitivity analysis. The costing model should also be expanded with additional data from other settings on the costs of febrile illness so that the effects of variation in cost parameters can be explored; some of this information is compiled in publicly available databases, for example through WHO-CHOICE [286]. In that vein, a probabilistic sensitivity analysis varying health systems parameters and costs was recently carried out using the five-day time step model [287].

Moreover, the complexity of health systems makes it difficult to characterize countries in terms of a few variables related to malaria case management. Countries may perform relatively well on certain aspects of case management and

relatively poorly on others. Therefore, allocation of countries to case management categories was not found to be feasible. Rather, it is considered more useful to simulate ranges for each variable, without referring to specific places, or to apply the model to specific settings where data is available.

Health systems are dynamic, and interventions to improve malaria case management may have numerous effects on the rest of the system. For example, a reduction in the end-user price of malaria drugs may modify patterns of treatment-seeking and self-treatment, prescribing practices and adherence [288]. The case management model offers the possibility to combine quantitative modeling of the feedback effects in health systems with dynamic models of malaria transmission and cost-effectiveness analysis. Whether the models can be useful to answer these types of questions, or whether they are best explored outside the models, is still uncertain.

Once the one-day time step models achieve a satisfactory fit to data, they should be illustrated by applying them to several simple questions. First, the effect of drug stock-outs could be simulated by varying case management coverage in time and exploring the effect on health and transmission outcomes, relative to constant coverage. Another immediate research question is the cost-effectiveness of different levels of diagnostic testing.

In the longer-term, it would be important to fit the parameters of the 14 sub-model variants, incorporating different assumptions about decay of immunity and heterogeneity in force of infection, treatment-seeking and co-morbidity with the one-day time step model. This would enable investigation of the impact of model uncertainty, and comparison of the predictions of the different models.

7.4. Conclusion

The rapidly changing malaria epidemiology due to factors such as intervention scale-up [26] and urbanization [289] in much of Africa requires that policy decisions be taken urgently. Models are necessary to inform these decisions, and the results of multiple models should be compared against one another towards assessing their validity. A major challenge for the next phase of the project is increasing the application of the models to help guide research and policy-making.

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