

Symptomatic illness and treatment of *Plasmodium falciparum* malaria in African children

A thesis submitted for the degree of *Doctor of Philosophy*

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Abstract

Plasmodium falciparum malaria is a major cause of morbidity and mortality globally, with a disproportionate fraction of cases and deaths in children under five years of age in sub-Saharan Africa. Estimating the proportion of infected individuals and symptomatic cases that receive effective antimalarial treatment is essential for assessing effectiveness of response efforts to reduce the malaria burden and for identifying coverage gaps for interventions. This thesis aims to provide new insights into the clinical malaria burden, and provides estimates of the proportion of malaria-infected children in sub-Saharan Africa that receive antimalarial treatment.

The first major theme of this thesis was to develop a framework for estimating the prevalence of paediatric fever in sub-Saharan Africa, distinguishing between malaria-attributable fevers (MAF), and non-malarial febrile illness (NMFI) with and without an asymptomatic *P. falciparum* infection. Using household survey data and Bayesian geostatistical methods, continental cartographic estimates of paediatric fever prevalence were produced, separated by underlying cause.

The second research focus was to develop an essential adjustment to household survey data to assess the duration a *P. falciparum*-infected individual remains positive via rapid diagnostic test after being treated with antimalarial medication. This adjustment was used in subsequent chapters, allowing for more accurate assessment of the likelihood of a febrile individual in the household survey datasets having experienced a MAF or NMFI in the two weeks preceding the survey.

Current malaria burden estimation approaches typically enumerate the total number of malaria-positive fevers expected at a national-level. This approach systematically overestimates the clinical burden of malaria, as many of these malaria-positive fevers are causally attributable to NMFI (and the malaria infection is asymptomatic). In the third research chapter, estimates were produced of the proportion of paediatric malaria-positive fevers that are causally attributable to either malaria or NMFI that present at public health facilities in sub-Saharan African countries. The results presented in this chapter provide estimates of the potential scale of overestimation of the *P. falciparum* malaria burden using conventional burden estimation approaches.

Finally, estimates of effective antimalarial coverage amongst children under 5 residing in 41 country-years with a household survey were presented, and individual-, community-, clinic-, and national-level coverage gaps for effective antimalarial coverage were identified. The results and conclusions from these studies are presented alongside recommendations and implications for both caregivers in malaria-endemic countries implementing paediatric fever management policy, and for epidemiologists studying the burden of malaria and non-malarial febrile illnesses.

Statement of Contribution and Associated Publications

The chapters presented in this thesis (excluding the Introduction and Discussion; Chapters 1 and 6) have been published, submitted or prepared for publication in academic journals. Chapters 2 to 5 were assembled as collaborative efforts from members of the Malaria Atlas Project, other members of the University, and external collaborators. Below, I summarise the contributions of all authors to each chapter.

Chapter 2: Quantifying the contribution of *Plasmodium falciparum* malaria to febrile illness amongst African children.

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Authors: Ursula Dalrymple (UD), Ewan Cameron (EC), Samir Bhatt (SB), Daniel J Weiss (DJW), Sunetra Gupta (SG), Peter W Gething (PWG).

Author contributions: UD conceived the study (with PWG and EC), aggregated all datasets, designed and implemented boosted regression tree analysis, generated outputs from Bayesian hierarchical model, generated all graphics and tables, wrote first draft of manuscript. EC conducted statistical analysis and implementation of Bayesian hierarchical model with input from UD and SB. DJW provided variables for BRT modelling. PWG oversaw the study. All authors reviewed and approved the final manuscript.

Chapter 3: How long do rapid diagnostic tests remain positive after anti-malarial treatment?

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Authors: Ursula Dalrymple (UD), Rohan Arambepola (RA) Peter W Gething (PWG), Ewan Cameron (EC).

Author contributions: UD conceived of and designed the research, and constructed the dataset. UD, RA and EC conducted the analysis and visualizations. PWG supported the analysis. UD and RA drafted the manuscript. All authors read and approved the final manuscript.

Chapter 4: Overestimation of the *Plasmodium falciparum* malaria burden in African children due to coincident infections with non-malarial febrile illnesses.

Status: Prepared for submission.

Authors: Ursula Dalrymple (UD), Ewan Cameron (EC), Rohan Arambepola (RA), Katherine E. Battle (KEB), Elisabeth G. Chestnutt (EGC), Suzanne Keddie (SK), Katherine A. Twohig (KAT), Daniel A. Pfeffer (DAP), Harry Gibson (HG), Daniel J. Weiss (DJW), Samir Bhatt (SB), Sunetra Gupta (SG), Peter W. Gething (PWG).

Author contributions: UD conceived the study with PWG and EC. UD assembled parasite density datasets (with assistance from KEB, EGC, SK and KAT in updating the set of studies meeting the inclusion criteria; UD extracted all information from studies). UD assembled all other literature review and household survey datasets, assembled Ministry of Health datasets (which were downloaded after an online search by KAT and DAP). UD designed and implemented Bayesian statistical analysis of the relationship between MAF and *Pf*PR with guidance from RA and EC. UD conducted boosted regression tree modelling; designed basic framework for, and analysed outputs from, Bayesian hierarchical model; generated all displayed graphics and tables; wrote first draft of manuscript.

EC conducted statistical analysis and implementation of Bayesian hierarchical model with input from UD and SB. EC provided first draft of sub-section "4.4.3.3. Fever attribution model", which was revised by UD.

DJW and HG provided variables for BRT modelling.

PWG oversaw the study.

All authors reviewed and approved the final manuscript.

Chapter 5: What proportion of malaria infections receive effective antimalarial treatment?

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Authors: Ursula Dalrymple (UD), Ewan Cameron (EC), Harry Gibson (HG), Jennifer Rozier (JR), Daniel J. Weiss (DJW), Sunetra Gupta (SG), Peter W. Gething (PWG).

Author contributions: UD conceived the study with PWG; assembled or digitised all datasets; conducted boosted regression tree modelling; designed basic framework for, and analysed outputs from, Bayesian hierarchical model; generated all displayed graphics and tables; wrote all sections of manuscript.

EC conducted statistical analysis and implementation of Bayesian hierarchical model with input from UD.

HG and DJW provided covariates.

JR provided maps of *Pf*PR displayed in Figure 5.2.

PWG conceived and oversaw the study.

All authors reviewed and approved the final manuscript.

As her supervisors, we certify that the statements of contribution listed here are a fair representation of Ursula Dalrymple's work:





Professor Peter W. Gething Dr Ewan Cameron Professor Sunetra Gupta

17th September 2018

* * *

During my DPhil I have also been involved with other projects conducted by the Malaria Atlas Project and collaborators that were not directly related to my thesis but were conducted in parallel with the work detailed above:

1. Weiss DJ, Nelson A, Gibson HS, Temperley W, Peedell S, Lieber A, et al. A global map of travel time to cities to assess inequalities in accessibility in 2015. Nature. 2018;553:333–336.
2. Gething PW, Casey DC, Weiss DJ, Bisanzio D, Bhatt S, Cameron E, et al. Mapping *Plasmodium falciparum* mortality in Africa between 1990 and 2015. N Engl J Med. 2016; 375 (25), 2435-2445.
3. Battle KE, Bisanzio D, Gibson HS, Bhatt S, Cameron E, Weiss DJ, et al. Treatment-seeking rates in malaria endemic countries. Malar J. 2016;15 (20).
4. Bhatt S, Weiss DJ, Mappin B, Dalrymple U, Cameron E, Bisanzio D, et al. Coverage and system efficiencies of insecticide-treated nets in Africa from 2000 to 2017. eLife. 2015; 4, e09672.
5. Mappin B, Cameron E, Dalrymple U, Weiss DJ, Bisanzio D, Bhatt S, et al. Standardizing *Plasmodium falciparum* infection prevalence measured via microscopy versus rapid diagnostic test. Malar J. 2015; 14 (460).

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Abbreviations

ACT	Artemisinin combination therapy
AFRO	World Health Organization Regional Office for Africa
AIC	Akaike information criterion
ARI	Acute respiratory infection
BRT	Boosted regression tree
BRT_{bg}	Boosted regression tree model of the suitability for fever without a malaria infection
BRT_{treat}	Boosted regression tree model of the propensity for all-cause fever treatment-seeking
DHS	Demographic and Health Survey
EIR	Entomological inoculation rate
EVI	Enhanced Vegetation Index
F-	Fever negative
F+	Fever positive
FIND	Foundation for Innovative New Diagnostics
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GLM	Generalised linear model
GPS	Global Positioning System
GRUMP	Global Rural-Urban Mapping Project
HMIS	Health management information system
IMCI	Integrated management of childhood illness
INLA	Integrated nested Laplace approximation
ITN	Insecticide-treated bed net
LST	Land Surface Temperature
MAF	Malaria-attributable fever

MAP	Malaria Atlas Project
MCF	Malaria-coincident fever
MDA	Mass drug administration
MIS	Malaria Indicator Survey
MSAT	Mass screen and treat
MSF	Médecins Sans Frontières
NMCP	National malaria control programme
NMFI	Non-malarial febrile illness
NTD	Neglected tropical disease
P-	*Plasmodium falciparum* negative
P+	*Plasmodium falciparum* positive
PAR	Population at risk
PCR	Polymerase chain reaction
*Pf*PR	*Plasmodium falciparum* parasite rate (prevalence)
$PfPR_{0-5}$	*Plasmodium falciparum* parasite rate in children under 5 years of age
$PfPR_{2-10}$	*Plasmodium falciparum* parasite rate in children aged 2-10 years of age
RDT	Rapid diagnostic test
SLOOCV	Spatial leave-one-out cross-validation
SMC	Seasonal malaria chemoprevention
UN	United Nations
WHO	World Health Organization
WHO/FIND PTP	World Health Organization/Foundation for Innovative New Diagnostics Product Testing Program (for RDTs)
WWARN	Worldwide Antimalarial Resistance Network

Chapter 1 - Introduction

1.1. Biology and epidemiology of *Plasmodium falciparum* malaria in Africa

Human malaria is caused by one of six species of the protozoal parasite *Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale curtisi, Plasmodium ovale wallikeri, Plasmodium malariae* and *Plasmodium knowlesi*, and is transmitted between humans (and long-tailed macaques, in the case of *P. knowelsi*) by *Anopheles* mosquitoes. In 2016, the World Health Organization (WHO) estimated that there were a total of 216 million cases of human malaria in 91 countries worldwide, with an estimated 445,000 deaths, 91% of which were in the WHO African Region [1]. Whilst *P. vivax* is geographically the most widespread of the human malarias [2], *P. falciparum* infection is associated with more severe disease, resulting in a higher burden of morbidity and mortality. The prevalence and incidence of *P. falciparum* malaria is highest in sub-Saharan Africa, where it is responsible for an estimated 99% of malaria cases [1].

Over the past two decades, prevalence, incidence and mortality from *P. falciparum* malaria infection have dramatically reduced across the African continent. A model utilising the most comprehensive dataset of *P. falciparum* prevalence observations from literature and surveys by Bhatt and colleagues [3] estimates that the prevalence of *P. falciparum* declined by 40% across the continent over the time period 2000-2015. This reduction in prevalence resulted in 663 million cases of *P. falciparum* malaria being averted within the same time period [3], and a decrease in *P. falciparum* malaria-attributable deaths from 12.5 per 10,000 population in 2000 to 5.4 in 2015 [4]. However, since 2015, decline in *P. falciparum* prevalence has begun to stagnate and plateau, with some countries seeing increases in reported malaria cases [1].

Funding for anti-malaria interventions increased by more than 2.5 times globally between 2005 and 2014, rising from US$ 960 million to US$ 2.5 billion [5]. The increased availability and utilisation of insecticide-treated bed nets, antimalarial treatments in the form of artemisinin combination therapies (ACTs) and indoor residual spraying is accredited with responsibility for the majority of the decline in prevalence over the time period in sub-Saharan Africa [3]. Funds received by sub-Saharan African countries during the period of decline were highly heterogeneous and, whilst countries with a higher population-at-risk (PAR) in general received higher levels of funding, there was inequity when funding levels are considered at a per-capita-at-risk scale [6, 7].

Despite the declines in malaria prevalence and incidence, malaria is still a major cause of morbidity and mortality in sub-Saharan Africa, and predominantly affects children under five years of age. Approximately three-quarters of *P. falciparum* associated deaths are amongst children under five years of age [4], and incidence is estimated to be markedly higher in children under five at all levels of transmission intensity [8]. Partial immunity to malaria is acquired with repeated malaria exposure over time, leaving children disproportionately affected by the disease. After the period of neonatal partial immunity from maternal antibodies ends, acquired immunity develops at a rate determined by the frequency of infection [9], leading to lower frequency of severe illness and lower parasite density infections amongst older children and adults in high exposure areas [10]. For this reason, immunonaive returning travellers also experience infections with higher parasite densities and more severe clinical illness. As children are disproportionately affected by severe illness from *P. falciparum* infection, many malaria monitoring and evaluation efforts focus primarily on targeting children under five years of age.

1.2. The role of treatment in reduction of *P. falciparum* prevalence and incidence

1.2.1. Available treatments for *P. falciparum*

Since 2006, the WHO has recommended ACTs as the first-line treatment for *P. falciparum* malaria infection. ACTs combine an artemisinin derivative (such as dihydroartemisinin, artesunate or artemether), which acts to clear parasites quickly and effectively from the blood, in combination with another antimalarial drug (such as lumefantrine, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, etc.), which persists in the blood longer, acting as both a prophylactic agent and to prevent recrudescence [11]. ACTs were developed in an era of increasing resistance to existing antimalarial medications as both a reliable drug for which resistance had not yet been observed, and as a method of preventing resistance to ACTs in the future by combining two or more antimalarial therapies. ACTs have been accredited with 19% of malaria prevalence reductions in sub-Saharan Africa amongst children aged 2-10 years between 2000 and 2015 [3]. ACT resistance has now been observed in a number of locations in South East Asia, and has been reported in returning travellers from Equatorial Guinea [12–15]. ACT resistance, should it become widespread amongst *P. falciparum* parasites, would undo years of prevalence declines and lead to increases in morbidity and mortality if an alternative, equally effective treatment does not emerge.

Within a clinical setting, a febrile child presenting symptoms at a health facility in a malaria-endemic country is not always guaranteed to receive an ACT. Multiple factors contribute to this potential outcome. First, the clinician must diagnose whether the child has a malaria infection. In most malaria-endemic countries, malaria is typically the suspected underlying cause of a fever, but in the absence of parasite-based diagnosis, many clinicians rely on clinical algorithms (typically involving identification of an enlarged spleen in addition to fever) to diagnose malaria infections [16]. In the past,

parasite-based diagnoses were uncommon in clinics, limited to those with microscopy facilities; and even then microscopic diagnosis had the potential to provide unreliable results unless conducted by a well-trained clinician [17]. In recent years, parasite-based diagnosis has become a mainstay for malaria diagnosis in clinics, due in part to a 2010 directive from WHO to recommend diagnosis with rapid diagnostic tests (RDTs) or microscopy before administering antimalarials [18]. Manufacturer deliveries and national malaria control program (NMCP) distributions of RDTs have risen sharply over the past decade. Disbursements of RDTs peaked in 2013 and have since begun to plateau; this is a worrying statistic given only 52% of suspected malaria cases presenting to public clinics received a parasitological test in surveys conducted between 2014 and 2016 [1]. Febrile children presenting at private clinics and informal clinics (such as pharmacies) are even less likely to receive a parasite-based diagnosis, with only 36% and 10% of febrile children receiving a diagnostic in the same surveys in private and informal clinics, respectively [1].

After a diagnosis of malaria is made (whether parasite-based or presumptive) the clinician will typically provide medication. Studies show that only 19.7% of paediatric *P. falciparum* cases (i.e. blood parasites and a fever) received an ACT in sub-Saharan Africa in 2015 [19]. Despite high treatment failure rates with other antimalarials, many barriers to receiving first-line treatment are present, including stock-outs in facilities [20], patients or their guardians opting for non-first-line antimalarials due to cost [21] (particularly a problem in informal facilities, and exacerbated in countries where travel times to formal facilities are high [22]), lack of education on the part of the child's caregiver [23], and poor staff training and adherence to guidelines [24–28].

In many sub-Saharan African countries, particularly those in the Sahel sub-region, malaria is highly seasonal and peaks during and shortly after the rainy season. Rainy

seasons are typically short-lived, with many African countries experiencing two or more rainy seasons each year. In highly-seasonal *P. falciparum* transmission settings the WHO has, since 2012, recommended seasonal malaria chemoprevention (SMC) [29] using sulfadoxine-pyremithine plus amodiaquine administered to at-risk children at one-month intervals throughout the high transmission season. The choice of non-first-line antimalarials for SMC allows ACT to be used for the treatment of clinical cases when SMC is ineffective. SMC antimalarial medications are also cheaper than ACTs, rendering them more cost-effective [30]. Based on seasonality and incidence data, up-scaling of SMC could prevent millions of cases and tens of thousands of deaths [31]. In 2016, 15 million children across 12 countries in sub-Saharan Africa were protected by SMC, including almost all administrative districts in Mali, Burkina Faso and Togo, with 91% of eligible children in SMC-implementation districts receiving SMC at least once [1]. Measuring the proportion of malaria infections that receive treatment is critical for both assessing coverage gaps in reducing malaria transmission, and for quantifying the effect that effective treatment has on reducing malaria prevalence and incidence [3]. In this thesis, I will provide estimates of the coverage of antimalarial medications amongst children with a *P. falciparum* malaria infection, and provide insights into the proportion of all paediatric fevers that would be resolved through antimalarial medication.

1.2.2. Barriers to seeking treatment

In household surveys conducted between 2014 and 2016, treatment was sought for 45.5% of children who had a fever at any point during the two weeks preceding the survey [32]. Febrile malaria cases that do not seek treatment for their symptoms pose a major problem for elimination of the disease; by combining high parasite densities (which are usually present in febrile individuals) and a lack of treatment, their potential for onward

transmission of the disease is high. Closing this treatment coverage gap is essential for elimination, but several noteworthy barriers make this endeavour challenging. Studies in Kenya show that affordability (of both medicines and transport to the health facility) is a common concern for febrile individuals and caregivers, and thus cost acts as a barrier to treatment-seeking [33–36]. Poor perceptions of the effectiveness of treatment received were also cited as reasons for not seeking treatment [37, 38]. Additionally, lack of trust in clinicians with regards to their training and knowledge can dissuade caregivers from seeking treatment, especially relating to visiting community health workers [39, 40]. Distance to the health facility is cited as a common reason for choosing not to seek care; this is exacerbated when combined with household wealth, owing to transportation costs [34, 40, 41]. Household-level factors may also affect the likelihood that a caregiver seeks treatment for their children. For example, studies in Sri Lanka and Uganda have shown differences in treatment-seeking by the birth order of the child [42, 43]. Finally, studies in Sudan, Zambia and Kenya show that caregivers for febrile children are likely to try home remedies first before seeking treatment. Such remedies include herbal medicines, antipyretics, or supplies of remaining antimalarial medications at home [44–46] that are unlikely to be first-line antimalarials and thus have a higher probability of treatment failure. While not technically a barrier to treatment-seeking, self-diagnosis and home remedies can delay or prevent the administration of effective treatment, both of which prolong the amount of time the infection is patent for onwards transmission.

1.2.3 Conventional burden estimation methodologies

The rate at which febrile individuals seek treatment is currently used as a critical adjustment for malaria case numbers during burden estimation [47, 48]. Burden estimates are published each year in the WHO World Malaria Report in the form of estimated total

cases within each malaria-endemic country for the preceding year. These estimates are derived from one of two sources. The first method, which is referred to throughout this thesis as the "cartographic approach" for burden estimation, relies on conversion of malaria prevalence maps into estimates of malaria incidence (i.e. estimates of the number of truly symptomatic malaria cases per year) through an established modelling approach [49]. The second method, referred to as the "adjusted case-count approach" throughout this thesis, generates burden estimates using a number of steps. First, the WHO receives information from the NMCP in each malaria endemic country, consisting of aggregated data from clinics across the country, which report to the NMCP via the country's health management information system (HMIS). The three metrics reported to the HMIS which are subsequently used for burden estimates are: *i)* the number of confirmed (i.e. received a diagnostic test) and unconfirmed (i.e. suspected malaria without diagnostic testing) cases; *ii)* the number of cases confirmed by microscopy or RDT; and *iii)* the total number of slide or RDT examinations undertaken. Next, the unconfirmed cases are multiplied by the positivity rate of microscopy examinations, and added to the confirmed cases to generate a "total" count of confirmed cases seen in clinics that report to the HMIS. Then the total number of cases in clinics is revised using a reporting completeness metric, which is self-reported by countries or approximated by the WHO, to adjust for the clinics that had missing reports, and further adjusted for the clinics that do not report to the HMIS (i.e. private or informal clinics). Finally, the estimated number of confirmed cases in all clinics (regardless of whether they report to the HMIS) is adjusted to account for the proportion of cases that do not seek treatment, as estimated using the treatment-seeking rate. This is derived using information on the treatment-seeking rate amongst children under five years of age with a fever of any cause, which is extracted from household survey datasets published by the DHS Program and by the UNICEF Multiple

Indicator Cluster Surveys (MICS). For the purposes of burden estimation, the treatment-seeking rate for adults and older children is assumed to be equivalent to the rate for children under five years of age [47].

In this thesis, several elements of current conventional burden estimation approaches are investigated. While the cartographic approach and the adjusted case-count approach ostensibly seek to measure the same metric (i.e. total number of malaria cases), they fundamentally measure different metrics. The cartographic approach, through use of models of the rate of symptomatic malaria-attributable illness at differing underlying *P. falciparum* prevalence levels, measures only the total number of malaria-attributable fevers (MAF). The adjusted case-count approach, however, uses "confirmed malaria cases" (i.e. malaria parasites and a fever, regardless of the fever's underling cause) reported to clinics. In practise, the estimates generated through this approach represent the total number of malaria infections that are accompanied by a fever of any underlying cause, rather than fevers that are causally attributable to malaria. This thesis also addresses an oversight of the adjusted case-count approach for estimating total community cases: is the treatment-seeking rate for MAF equivalent to the treatment-seeking rate for all-cause fever? If the proportion of MAF and non-malarial febrile illness (NMFI) presenting at clinics differs from the proportion of MAF and NMFI in the community, estimates of community malaria burden may be inaccurate if generated using treatment-seeking rate for all-cause fever.

1.3. Malaria attributable fever: definition, methods used for measurement in existing literature, and defining the difference from malaria-coincident fever

In this thesis, the term "malaria-attributable fever" defines any fever where a *P. falciparum* malaria infection is the true underlying cause of the fever. This definition includes co-infections where malaria and the NMFI are co-symptomatic, and are therefore jointly the underlying cause of the fever. This definition also includes fevers that are co-infections with an asymptomatic NMFI, as the malaria infection is the only underlying cause of the fever. This definition does *not* include co-infections where the malaria infection is asymptomatic and the NMFI is the only underlying cause of the fever.

Febrile illness is a major component of paediatric morbidity, with 37.4% of children in DHS Program datasets between 2006-2014 experiencing a fever within the past two weeks, as recalled by their caregiver [32]. Despite evidence that malaria prevalence has declined in recent years, many fevers are still presumptively treated as malaria [1, 50–53]. While presumptive treatment still persists, the roll-out of RDTs has led to a rapid increase in parasite-based diagnosis, with 87% of suspected cases in public, HMIS-reporting facilities in the WHO African region receiving a parasite-based diagnosis in 2016, up from 36% in 2010 [1].

While this increase in parasitological testing aids in reducing malaria overtreatment, it did not coincide with roll-outs of routine pathological diagnosis for other NMFIs. This is problematic because routine pathological diagnosis for other NMFIs is typically unavailable and clinicians must instead rely on physiological examinations of febrile individuals, as described in the next sub-section. The prevalence of non-malarial febrile illnesses is largely uncharacterised, and as such, an unknown proportion of malaria-positive fevers are likely to be coincidental with an NMFI. Asymptomatic malaria

infections are well-documented across all age groups [54–56], and often at parasite densities high enough to be detected by RDTs and microscopy [57–64]. NMFIs may be the underlying cause of the fever in cases when an individual also has an asymptomatic malaria infection, and as such could result in overestimation of the number symptomatic malaria cases in clinics.

Differentiating between a malaria-attributable fever and a malaria infection that is simply coincident with but not causing a fever is challenging, particularly when potential NMFI co-infections cannot be pathologically diagnosed. In previous analyses, numerous approaches have been employed for estimation of the proportion of malaria-positive fevers that are actually due to malaria. An often-utilised approach relies on knowledge of the parasite density of the infection, and defines a "pyrogenic threshold"; a parasite density over which malaria infections will cause fever. This pyrogenic threshold depends on a number of factors. Dicko *et al.* found that the pyrogenic threshold was highly dependent on seasonality, with a lower pyrogenic threshold in the dry season compared to the rainy season in a study in Bandiagara district, Mali [65]. Age has also been found to affect pyrogenic threshold (probably due to exposure-related immunity), with the pyrogenic threshold decreasing with age [66, 67], although a study by McGuiness and colleagues found a lower density was required to cause fever in infants compared to children [68]. Logistic regression methods have been used to define the pyrogenic threshold within sub-sets of populations, based on individual-level factors, including an analysis of the difference in the rate of MAF in the high and low season by age in Burkina Faso, and in the highlands of western Kenya [59, 69], and individual bed net use in a study in Dielmo, Senegal [70]. The pyrogenic threshold approach is also used to determine the probability of an infected individual developing symptoms within some transmission models of malaria. In the OpenMalaria transmission model, an age- and

exposure-related pyrogenic threshold is used to determine the probability of developing a symptomatic malaria infection [71]. The pyrogenic threshold is modelled indirectly in the Disease Transmission Kernel malaria transmission model, and is reliant on the level of pro-inflammatory cytokines, derived as a function of the number of infected red blood cells, which itself is a function of parasite density [72]. The pyrogenic threshold approach is not uniformly adopted across transmission models, however, with some deriving risk of clinical disease as a function of exposure-related immunity [73].

Empirical estimations of the proportion of fever cases attributable to malaria can be used as an alternative to pyrogenic threshold approach. Such estimates are made using the expected rate of non-malarial fever amongst malaria-positive febrile individuals, where the "excess" of fever in the malaria-positive febrile individuals not explained by non-malarial fever can be directly attributed to malaria. The rate of NMFI is derived by measuring the rate of fever in malaria-negative individuals, and therefore relies on having paired diagnoses of malaria and fever across a population [74, 75]. Such approaches are useful for datasets where parasite density is unknown, such as cross-sectional household surveys conducted by the DHS Program [32]. In this thesis, this empirical approach is used for defining the rate of malaria-attributable fever and thus underpins the predictive model utilised in the forthcoming chapters.

1.4. The burden and causative agents of fever amongst African children

The syndrome "fever", referring to heightened body temperature, can be caused by a variety of medical conditions of both infectious and non-infectious origins. Non-infectious fevers can originate from autoimmune conditions, environmental conditions (hyperthermia), inflammation, cancer, or can be drug-induced [76]. Infectious causes can be viral, bacterial, helminthic or protozoal in origin.

The precise burden of "fever" as a syndrome has not been quantified at a continental level (e.g. through the annual Global Burden of Disease study, which quantifies the burden of other syndromes such as diarrhoea [77] and anaemia [78]). National-level fever metrics can be extracted from household survey datasets from sources such as the DHS Program and national Ministries of Health in malaria-endemic countries, with the key metrics being the two-week fever recall that is typically included for groups at high risk of malaria (such as young children and pregnant women) [32]. Additionally, the HMIS in many malaria-endemic countries collect information on the number of fever cases presenting at health facilities by aggregating the number of suspected malaria cases (typically "suspected" due to the presence of a fever).

The WHO provide a step-by-step protocol for clinical diagnosis and treatment of paediatric fevers as part of their Integrated Management of Childhood Illness (IMCI) protocols, which has been implemented in more than 100 countries worldwide [79]. The IMCI protocols are a holistic approach to child health, which aim to improve both clinician training and paediatric health outcomes. For febrile illness in sub-Saharan Africa, IMCI guidelines recommend that the child first receives a parasite-based diagnosis for malaria (and antimalarial medication if the test is positive) and is examined for other symptoms of non-malarial infections (such as checking for rashes and respiratory observations) [80].

Parasite-based diagnostic tests for many of non-malarial febrile illnesses are uncommon in outpatient clinical settings, and typically require access to specialist equipment that is not cost- or time-effective for routine diagnosis. Rapid and reliable point-of-care tests exist for HIV and syphilis infection (in addition to malaria) [81], but these tests represent the exception, rather than the rule. Polymerase chain reaction (PCR) and serological testing are expensive and laborious procedures for disease diagnosis, but remain the only

methods available for pathogen-based diagnosis of a number of major important pathogens in sub-Saharan Africa. Similarly, point-of-care tests exist but are non-routine for Ebola virus disease which typically relies on diagnosis via PCR at regional laboratories [82]; brucellosis [83] and Q fever [84] both typically require PCR diagnosis; leptospirosis diagnosis relies on PCR or serological tests [85]; and yellow fever and arbovirus (dengue, chikungunya) diagnoses rely on serological tests post-infection. Routine, laboratory-based diagnostics are available for a number of other major causes of paediatric fever, but they are unable to provide an immediate diagnosis. In contrast, the Xpert MTB/RIF rapid diagnostic system has been developed for tuberculosis, but is not cost-effective for routine diagnosis [86]. As such, microbiological sputum examination (time-intensive) or chest X-ray (cost-prohibitive in most African clinics) remain the most heavily utilised for tuberculosis diagnosis. *Salmonella spp.* diagnosis requires culturing of stool or blood samples [87]; visceral leishmaniasis is diagnosed routinely using light microscopy, which requires laboratory equipment and a trained microscopist [88]. Diagnosis of *Streptococcus spp.* is typically achieved using bacterial culture, although rapid diagnostics are under development [89]; rapid diagnostic testing of *Cryptococcus spp.* has shown to be sensitive but has not yet been fully rolled-out across sub-Saharan Africa, where case fatality rates from cryptococcal meningitis can reach 30-50% [90]; and a complex array of laboratory procedures for rickettsiosis render diagnosis unlikely in a clinical setting [91]. Acute respiratory infections (ARI), which often cause paediatric fevers, are typically diagnosed using IMCI guidelines based on syndromes, and would benefit from a multiplex routine diagnostic to differentiate between bacterial and viral causes of ARI [81].

A corollary of the lack of rapid diagnostics for NMFI is that prevalence data (and often also consensus on the vectors, reservoirs, modes and seasonality of transmission [92]) for

these diseases is lacking and/or not well distributed over the spatial and temporal domain of the disease. These limitations constitute a barrier for quantitative estimations of disease burden, either through incidence counts or cartographic prevalence estimates. A number of initiatives have provided qualitative information on the distributions of NMFI worldwide. The Worldwide Antimalarial Resistance Network (WWARN) collates published studies on observations of NMFI, documenting both the global location and the prevalence of infection, and makes these data publicly available for visualisation [93]. These studies provide qualitative information on the geographical spread of NMFI in sub-Saharan Africa, but do not provide the requisite spatiotemporal coverage for geospatial modelling of individual NMFIs. Additionally, a recent review of causes of NMFI in Africa summarised recent studies concerning the pathogens that comprise NMFI in Africa and found that causes of NMFI in Africa were widespread. Diseases included in this study were: *i)* bacterial pathogens, such as *Salmonella enterica* and *S. enterica* serovar Typhi (which were together responsible for as many as 46% of fever cases in Malawi from 1998-2016 [94]), *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis*. Also included were *i)* zoonotic bacteria such as leptospirosis, Q fever, brucellosis and rickettsiosis; *ii)* protozoal infections such as trypanosomiasis; *iii)* fungal infections such as *Cryptococcus spp*; and *iv)* viral infections such as arboviruses (dengue, chikungunya), yellow fever, and viral infections of the lower respiratory tract [95]. The burden of a number of NMFIs are estimated annually as part of the annual Global Burden of Disease study [96], but predominantly only at national (or global) scales.

In addition to malaria mapping efforts, global or multinational cartographic estimates have been generated for a small number of infectious diseases, including a number that contribute to NMFI globally, such as dengue virus [97, 98], *P. vivax* malaria [99], *P. knowlesi* malaria [100], Zika virus [101], soil-transmitted helminths [102], lymphatic

fileriasis [103], and Lassa fever [104]. Despite these efforts, approximately only 4% of all global infectious diseases identified with a strong rationale for mapping have been mapped [105].

Understanding the spatial heterogeneity of NMFIs is crucial to understanding the probability of a malaria-positive fever coinciding with an NMFI, thus affecting the proportion of malaria-positive fevers that are likely to be malaria-attributable. In this thesis, I generate spatiotemporal estimates of all-cause fever, non-malarial fever, and malaria-attributable fever prevalence at a 5km x 5km pixel resolution across sub-Saharan Africa, bringing new insights into the spatial and temporal heterogeneities in fever prevalence.

1.5. Effective treatment rate: definition, previous attempts to measure from literature, rationale for our approach

Understanding the proportion of malaria infections that receive and adhere to effective treatment (and are subsequently cured) is critical for both understanding the burden of *P. falciparum* malaria and identifying coverage gaps in education, treatment-seeking and provision of effective antimalarial medication. While malaria prevalence and incidence has shown continuous decline over the past two decades, progress is slowing and reported malaria cases have begun to increase in a number of sub-Saharan African countries (in part as a consequence of increased diagnostic testing) [1]. Methodologies to measure the proportion of "clinical malaria events" (that is, a malaria infection followed by a malaria-attributable fever) take a multi-faceted approach, by first understanding the rate at which febrile individuals seek treatment, and for those that do seek treatment, understanding what happens to them at the treatment location they visit (i.e. receipt of a parasite-based diagnosis, and receipt of an effective antimalarial) [106]. Together, the

rates at which treatment is sought and effective treatment is appropriately prescribed at the clinic-level can be described as the "systems effectiveness"; that is the proportion of clinical malaria cases that are effectively treated by the national health system [106]. A major synthesis of health system effectiveness and the "effective treatment rate" – which includes home treatment and drugs obtained from informal sellers – was published by Galactionova *et al.* in 2015, using DHS Program datasets as response data [106]. In this study, Galactionova and colleagues present six key indicators for effective coverage and malaria service performance indicators for 43 sub-Saharan African countries in 2011-2012: *i)* effective coverage (i.e. the proportion of malaria-attributable fever episodes that are cured), *ii)* access to any care provider, *iii)* access to a formal care provider with provisions for treating *P. falciparum, iv)* compliance of facilities with the first-line antimalarial treatment, *v)* adherence of patients to antimalarial medication, and *vi)* the overall cure rate (i.e. what proportion of treated malaria-fevers are cured by the treatment received). An individual who is included amongst effective coverage should be, therefore, one who: *i)* had a malaria infection and a fever, ii) received effective treatment for the malaria infection (regarded in this study as treatment with the ACT artemether-lumefantrine, the first-line treatment recommended across sub-Saharan Africa [1]; additionally the "effective coverage" metric does not require that the child received the treatment from a formal clinic location, simply that they received an appropriate, high-quality dosage), and *iii)* adhered to the treatment and was subsequently cured. To measure this effective coverage metric, Galactionova and colleagues extracted DHS Program data on the two-week fever prevalence of children under 5 years of age, the rate at which they sought treatment for their fever, and the type of medications received at the treatment location. The DHS Program data is a comprehensive source of health information that can be mined to gather a semi-complete view of the path between

malaria infection and cure; however the authors did not utilise information on the parasitological diagnosis of malaria in surveyed children that is available from many of the DHS Program surveys. The authors also did not use information on whether the clinician tested the child with an RDT at the point of treatment (available in most DHS Program surveys), which can be used as an indicator of presumptive or parasite-based diagnosis. In their study, the authors augmented the DHS Program survey information with a literature review and health expenditure data characterising *i)* supply-side inefficiencies relating to drug supply (considering that many ACTs delivered to countries are not actually, for numerous reasons, prescribed to individuals with malaria infections; this can render the "theoretical efficiency" of ACTs to as low as 38% at the point of delivery [106, 107]); *ii)* compliance of health service providers to recommended first-line treatment; and *iii)* adherence of patients to antimalarial medication. With this additional information the authors were able to generate, for each country, a comprehensive overview of the national-level coverage gaps for treatment of malaria cases. The authors found that the total effective coverage for malaria cases varied significantly across sub-Saharan African countries, from 8% (of total malaria cases receiving and adhering to an effective cure) to 72%, with effective coverage particularly low in Central and North East Africa. Although this analysis effectively identifies gaps in particular areas that would help achieve higher effective coverage rates, it does not identify or quantify the effect of specific individual-level factors that are directly responsible for elements such as low treatment-seeking rates or low adherence rates [106]. The effect of individual-level factors on the probability of receiving an ACT was assessed by Bennett and Bisanzio *et al.* in 2017, utilising RDT results and treatment-seeking outcomes from individuals in DHS Program datasets by matching each individual with demographic information about their household to assess the effect these factors have on ACT coverage [19]. The authors

found that greater household wealth, higher levels of maternal education, and ownership of insecticide-treated bed nets increase the likelihood of an individual receiving an ACT. Additionally, the authors found that health clinics in the public sector were more likely to stock and issue ACTs compared to those in the private sector; this is a finding corroborated by literature [108, 109]. A review by Rao *et al.* collated indicators of barriers to successful malaria treatment at the clinic level, including published observations of ACT stock-outs, with delivery delays and poor resource allocation providing further bottlenecks. The authors also identify studies detailing poor health facility adherence to ACT prescription guidelines [22].

In this thesis, I aim to present an updated model for assessing systems effectiveness and effective coverage across sub-Saharan Africa, that addresses these individual-level factors, draws on all pertinent information from DHS Program surveys, and ultimately distinguishes between truly malaria-attributable fevers and those infections simply coincident with a non-malarial fever, to understand the proportion of fever cases that are effectively cured by antimalarial medication.

1.6. Thesis aims and rationale

This thesis aims to refine methodologies for estimating the burden of malaria, and provides estimates of the proportion of malaria infections in children under 5 that receive effective antimalarial treatment at a national level in malaria-endemic countries in sub-Saharan Africa. Malaria caused by *P. falciparum* remains a major cause of morbidity and mortality amongst African children, and the prevalence and incidence of *P. falciparum* across the continent has been well-characterised in recent years. However, non-malarial febrile illnesses, for which routine parasite-based diagnosis is uncommon, could be mistaken for malaria in a clinical setting, particularly when coincident with an

asymptomatic malaria infection. The prevalence of most non-malarial febrile illnesses is largely unknown, further confounding this issue.

The first research chapter of this thesis, Chapter 2, aims to provide spatiotemporal estimates of the prevalence of: *i)* all-cause fever, *ii)* malaria-positive fever, *iii)* malaria-attributable fever (both as a single metric, and as a proportion of malaria-positive fevers), and *iv)* non-malarial fever. This is achieved by collating paired observations of fever and malaria positivity amongst children under 5 years of age from nationally-representative household survey datasets, and using environmental and socio-demographic variables to generate a predictive model of all four fever metrics described above. By estimating these four metrics, the results presented in Chapter 2 show that only a fraction of malaria-positive fevers at community-level amongst children in sub-Saharan Africa are causally attributable to malaria. This refined understanding of febrile illness in malaria-positive children indicates that malaria burden estimations may overestimate clinical malaria cases (i.e. symptomatic illness causally attributable to malaria) if the adjusted case-count approach is used to generate burden estimates.

Chapter 3 aims to address confounding issues associated with using DHS Program datasets (and similar surveys) for pairing RDT diagnoses with fever recall. Within such surveys, parasite-based diagnoses of malaria positivity are conducted on the day of interview, but observations of fever positivity are based on two-week recall by the caregiver. As such, the possibility exists that a child who had a malaria infection and a fever in the past two weeks sought and received effective antimalarial treatment, and has since had their malaria infection cleared, with blood antigen concentrations reduced sufficiently to appear RDT-negative by the time of interview. This is problematic for the modelling approach used in the preceding chapter, which relies upon two-week fever recall and malaria positivity (derived from the interview RDT result) as paired

observations of concurrent malaria infection and fever. In Chapter 2, RDT outcomes were used as an indicator of malaria positivity during the two weeks preceding the survey, as they typically represent a more accurate observation of two-week malaria infection compared to microscopy (due to persistent antigenicity, as described above), but the possibility still exists that malaria antigens may have reached a sufficiently low quantity within two weeks to present negative by the time of interview. In Chapter 3, observations of persistent antigenicity via RDT from literature are collated, and a Bayesian survival model is used to predict the time taken for an infected individual to return a negative RDT. Additionally, the effects of RDT type (based on the specific antigens that the RDT detects), type of antimalarial medication received, and age of patients on the duration of persistent RDT positivity are presented. The outputs from this model are used in later chapters as an adjustment for DHS Program datasets to account for the possibility of individuals within household survey datasets with malaria-attributable fevers seeking and receiving effective treatment and becoming negative prior to the interview. In addition to improving the accuracy of household survey information, the results of this chapter may be instructive for clinicians who, when presented with an RDT-positive individual with a recent history of antimalarial treatment, must decide whether the individual is truly RDT-positive (via treatment failure, or re-infection) or whether to investigate further for potential non-malarial febrile illness as the underlying fever cause.

The results presented in Chapter 2 indicated that current burden estimates may overestimate the number of clinical malaria cases if data on the number of malaria-positive fevers at clinics (reporting to the HMIS) is used to generate burden estimates. In Chapter 4, I present estimates of the proportion of fevers presenting at public health clinics (i.e. clinics that are likely to report to the HMIS) that are *i)* malaria-attributable, *ii)*

attributable to co-symptomatic malaria and non-malarial causes, *iii)* caused by NMFI but co-incident with an asymptomatic *P. falciparum* infection, and *iv)* caused by NMFI without a *P. falciparum* infection in 41 country-years with a DHS Program household survey in sub-Saharan Africa. The results presented in this chapter are intended to give a more in-depth estimate of the scale of overestimation of malaria cases using burden estimation approaches that use the adjusted case-count approach to generate national burden estimates.

In Chapter 4, the estimates of the proportion of each fever type presenting at public health clinics for each survey are generated using two major steps. First, the relationship between *P. falciparum* malaria prevalence (*Pf*PR) and the prevalence of MAF is modelled. The relationship between malaria prevalence and the prevalence of malaria-attributable fever is not well-characterised. It is often assumed that in areas of low malaria prevalence, the proportion of malaria-positive infections that are directly attributable to malaria is higher than in areas of high malaria prevalence, due to exposure-related immunity that modulates malaria parasite density in the blood and prevents clinical malaria episodes [110]. However, in areas with lower transmission intensity, *P. falciparum* tends to have less population genetic diversity [111], suggesting that fewer overall exposures may be required to develop effective resistance. In order to model the underlying relationship between MAF and *Pf*PR, I present a dataset of collated observations of the proportion of fever episodes that are causally attributable to malaria from a variety of sources, each of which uses a variety of case definitions and methods for determining the presence of a fever (i.e. through measurement, or through personal recall over a defined period). By collating information from a wide variety of sources, I fit a model to determine the underlying relationship between *P. falciparum* malaria-attributable fever and *P. falciparum* prevalence in children under 5 years of age.

The second major step for estimation of the proportion of each fever type amongst febrile children presenting at public health clinics in sub-Saharan Africa involves using the coefficients of the fitted model to re-calibrate the Bayesian hierarchical model presented in the first research chapter. Using the re-calibrated model in conjunction with the adjustment presented in Chapter 3 and a host of new individual-level indicators from the DHS Program household surveys, a model is developed to assign a probabilistic likelihood of a malaria-attributable fever or a non-malarial febrile illness to each febrile individual within the DHS Program datasets. Using information on their subsequent treatment-seeking behaviour, I construct an analysis of the fraction of fevers presenting at public health clinics at a national level for sub-Saharan African countries that fall into each of the four fever types described above. Further, I collate reports of malaria "cases" (i.e. malaria-positive fevers) amongst children under 5 years of age from three sub-Saharan African Ministries of Health, and estimate the proportion that would be causally attributable to malaria in each country. The results presented in Chapter 4 aim to improve understanding of the malaria burden in sub-Saharan Africa by exploring how the raw number of malaria-positive fever cases presenting at health clinics is driven by the malaria prevalence, as well as the prevalence of non-malarial febrile illness.

Chapter 5 aims to draw on the research of all the preceding chapters to present revised estimates of the coverage of effective antimalarial medication for malaria-infected children in sub-Saharan Africa, and to generate estimates of the appropriateness of treatment and adherence to diagnostic guidelines. National estimates are generated of the proportion of malaria infections that do not receive effective ACT because they are *i)* asymptomatic, *ii)* do not seek treatment, *iii)* do not receive an antimalarial, and *iv)* receive a non-ACT antimalarial. Additionally, the model for individual probabilistic attribution of fever presented in the previous chapter is used to disaggregate malaria-

positive fevers into MAF and NMFI, in order to estimate a number of additional metrics to indicate the performance of health systems at treating malaria infections. The proportion of malaria-positive fevers that would not be resolved by ACT treatment alone (because they are causally attributable to NMFI) is estimated. Differences in the proportion of children with MAF that receive an ACT is estimated, and compared to the proportion of children with malaria-positive fevers that receive an ACT. The rates of presumptive treatment (i.e. antimalarial treatment without a parasite-based diagnosis) and under-treatment of malaria-positive fevers (i.e. the proportion that do not receive an antimalarial), and rate of over-treatment of NMFI without a *P. falciparum* infection is quantified for each country-year, separated by public and private clinics. Finally, individual-level sociodemographic indicators from the DHS Program dataset such as wealth, age, education, and insecticide-treated bed net use are investigated to assess their effects on the probability of children being infected with *P. falciparum*, experiencing non-malarial febrile illness, on subsequent treatment-seeking behaviour, and of receiving an ACT at their treatment location.

The outputs presented in this chapter are intended to provide an overview of the proportion of malaria infections that are effectively treated within the country-years with a household survey, identify individual-level, household-level, community-level and clinic-level coverage gaps for reducing the prevalence of malaria-attributable fevers. Sub-sections of the population less likely to seek treatment are identified, and the progress made in over the past decade in increasing diagnostic testing and provision of ACT antimalarial drugs in clinics across sub-Saharan Africa is highlighted.

The research presented in this thesis aims to provide new insights into the true burden of malaria amongst children in sub-Saharan Africa. The disaggregation of malaria-positive fevers into those that are truly malaria-attributable and those that are asymptomatic

malaria infections coincident with a non-malarial febrile illness provides a new understanding of the proportion of fevers that would be resolved by effective antimalarial medication. Coverage gaps are identified in both systemic non-adherence to clinical treatment guidelines, and inequities in ACT coverage and treatment-seeking dependent on factors across multiple societal levels. The identified coverage gaps can be used to guide intervention efforts and improve health system efficiency. This thesis also represents a comprehensive analysis of malaria indicators from household survey datasets from the DHS Program, which will continue to provide new, consistent surveys in the future, allowing the analysis presented here to be updated and for future progress in closing coverage gaps to be assessed.

Lastly, by estimating the continental prevalence of all-cause fever, and the contribution of malaria and non-malarial causes, I provide the first cartographic estimates of non-malarial fever prevalence for sub-Saharan Africa, which can be further utilised for guiding research on the causes of, and treatment for, non-malarial febrile illness.

In summary, the overarching aims of this thesis are:

- To establish a framework for estimating the proportion of paediatric fevers that are causally attributable to malaria, and sub-divide malaria-positive fevers into those that are causally attributable to malaria and those that are causally attributable to NMFI with an asymptomatic malaria infection.
- To map the prevalence of febrile illness amongst sub-Saharan African children, subdividing fevers into MAF and NMFI.
- To extend the framework to encompass the prevalence of MAF and NMFI (both with and without an asymptomatic *P. falciparum* infection) presenting at public health clinics in order to assess the potential for burden overestimation via the adjusted case-count approach.

- To measure ACT coverage amongst malaria-infected children in sub-Saharan Africa.

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Chapter 2 - Quantifying the contribution of *Plasmodium falciparum* malaria to febrile illness amongst African children

This chapter presents cartographic estimates of the prevalence of malaria-attributable fever (MAF), non-malarial febrile illness (NMFI), and all-cause fever (ACF) in children under 5 years of age in an average two-week window annually, between 2006 and 2014. In this chapter, malaria-positive fevers are sub-divided into MAF (where malaria is the underlying cause of the febrile illness), and malaria-coincident fever (MCF, where the underlying cause of the fever is NMFI, and the malaria infection is asymptomatic). The results presented in this chapter were intended to refine the interpretation of the burden of malaria, and present the groundwork for a core concept of this thesis: not all malaria-positive fevers are causally due to malaria. The maps of NMFI and ACF presented in this thesis were also intended to be of interest to researchers trying to define the spatial limits and epidemiology of non-malarial febrile illnesses, and represent the first published continental maps of febrile illness not caused by malaria.

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There are 6 Supplementary Figures and Files associated with this chapter, which can be found in the Appendix to this thesis. Figure 1 – Figure Supplement 1 shows the histogram of the probability integral transform diagnostic used for model validation. Figure 5 – Figure Supplement 1 shows further model fits and validation. Supplementary File 1 shows yearly population-weighted percentages for all-cause fever prevalence, and malaria-attributable fever, malaria-positive fever, and non-malarial febrile illness within all-cause fever amongst population at risk in children under 5 years of age in malaria-endemic Africa, 2006–2014. Supplementary File 2 shows household survey data used in analysis. Supplementary File 3 shows covariates used in BRT, listed by contribution to the final model. Supplementary File 4 shows model parameters and credible intervals of the final multinomial model; final model coefficients.

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RESEARCH ARTICLE

Quantifying the contribution of *Plasmodium falciparum* malaria to febrile illness amongst African children

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Abstract Suspected malaria cases in Africa increasingly receive a rapid diagnostic test (RDT) before antimalarials are prescribed. While this ensures efficient use of resources to clear parasites, the underlying cause of the individual's fever remains unknown due to potential coinfection with a non-malarial febrile illness. Widespread use of RDTs does not necessarily prevent over-estimation of clinical malaria cases or sub-optimal case management of febrile patients. We present a new approach that allows inference of the spatiotemporal prevalence of both *Plasmodium falciparum* malaria-attributable and non-malarial fever in sub-Saharan African children from 2006 to 2014. We estimate that 35.7% of all self-reported fevers were accompanied by a malaria infection in 2014, but that only 28.0% of those (10.0% of all fevers) were causally attributable to malaria. Most fevers among malaria-positive children are therefore caused by non-malaria illnesses. This refined understanding can help improve interpretation of the burden of febrile illness and shape policy on fever case management.

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Introduction

Following new case management guidelines issued by the World Health Organization in 2010, individuals presenting with fever at a health clinic in sub-Saharan Africa have an increased chance of receiving a rapid diagnostic test (RDT) prior to receiving antimalarial treatment (***World Health Organization, 2015***). This reduces the over-prescription of antimalarial drugs to uninfected patients while ensuring patent infections are identified and the parasites cleared through treatment. However, in highly endemic areas, malaria infections are both common and frequently asymptomatic (***Bousema et al., 2014***), meaning that for many patients presenting at health care facilities, their fever and parasitaemia are not causally related.

Ambiguity around causality in RDT-positive fever cases is problematic from both the disease surveillance and health system perspectives. Routine case surveillance systems generally report the incidence of clinical malaria based on counts of febrile individuals with a presumed or confirmed malaria infection (***World Health Organization, 2016***). If the malaria infections in many of these cases are in fact asymptomatic then the resulting case reports will over-represent clinical malaria, even where RDT testing is ubiquitous, leading to an overestimation of morbidity due to malaria. Conversely, fevers caused by another pathogen but coincident with a malaria infection will suffer a systematic under-reporting under this protocol and consequently the disease burden of non-malarial febrile illness (NMFI) will be underestimated. In instances where a febrile individual has both a malaria infection and a NMFI, both infections can simultaneously be the cause of the fever. Indeed co-infections

have been known to modulate both the parasite load of both diseases and the severity of the individual's fever (**French et al., 2001**; **Hartgers and Yazdanbakhsh, 2006**).

Diagnosing and treating NMFI is challenging as symptoms of many of these diseases can be non-specific and similar to malaria, for example bacterial infections such as pneumonia (**Hildenwall et al., 2016**; **Källander et al., 2004**) and meningitis (**Gwer et al., 2007**). Additionally, routine diagnostic tests have not yet been developed or are not commonplace for many of these diseases (**Chappuis et al., 2013**). From the health systems perspective, case management may be inadequate if individuals who receive a positive RDT result but have a co-infection with another pathogen do not receive effective treatment for their fever. For these reasons, there is a pressing need to understand the contribution of malaria to febrile illness and how this varies spatially and temporally across endemic Africa.

Estimating malaria-attributable fever prevalence

The rate of fever associated with (but not necessarily caused by) a malaria infection has been shown to have declined over time in some settings, halving between 1986 and 2007 in one collation of field studies (**D'Acremont et al., 2010**); a trend likely driven by the declining prevalence of malaria over the latter portion of that time period. Estimating the fraction of these fevers in which the malaria infection is the causal pathogen (i.e. the malaria-attributable fraction) is challenging, and various methods have been developed. Attempts have been made to measure the malaria-attributable fraction arithmetically using case-control trials, where the difference in the rate of malaria positivity in febrile and afebrile individuals is used to calculate the attributable fraction (**Ehrhardt et al., 2006**; **Schellenberg et al., 1994**; **Smith et al., 1994**). Alternatively, logistic regression approaches have been developed to estimate causal fractions based on measurements of blood parasite density. This approach has been demonstrated in numerous field trials, including various settings in Kenya (**Afrane et al., 2014**; **Bloland et al., 1999**), in an area of seasonal transmission in Burkina Faso (**Bisoffi et al., 2010**), and in a national survey in Mozambique (**Mabunda et al., 2009**). Computational simulations of malaria transmission can also be adapted to estimate an upper bound on the malaria-attributable fraction of fevers at varying levels of *Plasmodium falciparum* prevalence (*Pf*PR), by monitoring the proportion of parasite-positive individuals within a simulation with a symptomatic infection (here, a symptomatic infection is synonymous with a malaria attributable fever, as co-infections with other pathogens are not typically simulated) (**Griffin et al., 2010**; **Ross et al., 2006**). None of these approaches make use of the rich trove of national household survey data recording malaria infection status as well as fever history that are now available for multiple countries and years from sources such as the DHS Program (**DHS Program, 2017**) and the UNICEF Multiple Indicator Cluster Surveys (**UNICEF, 2017**).

Using household survey data to model malaria-attributable fever and non-malarial febrile illness

Household survey data on malaria infection status and two-week fever history do not allow direct attribution of malaria causality at the individual level. However, when data from multiple individuals are combined, then the causal contribution of malaria infections to fevers within the group can be explored by measuring the extent to which fevers are more common in infected versus uninfected individuals. Building on this intuitive logic, we have developed a multinomial geospatial model (described in detail in Materials and methods) that uses the georeferenced survey data on individual-level malaria infection and fever status to infer the community-level fraction of malaria positive fevers that are either caused by or coincident with underlying malaria infections, and subsequently to map these quantities across sub-Saharan Africa. This refined understanding of the contribution of malaria versus other causes to febrile illness can improve disease burden estimation and interpretation and thus inform case management policy in sub-Saharan Africa.

Results

Model overview

Using a total of 38 household surveys in 24 Saharan African countries collected between 2006 and 2014, we collated 155,369 observations of two-week fever prevalence and RDT diagnostic outcome

for *P. falciparum* in children from 10,606 locations with two modelled predictor variables: *P. falciparum* prevalence in children under five years of age ($Pf PR_{0-5}$); and suitability for fever without a malaria infection. The final hierarchical Bayesian model predicted the proportion of individuals with a fever directly attributable to malaria (hereafter Malaria Attributable Fever, MAF) and the proportion of individuals with a fever not attributable to malaria (hereafter Non-Malarial Febrile Illness, NMFI) within each 5 × 5 km pixel across the stable *P. falciparum* transmission zones on the African continent for each year 2006–2014. These maps were used to derive a series of further metrics as outlined below. Details of model validation are provided in Materials and methods and ***Figure 1—figure supplement 1***.

Prevalence of all-cause fever

All-cause fever prevalence was calculated as the sum of the two metrics estimated by the model: prevalence of *P. falciparum* malaria-attributable fever (MAF) and non-malarial febrile illness (NMFI). In 2014, the prevalence of fever of any cause across the stable limits of *P. falciparum* transmission was 31.0%, and increased slightly over the study period, from 27.0% in 2006. Countries were highly heterogeneous in their overall fever burden, with Niger (53.4%), Gabon (44.9%) and Nigeria (42.8%) having the highest all-cause fever prevalence in 2014. The countries with the lowest fever burden in the same year were Swaziland (4.60%), Eritrea (5.3%) and Somalia (10.1%) The mapped posterior prediction of all-cause fever prevalence across Africa is shown in ***Figure 1***.

Malaria-attributable fevers among malaria-infected children

In 2014, we estimate that less than one-third (28.0%) of all fevers in *P. falciparum* malaria-infected children under five were attributable to *P. falciparum* in any given two-week period. This fraction varied geographically, as shown in ***Figure 2***, with the largest contribution of MAF to malaria-positive fevers in 2014 in Swaziland (86.9%), Eritrea (81.9%) and Somalia (69.9%) and the lowest in Niger (14.7%), Gabon (20.9%) and Nigeria (20.9%). The fraction also varied though time, decreasing continent-wide from 36.1% in 2006 to 28.0% in 2014. Time-series estimates for all countries are shown in ***Figure 3***.

Age of the child was also shown to have an effect on the likelihood of a child developing a malaria-attributable fever. ***Figure 4*** shows the fitted relationship between local $Pf PR_{0-5}$ and the probability of a malaria-attributable fever in the past two weeks, for all children under five years of age in ***Figure 4a*** and in individuals over and under two years of age in ***Figure 4b***. For all children, the probability of an attributable fever grew with $Pf PR_{0-5}$, with a decreasing gradient as $Pf PR_{0-5}$ increases. ***Figure 4b*** shows that this trend is also true for children over two years of age, but the probability of a malaria-attributable fever increases linearly with $Pf PR_{0-5}$ for children under two years of age.

Malaria infections within all fevers

In 2014, we estimate that 35.7% of all fevers in children under five were accompanied by an RDT-patent *P. falciparum* infection, and that this fraction has declined from 48.5% in 2006. The countries with the highest proportion of malaria-positive fevers in 2014 were the Central African Republic (71.0%), Equatorial Guinea (66.2%) and Guinea (65.7%) and the lowest were Ethiopia (1.4%), Botswana (1.6%) and Swaziland (2.9%). ***Figure 5*** highlights the large disparity between the fraction of all fevers that are malaria positive (35.7% continent-wide in 2014) and the fraction of all fevers that are causally attributable to malaria (10.0% continent-wide in 2014).

Contribution of non-malarial febrile illness to all fevers

Non-malarial febrile illness (NMFI) arises in two forms: (i) fevers in malaria-negative individuals, and (ii) fevers in *P. falciparum* malaria-positive individuals where the fever is coincident with but not caused by the malaria infection (hereafter referred to as Malaria-Coincident Fevers, MCF). The sum of these two types of febrile illness are referred to here as NMFI, and are estimated directly by the model. The fraction of all fevers that are due to NMFI increased over the study period, from 82.5% in 2006 to 90.0% in 2014. The countries with the largest fractions of NMFI to all fevers were Ethiopia (99.4%), Botswana (99.2%) and Gambia (98.5%), and the smallest were Guinea (58.2%), Equatorial Guinea (60.4%) and Central African Republic (64.6%).

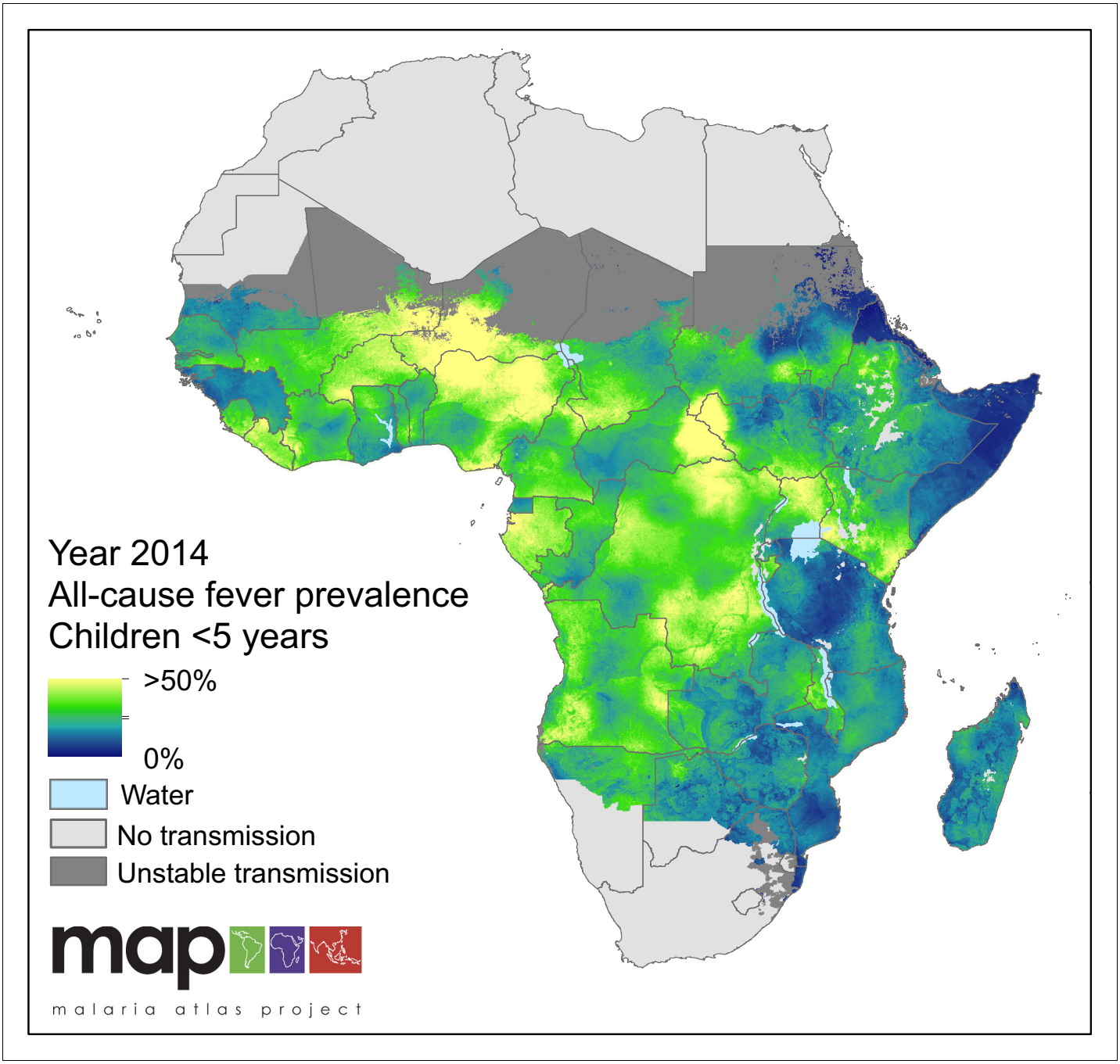


Figure 1. Predicted all-cause fever prevalence within limits of stable *P. falciparum* transmission in children under 5 years of age in 2014.
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The following figure supplement is available for figure 1:

Figure supplement 1. The histogram of the probability integral transform diagnostic.
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The proportion of MCF within NMFI fell over the study period, from 37.6% in 2006, to 28.6% in 2014. The countries that had the highest prevalence of MCF within NMFI were the Central African Republic (55.2%), Burkina Faso (54.9%) and Equatorial Guinea (44.2%), and the countries with the lowest prevalence of MCF within NMFI were Swaziland (0.4%), Botswana (0.8%) and Ethiopia (0.8%). A corollary of this is that Swaziland, Botswana and Ethiopia were also the countries with the lowest

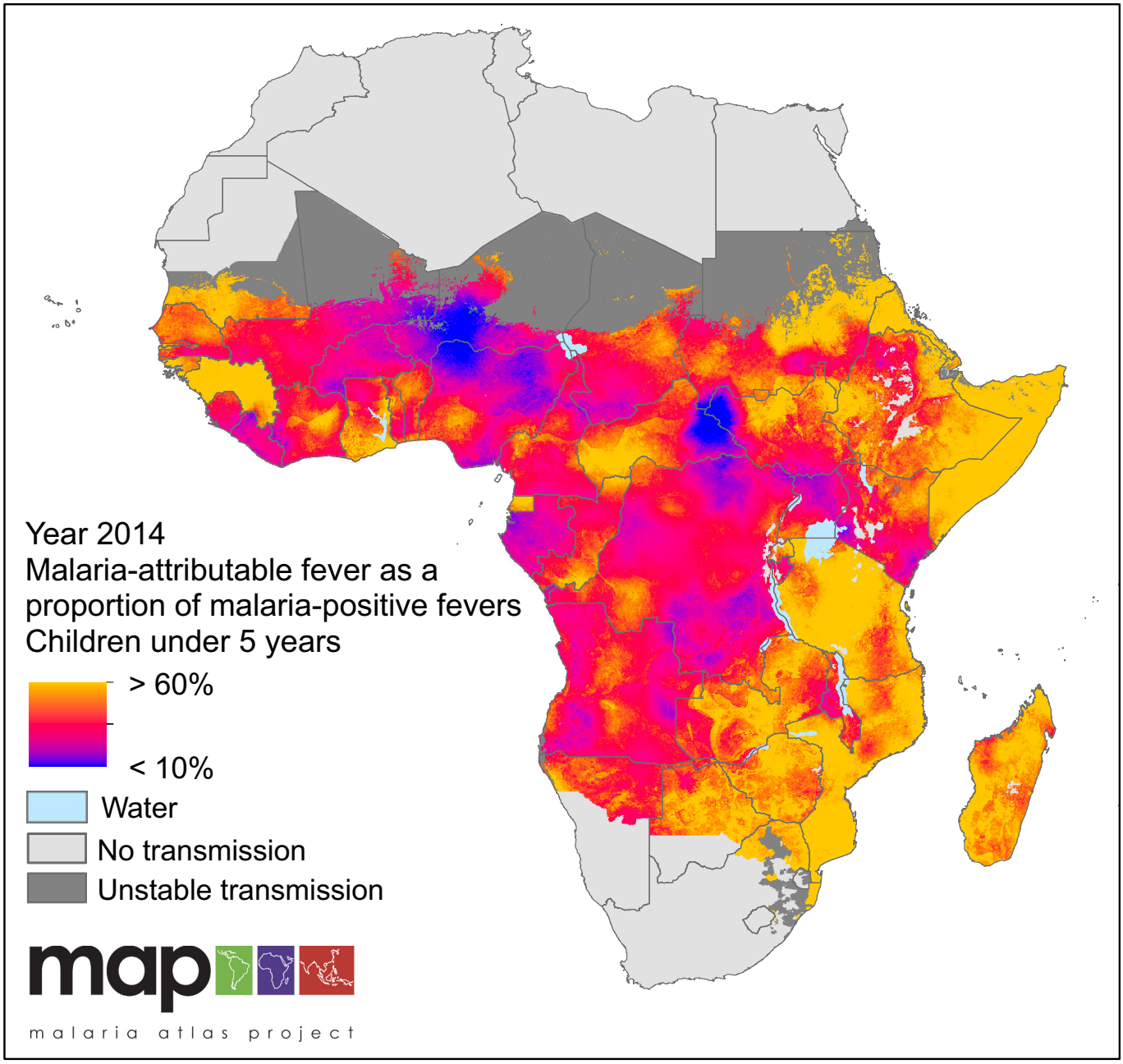


Figure 2. Predicted malaria-attributable fevers as a proportion of malaria-positive fevers (children under 5 years of age, 2014). Predictions are shown within the limits of stable *P. falciparum* transmission.

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proportion of malaria-positive individuals within the national cases of NMFI. The posterior estimation of prevalence of NMFI in children less than five years of age within the spatial limits of *P. falciparum* transmission is shown in ***Figure 6***.

Full details national-level estimates of MAF, MCF, malaria-positive fevers and NMFI can be found in ***Supplementary file 1***. A plot detailing the relationship between all-cause fever, malaria-positive fevers, and MAF with varying *P. falciparum* transmission intensity in both response data and predictions can be found in ***Figure 5—figure supplement 1***. These plots of our estimates are displayed

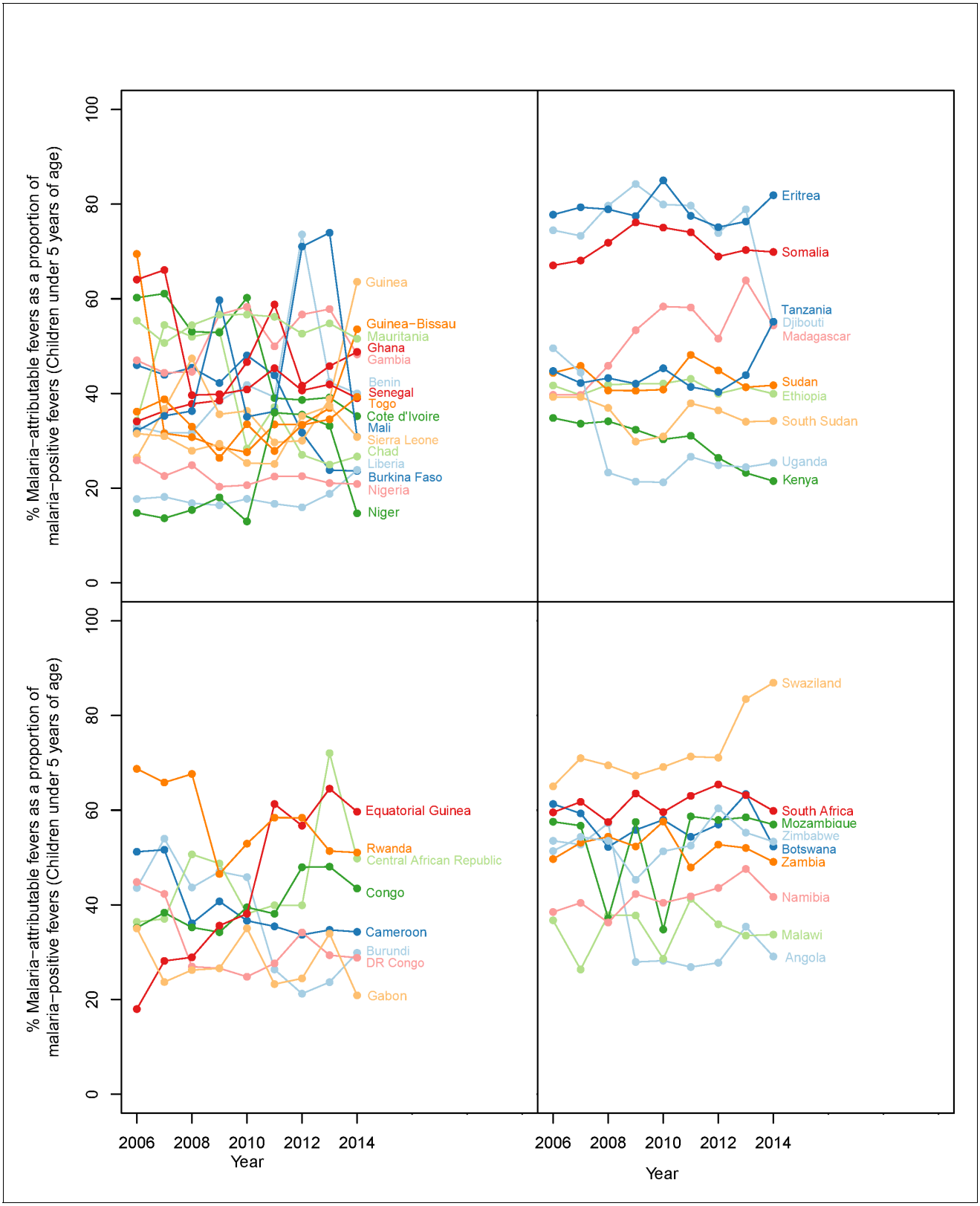


Figure 3. Malaria-attributable fevers as a proportion of malaria-positive fevers (children < 5 years of age). Plotted values are the population-weighted mean for 43 sub-Saharan African countries over the study period, 2006–2014. Countries have been grouped by region to improve clarity.

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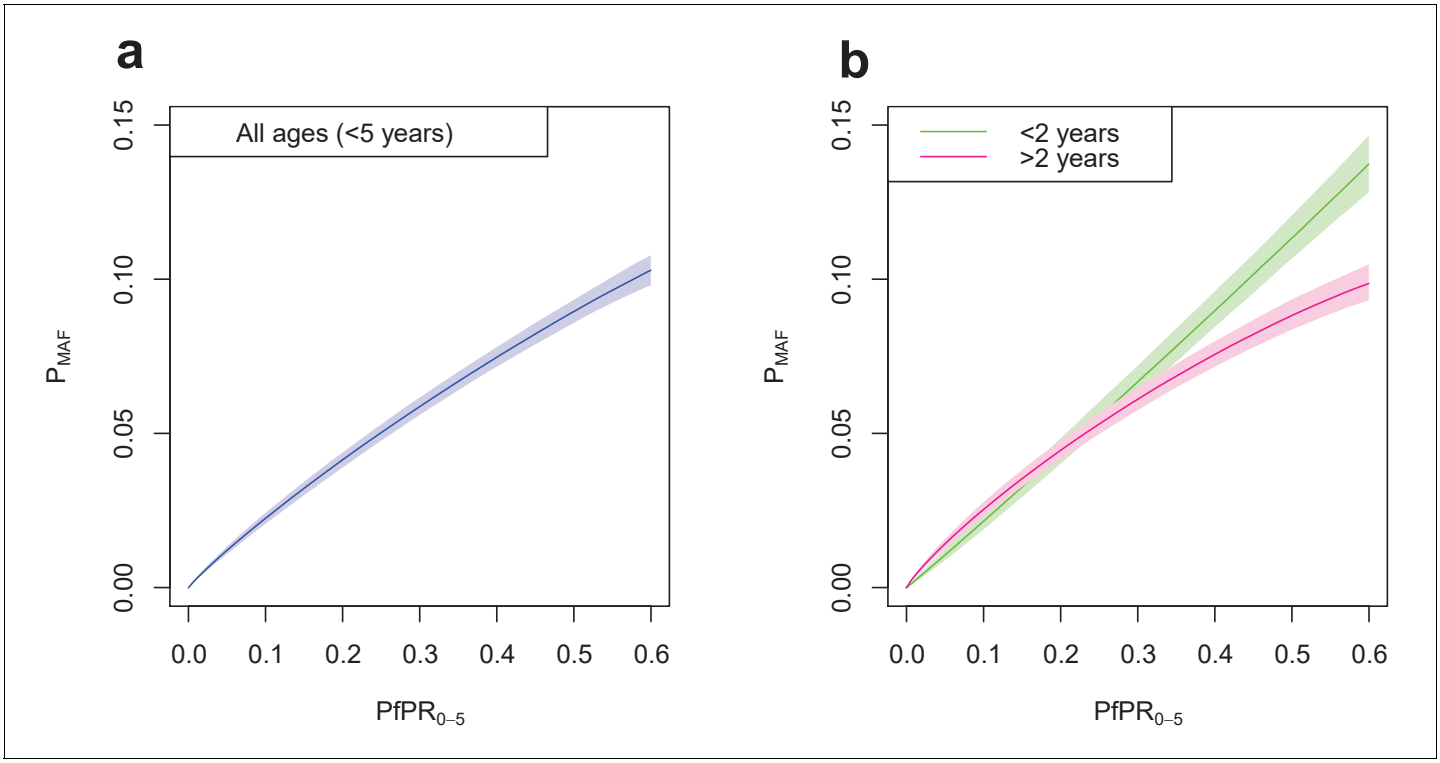


Figure 4. Final fitted relationship between *Pf*PR_{0-5} and probability of a malaria-attributable fever (MAF) in the past two weeks. (**a**) shows this relationship in children under five years of age, and (**b**) disaggregated into children under 2 years of age, and children aged 2–4 years. The probability of MAF in the past two weeks is greater for children under 2 years of age than for children above 2 years of age in areas with a *Pf*PR_{0-5} higher than approximately 0.3. Median values of the posterior distribution are shown, with shaded 95% credible intervals.

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with overlaid estimations of clinical incidence over the duration of the past zero to two, and two to four weeks, with increasing *Pf*PR_{0-5} from an ensemble of transmission models (***Cameron et al., 2015***). The breakdown of the contribution of NMFI, malaria-coincident fevers, and fevers without a patent malaria infection to all-cause fever varied considerably by country; this breakdown is displayed in detail for 2014 in ***Supplementary file 5***.

Discussion

The analysis presented here shows that although the proportion of fever cases that are accompanied by an RDT-patent *P. falciparum* infection remains high, only approximately a third of these fevers are causally attributable to malaria. The majority of febrile illness in Africa is caused by pathogens other than *P. falciparum* malaria, even in areas where malaria is highly endemic, and the proportion of all fevers caused by NMFI has risen since 2006. We estimate here that over a typical two-week period in 2014 one in four children under five years old residing in the limits of stable malaria transmission will suffer a fever not caused by *P. falciparum* malaria, whereas only one in every 32 children will suffer a fever directly caused by *P. falciparum*. We show that current estimations of malaria burden in Africa based on RDT-positive cases of fever may be overestimating the burden by up to two-thirds, and the level of overestimation is likely to be highly heterogeneous between different countries (***Figure 3***). For example, countries such as Niger, Gabon and Nigeria, where fewer than 21% of malaria-positive fever cases are causally attributable to malaria, may be substantially overestimating the morbidity caused by malaria (and systematically underestimating the burden of other diseases that may be co-infecting and causal). Additionally, these results have implications for the effectiveness of treatment received at point of care, as a substantial proportion of RDT-positive fevers are likely to be coincident with and caused by a NMFI. Our estimations of MAF prevalence in the past two weeks are comparable to estimations of clinical incidence from an ensemble of transmission models

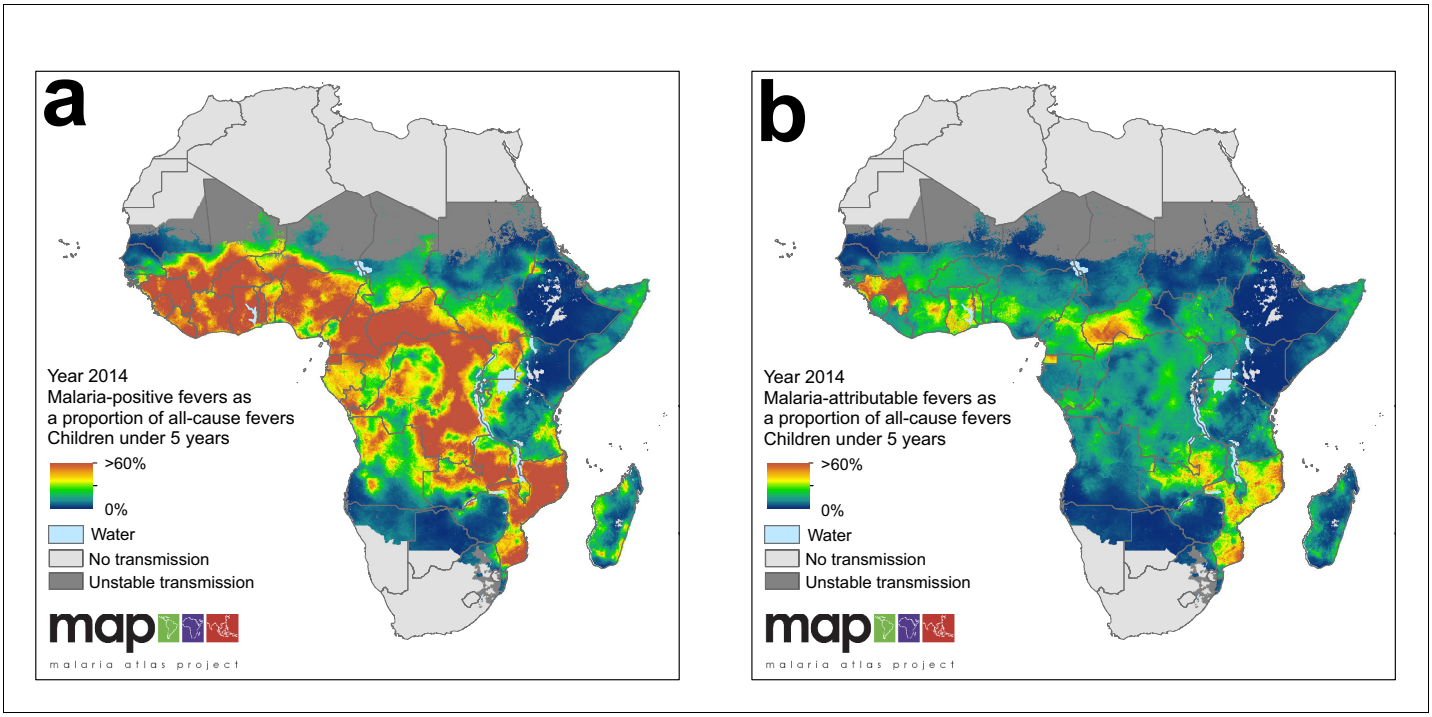


Figure 5. (**a**) Predicted malaria-positive fevers as a proportion of all fevers; (**b**) predicted malaria attributable fevers (MAF) as a proportion of all fevers. Both maps are shown for the year 2014, for children under 5 years of age and bounded by the limits of stable *P. falciparum* transmission.

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The following figure supplement is available for figure 5:

Figure supplement 1.

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(***Figure 5—figure supplement 1***) (***Cameron et al., 2015***) although our estimates match more closely to transmission model estimations of the prevalence of febrile illness lasting the duration of the past two-to-four weeks, rather than the past zero-to-two. For 13 of the 38 household surveys used in this analysis, the number of days since the onset of the child's fever was available. Children in these surveys had a fever for on average 5.38 days (±3.85 days) prior to the interview. This disparity between fever duration in our estimates and transmission model estimates can perhaps be explained by the cross-sectional nature of the surveys; the transmission models estimate the full course of the fever without treatment, whereas the household surveys aim to curtail the fever at the interview by administering appropriate medication to febrile children.

The total number of fever cases accompanied by an RDT-patent *P. falciparum* infection declined substantially over the study period (from 48.5% in 2006 to 35.7% in 2014), linked with declining $Pf\text{PR}_{0\text{-}5}$ over the same time (***Bhatt et al., 2015***; ***Smith et al., 2007***). The only country with a noteworthy increase in malaria-positive fevers over the study period was Gabon, which also experienced an increase in $Pf\text{PR}_{0\text{-}5}$ between 2006 and 2014.

This modelling approach makes use of household survey datasets in a novel way; no previous attempts have been made to measure childhood fever prevalence (and the malaria/non-malaria causality of the fever) from surveys recording two-week fever history. This approach has some drawbacks: it relies on two-week recall of fever from the child's caregiver, the accuracy of which can be subject to biases such as (i) length of time since the fever; (ii) the child's frequency of febrile episodes, (iii) the economic status of the family, and (iv) even the child's sex (***Das et al., 2012***; ***Rockers and McConnell, 2017***). We also include fever caused by *P. vivax* malaria as a NMFI by definition, as not all household surveys tested for *P. vivax* with RDT and thus only *P. falciparum* outcomes were used in this analysis. This is unlikely to have a major effect on most of Africa due to high Duffy negativity resulting in unstable *P. vivax* transmission, and very low levels of stable transmission in Madagascar and the horn of Africa (***Gething et al., 2012***; ***Howes et al., 2011***). One drawback of

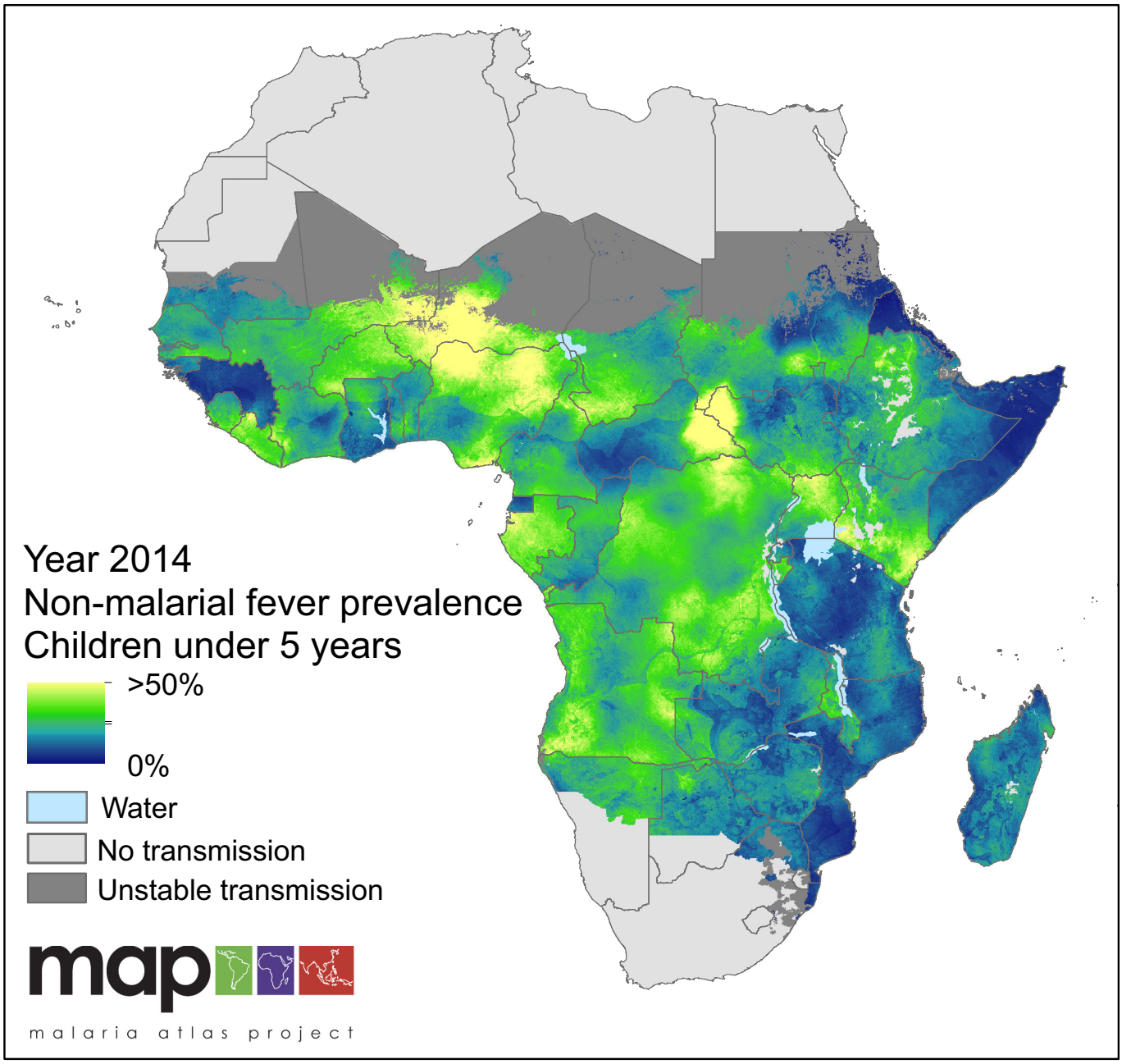


Figure 6. Predicted non-malarial febrile illness (NMFI) prevalence in children under 5 years of age. NMFI prevalence is defined as the sum of the prevalence of febrile illness without a *P. falciparum* malaria infection and the prevalence of febrile illness coincident with, but not caused by, a P. falciparum malaria infection (MCF), for children under 5 years of age and bounded within the spatial limits of stable *P. falciparum* transmission in 2014.
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using household survey data to generate predictions such as those presented here is that the survey data interviews children on one day within the time frame that the survey is conducted (typically two to four months). It is not necessarily the case that children who present a patent malaria infection but no history of infection over two weeks prior to their survey date have never, or will never, develop a malaria-attributable fever, and may have already done so outside of the two-week recall period of the survey interview. Additionally, co-infections may lead to a fever that would not have occurred had the child only had a monoinfection with malaria or the NMFI (***French et al., 2001***;

Hartgers and Yazdanbakhsh, 2006).This study does not consider the effects of co-morbidity in this sense, and fevers that fall into this category are accounted for within NMFI. We also incorporate no predictor variables at resolutions below the pixel-level (e.g. individual or household level), which are likely to be significantly predictive of both MAF and NMFI prevalence. Predictors such as household wealth and other associated health indicators are available within the household survey datasets, but owing to the heterogeneity of individual level variables measured in different surveys and the lack of a common set of information directly representative of those variables outside of surveyed countries, we have not incorporated them in the current model.

The low prevalence of malaria-positive fevers at all levels of *P. falciparum* endemicity suggests that passive case detection alone may not be enough to halt transmission of malaria, as many infected children are afebrile at any one time (regardless of whether their fever is attributable to the malaria infection or not). Further, this study estimates MAF prevalence in children less than two years of age, and between two and four years of age. We find that the relationship between MAF prevalence and *Pf*PR is not equivalent across all age groups (*Figure 4*), with children under two years of age having a higher probability of developing a malaria-attributable fever than children older than two in areas where $PfPR_{0\text{-}5}$ is greater than 30%. For older children living in high *Pf*PR locations, a higher proportion of the population will have acquired immunity to malaria infection (*Doolan et al., 2009*), and therefore may be less likely to present with a malaria-attributable fever. Although there is uncertainty over how long malaria immunity lasts (*Filipe et al., 2007*; *Wipasa et al., 2010*), in areas of rapid decline of malaria prevalence that are now moving towards elimination, this residual acquired immunity may present problems for elimination if programs rely on passive case detection and treatment to halt transmission. Again, the limitation of our estimates which use a two-week window for reporting of symptoms means that, in order to assert with confidence that passive case detection would be insufficient to halt transmission, evidence for a high prevalence of never-symptomatic infections would also be necessary.

Despite all malaria-endemic countries now adopting the official policy of parasite-based diagnosis of suspected malaria cases before issuing antimalarials, a large number of suspected malaria cases still do not receive a diagnostic test before treatment (*Hertz et al., 2013*; *World Health Organization, 2015*). This proportion has decreased over the time period of this study, from 64% of suspected cases not receiving a diagnostic test in 2005 to only 35% in 2014 (*World Health Organization, 2015*). The reasons for this high proportion of suspected cases not receiving parasite-based diagnosis lies predominantly in resource limitation in rural health clinics in malaria endemic countries (*Ghai et al., 2016*). This remaining proportion of NMFI that is assumed to be caused by malaria, and thus treated with an antimalarial, exacerbates the problem of over-prescription of antimalarials. By enumerating the proportion of NMFI, this study provides evidence of the on-going need to test febrile individuals for parasitaemia, but can also be used identify different geographic and malaria-burden settings where administering antimalarials in the absence of a positive test for *P. falciparum* is least warranted.

This suite of maps demonstrates the need for better diagnostic tests for other pathogens causing NMFI in Africa, which will in turn lead to a better understanding of the range of diseases that make up the non-malarial fraction of all-cause fever prevalence. Whilst the spatial distribution of pathogens that cause NMFI is largely unknown, occurrence data for these diseases are becoming more widely available, particularly in the context of identifying diseases with similar symptomatic presentations as malaria. The Worldwide Antimalarial Resistance Network (WWARN) now collects clinical evidence of non-malarial febrile illness (NMFI) caused by neglected tropical diseases from peer-reviewed case studies of fever diagnoses from across the malaria-endemic world (*Worldwide Antimalarial Resistance Network, 2017*). The collation of these studies is designed to give an overview of the presence of fever-causing pathogens in areas of overlapping endemicity with malaria, but cannot presently be used to quantify the spatiotemporal distribution of NMFI, nor can it be used to measure the individual contribution of each disease as an underlying cause of febrile illness. For example, a major review of 146 case studies in the Mekong region of Southeast Asia (*Acestor et al., 2012*), showed that misdiagnosis and mistreatment of the fever was a common outcome for individuals who were co-infected with malaria and other diseases with overlapping symptoms (e.g., Dengue fever virus, *Orientia tsutsugamushi* and *Rickettsia* species). In addition to implicating potential overestimation of the burden of malaria in the past, the results of this study suggest that current WHO guidelines for integrated management of childhood illness (IMCI) is

currently suboptimal for the treatment of non-malarial fever. Whilst treating positive malaria infections is the correct strategy for slowing malaria transmission, removing the malaria-attributable fevers from the population, and reducing the reservoir of infected individuals that perpetuate transmission; current procedures may lead to systematic mismanagement of NMFI. This study shows the need for increased efforts to develop and distribute routine diagnostics for NMFI-causing pathogens.

Materials and methods

Household survey data

Thirty-eight cross sectional, nationally-representative georeferenced surveys of malaria prevalence in children less than five years of age across 24 countries in sub-Saharan Africa were obtained from the Malaria Atlas Project database (**Guerra et al., 2007**; **Malaria Atlas Project , 2017**). These surveys originate from a variety of sources such as the DHS Program, UNICEF Multiple Indicator Cluster Surveys, and national Ministries of Health in malaria-endemic countries. Full details of the surveys used can be found in **Supplementary file 2**.

In these surveys, a blood sample was taken from any children present and tested for malaria parasites with both a RDT and Giemsa-stained microscopy. Here, we used the RDT-derived diagnostic outcome as an indicator of malaria positivity within the last two weeks, to lessen the possibility of a recent infection having been cleared via artemisinin combination therapy (ACT) (and therefore presenting as a negative result by microscopy). RDTs offer a more accurate representation of two-week infection than microscopy due to the persistence of histidine-rich protein II in the blood for up to 14 days after parasite clearance with ACT (**Mayxay et al., 2001**). Diagnostic and fever history outcomes from a total of 155,369 children that were aggregated within 5 × 5 km raster cells, resulting in a total 10,606 data points. In addition to the diagnostic and fever history outcomes, the wealth quintile (i.e. poorest, poorer, middle, richer, richest) of the individual's household was also extracted for use as an household-level predictor of fever in the final multinomial model.

Covariates

Independent model-based spatiotemporal predictions of both the prevalence of *P. falciparum* infection ($Pf PR_{0-5}$) and for the environmental suitability for background (non-malarial) fevers in children under five years of age across Africa for each year within the span of the household survey data (2006–2015) were constructed as covariates for use in the final multinomial model.

The $Pf PR_{0-5}$ covariate was generated for each year using the $Pf PR_{2-10}$ modelled predictions of slide-patent African *Pf*PR from the Malaria Atlas Project (**Bhatt et al., 2015**), age-standardised to 0–5 years using the 'agestand' package in R, based on a previously described age-standardisation procedure for *Pf*PR (**Smith et al., 2007**), and transformed to predict RDT-based prevalence via an microscopy-to-RDT relationship identified in earlier work (**Mappin et al., 2015**).

Prior to this study, no mapped estimates of environmental suitability for background fever existed for the African continent, hence a modelled estimate of environmental suitability for background fever was constructed using a boosted regression tree (BRT) model. The BRT approach generates a flexible regression model in two steps. Initially, response data are split recursively by predictor variables, where predictor variables that maximise the partitioned response data's homogeneity are selected more frequently in subsequent steps. This is followed by a 'boosting' step, where the regression tree models are combined to reduce the model's overall predictive deviance (**Elith et al., 2008**), and at each iterative step cross-validated against a randomly held-out subset to avoid overfitting (**Bhatt et al., 2013**).

Firstly, a training dataset was constructed, consisting of a subset of the household survey dataset where survey cells with ten or fewer tested individuals were removed in order to increase the reliability of observed prevalence values. This procedure reduced the final number of data points in the training dataset to 5320. Background fever prevalence was obtained at each data point through aggregation of individuals with a fever in the previous two weeks without a patent malaria infection.

A large suite of potential environmental and socio-demographic covariates was assembled, as described elsewhere (**Weiss et al., 2015**). Briefly, 5 × 5 km resolution surfaces across the African continent of different environmental and sociodemographic covariate types—elevation, land cover,

population density, precipitation, enhanced vegetation index (EVI), land surface temperature (LST), *P. falciparum* temperature suitability index (TSI) (**Weiss et al., 2014**), tasselled cap wetness (TCW), tasselled cap brightness (TCB), nighttime lights, Global Urban Footprint (**Esch et al., 2012**), and national-level World Bank indicators of poverty and healthcare quality (**World Bank, 2017**)—were obtained from the Malaria Atlas Project database and leveraged by constructing pixel-level spatial summaries (maximum, mean, minimum, standard deviation and range). These summarisations produced a total of 986 spatially- and temporally-contemporaneous covariates from which we extracted results for each of the 5320 georeferenced response data points.

To reduce the number of covariates an exploratory BRT model was constructed using background fever prevalence as the response variable and the covariates as predictor variables using the 'gbm. step' function in the 'dismo' package in R (**Elith et al., 2008**). The BRT model was parameterised with a tree complexity of 5, a learning rate of 0·05, a hold-out fraction of 0·05 and an error structure within the family 'gaussian' after a suitable inverse-sigmoid transform of the observed background fever prevalences. Each of the 986 covariates was ranked by their contributions to the fitted exploratory model. To reduce redundancy, each variable within the assembled suite of covariates was tested for collinearity with every other variable. Covariates were considered collinear if a correlation of greater than 0.7 existed between the two covariates, and when collinearity was identified only higher-ranked covariate was retained. This approach left a final dataset of 174 predictor variables for each of the 5320 response data points.

The final model, using the reduced set of 174 non-collinear predictor variables, was fitted with 2000 trees, a tree complexity of 5, and a reduced learning rate of 0.01 (reducing the learning rate improves model performance [**Elith et al., 2008**]). A list of the 174 predictor variables and each variable's contribution to the final model used can be found in **Supplementary file 3**. Predictions for the environmental suitability for background fever amongst children under five years old for each month between January 2006 and December 2014 across the area of stable malaria transmission in Africa were generated using the fitted BRT model and the 174 predictor variables. For a number of predictor variables, data were unavailable in November and December 2014, so data from the same month in the previous year were used instead. Yearly predictions for 2006–2014 were generated as a mean of each monthly prediction for use in the multinomial model. Gaps in the resulting predicted layers, caused by small gaps in the remotely-sensed covariate layers, were filled by recursively scanning through each raster cell by cell, and filling in cells with no data with the mean of the first layer of surrounding cells until no gaps remained.

Multinomial model

A training dataset for the multinomial model was constructed from all 10,606 points in the household survey dataset. Of these points, 25% (2,652) were selected for the holdout dataset, where probability of selection was directly proportional to the distance of the nearest neighbouring point, to avoid clustering of hold-out points in areas of dense data coverage. The remaining 75% of points (7,954) were used in the training dataset.

The observed data at each site, i (a 5 $\times$ 5 km pixel), with $N^i_{\text{tot.}}$ surveyed individuals may be represented as a two-by-two categorical table of counts according to fever status (febrile or afebrile) and RDT-based *P. falciparum* parasite status (positive or negative). The hierarchical Bayesian model we construct here thus takes a top-level likelihood with multinomial distribution having four unknown parameters, $\{q^i_1, q^i_2, q^i_3, q^i_4\}$, that describe the expected proportion of counts in each category; i.e.,

$$\left[N^i_{\text{feb. \& pos.}}, N^i_{\text{feb. \& neg.}}, N^i_{\text{afeb. \& pos.}}, N^i_{\text{afeb. \& neg.}}\right] \sim \text{Multinomial}\left[\{q^i_1, q^i_2, q^i_3, q^i_4\} | N^i_{\text{tot.}}\right].$$

Since each expected proportion must lie between zero and one while their joint sum is strictly unity, the effective dimension of unknown parameters here is three, with constraint to the standard 3-simplex. Our parameterisation takes three components accordingly, which we define so as both to respect these constraints and to represent the key targets of our inference as shown in **Table 1**.

Here $p^i_{\text{pos.}}$ is the expected prevalence of malaria parasites in children under five years of age, p^i_{bg} is the expected prevalence of background fever (within a two-week window) in the same cohort, and r^i_{maf} gives the expected proportion of *P. falciparum* positives reporting a fever attributable to malaria. By convention (and in line with our objectives) we define the prevalence of these 'malaria-

Table 1. Four-way infection outcome table and formulae for deriving targets of inference.

	Pf pos.	*Pf* neg.
Febrile	$q_1^i = p_{\text{pos.}}^i \left(r_{\text{maf}}^i \left(1 - p_{\text{bg}}^i \right) + p_{\text{bg}}^i \right)$	$q_2^i = \left(1 - p_{\text{pos.}}^i \right) p_{\text{bg}}^i$
Afebrile	$q_3^i = p_{\text{pos.}}^i \left(1 - r_{\text{maf}}^i \right) \left(1 - p_{\text{bg}}^i \right)$	$q_4^i = \left(1 - p_{\text{pos.}}^i \right) \left(1 - p_{\text{bg}}^i \right)$

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attributable fevers', p_{maf}^i, as $p_{\text{maf}}^i = p_{\text{pos.}}^i r_{\text{maf}}^i \left(1 - p_{\text{bg}}^i \right)$; that is, excluding causal fevers 'coexisting' with a background fever.

Our representation of the local parasite prevalence in children under five years of age takes the form of a spatial generalized linear model (GLM) in which the logit transform of predicted prevalence from the MAP *Pf*PR$_{2\text{-}10}$ space-time cube (***Bhatt et al., 2015***), age-standardised to *Pf*PR$_{0\text{-}5}$ (***Smith et al., 2007***), is used as a linear predictor for the logit transform of the under-five year old prevalence, augmented with a latent (spatial) Gaussian random field (GRF). That is,

$$\text{logit}\, p_{\text{pos.}}^i = \text{logit}\, Pf\text{PR}_{\text{MAP}}^i + f_{x(i),}$$

$$f \sim GRF_{\theta.}$$

An identical model is used for the rate of background fevers in this cohort, except that the predictor variable is now the logit of the environmental suitability for background fevers predicted by the BRT model outlined above. Hence,

$$\text{logit}\, p_{\text{bg}}^i = \text{logit}\, \text{FEV}_{\text{BRT}}^i + g_{x(i),}$$

$$g \sim GRF_{\phi.}$$

Our model for the proportion of parasite positives with a causal malaria fever is a simple quadratic dependence on the local prevalence, motivated by the form observed in a previously described transmission model (***Maire et al., 2006***; ***Ross et al., 2006***; ***Smith et al., 2006a***; ***Smith et al., 2006b***). Namely,

$$\text{logit}\, r_{\text{maf}}^i = \delta + \psi \times \text{logit}\, p_{\text{pos.}}^i + \xi \times \left(\text{logit}\, p_{\text{pos.}}^i \right)^2.$$

For computational tractability we adopt a Gaussian Markov Random Field (GMRF) approximation to the continuous GRF components of our model using the version for Matern GRFs identified by Lindgren et al. (***Lindgren et al., 2011***) from the INLA package (***Rue et al., 2009***). Implementation of this model requires construction of a mesh-based tessellation enclosing the African continent (plus Madagascar) which we also perform with the INLA package using 6280 mesh nodes. We fixed the smoothness of both GMRFs used in our model to $\nu = 1$ $(\alpha = 2, d = 2)$ and set (weakly informative) standard Normal priors on the logarithm of the hyperparameters for each, κ $\left(\text{i.e., } 2\sqrt{2} \times \text{inverse range}\right)$ and τ $(\text{i.e., inverse variance})$. Finally, we complete our model by placing priors on the intercept and two slope coefficients of the $\text{logit}\, r_{\text{maf}}^i$ model:

$$\delta \sim \text{Normal}\left[-2, 1.0^2\right], \quad \psi \sim \text{Normal}\left[0, 0.25^2\right], \qquad \text{and} \qquad \xi \sim \text{Normal}\left[0, 0.25^2\right].$$

Model fitting was performed with the TMB package (***Kristensen et al., 2015***) for automatic differentiation, which returns functions for the likelihood plus gradient and Hessian matrices with respect to all parameters of our model after (approximate) marginalisation over the random fields via a Laplace approximation. These are then plugged into the 'nlminb' function in R and optimised to find the empirical Bayes solution with the local Hessian used to form approximate credible intervals as summarized in ***Supplementary file 4***. Additional model fits to response data disaggregated by age

(children over and under two years of age) were conducted to assess the age-effect on the likelihood of developing MAF with varying *Pf*PR.

Model validation was perform via an initial fit of the above model to a sub-sample (75%) of the full dataset using a spatial leave-one-out cross validation procedure (***Le Rest et al., 2014***). The probability integral transform diagnostic (***Angus, 1994***; ***Diebold et al., 1997***) for multinomial probabilities at the holdout sites estimated from the empirical quantiles of draws from the posterior predictive was used as a qualitative check on the calibration of our posterior uncertainties (***Figure 1—figure supplement 1***). All code for the multinomial model and the BRT model are available on GitHub (***Dalrymple, 2017***; a copy is available at https://github.com/elifesciences-publications/MAF-NMFI).

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Additional files

Supplementary files

- Supplementary file 1. Yearly population-weighted percentages for all-cause fever prevalence, and malaria-attributable fever, malaria-positive fever, and non-malarial febrile illness within all-cause fever amongst population at risk in children under 5 years of age in malaria-endemic Africa, 2006–2014.

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- Supplementary file 2. Household survey data used in analysis.

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• Supplementary file 3. Covariates used in BRT, listed by contribution to the final model.
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• Supplementary file 4. Model parameters and credible intervals of the final multinomial model; final model coefficients.
DOI: https://doi.org/10.7554/eLife.29198.014

• Supplementary file 5. National breakdown of contribution of NMFI, MAF and MCF (malaria-coincident fever) to all-cause fever in 2014. NMFI is represented here as a fever without a patent malaria infection, MCF as a fever with a patent malaria infection where the fever is caused by a co-infection with an NMFI, and MAF where the malaria infection is the sole cause of the individual's fever. This file is supplementary to ***Figure 5***.
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• Transparent reporting form
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Major datasets

The following previously published datasets were used:

Author(s)	Year	Dataset title	Dataset URL	Database, license, and accessibility information
UNICEF MICS	2011	UNICEF MICS Ghana 2011	https://www.unicef.org/ghana/Ghana_MICS_Final.pdf	Available upon request from UNICEF MICS (http://mics.unicef.org/surveys)

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Chapter 3 - How long do rapid diagnostic tests remain positive after anti-malarial treatment?

During exploration of the limitations of the results presented in Chapter 2, implications of the timing mismatch between recall of paediatric febrile illness (two weeks preceding the survey) and rapid diagnostic test (RDT)-measured malaria diagnosis in household survey datasets were investigated. This chapter addresses one such limitation. Children who test RDT-negative at the point of interview, but who were known to have been febrile in the two weeks preceding the survey, sought treatment, and received an anti-malarial may have been RDT-positive at the time of treatment, but the antigens associated with their infection may have cleared sufficiently by the point of interview to return a negative RDT. RDT-derived diagnosis (as opposed to microscopic analysis) was used in Chapter 2 to account this effect, with the underlying assumption that any RDT-positive child who received an anti-malarial medication in the two weeks preceding the survey would still be RDT-positive by the time of interview. In this chapter, this assumption is tested. Using a dataset compiled from a systematic literature review of persistence of RDT positivity after anti-malarial treatment, a Bayesian survival model was constructed to estimate the duration after anti-malarial treatment that a child may remain RDT-positive.

In Chapters 4 and 5, the outcomes of this chapter are used as an adjustment to account for the probability of a recently-treated child in the household survey dataset reverting to RDT-negative by the time of interview.

This chapter was published in *Malaria Journal* in June 2018 and is shown below in its published format. There are two Additional Files associated with this Chapter which can be found in the Appendix. Additional File 1 shows details of the publications used in analysis, and Additional File 2 shows the Bayesian survival model priors and likelihoods.

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How long do rapid diagnostic tests remain positive after anti-malarial treatment?

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Abstract

Background: Rapid diagnostic tests (RDTs) are increasingly becoming a paradigm for both clinical diagnosis of malaria infections and for estimating community parasite prevalence in household malaria indicator surveys in malaria-endemic countries. The antigens detected by RDTs are known to persist in the blood after treatment with anti-malarials, but reports on the duration of persistence (and the effect this has on RDT positivity) of these antigens post-treatment have been variable.

Methods: In this review, published studies on the persistence of positivity of RDTs post-treatment are collated, and a bespoke Bayesian survival model is fit to estimate the number of days RDTs remain positive after treatment.

Results: Half of RDTs that detect the antigen histidine-rich protein II (HRP2) are still positive 15 (5–32) days post-treatment, 13 days longer than RDTs that detect the antigen *Plasmodium* lactate dehydrogenase, and that 5% of HRP2 RDTs are still positive 36 (21–61) days after treatment. The duration of persistent positivity for combination RDTs that detect both antigens falls between that for HRP2- or pLDH-only RDTs, with half of RDTs remaining positive at 7 (2–20) days post-treatment. This study shows that children display persistent RDT positivity for longer after treatment than adults, and that persistent positivity is more common when an individual is treated with artemisinin combination therapy than when treated with other anti-malarials.

Conclusions: RDTs remain positive for a highly variable amount of time after treatment with anti-malarials, and the duration of positivity is highly dependent on the type of RDT used for diagnosis. Additionally, age and treatment both impact the duration of persistence of RDT positivity. The results presented here suggest that caution should be taken when using RDT-derived diagnostic outcomes from cross-sectional data where individuals have had a recent history of anti-malarial treatment.

Keywords: Malaria, Fever, RDT

Background

With resistance to first-line anti-malarials becoming increasingly widespread [1], malaria-endemic countries have made a shift towards parasite-based diagnosis of malaria infections in clinics rather than presumptive diagnosis of suspected cases in order to prevent over-prescription of anti-malarials and to curb anti-malarial resistance, owing in part to a change of World Health Organization (WHO) recommendation in 2010 [2]. Between 2010 and 2015, sales of rapid diagnostic tests (RDTs) from manufacturers worldwide tripled from 90 to 270 million, and in 2015 RDTs constituted 74% of diagnostic testing for suspected malaria cases [3]. RDTs have now joined microscopy as a mainstay of malaria diagnosis in household surveys, with a number of the most recent malaria indicator surveys (MIS) from the Demographic and Health Surveys (DHS) Programme using only RDTs, without microscopy [4, 5]. These data from national surveys have been used to produce spatiotemporal maps of malaria prevalence and mortality at a continental scale [6, 7] (after careful standardization across different diagnostic methods [8]), to estimate the proportion of febrile illness in African children that is attributable to malaria versus other causes [9], and to generate estimates of the

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effectiveness of health systems in malaria-endemic countries, amongst numerous other applications.

RDTs typically detect at least one of two antigens: histidine-rich protein II (HRP2), a protein occurring in the cytoplasm of *Plasmodium falciparum*; and *Plasmodium* lactate dehydrodgenase (pLDH), a glycolytic enzyme produced by live *Plasmodium* parasites of all human-infecting species. RDTs that detect pLDH either detect pan-pLDH (also commonly referred to as the pan-malarial antigen, or PMA), which is common to all human-infecting species, or species-specific pLDH. Most commonly, RDTs fall into two categories: detecting HRP2 only, or detecting both HRP2 and pan-pLDH. Of the 57 national surveys conducted by the DHS Programme released before the end of 2017, 21 surveys used HRP2-only RDTs, 33 used HRP2/pan-pLDH combination RDTs, 5 used HRP2/*Plasmodium vivax*-pLDH combination RDTs, and one used a pan-pLDH-only RDT (Pers. comm. from DHS Program, 2017). Within these surveys, 43.2% of individuals with negative RDT results at time of observation but who had sought treatment for their fever within the previous 2 weeks reported to have received anti-malarial medication at their treatment location. Some fraction of these individuals (who would typically be identified as non-malarial fever cases by end-users of the household survey dataset) may in fact have had a symptomatic malaria infection that was successfully treated in time to allow the malaria antigen concentration in their blood to reduce below the threshold for RDT detection at the survey interview. Amongst these (at-survey) RDT-negative patients who sought treatment and received an anti-malarial, 45.1% received an RDT diagnosis at their treatment location. Although the interviewers do not ask the result of the RDT administered at the treatment location, this figure is indicative of a high rate of RDT positivity at the time of treatment; a 2016 review of health worker compliance in clinics in malaria-endemic countries showed that only 1.5% of RDT-positive patients in clinics do not receive an anti-malarial, and that 19.1% of RDT-negative patients receive an anti-malarial (overtreatment) [10]. Understanding the quantitative impact of prior treatment on observed RDT status is an important step towards adding value from fever status records to the enumeration of malaria burden.

False negativity in RDT diagnosis, defined as the failure to register a positive result for patients having any non-zero parasite load, usually arises through parasite antigen concentrations within the blood being lower than the threshold of detection for RDTs, which accounts for approximately half of *P. falciparum* infections in malaria-endemic populations [11]. This threshold depends on the particular RDT and the expertise of the individual administering the diagnostic, but typically falls in the range of 5-15 parasites per μL [12]. Additionally, *P. falciparum* parasites with histidine-rich protein II (HRP2) deletions have been reported in more than 10 countries [3], which would lead to false negative results in RDTs that detect only the HRP2 antigen. Conversely, false positive results have been reported in patients expressing rheumatoid factor [13], and it remains a possibility that they could arise through non-specific binding of heterophilic antibodies [14]. The evidence collated in this review describes another route through which an individual without a current malaria infection could still present with a positive RDT: the persistence of malaria antigens after recent parasite clearance through anti-malarial medication. There is a temptation to view this outcome as a 'false positive' when imagining RDT as a proxy for microscopic detection, but when using RDTs for survey-based estimation of disease transmission intensity this is precisely the desired measure: evidence of recent parasite exposure. Understanding the duration of positivity after successful parasite clearance is also critical for accurate diagnosis of re-infection after a previous infection has been treated; if antigens from the first infection are still present in great enough quantities after treatment, an individual will still return a positive RDT after treatment, and may be misinterpreted as a re-infection, or, indeed, re-infections may be missed.

The amount of time necessary for RDTs to turn negative after treatment of an RDT-patent malaria infection is shaped by the different rates at which HRP2 and pLDH persist in the blood post-treatment; hence the type of RDT used is likely to be important. Additionally, the type of treatment the patient receives is critical to the speed and completeness of parasite clearance [15], and is, therefore, also likely to affect the time taken for the RDT to become negative. Parasite density at the time of anti-malarial medication has also been reported to correlate with increased duration of persistent positivity [16], so in malaria-endemic areas the age of the individual may influence the likelihood of persistent positivity given the link between acquired immunity, parasite density and age. Numerous studies that state that persistent antigenicity may pose a limitation to their findings typically reference one or two examples of persistent antigenicity in other publications [18–27]; however, the reported length of persistent antigenicity is highly variable amongst studies. In this analysis, data from published reports of persistent antigenicity are collated, systematically reviewing and synthesizing all information available on the length of time required for RDTs to turn negative after treatment of a malaria infection, and a Bayesian survival model is fit to estimate the length of time RDTs can be expected to remain positive after treatment, exploring how this duration is affected by the type of RDT used,

the anti-malarial drugs administered, and the age of the individuals.

Methods

Systematic literature review

A systematic review of publications on the persistence of antigenaemia and positivity of RDTs after treatment was conducted using the search term "antigen persist RDT" on Google Scholar. Due to persistence of antigenicity typically being reported as a secondary result in publications evaluating RDT performance, indexing sites such as PubMed or Web of Science returned few results due to the inconsistency of terminology both in title and content for this type of publication (12 results on PubMed and 13 on Web of Science for the same search terms used in the Google Scholar review). Other search terms ("HRP2 persist", "pLDH persist", and "RDT persist positivity") were attempted on PubMed and Web of Science and each yielded 5 or fewer results, all of which were non-relevant or identified in the final Google Scholar review. The Google Scholar search yielded more than 4100 results, sorted by relevance. The search continued until 10 consecutive pages of results yielded no more publications meeting the following inclusion criteria: they (i) treated patients for symptomatic malaria infections; and, (ii) followed up with RDT-based diagnosis over a number of days. The proportion of individuals who still tested positive via RDT was extracted for each day of follow-up and analysed as a time series. In addition to the proportion of positive tests, information on other factors that may affect RDT positivity in the follow up period was also extracted: (i) RDT type (antigens detected); (ii) treatment received (artemisinin-based combination therapy (ACT) or non-ACT); and, (iii) age range of patients (children 5 years of age or under, or adults over 14 years of age). There were two studies where the treatment regimen was unknown; 3 were conducted prior to 2001 so it was assumed that individuals received a non-ACT anti-malarial [28–30], and one conducted in 2011 so it was assumed that individuals received an ACT [23]. All studies meeting the inclusion criteria are documented in full in Additional file 1: Table S1.

Bayesian survival model

The data was fit with a Bayesian survival model, where the time taken for an event to occur—in this case an individual becoming RDT-negative—is modelled. This time is determined by a hazard function $h(t)$ which represents the instantaneous probability of the event occurring given it has not already occurred. Therefore a high value of $h(t)$ corresponds to a high probability that an individual will become RDT-negative at time t, given they were not already RDT-negative. Given a hazard function $h(t)$, a survival curve $S(t)$ can be calculated which represents the probability of an individual still being RDT-positive at time.

It was assumed that there was a common baseline hazard function for all study groups, analogous to assuming the overall shape of a survival curve will be similar regardless of drug type, RDT type or age of the individual. Each of the variables (drug type, RDT type, age, year) then scaled the hazard function by a constant—a variable increasing the hazard function would corresponding to individuals being likely to become RDT-negative earlier.

A piecewise-constant baseline hazard function $h(t)$ was assumed across all study groups,

$$h(t) = c_i$$

for $t_i < t < t_{i+1}$, with c_i a non-negative constant and the time points, t_i, the times at which an RDT was carried out in any study. The group-specific hazard function for the jth study group, $h_j(t)$, was assumed to be this baseline hazard function modulated by the effect of covariates, X_j, and a study group-level random effect, Z_j, as follows:

$$h_j(t) = h(t) \times \exp\left(-\left(X_j^T \beta + Z_j\right)\right).$$

The covariates were all categorical and included: (i) age (child, unknown, adult); (ii) RDT type (HPR2 or pLDH, either alone or in combination with HRP2); (iii) drug type (ACT or non-ACT); and, (iv) year of study (i.e. the year the research was conducted rather than publication year; separated into 5 categories: 1990–1995, 1996–2000, 2001–2005, 2006–2010, and 2011–2013).

The cumulative hazard function $H_j(t)$ is given by the integral of the hazard function,

$$H_j(t) = \int_0^t h_j(t)dt$$

and the survival curve, $S_j(t)$, is given by $S_j(t) = \exp\left(-H_j(t)\right)$. The value, $S_j(t)$, represents the probability of individual becoming RDT-negative at time, t, or later.

Finally, a probability of treatment failure, p_{fail}, was incorporated, and assumed dependent on all previous covariates except RDT type:

$$p_{\text{fail}} = \text{logit}^{-1}\left(X_j' \beta_{\text{fail}}\right) = \frac{1}{1 + \exp\left(-X_j'^T \beta_{\text{fail}}\right)}$$

where X_j' are the covariates other than RDT type and β_{fail} are slopes learnt during the model fit.

Choosing suitable priors (see Additional file 2 for full details of priors and likelihoods), posterior distributions for c, Z_j were approximated, and survival curves predicted by choosing the desired covariates and setting Z_j to zero. Model fitting was performed in R using the TMB package for automatic differentiation [30].

As the model does not allow individuals to test positive after testing negative, any study groups where the percentage of still-positive individuals increased by more than 15% points between time points were removed. For study groups with smaller increases over time this data was included but with increases removed, as the general trend of the data would still be informative. Leave-one-out cross-validation was conducted to analyse predictive performance.

Results

Data

A total of 31 separate publications met the inclusion criteria, yielding 67 individual study groups, as some publications followed up multiple groups of individuals post-treatment. The studies included were conducted between 1994 and 2013. The number of individuals within each study group varied highly, ranging from 10 to 386 individuals (mean = 104.1, SD = 92.2). All studies incorporated only uncomplicated malaria cases, with the exception of one study group which incorporated both severe and uncomplicated malaria cases [31]. Twenty-eight of the study groups were confined to children 5 years of age or under, 3 to adults 14 years or older, 12 study groups were of mixed age, and the age range was unknown in 24 study groups. The anti-malarial received was recorded for all study groups; 44 of these study groups received an ACT while the remaining 23 study groups received a non-ACT anti-malarial. HRP2-only RDTs were used in 40 of the study groups, RDTs detecting pLDH-only were used in 21 study groups, and combination RDTs detecting both HRP2 and pLDH were used in 6 study groups. A total of 5 study groups were omitted entirely due to increases of over 15 percentage points in the proportion of positive individuals between consecutive measurements, and a further 9 study groups had outcomes from one or more days removed due to smaller increases. Full details of the extracted data, along with study references, can be found in Additional file 1: Table S1.

Model fit

Table 1 summarizes the estimated baseline hazard function. The value of the hazard function remains relatively constant until day 17 after treatment, suggesting a constant probability of reverting to RDT negative until that time. The value of the hazard function increases after 17 days post-treatment, indicative of an increasing probability of an individual who is still RDT-positive reverting to RDT-negative with each successive day post-treatment. The standard deviation of the baseline hazard function increases with time, likely due to the paucity of data more than 42 days post-treatment (Table 1). To test the predictive performance of the model leave-one-out cross-validation was performed. Each study group was removed iteratively from the response data and then compared the predicted and observed proportion of RDT-negative individuals in this group at 14 and 28 days. Correlations of 0.75 and 0.78 were found between observed and predicted values at 14 and 28 days, respectively (summarized in Fig. 1) showing good predictive performance.

Table 1 Estimated baseline hazard function for probability of RDTs reverting from positive to negative 0–63 days after treatment

Time interval (days)	Log hazard function (log c_i)	
	Mean	Standard deviation
$0 \leq t < 1$	−2.14544	0.59800
$1 \leq t < 2$	−2.33424	0.59788
$2 \leq t < 3$	−2.22978	0.59812
$3 \leq t < 4$	−1.95530	0.59871
$4 \leq t < 5$	−2.06535	0.59897
$5 \leq t < 6$	−2.63433	0.59984
$6 \leq t < 7$	−2.88932	0.60210
$7 \leq t < 10$	−2.30567	0.61558
$10 \leq t < 14$	−2.11019	0.60812
$14 \leq t < 17$	−2.00743	0.62575
$17 \leq t < 21$	−1.82409	0.61273
$21 \leq t < 28$	−1.64152	0.60006
$28 \leq t < 35$	−0.95173	0.59972
$35 \leq t < 42$	−0.76698	0.60509
$42 \leq t < 49$	−0.40862	0.66399
$49 \leq t < 56$	−0.32584	0.73220
$56 \leq t \leq 63$	0.06540	0.89587

Table 2 summarizes the model-estimated coefficients for factors affecting duration of persistent positivity. Higher values correspond to a lower hazard function and thus increased probability of a longer duration of persistent RDT positivity. In addition to the primary factors (age, RDT type, anti-malarial medication type) described in more detail below, the effect of year of study on the hazard function was investigated. A small effect was observed that older studies (pre-2000) and those conducted between 2006 and 2010 show shorter durations of persistent positivity than those conducted between 2001 and 2005 and those conducted between 2011 and 2013. The coefficients for all variables affecting the likelihood of treatment failure are outlined in Table 3.

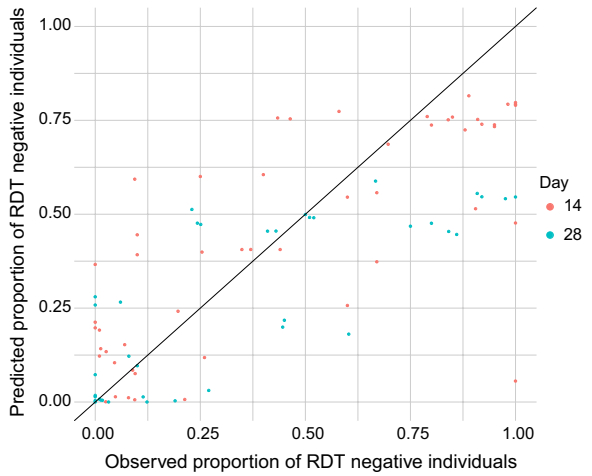


Fig. 1 Observed and predicted proportion of RDT negative individuals at 14 and 28 days after treatment from leave-one-out cross-validation. The black line represents 1:1 for observations and predictions

Table 2 Estimated coefficients for variables affecting duration of persistent positivity

Variable	β	
	Mean	Standard deviation
Age		
Child	0.47259	0.34271
Unknown	−0.17405	0.34302
Adult	−0.31372	0.35144
RDT type		
HRP2	0.92519	0.33919
pLDH	−1.04777	0.33905
Combination	0.10741	0.34083
Drug type		
ACT	0.25571	0.41472
Non-ACT	−0.27088	0.41472
Year of study		
1990–1995	−0.32517	0.29396
1996–2000	−0.0111	0.26762
2001–2005	0.36172	0.26733
2006–2010	−0.08271	0.26692
2011–2013	0.04209	0.26782

Higher coefficient values correspond to a lower hazard function and thus increased probability of a longer duration of persistent RDT positivity

Overall survival estimate

Overall, there was substantial variability in the proportion of RDTs that remained positive 1–63 days after treatment. In some study groups, the RDTs of all patients were negative 2–3 days after treatment, but in one study group some individuals still returned a positive RDT 56 days after treatment. Clustering in measurement days at 7, 14, 21, and 28 days after treatment was observed, with sparsity in measurements in the intervening days. Figure 2 shows the fitted estimate of persistence of RDT positivity 0–63 days after treatment for all study groups, overlain with the proportion of individuals still positive within each study group at each time point. The fitted Bayesian survival model estimates that, in any given cross-sectional population, 50% of treated individuals will present a negative RDT at 7 days (2–20 days, 95% CI) post-treatment, and that 95% of individuals will present a negative RDT by 24 days (8–43 days, 95% CI) post-treatment.

Likelihood of persistent positivity by RDT type

Study groups were separated by the type of RDT used in the analysis; HRP2-only RDTs were used in 40 study groups. 21 study groups were analysed pLDH-only RDTs (including pan-*Plasmodium* pLDH and *P. falciparum* pLDH variants). 6 study groups included combination RDTs which tested for both HRP2 and pan-*Plasmodium*-pLDH. Two study groups using HRP2 RDTs and 3 study groups using combination RDTs were removed prior to analysis due to increases in proportion of positive individuals over time. RDTs from a total of 7 different manufacturers were used across the study groups (Additional file 1: Table S1). For 3 of the studies, a single combination HRP2/pan-pLDH RDT was used, but instead of a binary positive/negative result, the result for each individual band was given [32–34]. These studies are included as two separate study groups in both the HRP2-only group and the pLDH RDTs group, with the result for the relevant band included in each group. The binary results for all other combination tests where individual band positivity was unknown were included in the combination RDTs group.

In Fig. 3, the fitted survival model estimate for each of the 3 RDT types is shown. Table 2 shows the model-estimated coefficients for the effect of RDT type, with HRP2 RDTs showing a significantly higher probability of experiencing a longer duration of persistent positivity than other RDTs. The model predicts that, within a population monitored using HRP2 RDTs, 50% of treated individuals would present with a negative RDT by 15 days (5–32 days, 95% CI) after treatment, and 95% of individuals would present with a negative RDT by 36 days (21–61 days, 95% CI) after treatment. For RDTs detecting pLDH only, 50% of individuals would present with a negative RDT by 2 days (1–7 days, 95% CI) after treatment, and 95% of individuals present with a negative 10 days (3–24 days, 95% CI) after treatment. Duration of persistent positivity for combination RDTs that detect both HRP2 and pLDH falls between HRP2 and pLDH RDTs,

Table 3 Estimated coefficients for variables affecting probability of treatment failure

Variable	β_{fail}	
	Mean	Standard deviation
Age		
Child	−3.46444	2.57147
Unknown	−0.07017	2.15373
Adult	−0.39833	2.2029
Drug type		
ACT	−2.00807	2.38318
Non-ACT	−1.42487	2.38322
Year of study		
1990–1995	−0.00101	1.66774
1996–2000	−0.90702	1.61296
2001–2005	−0.9747	1.61356
2006–2010	−0.54851	1.6232
2011–2015	−2.5017	3.76325

Higher coefficient values correspond to a higher probability of treatment failure

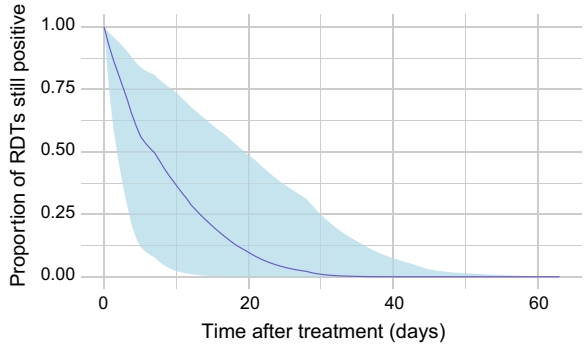


Fig. 2 Fitted relationship between proportion of RDTs still positive within a given sample of individuals, and length of time (number of days) after treatment was first administered. All study groups were used in this fitted relationship. The posterior distribution median (blue line) and 95% credible intervals (light blue shaded area) is displayed

with 50% of RDTs presenting a negative result by 7 days (2–20 days, 95% CI) and 95% of RDTs presenting a negative result by 24 days (11–43 days, 95% CI).

Likelihood of persistent positivity by type of therapy received

Type of treatment received on day 0 of the analysis was known for all study groups. Treatment regimens were grouped based on whether or not they were considered ACT (i.e., an artemisinin derivative coupled with a partner anti-malarial drug). Non-ACT included artemisinin monotherapy, chloroquine, quinine, primaquine, sulfadoxine–pyrimethamine, and mefloquine (full details of all treatment regimens can be found in Additional file 1: Table S1). In total, 44 study groups received ACT, and 23 study groups received non-ACT treatment. Three study groups receiving non-ACT and two study groups receiving ACT were removed prior to analysis due to increases in proportion of positive individuals over time.

Table 2 shows the model-estimated coefficients for the effect of treatment, with individuals who received an ACT showing a higher probability of experiencing a longer duration of persistent positivity than those who received a non-ACT, although the magnitude of the difference between the coefficients is less pronounced than the effect of RDT type, and the credible intervals for these estimates include zero, indicating a higher level of uncertainty. The fitted relationship between persistent RDT positivity and length of time since treatment, separated by the type of therapy received, is shown in Fig. 4. The model predicts that 50% of patients who received an ACT would test negative via RDT by day 8 (3–21, 95% CI), compared to day 4 (2–14, 95% CI) for patients that received a non-ACT anti-malarial. It is predicted that 95% of patients that received an ACT would test negative via RDT by day 27 (13–43, compared to day 19 (8–34, 95% CI) for patients that received a non-ACT anti-malarial.

Combined effect of RDT type and therapy received

Figure 5 shows the effect of type of anti-malarial therapy received on the fitted relationship when separated by RDT type. For both categories of anti-malarial, persistent positivity is predicted for a longer duration when using HRP2 RDTs than when using pLDH-only or HRP2/pLDH combination RDTs. When using HRP2-only RDTs during follow-up, the model predicts that 50% of patients would present with a negative test by day 19 (10–31, 95% CI) when given an ACT on day 0, or by day 13 (5–22, 95% CI) when given a non-ACT at day 0; and the model predicts that, using a HRP2 RDT, 95% patients would present with a negative test by day 41 (29–59, 95% CI) when given an ACT on day 0, or by day 32 (21–46, 95% CI) when given a non-ACT at day 0. When using pLDH-only RDTs during follow-up, the model predicts that 50% of patients would present with a negative test by day 3 (1–6, 95% CI) when given an ACT on day 0, or by day 2 (1–4, 95% CI) when given a non-ACT at day 0; and, using pLDH-only RDTs, 95% patients would present with a negative test by day 13 (5-23, 95% CI) when given an ACT on day 0, or by day 8 (3–16, 95% CI) when given a non-ACT at day 0. For HRP2/pLDH combination RDTs, 50% of patients would present with a negative test by day 10 (4–18, 95% CI) when given an ACT on day 0, or by day 5 (2–12, 95% CI) when given a non-ACT at day 0; and, 95% patients would present with a negative test by day 29 (16–41, 95%

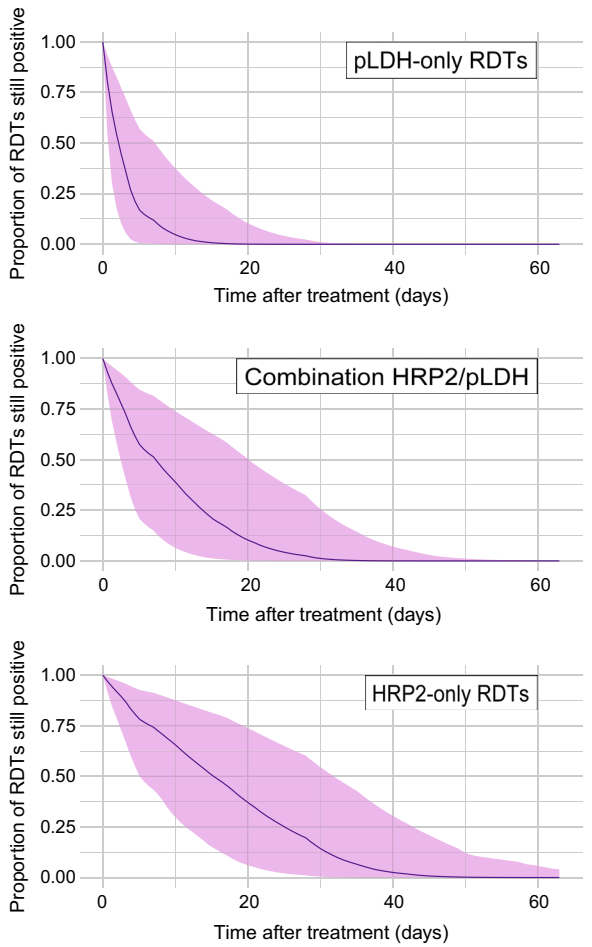


Fig. 3 Fitted relationship between proportion of RDTs still positive within a given sample of individuals, and length of time (number of days) after treatment was first administered, separated by the type of RDT used to monitor patients during the follow-up period. The fitted relationship for study groups monitored with RDTs that detect pLDH only (*N* study groups = 21) is shown in the top panel (with shaded 95% credible intervals), and the fitted relationship for study groups monitored with RDTs that detect pLDH in combination with HRP2 (*N* study groups = 6) is in the middle panel (with shaded 95% credible intervals), and the fitted relationship for study groups monitored with RDTs that detect HRP2 only (*N* study groups = 40) is in the bottom panel (with shaded 95% credible intervals)

CI) when given an ACT on day 0, or by day 21 (10–32 95% CI) when given a non-ACT at day 0.

Likelihood of persistent positivity by age of patient

The age of sampled individuals was known for 41 of the 67 study groups. Of these, 28 of the study groups were confined to children 5 years of age or under, 3 to adults 14 years or older and 12 study groups were of mixed age (Additional file 1: Table S1). One study group concerning children 5 years of age or under and one study group concerning adults were removed prior to analysis due to increases in proportion of positive individuals over time. In Table 2, the model-estimated coefficients for the effect of age of individuals can be found. The model predicts that children are more likely to experience longer durations of persistent positivity than adults, although again the magnitude of the difference between the coefficients is less pronounced than the effect of RDT type, and again, the credible intervals for the estimate for adults are wide, indicating a high level of uncertainty. In Fig. 6, the fitted relationship between persistent positivity and days since treatment is shown, confined separately to only children 5 years of age or under, and only adults 14 years of age or older. Children were estimated to have a slightly longer duration of persistent positivity than adults; it is estimated that 50% of children would present a negative RDT by day 11 (3–25, 95% CI), whereas 50% of adults would present a negative RDT by day 4 (1–15, 95% CI). The model estimates that 95% of children would present a negative RDT by day 31 (14–49, 95% CI), and 95% of adults would present a negative RDT by day 19 (6–36, 95% CI).

Discussion

In this study, published data on persistence of positive RDT results after anti-malarial treatment is collated. Amongst the study groups, the proportion of individuals who still test positive at increasing numbers of days after treatment is highly variable (Fig. 2) but shows more discernible trends when grouped by the type of RDT used to detect the infection (Fig. 3) and the treatment that the individuals receive at day 0 (Fig. 4). The Bayesian survival model estimates presented here can be used as a tool to estimate the proportion of individuals within a given study group that would still present a positive RDT for 2 months after anti-malarial treatment, and allow further distinction depending on: (i) RDT type used for analysis; (ii) type of treatment administered at day 0; and, (iii) age of patients. On average, the model predicts that half of RDTs will be negative 7 days after treatment has been received.

RDT type

The finding that HRP2 RDTs show persistent positive results after treatment for longer than combination or pLDH RDTs (Figs. 4, 5) corroborates direct comparisons between HRP2 and pLDH RDTs amongst the same patients [17, 35, 36], owing to the slower degradation of HRP2 compared to pLDH after parasite clearance. The duration of persistent positivity for combination RDTs that detect both HRP2 and pLDH falls between the durations for RDTs that detect only one antigen; this suggests that the positivity of the HRP2 line on the combination

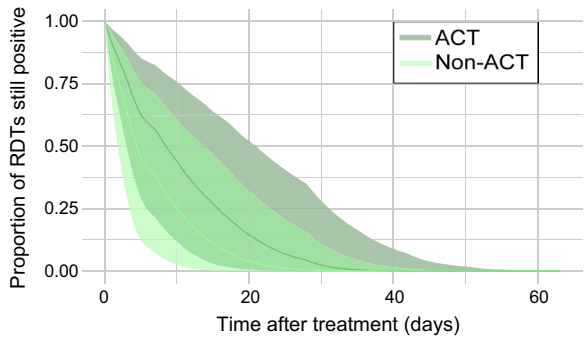


Fig. 4 Fitted relationship between proportion of RDTs still positive within a given sample of individuals, and length of time (number of days) after treatment was first administered, separated by the type of anti-malarial medication administered to patients on day 0 of the analysis. The dark green line (with shaded 95% credible intervals) shows the fitted relationship for individuals who received an ACT on day 0 (*N* study groups = 44), and the fitted relationship for individuals who received a non-ACT anti-malarial medication (either artemisinin monotherapy, chloroquine, quinine, primaquine, sulfadoxine-pyrimethamine, and mefloquine—full details in Additional file 1: Table S1; *N* study groups=23) is shown by the light green line (with shaded 95% credible intervals)

test is behaving similarly to HRP2-only tests and that studies are often reporting an RDT to be positive if the HRP2 line indicates a positive result, even if the pLDH line does not indicate a positive.

Despite most study groups using HRP2 RDTs, more variability was observed in the length of time HRP2 RDTs returned positive results than for other RDTs, as demonstrated by the width of the credible intervals in Fig. 3. Mayxay et al. [31] measured the persistence of detectable levels of HRP2 post-treatment and found a clear relationship between longer persistence and higher levels of initial blood parasite density. In the dataset collated for this study, parasite density ranges were known for 22 of the 67 study groups (Additional file 1: Table S1) but the ranges of parasite density are wide and irregular, making analysis by initial parasite density unreliable and challenging. Future extensions of studies on persistent antigenicity would benefit from recording parasite density, or even the severity of a patient's symptoms, as fever severity is linked to increased parasite density [37]. Although pLDH degrades faster than HRP2, both RDTs return positive results for a long time post-treatment; the model estimates that some HRP2 RDTs will still be positive more than 36 days after treatment, and RDTs detecting pLDH for more than 10 days after treatment. Positive pLDH RDTs could result from the persistence of malaria gametocytes, as they are unaffected by some anti-malarials but are known to produce pLDH in mature gametocytes (but not HRP2, which is only produced by immature gametocytes) [38, 39]. Persistent positivity of combination RDTs could be due to ambiguity in the reporting of a "positive" result with HRP2/pLDH combination RDTs. For example, if a recently treated individual returns a positive HRP2 band and a negative pan- or *Pf*-pLDH band on the same RDT, whether or not this result would be interpreted as a true or false positive would depend on the training of the clinician and the perceived reliability of the test. Differences in positivity by HRP2 band and pLDH band were not reported for a number of the studies that included combination RDTs. In a number of publications, a test was considered "positive" if either band was clearly visible. Clear division in the positivity of each band would help characterize the different reactivities of HRP2 and pLDH bands to blood after anti-malarial treatment, as combination RDTs with only a HRP2 band visible (caused by the prolonged degradation of HRP2) may simply be recorded as "positive", thus skewing the results for combination RDTs in favour of longer positivity duration. This method of defining malaria "positivity" also presents a problem from a converse perspective: if a treated *P. falciparum* infection generated a negative HRP2 band and a positive pan-pLDH band (due, perhaps, to circulating mature gametocytes not cleared by anti-malarial medication and producing pLDH), then the RDT may be misreported as a malaria infection by a species other than *P. falciparum* [39]. This type of false negativity of HRP2 bands could also arise should the parasite be carrying a HRP2 deletion, which while currently not thought to be widespread, has been reported in 5 countries in sub-Saharan Africa [40] and 10 countries worldwide [3].

Type of anti-malarial therapy received

In Fig. 4, the proportion of individuals still positive at increasing numbers of days shows that the study groups who received ACT are highly variable in the rate at which RDTs become negative, compared to the groups who received non-ACT. When broken down by the type of RDT used to measure persistent positivity, individuals who took ACT remained persistently positive for longer than individuals who took non-ACT anti-malarials. The reasons for this are unclear, and may seem counterintuitive. A potential explanation could relate to individuals who received ACT being tested in later years due to introduction of ACT as the first-line anti-malarial in 2006 (the publications included here have a mean study date of 2007 for those who receive ACT), compared to non-ACT anti-malarials (mean study date of 2001 for those who receive non-ACT), which may not have been fully captured in the random study effect. Over the past 2 decades, RDTs have increased greatly in sensitivity, as reported by the World Health Organization's Malaria

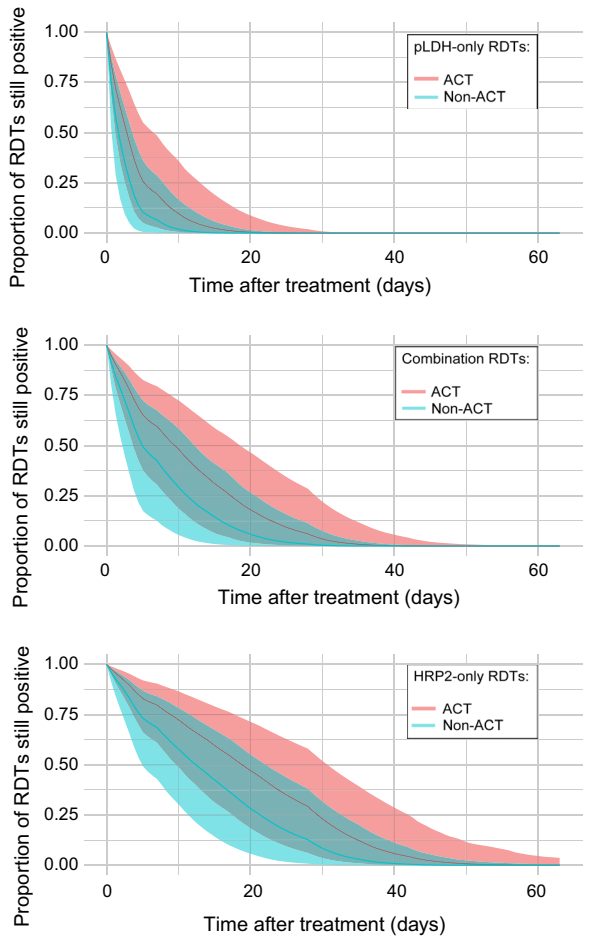


Fig. 5 Both panels show the fitted relationship between proportion of RDTs still positive within a given sample of individuals, and length of time (number of days) after treatment was first administered, separated by the type of anti-malarial medication administered to patients on day 0 of the analysis. Top panel: fitted relationship by type of anti-malarial medication amongst study groups tested with a pLDH-only RDT. Middle panel: fitted relationship type of anti-malarial medication amongst study groups tested with a HRP2/pLDH combination RDT. Bottom panel: fitted relationship by type of anti-malarial medication amongst study groups tested with a HRP2-only RDT. In each panel, the fitted relationship for individuals who received an ACT is shown by the pink line (with shaded 95% credible intervals), and the fitted relationship for individuals who received a non-ACT is shown by the blue line (with shaded 95% credible intervals)

Rapid Diagnostic Test Performance, which has undergone 7 rounds of product testing of RDTs, with the latest round conducted in 2015–2016 [41].

Studies comparing persistent antigenicity with separate groups testing ACT and non-ACT anti-malarials find variable differences in HRP2-only RDT positivity between trial groups: including a study by Houze et al. comparing ACT and sulfadoxine-pyrimethamine which found no difference [35], and a study by Tjitra et al. comparing sulfadoxine-pyrimethamine and artesunate with sulfadoxine-pyrimethamine (AS-SP) which found that AS-SP had approximately one-third fewer persistently positive RDTs in the first 7 days after treatment, and then roughly equivalent rates [42].

Due to the small number of study groups tested with non-ACT anti-malarials, and the variety of anti-malarials used within this group, non-ACT anti-malarials were not disaggregated into individual drugs. As the particular drug used tends to be a known variable in both clinical settings and for prevalence surveys, the analysis presented here could be improved by repeating for individual non-ACT drugs (and even different combinations within the ACT category) if more data from non-ACT study groups were available.

Relationship between patient age and persistent RDT positivity

The results presented here show that children are more likely to remain positive for a longer time after anti-malarial treatment than adults, although the model fits have significant overlap in their 95% credible intervals. This significant overlap is in part due to the small sample size of study groups formed of only adults; age range was unknown for 24 of the study groups, and the remainder included individuals of all ages, and disaggregating observations by the age of individuals was not possible. Children are less likely to have developed acquired immunity to malaria than adults [43]. Acquired immunity leads to lower parasite densities [44], which has been reported to lead to a shorter duration of persistent RDT positivity after treatment [16]. The finding is also strengthened by the model estimates for unknown or mixed age individuals (represented by the dotted line in Fig. 6), which falls between the estimates for children and adults.

Applications and limitations of findings

Many of the publications included as data points in this analysis report persistent antigenicity as a secondary finding of other analyses, such as evaluations of new RDTs [45–47] or testing RDTs in a new setting, such as introducing RDTs into clinics in malaria-endemic areas where previously only microscopy or presumptive diagnosis were available [18, 48–51]. A pitfall of this opportunistic data gathering approach is that the studies do not all follow the same protocol, and are conducted in a variety of settings. The findings of this review could be built on by a study designed with persistent antigenicity as the main subject of analysis, following rigorous protocol and testing the same subjects with a variety of RDTs (as some of the studies included here show persistent antigenicity as a main goal, but use only one type

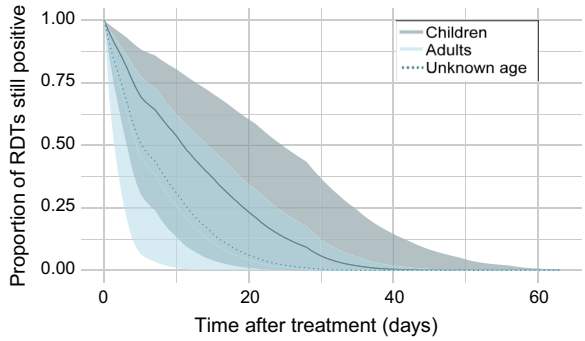


Fig. 6 Fitted relationship between proportion of RDTs still positive within a given sample of individuals, and length of time (number of days) after treatment was first administered, separated by age. Children 5 years of age or under (*N* study groups = 28) are represented by the dark blue line and shaded 95% credible intervals; adults 14 years of age or older (*N* study groups = 3) are represented by the light blue line and shaded 95% credible intervals. Mixed and unknown ages (*N* study groups = 36) are represented by the dotted blue line (credible intervals are not shown)

of RDT [37, 52–55]), although it would be unethical to provide RDT-positive subjects with anything other than first-line anti-malarial treatment. Additionally, many of the studies did not confirm (using microscopy or PCR) the species of *Plasmodium* infecting study groups. Many of the studies were conducted in sub-Saharan Africa and thus were likely to be reporting *P. falciparum* infections only [55] and most study groups used HRP2 RDTs (Additional file 1: Table S1), thus meaning only *P. falciparum* infections would be detected, but the possibility remains that some of the infections in study groups using pLDH or combination RDTs reported other species of *Plasmodium.* Antigen concentrations may differ between different *Plasmodium* species infections, so further analyses of persistent positivity would benefit from separating analysis by species.

A number of studies included here did not control for treatment failure or re-infection over the study period. The probability of treatment failure was controlled within the model, using known treatment failure rates as collated by the WHO [56]; however there is a small possibility that some of the still-positive RDTs seen in later days of the study period could be due to re-infection rather than persistent antigenicity. Re-infection is somewhat unlikely given the duration of the follow-up period in most of the studies included here, in addition to the prophylactic effect of the drugs administered at day 0, and the incubation time of malaria (9–15 days for *P. falciparum* and 12–17 days for *P. vivax* [57]).

Some of the studies included in this analysis described intensity of the indicator bands on the RDTs, but not a sufficient number, and for those that did include this information it was not sufficiently consistent for direct comparison. Band intensity is an indicator of parasite density (and subsequently antigen concentration) [58]. Further analysis of the band intensity change during the follow-up period after treatment may allow differentiation between persistent antigenicity and recrudescence or reinfection.

The WHO and the Foundation for Innovative New Diagnostics test the performance of RDTs systematically in the Product Testing Programme, using panel detection scores (PDS) as a guide to test sensitivity and specificity, and currently recommend that only RDTs with a panel detection score of over 75% are procured by national malaria control programmes (NMCP) [42] (although over the period 2011–2014, many NMCPs were not completely adherent to this criteria, especially amongst RDTs supplied to the private sector [59]). A number of the RDTs included in this analysis fall below the PDS threshold, although this threshold has moved over time, and many RDTs that currently fall below the PDS threshold were acceptable at the time the study was conducted. The RDTs included here show some intra-specific variation amongst RDTs that detect the same antigen(s), and future analyses would benefit from separating RDTs by the model rather than just the antigens detected, which was not possible in this analysis due to lack of reporting of RDT model number in the included studies. End-users of these results should take note of the sensitivity of the RDT used in their analysis relative to the sensitivities of the RDTs included in this study; more sensitive RDTs are likely to display longer durations of persistent positivity than the results presented here would indicate.

The findings presented here can be used to assess the reliability of positive RDTs in situations where it is known that the patient was treated for a patent malaria infection in the recent past. From the clinical perspective, the data presented here may be used to assess the likelihood of a non-malarial febrile illness as the underlying cause of an individual's fever, should that individual present with a positive RDT but has also been known to have received anti-malarial treatment in the recent past. A recent study estimates that 72% of RDT-positive fevers in sub-Saharan African children are actually due to non-malarial causes [9], suggesting potential for improvements to the management of paediatric non-malarial fevers. For individuals with a current fever and a recent history of anti-malarial treatment, a positive RDT after successful anti-malarial treatment has potential as an indicator for non-malarial febrile illness (for which routine diagnostic tests are often unavailable) as the fever's underlying cause is likely to be a non-malarial fever in this scenario, especially if the anti-malarial treatment received was an ACT. From the perspective of an analyst using household

survey data on malaria prevalence, these results show that caution must be taken when a positive RDT from an individual who has also received recent anti-malarial treatment is observed. The Bayesian survival model estimates presented here can be used to give an estimate of the likelihood of persistent positivity, given the RDT used in the household survey, the treatment the individual has received, the age of the individual, and the number of days since the completion of treatment.

Conclusion

This study shows that RDTs remain positive for a highly variable amount of time after treatment with anti-malarials. When grouped by antigen, RDTs that detect HRP2 only are found to show longer durations of persistent positivity than RDTs that detect pLDH; this difference is the most distinct effect from any of the factors investigated in this analysis. The model estimates that individuals receiving ACT are more likely to experience a longer duration of persistent positivity than individuals who receive non-ACT anti-malarials; this may, however, be an artefact of the coincident trend towards use of ACT as front-line anti-malarials and ever-increasing RDT sensitivities not fully captured by the random effects structure used in this analysis. Additionally, the results show that children are more likely to experience a longer duration of persistent positivity than adults. Epidemiologists combining RDT-derived household survey data on malaria prevalence with fever status reports and clinicians diagnosing malaria infections alike should take consideration of previous anti-malarial diagnosis and treatment, given the high likelihood of persistent positivity in the weeks succeeding anti-malarial treatment.

Additional files

Additional file 1: Table S1. Details of the publications used in analysis.

Additional file 2. Bayesian survival model priors and likelihoods.

Authors' contributions

UD conceived of and designed the research, constructed the dataset. UD, RA and EC conducted the analysis and visualizations. PWG supported the analysis. UD and RA drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its additional file].

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Chapter 4 - Overestimation of the *Plasmodium falciparum* malaria burden in African children due to coincident infections with non-malarial febrile illnesses

This chapter aimed to quantify the overestimation of symptomatic *Plasmodium falciparum* infections amongst *P. falciparum*-positive febrile children presenting to public health clinics in sub-Saharan Africa, by probabilistically distinguishing between true *P. falciparum*-attributable fevers and non-malarial febrile illness (NMFI) coincident with an asymptomatic *P. falciparum* infection. This was accomplished in two steps. First, the underlying relationship between malaria-attributable fever (MAF) and *P. falciparum* prevalence (*Pf*PR) presented in Chapter 2 was recalibrated using a large dataset compiled from multiple literature sources to incorporate both measured and self-reported fevers. This recalibration addressed potential bias introduced in the earlier approach by relying only on self-reported fevers in the household survey dataset. Second, the recalibrated relationship was used to adapt the Bayesian hierarchical model presented in Chapter 2 to make probabilistic classifications of each febrile individual in the household survey dataset as having either a malaria-attributable fever, a rapid diagnostic test (RDT)-positive non-malarial febrile illness, or an RDT-negative non-malarial febrile illness. The Bayesian hierarchical model was further adapted to increase the power to probabilistically assign fever type through incorporation of: *i)* individual-level covariates, and *ii)* utilisation of the adjustment for recent antimalarial treatment presented in Chapter 3. Each febrile individual's subsequent treatment-seeking behaviour, as reported in the household survey, was then tracked to estimate the proportion of MAF and NMFI

coincident with an asymptomatic malaria infection presenting at public health clinics in sub-Saharan Africa.

This chapter has been prepared for publication and is shown here in its pre-submission format, with figures integrated at appropriate locations within the text. There are five additional tables and two additional files associated with this manuscript, which are included in the Appendix. Additional Table 1 contains details of the parasite density literature review, Additional Table 2 contains details of the household survey dataset used in this analysis, Additional Table 3 contains details of further additional datasets used in the analysis, and Additional Tables 4 and 5 contain details of covariates used in the boosted regression tree modelling. Additional Files 1 and 2 contain the R and C++ code used within the TMB model to generate the individual-level attributions of MAF and NMFI for individuals within the household survey dataset.

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Author contributions: UD conceived the study with PWG and EC. UD assembled parasite density datasets (with assistance from KEB, LC, SK and KAT in updating the set of studies meeting the inclusion criteria; UD extracted all information from studies). UD assembled all other literature review and household survey datasets, assembled Ministry of Health datasets (which were downloaded after an online search by KAT and DAP). UD designed and implemented Bayesian statistical analysis of the relationship between MAF and *Pf*PR with guidance from RA and EC. UD conducted boosted regression tree modelling; designed basic framework for, and analysed outputs from, Bayesian hierarchical model; generated all displayed graphics and tables; wrote first draft of manuscript.

EC conducted statistical analysis and implementation of Bayesian hierarchical model with input from UD and SB. EC provided first draft of sub-section "4.4.3.3. Fever attribution model", which was revised by UD.

DJW and HG provided variables for BRT modelling.

PWG oversaw the study.

All authors reviewed and approved the final manuscript.

4.2. Abstract

The community-level disease burden of *Plasmodium falciparum* malaria illness is generally estimated using one of two distinct approaches: either by transforming survey-based malaria prevalence estimates to malaria incidence estimates using conversion formulae based on mechanistic malaria transmission models; or by adjusting counts of recorded malaria cases from clinics for various sources of incompleteness (e.g. in reporting, diagnosis and treatment-seeking). Whilst both ostensibly seek to evaluate malaria disease burden, there is an implicit, often unacknowledged, difference in the metric being estimated. The first aims to enumerate only symptomatic malaria cases (i.e., febrile episodes due to a high blood-stage parasite density), while the second enumerates all febrile episodes coincident with a microscopically-patent or rapid diagnostic test (RDT)-patent malaria infection, regardless of the fever's underlying cause. This distinction renders interpretation of and comparison between estimates problematic. Here, a novel approach was used to triangulate multiple community-based data sources capturing individual-level fever, parasite infection, and care-seeking status to estimate the fraction of malaria-positive fevers presenting at health facilities that are attributable to malaria versus other non-malarial causes.

First, records of paired malaria and fever diagnoses from a variety of sources were collated to model the underlying relationship between paediatric malaria-attributable fever (as a proportion of malaria-positive fevers) with *P. falciparum* malaria prevalence. Second, the fitted relationship was used to calibrate a hierarchical Bayesian model to assign likelihoods of malaria-attributable fever (MAF) and non-malarial fever (NMFI) to febrile children under 5 from a dataset of 41 nationally representative household surveys from 21 countries in sub-Saharan Africa surveyed between 2006 and 2016. Using treatment-seeking outcomes from the dataset, the proportion of MAF and NMFI amongst

malaria-positive febrile children presenting at public clinics was estimated. These results were compared to malaria cases reported amongst children under 5 for three contemporaneous country-years from national Ministry of Health reports, and the proportion of reported malaria-positive fevers that were causally due to non-malarial infections was estimated. Across all surveyed malaria-positive febrile children who sought care at public clinics, malaria was estimated to be the underlying cause of only 37.7% (31.1 – 45.4, 95% CrI) of malaria-positive fevers. This proportion showed significant geographical and temporal heterogeneity, from 5.3% (1.8 – 12.4, 95% CrI) in Tanzania in 2007-2008, to 81.5% (77.7 – 84.5, 95% CrI) in Mali in 2012-2013. The results presented here improve comparability of case reporting-based versus prevalence-based estimates of malaria cases, with significant implications for national and global estimation of malaria burden.

4.3. Introduction

Despite significant gains in reducing malaria prevalence, *Plasmodium falciparum* malaria remains a significant public health burden, with 216 million cases and 445,000 deaths estimated globally in 2016 [1–3]. For estimation purposes, malaria cases are currently defined as a parasitologically confirmed malaria infection [4], measured in practice from aggregated reports of diagnostic testing amongst fever cases in health clinics reporting to the health management information system (HMIS) in malaria-endemic countries. Current burden estimation methodologies for enumerating total community cases in malaria-endemic countries rely on either: *i)* aggregating total numbers of confirmed cases reported to the HMIS, then adjusting for the completeness of reporting, adjusting unconfirmed cases by the diagnostic positivity rate of confirmed cases, and finally

adjusting for the proportion of fever cases that seek treatment (henceforth "adjusted case-count approach"), or *ii)* applying a prevalence-to-incidence conversion [5] where cartographic models of malaria prevalence [6] are used to determine the number of infections that become symptomatic at a national level (henceforth "cartographic approach"). These two methodologies, while both used to estimate national case counts, do not follow the same strict definition of a malaria "case".

The first step of the adjusted case-count approach enumerates the number of fever cases presenting at clinics that are coincident with a patent malaria infection, before adjusting to produce estimates of the total number of community cases. By enumerating malaria-positive fevers, no distinction is made between malaria-attributable fevers and non-malarial fevers coincident with a patent, asymptomatic malaria infection, and both are reported as confirmed malaria cases by the clinic to the HMIS.

Conversely, the cartographic approach relies on mechanistic models of the proportion of infected individuals who go on to experience a symptomatic infection [5, 7–9]. By this rationale, the cartographic approach only estimates malaria-attributable fevers, and not fevers that are coincident with, but not caused by, a patent malaria infection. Burden estimates derived using this methodology will therefore produce estimates of malaria cases that are systematically lower than those produced using the adjusted case-count approach.

The adjusted case-count approach is typically used where observations of community malaria prevalence (which are required to utilise the cartographic approach) are sparse or parasite prevalence is low [1, 2, 10] (e.g. in much of Asia and the Americas). Conversely, using the adjusted case-count approach is challenging in many African countries, where health system surveillance systems are often incomplete, with data reported only from some public clinics, often without parasitological diagnosis [3, 10, 11]. In these

countries, where national household surveys of malaria prevalence are common [12], the cartographic approach is most typically used. In the most recent World Malaria Report, the number of malaria cases rose in a number of sub-Saharan African countries, when estimated via the adjusted case-count approach [3]. In response to this, differences between the adjusted case-count and the cartographic approaches were compared and presented in the report, revealing stark differences in a number of countries between these two estimation techniques, with the cartographic approach predicting far fewer cases than the adjusted case-count approach [3]. A better understanding of the difference between the rate of malaria-attributable fevers and malaria-positive fevers (and by extension, the metrics produced via the adjusted case-count and cartographic approaches) is required to estimate the true burden of malaria.

The proportion of malaria-positive fevers that are directly attributable to malaria rather than non-malarial causes has been estimated in literature using a number of different methods. Parasite density thresholds can be used, where febrile malaria-positive individuals are said to have a "causal" fever when their malaria infection is over a blood parasite density threshold (the "pyrogenic" threshold). Within this approach, all other febrile individuals with malaria infections under this threshold are presumed to have a non-malarial febrile illness that is the underlying cause of their fever. This method has been used frequently in passive and active case detection studies [13–16]. Logistic regression can augment this method by providing different pyrogenic thresholds for sub-sets of populations based on individual-level factors. Publications documenting this method include an analysis of the difference in the rate of malaria-attributable fevers in the high and low season by age in Burkina Faso [17], and in the highlands of western Kenya [18], and an analysis of the effect of individual insecticide-treated bed net use on clinical malaria cases [19]. The pyrogenic threshold approach is also used to determine

the probability of an infected individual developing symptoms within some mechanistic transmission models of malaria. In the OpenMalaria transmission model, an age- and exposure-related pyrogenic threshold is used to determine the probability of developing a symptomatic malaria infection [20]. Similarly, probability of developing a malaria-attributable fever is modelled indirectly in the Disease Transmission Kernel malaria transmission model, where probability of a malaria-attributable fever is reliant on the level of pro-inflammatory cytokines, derived as a function of the number of infected red blood cells, which itself is a function of parasite density [21].

If the parasite densities of malaria infections in a population of febrile individuals is unknown (for example, if parasite detection is conducted with a rapid diagnostic test or PCR), empirical methods can be utilised to estimate the proportion of malaria-positive fevers that are directly attributable to malaria. Empirical methods assess the background rate of non-malarial febrile illness, applying the same proportion of non-malarial fevers to the malaria-positive febrile individuals, with the excess of fever in malaria-positive febrile individuals representing the malaria-attributable fraction of fevers within the population [22, 23]. This approach can be applied to large-scale nationally representative household surveys such as those conducted by the DHS Program [12] if the survey collected paired individual-level observations of malaria positivity (typically measured by rapid diagnostic test (RDT) and microscopy) and fever status or recent fever history [12]. This approach was used in an earlier study as the basis for a model predicting the prevalence of all-cause, non-malarial, and malaria-attributable fever amongst children at a 5km x 5km resolution across sub-Saharan Africa, which estimated that only 10% of all paediatric fevers (and 30% of malaria-positive fevers) were causally attributable to *P. falciparum* malaria [24].

Studies and surveys estimating malaria-attributable fever use a variety of different definitions for fever, either through recall of recent self-diagnosed fever (used primarily in household surveys) [12, 25, 26], or through direct axillary temperature measurement by the interviewer [13, 27, 28]. Although the prevalence of fever when measured via recall over a period of time (for example, two weeks in most household surveys) is typically higher than when the same population receives axillary temperature measurement at the end of the time period [29–32], ambiguity exists over whether or not the fraction of malaria-positive fevers that are causally attributable to malaria differs between recalled and measured fevers.

Here, estimates of causal and non-causal malaria-positive fevers were collated from a wide variety of sources (with different definitions of causality, and differing fever definitions) and the relationship between the proportion of malaria-positive fevers that are causally attributable to malaria in a given community and the corresponding *P. falciparum* parasite prevalence (*Pf*PR) was modelled. Using this informative relationship, a Bayesian hierarchical model was fit to household survey data to predict whether febrile individuals under five years of age in this dataset had a non-malarial fever, a malaria-attributable fever, or a malaria-coincident fever (where the individual has a malaria infection, but it is not the underlying cause of their fever). Individuals' subsequent treatment-seeking behaviour was then followed to generate estimates of the proportion of febrile individuals under five years of age presenting at health clinics with fevers due to the following underlying causes: *i)* malaria-attributable fever (MAF), *ii)* co-symptomatic MAF and non-malarial febrile illness (NMFI), *iii)* NMFI coincident with an RDT-patent asymptomatic *P. falciparum* infection, and *iv)* NMFI without an RDT-patent *P. falciparum* infection. These estimates were compared to malaria case counts in children under five years of age obtained from Ministry of Health reports from three malaria-

endemic countries, to estimate the proportion of malaria-positive fevers with a non-malarial underlying cause. These findings highlight the difference between malaria-positive fevers presenting at clinics (considered "cases" under the adjusted case-count approach) and the true burden of symptomatic malaria-attributable infections (the metric estimated under the cartographic approach). The results further indicate the proportion of malaria-positive fevers that would not be resolved by antimalarial medication alone.

4.4. Methods

The following steps were followed in order to generate estimates of the proportion of malaria-positive fevers presenting in public clinics that were/were not causally attributable to malaria in 41 sub-Saharan African country-years. First, observations of malaria-attributable fevers amongst febrile, malaria-infected children were collated from a variety of sources (household surveys, and literature reviews using a range of criteria for defining malaria-attributable fever). Second, these observations were used to model the underlying relationship between the proportion of malaria-positive fevers that are due to MAF and *Pf*PR amongst children under 5 years of age. Third, this modelled relationship was used to calibrate another model to individually attribute the probability of each of four fever types (MAF, NMFI with an asymptomatic *P. falciparum* infection, NMFI without an asymptomatic *P. falciparum* infection, and co-symptomatic MAF and NMFI) to febrile children within a household survey dataset from 41 country-years in sub-Saharan Africa. The subsequent treatment-seeking outcomes for febrile children were then used to derive the proportion of malaria-positive fevers presenting in public clinics that were/were not causally attributable to malaria presenting at public clinics in sub-Saharan Africa.

The methods below are separated into two datasets and models for producing both of these metrics are described in turn below.

4.4.1. Modelling the relationship between malaria-attributable fever and malaria prevalence

Four different primary datasets were assembled and used to measure the relationship between MAF and *P. falciparum* prevalence in children under 5 years of age ($Pf\text{PR}_{0\text{-}5}$). The four datasets fall broadly into two categories: defining MAF using a pyrogenic parasite density threshold for malaria-infected individuals, above which malaria-positive fevers are defined as MAF (one dataset); and datasets which record paired observations of malaria positivity and fever (either measured fever at the point of diagnosis, or recalled recent fever history) allowing for empirical estimation of MAF (three datasets).

4.4.1.1. Data: parasite density estimates of MAF

Estimates of the proportion of malaria infections above and below a pyrogenic parasite density threshold at varying levels of $Pf\text{PR}_{0\text{-}5}$ were derived from active case detection studies. Analysis was restricted only to active case detection studies as these fully enumerate all febrile illnesses within the study site. The parasite density threshold dataset comprised a subset of the exhaustive dataset of *P. falciparum* active case detection studies compiled by Battle *et al* [33], updated to include all studies published until the end of 2017. Full inclusion criteria for this analysis were as follows: *i)* parasite densities of febrile individuals were given (either as raw values or above/below a case definition parasite density threshold; for studies that presented multiple case definition thresholds the threshold closest to 5,000 parasites/μl was used), *ii)* the study reported observations

for children between 0 and 5 years of age, and *iii) Pf*PR_{0-5} was recorded. For each study, the total number of microscopically-diagnosed *P. falciparum* positive febrile individuals above and below the malaria case definition threshold of 5,000 parasites/μl was collated, for consistency with previous models [5]. A total of 11 studies met the inclusion criteria, resulting in 31 active case detection records. Full details of the studies utilised are given in Additional Table 1.

4.4.1.2. Data: empirical estimates of MAF

The remaining three datasets consisted of paired records of fever and malaria positivity, from which the proportion of malaria-positive fever cases where the malaria infection was the underlying cause of the fever was derived empirically, by accounting for the rate of malaria-negative fever in the population. N_{MAF}, the number of malaria-attributable fevers, is given by

$$N_{MAF} = N_{P^+F^+} - (N_{P^+} \times \frac{N_{P^-F^+}}{N_{P^-}})$$

Where $N_{P^+F^+}$ is the number of individuals who are both *P. falciparum*-positive and fever-positive, N_{P^+} is the total number of *P. falciparum*-positive individuals, $N_{P^-F^+}$ is the total number of individuals who are both *P. falciparum*-negative and fever-positive, and N_{P^-} is the total number of *P. falciparum*-negative individuals. This empirical calculation assumes that the rate of fever caused by NMFI is the same in both the *P. falciparum*-positive and *P. falciparum*-negative populations, and as such calculates the "excess" number of fevers within the febrile *P. falciparum*-positive individuals not

explained by the background NMFI rate. Three datasets from varying sources were collated to estimate MAF empirically, as outlined below.

The first dataset used for empirical estimations of MAF composed of 41 cross-sectional, nationally-representative georeferenced surveys of malaria prevalence in children less than five years of age across 21 countries conducted between 2006-2016 in sub-Saharan Africa, obtained from the Demographic and Health (DHS) Program [12]. Full details of the surveys used can be found in Additional Table 2. In each of these surveys, interviewers visited houses (selected as a geographically and demographically representative sample of the population) and a finger- or heel-prick blood sample was taken from any children under five years of age present and tested for malaria with an RDT. For each child receiving a malaria diagnosis, their caregiver was asked whether, in the past two weeks, the child had a fever. Diagnostic and fever history outcomes were collated from each child, with children aggregated at geo-located cluster-level to represent community-level groups, resulting in a total of 156,670 paired observations of malaria positivity and fever history in the same individuals. A limitation of these data is that an individual who was malaria-positive at a previous point during the two weeks preceding the interview may have sought and received antimalarial treatment, and their blood antigen concentration may have reduced sufficiently to appear RDT-negative by the time of interview (henceforth referred to as the "treatment effect"). The treatment effect is accounted for in both models described in subsequent sections.

The second dataset for empirical estimation of MAF was collated from published articles documenting paired observations of malaria positivity and fever. Two search strategies were utilised to identify these studies. First, every article published between 2006 and 2017 cited within the Malaria Atlas Project database (the largest repository of global

malaria prevalence data, updated annually via exhaustive reviews of published literature) [33], was systematically searched for paired observations of fever and malaria positivity. Second, a systematic literature review of the PubMed database using the MeSh terms "malaria", "fever" and "diagnosis" was conducted. For both data sources, studies assessing a population in a malaria-endemic community were collated, using the following inclusion criteria: *i)* malaria diagnosis was conducted (using any diagnostic), and *ii)* diagnostic outcomes were paired with individual fever status, whether measured at the time of diagnosis or individually recalled recent fever history. For each study meeting the inclusion criteria, the location of study was recorded and the number of individuals in each community falling in to each of the following four categories was documented: *i) P. falciparum* positive and fever positive, *ii), P. falciparum* positive and fever negative, *iii) P. falciparum* negative and fever positive, and *iv) P. falciparum* negative and fever negative. The review of the MAP *Pf*PR database and the PubMed review yielded 71 and 23 observations, respectively, of community-level paired malaria and fever measurements, comprising a total of 123,649 individuals.

The third database utilised for empirical estimates of MAF was sourced from the *Program for Resistance, Immunology, Surveillance and Modeling of Malaria in Uganda* (PRISM) study [34]. The PRISM study collected data over five years (2011-2016) on malaria-related metrics across three sites of differing malaria transmission intensity in Uganda, with the aim of improving understanding of the complex relationships between malaria parasite, host, and vector. In each of the three Ugandan sites, approximately 100 households were enrolled between 2011 and 2013 and followed up longitudinally for malaria infection. The malaria diagnostic outcome of all individuals at enrolment was collated, and paired with measured fever (axillary temperature > 38°C) at the time of diagnosis.

Combined, the literature review and PRISM datasets yielded observations from a total of 112 study sites, but only 27 were used for modelling (82 were excluded because they focused only on individuals 5 years of age or above; and a further 3 amongst children under 5 years of age were excluded as they diagnosed malaria using RDT or PCR; only microscopic diagnosis was included as the majority of observations were conducted via microscopy, and to retain consistency between the parasite density dataset, the literature review dataset, and the PRISM dataset). Full details of the literature review data, including observations amongst adults and children over 5 years of age that were not included in the final analysis, can be found in Additional Table 3.

4.4.1.3. Modelling approach

For this analysis, a model was applied where the relationship between MAF in children under 5 years of age and *Pf*$PR_{0\text{-}5}$ was learned. The DHS Program data was used to inform the shape of the relationship, and the remaining three datasets described above were subsequently used to learn scaling factors, as these datasets are informative for higher values of *Pf*$PR_{0\text{-}5}$ but lack MAF observations where *Pf*$PR_{0\text{-}5}$ <0.1. Additionally these datasets were unbiased by the treatment effect described for the DHS Program data, described in the previous subsection.

We assume this relationship takes the following form, the motivation for which was informed by localised regression fits to the response data detailed above:

$$p_{MAF} = \beta\left(e^{-\lambda \times p_{pos}} + \alpha \right)$$

Where

$$p_{MAF} = \frac{N_{MAF}}{N_{MF}}$$

Where N_{MAF} is the number of individuals in a given population with a malaria-attributable fever, N_{MF} is the number of individuals in a given population with a malaria-positive fever (regardless of fever causality) and p_{MAF} is the proportion of malaria-positive fevers that are causally due to malaria. It was assumed that this proportion is negatively exponential and is shaped by three parameters, α, λ and β, where α controls the minimum proportion of malaria-positive fevers in a population that can be due to malaria, and λ controls the rate of decline with increasing *Pf*$PR_{0\text{-}5}$ until the minimum proportion of fevers, α, is reached. The relationship is scaled by the parameter β. p_{pos} represents the proportion of individuals who are *P. falciparum*-positive (whether febrile or not). The model used a numerical optimisation function to learn the parameters α, λ, and β (plus an additional standard deviation/observational noise parameter, σ) to fit the relationship between malaria-attributable fevers (as a proportion of malaria-positive fevers) and *Pf*$PR_{0\text{-}5}$ in a two-step process: first, all four parameters were optimised using only the DHS Program dataset, allowing the shape of the relationship to be learnt; second, λ and α were fixed to the optimised values identified in the first model fit using the household survey dataset, and the model re-fit β and σ, using the remaining datasets. Using this method, the intercept and rate of decline in p_{MAF} was learnt using the DHS Program dataset, and then the relationship was re-scaled by the non-DHS Program datasets (i.e. the parasite-density literature review dataset, the paired observations of fever and malaria dataset, and PRISM dataset, as detailed above). For direct comparability between datasets, only observations for children under five years of age were included.

Additional factors which may impact the relationship between MAF and *Pf*PR_{0-5} were also investigated. First, recent declines in *Pf*PR_{0-5} may affect the relationship due to residual exposure-dependent immunity, so DHS Program data were segregated by the magnitude of declines in *Pf*PR_{0-5} during the two years preceding the survey (measured at cluster-level for each 5km x 5km pixel) using cartographic model-based geostatistical estimates for 2000-2016 [6] and the model was fit to each data subset to investigate differences. Second, the parasite density threshold dataset (used for the secondary model calibration) was based on active case detection studies, meaning that the prompt and effective treatment rate for malaria cases is typically close to 100% [5]. The treatment rate in all the other datasets was far more variable. The potential effect of differing treatment rates on the relationship between MAF and *Pf*PR_{0-5} was investigated by segregating the DHS Program data by the treatment-seeking rate within each cluster. All modelling described above was completed in in R using the TMB package [35].

4.4.2. MAF-NMFI model and generation of clinic-level estimates

4.4.2.1. Household survey data

To inform the estimates of the proportion of malaria-attributable and non-malarial fevers presenting at health facilities, the household survey dataset described in the previous sub-section was utilised. Full details of the surveys used can be found in Additional Table 2. In addition to the RDT-derived parasitaemia and two-week fever outcomes described in the previous sub-section, the following information was also extracted for each child: *i)* a geo-referenced location for each child (for matching with remotely sensed explanatory variables, as explained below), *ii)* information about treatment-seeking behaviour at formal public health clinics that would be likely to report to the HMIS (locations such as

shops, pharmacies, markets, drug peddlers, friends and relatives, or traditional healers, and formal private health clinics were not included in this analysis), and *iii)* information about the child's age, household wealth, maternal education, and child usage of insecticide-treated bed nets the night preceding the household survey. These variables were used in the Bayesian hierarchical model described below as predictors of likelihood of experiencing MAF and NMFI in the two weeks preceding the survey. A total of 156,670 observations were collated from the 41 surveys.

4.4.2.2. Covariates

Three model-derived spatiotemporal estimates were utilised as predictor variables for probabilistic attribution of MAF or NMFI for each febrile individual within the household survey dataset. In order to increase computational efficiency whilst retaining use of the large repository of remotely-sensed data and malaria-related health metrics created and/or collated within the Malaria Atlas Project database, three modelled estimates that incorporate these metrics as predictor variables were used. These three predictor variables were: *i)* *Pf*$PR_{0\text{-}5}$, *ii)* suitability for fever without a malaria infection in children under 5 years of age, and *iii)* caregivers' propensity to seek treatment for fever of any cause for children less than 5 years of age. All three variables were generated as cartographic predictions, at a 5km x 5km resolution within areas of stable *P. falciparum* transmission across sub-Saharan Africa, and are described in full below.

The *Pf*$PR_{0\text{-}5}$ variable was generated by age-transforming estimates of malaria prevalence via microscopy diagnosis in children 2-10 years of age in Africa, as presented by Bhatt and colleagues [6], using the 'agestand' package in the R programming language, based

on the age-standardisation procedure for *Pf*PR described by Smith *et al* [36]. These estimates were then standardised to RDT-based prevalence estimates of malaria using the methods described by Mappin *et al* [37].

The remaining two covariates were generated using a boosted regression tree (BRT) approach, and are henceforth referred to as "BRT_{bg}" for suitability for fever without a malaria infection (a "background" fever, hence BRT_{bg}), and "BRT_{treat}" for propensity for all-cause fever treatment-seeking. The approach used is an adapted version of a methodology outlined previously [24]. To generate the two BRT variables, a training dataset was constructed, comprised of the household survey data points described above aggregated into 5km x 5km groups (to match the resolution of the predictor variables), including only clusters with more than ten children interviewed (to remove outliers due to small sample sizes), resulting in a training dataset of 5,262 clusters. For the BRT_{bg} model, the response variable was the empirical logit of the prevalence of fever without an RDT-patent malaria infection. For the BRT_{treat} model, the response was the empirical logit of the treatment-seeking rate amongst febrile individuals within each cluster. For both of these models, a suite of 157 environmental and socio-demographic covariates were initially assembled. These covariates, for the area of stable *P. falciparum* transmission in Africa, included 5km x 5km resolution remotely-sensed covariates (and derived products of remotely sensed variables) [38], and annual national-level demographic and poverty indicators supplied by the World Bank [39]. The World Bank data were incomplete for a number of country years, and were gap-filled using a Gaussian process regression approach. The temporal resolution of these datasets was either monthly, yearly, or stationary across the study period. Full details of the variables used and each variable's contribution to each final BRT model are given in Additional Tables 4 and 5.

For both the BRT_{bg} and BRT_{treat} covariates, a BRT model using the response dataset and the 157 covariate layers was constructed in the 'dismo' package in R developed by Elith *et al* [40]. The BRT split response data repeatedly by covariates, and the covariates that maximised the homogeneity of each of the two partitioned response datasets were selected more frequently in subsequent steps. The regression tree models were then "boosted", where models were combined to reduce overall predictive deviance. Both models were parameterised using a tree complexity of 5, a learning rate of 0.01, and the number of trees was determined by the optimal solution found by the 'gbm.step' function. Spatial predictions of BRT_{bg} and BRT_{treat} were generated across stable *P. falciparum* transmission zones in sub-Saharan Africa on a monthly basis from January 2006 to December 2016. Any gaps in these modelled predictions, caused by areas of missing data in the remotely sensed covariates, were filled with the average value from the eight surrounding cells.

4.4.2.3. Fever attribution model

The model utilised in this analysis is a further adaptation of a previously presented model for estimating the prevalence of MAF and NMFI at a 5km x 5km spatial resolution across sub-Saharan Africa from 2006-2014 [24]. Here, this model was modified to take into account additional individual-level data on socioeconomic status and treatment-seeking behaviour in the two weeks preceding the survey. This individual-level data can markedly improve the precision of the probabilistic estimations of fever type (i.e. MAF or NMFI), but since it is unavailable as a continuous spatial covariate, population-level estimates cannot be formed by applying the modified model across all pixels within a given country or district. Instead, a mixed estimation strategy is presented in this analysis

in which Bayesian posterior samples of predicted fever type were compiled using the design weights of the original survey, as described below.

The individual-level model presented in this analysis assigned a probability of each individual experiencing within the past 14 days a NMFI, a MAF, or both (i.e. a co-symptomatic MAF and NMFI). Conditional on those events a further set of probabilities was computed: probability of treatment-seeking, of receiving a heel-prick diagnosis (used as a proxy for RDT-based malaria diagnosis), of receiving antimalarials, and of clearing any parasites/antigens early enough to clear an RDT test at time of survey (as defined by the adjustment presented in [41]). Each individual's observed category according to their RDT test result and response to the corresponding survey questions informed their contribution to the likelihood function. The probabilities assigned to parasite positivity status ($p_{\text{pos.}}$), NMFI status (background fever; p_{bg}), and of treatment-seeking under each of the three fever cases—MAF-only ($p_{\text{treat|maf}}$), NMFI-only ($p_{\text{treat|bg}}$), or both ($p_{\text{treat|both}}$)—were estimated from the combination of individual level covariates—mother's education (m_i), child's age (a_i), household wealth (w_i), and bed net use (b_i)—and separate spatial random fields ($f_{\text{pos.}}$, f_{bg}, $f_{\text{treat|maf}}$, $f_{\text{treat|bg}}$, $f_{\text{treat|both}}$). Spatial covariates from high resolution imaging were introduced as described in the previous sub-section via treatment-seeking ($\text{BRT}_{\text{treat}}$) and malaria-negative fever prevalence (BRT_{bg}) predictions from separate BRT models, and malaria prevalence predictions ($\text{MAP}_{\text{pos.}}$) from a published *P. falciparum* prevalence model [6]. The probabilities of each stage of diagnosis and treatment response were assigned survey-level random effects: the probability of receiving a heel-prick test (p_{prick}), the probability of (explicit) 'under-treatment' (not receiving antimalarials despite a positive test result, $p_{\text{undertreat}}$), the probability of (explicit) 'over-treatment' (probability of receiving antimalarials despite a negative test result, $p_{\text{overtreat}}$), and the probability of presumptive treatment (receiving

antimalarials without a heel-prick test, $p_{\text{presumptive}}$). Again, the probability of experiencing a MAF given a patent parasite level infection was given by a polynomial function of the background community prevalence to reflect the role of exposure-based immunity [20, 24, 42, 43]. For individuals who were RDT-negative at the time of interview but were known to have received antimalarials within the past two weeks, the probability of the individual having been RDT-positive at the time of treatment and subsequently cured to the point of their blood antigen concentration reducing sufficiently to appear RDT-negative by the time of interview, $p_{\text{cured and reverted}}$, was assigned using the adjustment presented previously [41]. The probability of the success of each individual's antimalarial treatment was derived from treatment failure data compiled by the World Health Organization, matching the type of antimalarial to the country and year in which it was received [44, 45].

In Bayesian hierarchical notation all these layers sitting below the likelihood function may be written as follows:

for i in $1, \ldots, N_{\text{individuals}}$:

$$\text{logit}\, p_{\text{pos.}[i]} = \beta_m^{\text{pos.}} m_i + \beta_a^{\text{pos.}} a_i + \beta_w^{\text{pos.}} w_i + \beta_b^{\text{pos.}} b_i + \text{logit}\, \text{MAP}_{\text{pos.}[i]} + f_{\text{pos.}}(\text{location}_i)$$

$$\text{logit}\, p_{\text{bg}[i]} = \beta_m^{\text{bg}} m_i + \beta_a^{\text{bg}} a_i + \beta_w^{\text{bg}} w_i + \beta_b^{\text{bg}} b_i + \text{logit}\, \text{BRT}_{\text{bg}[i]} + f_{\text{bg}}(\text{location}_i)$$

$$\text{logit}\, p_{\text{treat|maf}[i]} = \beta_m^{\text{treat}} m_i + \beta_a^{\text{treat}} a_i + \beta_w^{\text{treat}} w_i + \beta_b^{\text{treat}} b_i + \text{logit}\, \text{BRT}_{\text{treat}[i]} + f_{\text{treat|maf}}(\text{location}_i)$$

$$\text{logit}\, p_{\text{treat|bg}[i]} = \beta_m^{\text{treat}} m_i + \beta_a^{\text{treat}} a_i + \beta_w^{\text{treat}} w_i + \beta_b^{\text{treat}} b_i + \text{logit}\, \text{BRT}_{\text{treat}[i]} + f_{\text{treat|bg}}(\text{location}_i)$$

$$\text{logit}\, p_{\text{treat|both}[i]} = \beta_m^{\text{treat}} m_i + \beta_a^{\text{treat}} a_i + \beta_w^{\text{treat}} w_i + \beta_b^{\text{treat}} b_i + \text{logit}\, \text{BRT}_{\text{treat}[i]} + f_{\text{treat|both}}(\text{location}_i)$$

$$\text{logit}\, \text{maf}_{[i]} = \alpha_0 + \alpha_1\, p_{\text{pos.}[i]} + \alpha_2 \left(p_{\text{pos.}[i]}\right)^2$$

for j in $1, \ldots, N_{\text{surveys}}$:

$$\text{logit}\, p_{\text{prick[j]}} \sim \text{Normal}\left(\mu_{\text{prick}}, \sigma^2_{\text{prick}}\right)$$

$$\text{logit}\, p_{\text{undertreat[j]}} \sim \text{Normal}\left(\mu_{\text{undertreat}}, \sigma^2_{\text{undertreat}}\right)$$

$$\text{logit}\, p_{\text{overtreat[j]}} \sim \text{Normal}\left(\mu_{\text{overtreat}}, \sigma^2_{\text{overtreat}}\right)$$

$$\text{logit}\, p_{\text{presumptive[j]}} \sim \text{Normal}\left(\mu_{\text{presumptive}}, \sigma^2_{\text{presumptive}}\right)$$

$$f_{\text{pos.}}(\cdot) \sim \text{Gaussian Process}\left[\theta_{\text{pos.}}\right]$$

$$f_{\text{bg}}(\cdot) \sim \text{Gaussian Process}\left[\theta_{\text{bg}}\right]$$

$$f_{\text{treat|maf}}(\cdot) \sim \text{Gaussian Process}\left[\theta_{\text{treat|maf}}\right]$$

$$f_{\text{treat|bg}}(\cdot) \sim \text{Gaussian Process}\left[\theta_{\text{treat|bg}}\right]$$

$$f_{\text{treat|both}}(\cdot) \sim \text{Gaussian Process}\left[\theta_{\text{treat|both}}\right]$$

All free parameters and hyper-parameters are assigned suitable priors (details may be found in the TMB model code given in the Appendix (Additional Files 1 and 2).

The top layer of the hierarchical model corresponds to the categorical likelihood for each category form by an individual's observed RDT test result (P: 0 = negative, 1 = positive),

caregiver-reported fever status within the past 14 days (F: 0 = no, 1 = yes), treatment sought response (T: 0 = no, 1 = yes), heel-prick conducted response (H: 0 = no, 1 = yes, 2 = missing data), and antimalarials received response (A: 0 = no, 1 = yes).

The probability of each category was found by enumerating each possible scenario whereby an individual could end up in that category. These are written mathematically below with explanatory notes. Calculations are omitted for cases with unknown heel-prick status for brevity: these are simply compiled by summation of the equivalent probabilities for the remaining outcomes with and without a heel-prick, weighted by the probability of having or not having received a heel-prick.

$\boldsymbol{P = 1, F = 0}$:

$$p_{\text{pos}[i]} \times \left(1 - \text{maf}_{[i]}\right) \times \left(1 - p_{\text{bg}[i]}\right)$$

The patient has an RDT-patent parasite load but has had neither a causal nor background fever in the past 14 days.

$\boldsymbol{P = 1, F = 1, T = 1, H = 1, A = 1}$:

$$p_{\text{pos}[i]} \times \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times p_{\text{treat|maf}[i]} + (1 - \text{maf}_{[i]}) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} + \text{maf}_{[i]} \times p_{\text{bg}[i]} \times p_{\text{treat|both}[i]}\right) \times p_{\text{prick[survey}[i]]} \times \left(1 - p_{\text{undertreat[survey}[i]]}\right) \times \left(1 - p_{\text{cured and reverted}[i]}\right)$$

The patient has one of the three possible fever types and has sought treatment accordingly; at treatment they received a heel-prick, were not explicitly under-treated (i.e. received antimalarials), but had not cleared their parasite load and reverted to RDT negative by the time of survey.

$\boldsymbol{P = 0, F = 1, T = 1, H = 1, A = 1}$:

$$\left(1 - p_{\text{pos}[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} \times p_{\text{prick}[\text{survey}[i]]} \times p_{\text{overtreat}[\text{survey}[i]]} + p_{\text{pos}[i]} \times \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times p_{\text{treat|maf}[i]} + \left(1 - \text{maf}_{[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} + \text{maf}_{[i]} \times p_{\text{bg}[i]} \times p_{\text{treat|both}[i]}\right) \times p_{\text{prick}[\text{survey}[i]]} \times \left(1 - p_{\text{undertreat}[\text{survey}[i]]}\right) \times p_{\text{cured and reverted}[i]}$$

Either the patient followed the course of events in the scenario above but *did* successfully clear their parasite load and revert to RDT negative by the time of survey; *or*, they had only a background fever, received a heel-prick that presumably returned a negative result but were given antimalarials anyway (explicit over-treatment).

$\boldsymbol{P = 0, F = 1, T = 1, H = 0, A = 1}$:

$$\left(1 - p_{\text{pos}[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} \times \left(1 - p_{\text{prick}[\text{survey}[i]]}\right) \times p_{\text{presumptive}[\text{survey}[i]]} + p_{\text{pos}[i]} \times \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times p_{\text{treat|maf}[i]} + \left(1 - \text{maf}_{[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} + \text{maf}_{[i]} \times p_{\text{bg}[i]} \times p_{\text{treat|both}[i]}\right) \times \left(1 - p_{\text{prick}[\text{survey}[i]]}\right) \times p_{\text{presumptive}[\text{survey}[i]]} \times p_{\text{cured and reverted}[i]}$$

The same range of possibilities as above except that since no heel prick was given this is considered a presumptive treatment event; whether or not that treatment could be considered implicit over-treatment or not of course depends on whether or not they did indeed have RDT-patent parasitemia at the point of treatment (to which a probability is assigned, although the definitive outcome is unknown).

$\boldsymbol{P = 1, F = 1, T = 1, H = 1, A = 0}$:

$$p_{\text{pos}[i]} \times \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times p_{\text{treat|maf}[i]} + \left(1 - \text{maf}_{[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} + \text{maf}_{[i]} \times p_{\text{bg}[i]} \times p_{\text{treat|both}[i]}\right) \times p_{\text{prick}[\text{survey}[i]]} \times p_{\text{undertreat}[\text{survey}[i]]}$$

Here it is assumed that the probability of a patient becoming parasite positive in between seeking treatment for their fever in the past 14 days and the time of survey is negligible; therefore the patient must have been parasite positive at time of seeking treatment so failure to receive antimalarials counts as an explicit under-treatment.

$\boldsymbol{P = 1, F = 1, T = 1, H = 0, A = 1}$:

$$p_{\text{pos}[i]} \times \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times p_{\text{treat|maf}[i]} + \left(1 - \text{maf}_{[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} + \text{maf}_{[i]} \times p_{\text{bg}[i]} \times p_{\text{treat|both}[i]}\right) \times \left(1 - p_{\text{prick}[\text{survey}[i]]}\right) \times p_{\text{presumptive}[\text{survey}[i]]} \times \left(1 - p_{\text{cured and reverted}[i]}\right)$$

Since no heel-prick test was conducted but antimalarials were given this is considered a case of presumptive treatment.

$\boldsymbol{P = 1, F = 1, T = 1, H = 0, A = 0}$:

$$p_{\text{pos}[i]} \times \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times p_{\text{treat|maf}[i]} + \left(1 - \text{maf}_{[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} + \text{maf}_{[i]} \times p_{\text{bg}[i]} \times p_{\text{treat|both}[i]}\right) \times \left(1 - p_{\text{prick}[\text{survey}[i]]}\right) \times \left(1 - p_{\text{presumptive}[\text{survey}[i]]}\right)$$

No heel-prick test was conducted and no antimalarials were given; since we again assume that the probability of the patient acquiring their parasite positive status after

seeking treatment but before the survey, this will be counted later as a case of (implicit) under-treatment (a missed opportunity).

$\boldsymbol{P = 1, F = 1, T = 0}$:

$p_{\text{pos}[i]} \times \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times \left(1 - p_{\text{treat|maf}[i]}\right) + \left(1 - \text{maf}_{[i]}\right) \times p_{\text{bg}[i]} \times \left(1 - p_{\text{treat|bg}[i]}\right) + \text{maf}_{[i]} \times p_{\text{bg}[i]} \times \left(1 - p_{\text{treat|both}[i]}\right)\right)$

The patient has one of the three fever types but has not sought treatment.

$\boldsymbol{P = 0, F = 1, T = 1, H = 1, A = 0}$:

$\left(1 - p_{\text{pos}[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} \times p_{\text{prick}[\text{survey}[i]]} \times \left(1 - p_{\text{overtreat}[\text{survey}[i]]}\right)$

Since the patient experienced a fever but has no patent parasite load and did not receive antimalarials it is inferred that they must have had a background fever; in this case they were given a heel-prick and not inappropriately treated with antimalarials (explicit over-treatment).

$\boldsymbol{P = 0, F = 1, T = 1, H = 0, A = 0}$:

$\left(1 - p_{\text{pos}[i]}\right) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} \times \left(1 - p_{\text{prick}[\text{survey}[i]]}\right) \times \left(1 - p_{\text{presumptive}[\text{survey}[i]]}\right)$

Since the patient experienced a fever but has no RDT-patent parasite load and did not receive antimalarials it is again inferred that they must have had a background fever; in this case they were not given a heel-prick but were also not presumptively (over-)treated.

$\boldsymbol{P = 0, F = 1, T = 0}$:

$$\left(1 - p_{\text{pos}[i]}\right) \times p_{\text{bg}[i]} \times \left(1 - p_{\text{treat|bg}[i]}\right)$$

Since the individual experienced a fever but has no patent parasite load and did not seek treatment (nor therefore receive antimalarials) it is again inferred that they must have had a background fever.

$\boldsymbol{P = 0, F = 0}$:

$$\left(1 - p_{\text{pos}[i]}\right) \times \left(1 - p_{\text{bg}[i]}\right)$$

The individual had neither a patent parasite load, nor a background fever during the past 14 days.

Once this model was coded in TMB and fit against the observed data, it was possible to arithmetically compute the posterior probabilities of each individual's fever type, though the diversity of possible observed categories made this is a formidable book-keeping exercise. The full set of calculations can be seen in the R script provided in the Appendix (Additional Files 1 and 2), but one case is explained below to illustrate the procedure.

$\boldsymbol{P = 1, F = 1, T = 1, H = 1, A = 1}$:

To compute the probability that an individual in this category had a malaria-attributable fever (with no background fever) this component of the class probability is divided by the sum of all components.

$$P(\text{maf only})[\text{i}] = \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times p_{\text{treat|maf}[i]}\right) / \left(\text{maf}_{[i]} \times \left(1 - p_{\text{bg}[i]}\right) \times p_{\text{treat|maf}[i]} + (1 - \text{maf}_{[i]}) \times p_{\text{bg}[i]} \times p_{\text{treat|bg}[i]} + \text{maf}_{[i]} \times p_{\text{bg}[i]} \times p_{\text{treat|both}[i]}\right)$$

In this calculation it can be seen that the posterior probability assigned to the individual's fever type depends on the relative probabilities that they would have each type of fever *and* the conditional probabilities that they would seek treatment. Since individual-level covariates and random field models inform both these calculations, the model is both tailored to each individual's circumstances and borrows strength from the observed behaviour of their neighbours. When these fever type probabilities were summed to produce survey-level estimates (e.g. of the relative fraction of malarial and non-malarial fevers amongst malaria-positive individuals), the accompanying design weights were used as supplied within the DHS Program surveys. The surveys were designed so that the stratification applied to the sampling relative to the total population was encapsulated in these design weights such that nationally-representative estimates were recovered upon application of the weights.

4.4.2.4. Ministry of Health malaria cases in children under 5 years of age

Reports of confirmed cases in children under five years of age were used to compare the estimated proportions of malaria-attributable fevers amongst malaria-positive febrile individuals in clinics, as predicted by the model presented above, for 41 country-years in sub-Saharan Africa. Confirmed case counts (i.e. those that received a parasitological diagnosis, rather than presumed or suspected cases) are presented for all malaria-endemic countries in the annual World Malaria Report, but are not disaggregated by age, preventing a direct comparison with our modelled estimates for cases amongst children

under 5 years of age. Instead, Ministry of Health and National Statistical Office websites for sub-Saharan African countries were systematically searched for reports of parasitologically confirmed malaria cases restricted to children under five years of age. Of the 41 country-years for which estimates were generated in this analysis, only three had age-disaggregated confirmed case data, collated at the closest contemporaneous year to the household survey (Benin 2010 [46], Burundi 2012 [47], and Kenya 2015 [48]).

4.5. Results

4.5.1. Relationship between malaria-attributable fever and *P. falciparum* prevalence

The proportion of malaria-positive fevers that are causally attributable to malaria was estimated to decline exponentially from 0.82 at $Pf\text{PR}_{0\text{-}5} \sim 0$, until $Pf\text{PR}_{0\text{-}5} > 0.4$ where the proportion becomes near-stationary at approximately 0.42. The coefficients for the fitted model are given in Table 4.1, and the final fitted model (with 68% and 95% credible intervals) are shown in Figure 4.1.

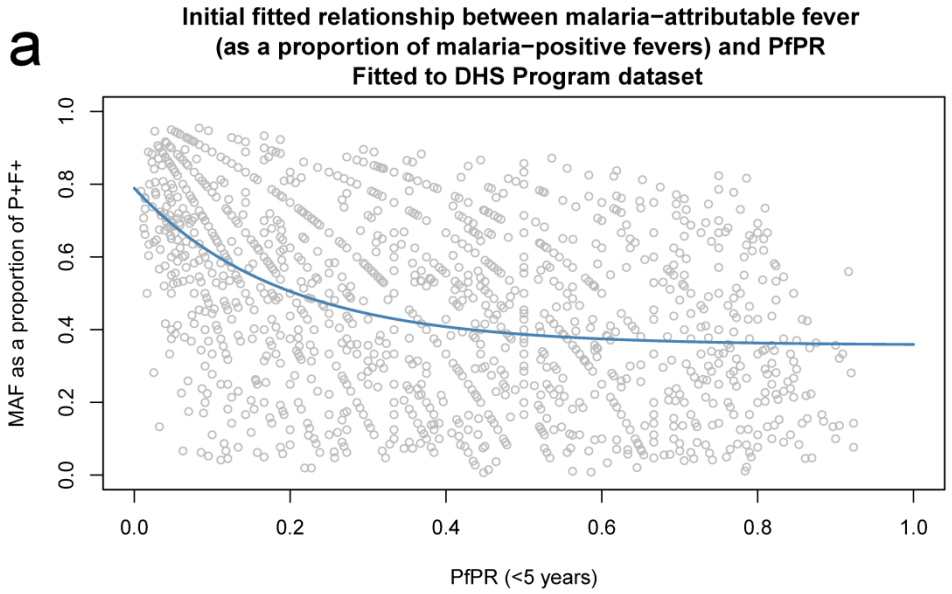
Limited effects were found of recent declines in $Pf\text{PR}_{0\text{-}5}$ (Figure 4.2), with non-significant differences between the relationships when fitted to DHS Program data points where the individuals lived in locations that had experienced large declines in $Pf\text{PR}_{0\text{-}5}$ (> 5% reduction in $Pf\text{PR}_{0\text{-}5}$ in the two years preceding the survey), compared to lesser declines (< 5% reduction) or $Pf\text{PR}_{0\text{-}5}$ increases. Differences in the fitted relationship by age were observable with older children (3 or 4 years of age) experiencing continual declines in the proportion of malaria-positive fevers that are causally attributable to malaria with increasing $Pf\text{PR}_{0\text{-}5}$, whereas children 2 years of age or younger (Figure 4.2) experience rapid exponential declines until approximately $Pf\text{PR}_{0\text{-}5} > 0.4$. Older children

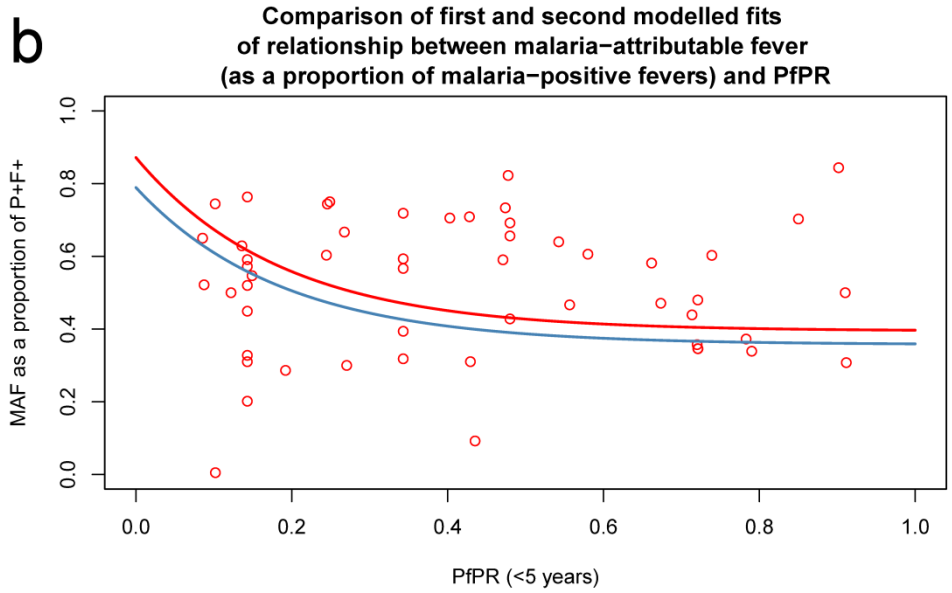
show a lower proportion of malaria-positive fevers causally attributable to malaria infection at higher *Pf*$PR_{0\text{-}5}$.

Background treatment-seeking rate (used as a proxy for underlying treatment rate for malaria infections) was not found to have a significant impact on the relationship between malaria-attributable fever (as a proportion of malaria-positive fevers) and *Pf*$PR_{0\text{-}5}$. Figure 4.3 shows the relationship between malaria-attributable fever (as a proportion of malaria-positive fevers) and *Pf*$PR_{0\text{-}5}$ for DHS Program clusters where the treatment-seeking rate for febrile illnesses within the cluster was over and under 30%, showing non-significant differences between the two subsets.

Table 4.1. Final model coefficients. β_{Final} represents the value of β after the second model-fitting (to the literature review data) and $\beta_{Initial}$ represents the value of β after the first model fitting (to the DHS Program data), which is not used in the final model fit.

Coefficient	**Value**
β_{final}	0.477
λ	5.354
α	0.827
σ	0.215
$\beta_{Initial}$	0.432


a
Initial fitted relationship between malaria−attributable fever
(as a proportion of malaria−positive fevers) and PfPR
Fitted to DHS Program dataset
MAF as a proportion of P+F+
PfPR (<5 years)
0.0
0.2
0.4
0.6
0.8
1.0


b
Comparison of first and second modelled fits
of relationship between malaria−attributable fever
(as a proportion of malaria−positive fevers) and PfPR
MAF as a proportion of P+F+
PfPR (<5 years)
0.0
0.2
0.4
0.6
0.8
1.0

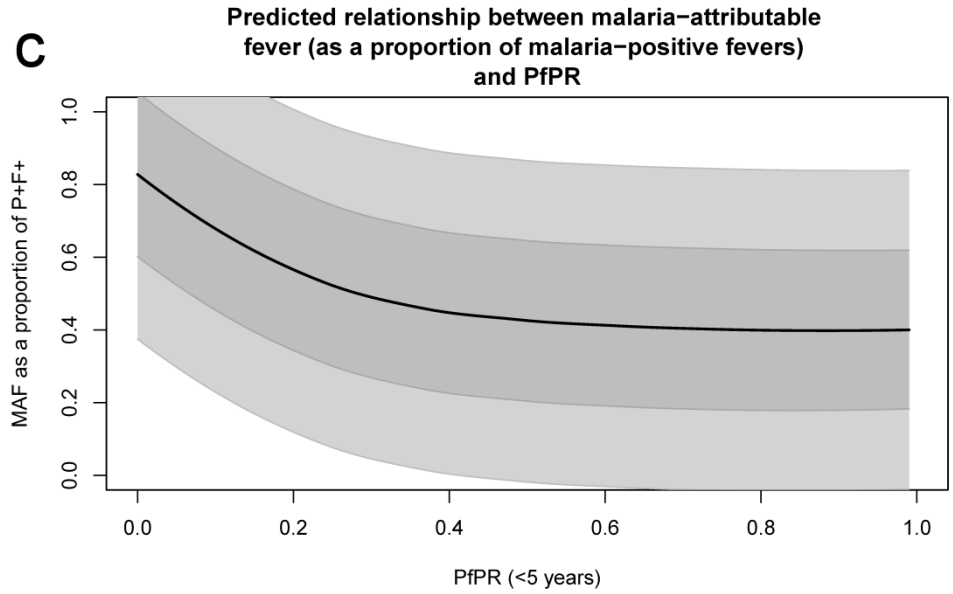
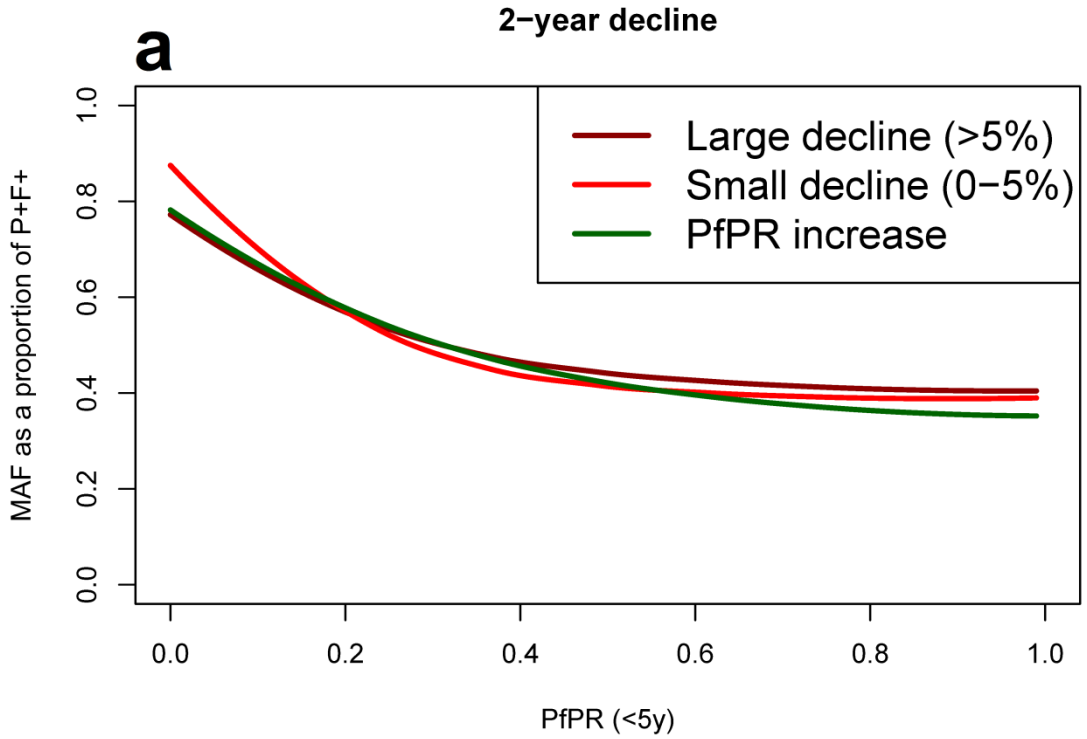
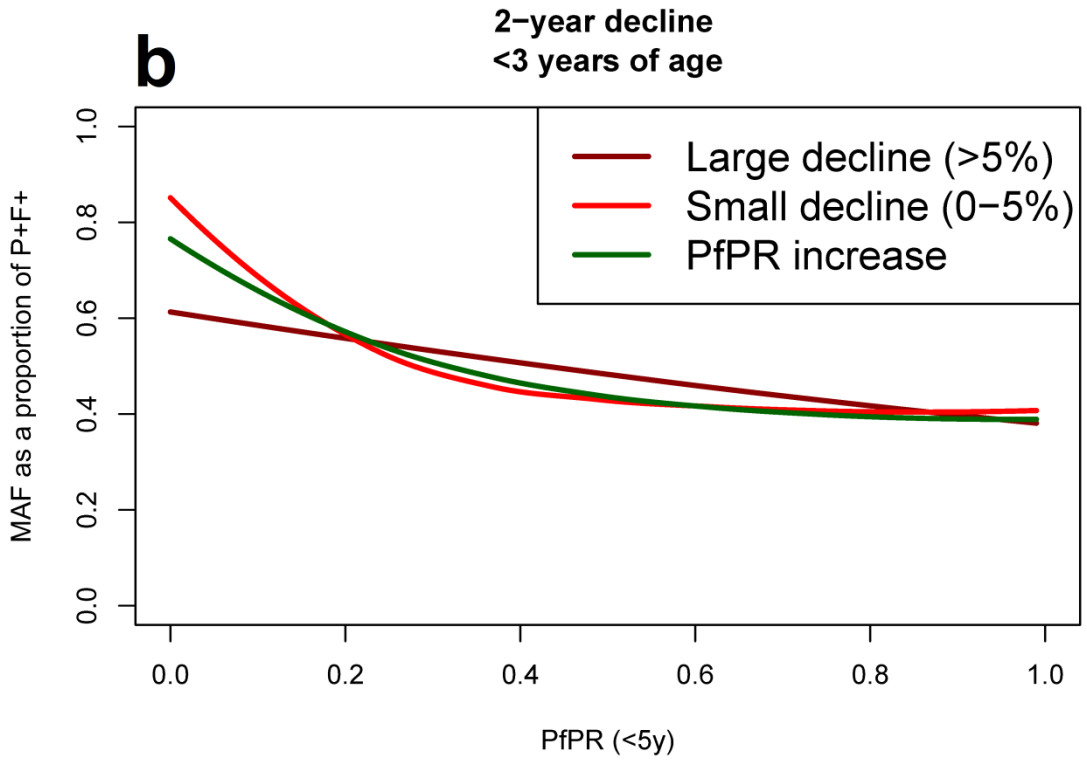

c
Predicted relationship between malaria−attributable
fever (as a proportion of malaria−positive fevers)
and PfPR
MAF as a proportion of P+F+
PfPR (<5 years)
0.0
0.2
0.4
0.6
0.8
1.0

Figure 4.1. a) Initial modelled relationship (blue line) between MAF (as a proportion of malaria-positive fevers) in children under 5 years of age, and *Pf*PR_{0-5}, fit only to empirical observations of MAF from the DHS Program household survey dataset, with survey data-points (grey points) overlain; **b)** original modelled relationship as described in the previous plot (blue line), and final rescaled model fit (red line), after optimising scaling parameters using the remaining three literature-derived datasets. Observation points from the three literature-derived datasets are overlain (red points); and **c)** final fitted relationship between MAF (as a proportion of malaria-positive fevers) in children under 5 years of age, and *Pf*PR_{0-5}. The black line represents the median, with decreasing grey shading representing the 68% and 95% credible intervals, respectively.


a
2−year decline
Large decline (>5%)
Small decline (0−5%)
PfPR increase
MAF as a proportion of P+F+
PfPR (<5y)
0.0
0.2
0.4
0.6
0.8
1.0


b
2−year decline
<3 years of age
Large decline (>5%)
Small decline (0−5%)
PfPR increase
MAF as a proportion of P+F+
PfPR (<5y)
0.0
0.2
0.4
0.6
0.8
1.0

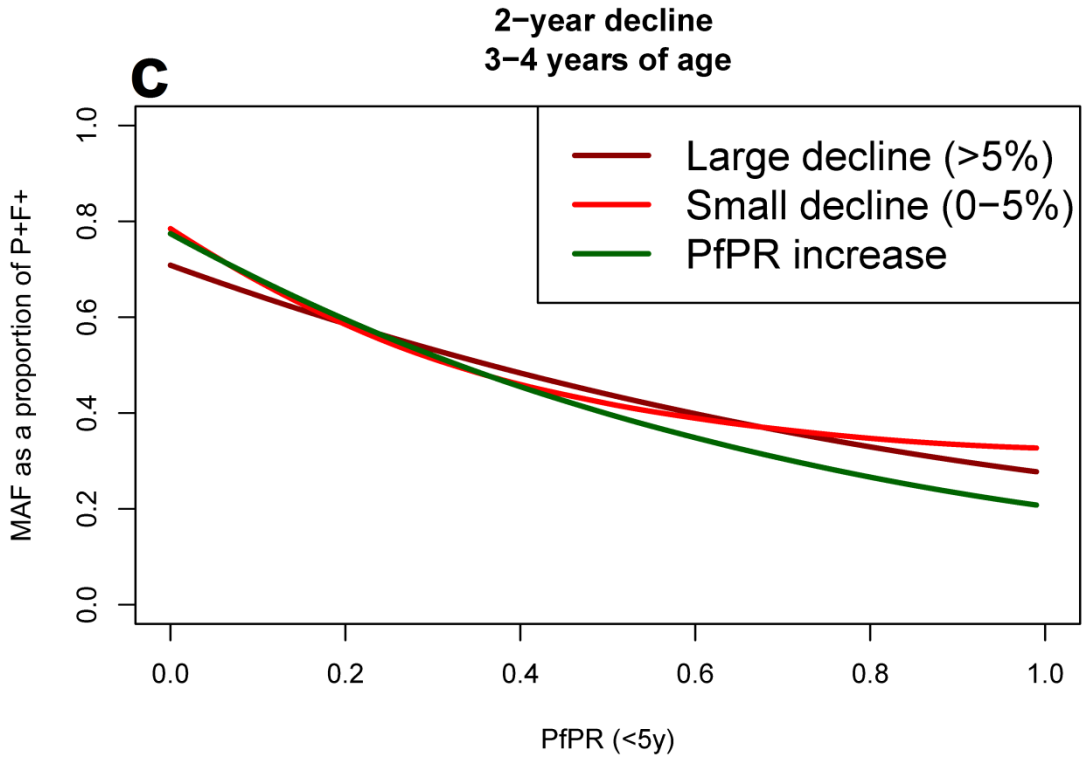


Figure 4.2. Fitted relationship between MAF and *Pf*PR_{0-5} when stratified by the magnitude of *Pf*PR_{0-5} decline in the two years preceding data collection. The top panel (**a**) shows the fitted relationship for all children under 5 years of age, with children located in areas where *Pf*PR_{0-5} declined by more than 5% in the two years preceding the survey in dark red, children located in areas where *Pf*PR_{0-5} declined by between 0 and 5% in red, and children located in areas where *Pf*PR_{0-5} increased in green. In the central panel (**b**) and bottom panel (**c**) the three decline categories are indicated by the same colours as (**a**); (**b**) shows the relationship only amongst children aged two years or younger, and (**c**) shows the relationship only amongst children aged three or four years. Declines in *Pf*PR_{0-5} were extracted from annual *Pf*PR predictions produced by Bhatt et al. [6].

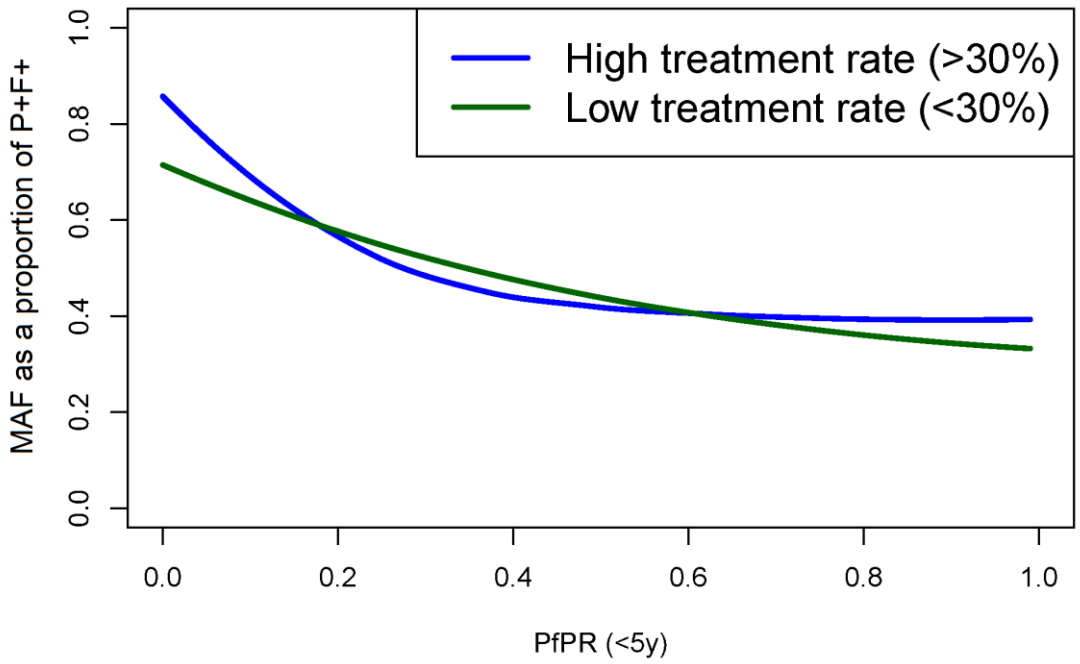


Figure 4.3. Fitted relationship between MAF and *Pf*PR_{0-5} when segregated by treatment-seeking rate within DHS Program clusters. The blue line represents the fitted relationship for clusters where the treatment-seeking rate for febrile children was ≥30%, and the green line for clusters where the treatment-seeking rate was <30%.

4.5.2. Ratio of MAF and NMFI amongst febrile children presenting to public health clinics

The final fitted relationship between malaria-attributable fever (as a proportion of malaria-positive fevers) and *Pf*PR_{0-5} was implemented in the Bayesian hierarchical model to attribute fevers amongst the surveyed individuals to either malaria or non-malarial causes. For each survey, the rate at which MAF and NMFI cases (which can be RDT-positive or RDT-negative) sought treatment was collated to produce an estimate of the proportion of each fever type presenting at public health clinics in that country-year.

Figure 4.4 illustrates the proportion of fevers in each survey estimated to fall into each of the four categories: MAF, fever causally due to co-symptomatic MAF and NMFI, NMFI coincident with an RDT-patent asymptomatic malaria infection, and NMFI without an RDT-patent malaria infection. On average, 37.7% (31.1 – 45.4, 95% CrI) of malaria-positive fevers presenting at clinics were causally attributable to malaria, ranging from 5.3% (1.8 – 12.4, 95% CrI) in Tanzania in 2007-2008, to 81.5% (77.7 – 84.5, 95% CrI) in Mali in 2012-2013. A corollary of this is that only the truly malaria-attributable fevers amongst all malaria positive fevers presenting at clinics across the surveyed country years would be resolved by effective antimalarial treatment, and the remainder are causally attributable to non-malarial causes which would require additional treatment (or time for the fever to be self-resolved). Overall, the estimates presented here show that the burden of malaria, if estimated using the adjusted case-count approach, may overestimate the burden of symptomatic *P. falciparum* malaria by 3.6 times on average, with the largest disparities in Tanzania 2007-2008, Angola 2006-2007 and Senegal 2008-2009 with overestimations of 19.0, 6.8, and 6.6 times, respectively. The countries with the least disparity (i.e. where most malaria-positive fevers presenting at public health clinics were causally attributable to malaria) were Mali 2012-2013, Benin 2011-2012, and Senegal 2010-2011. In these three country-years, the model estimated that the adjusted case-count approach would overestimate the burden of symptomatic malaria by 1.2, 1.4, and 1.4 times, respectively.

Amongst the surveyed country-years, six countries were surveyed three or more times between 2006-2016 (Angola, Liberia, Madagascar, Senegal, Tanzania, Uganda). The proportion of malaria-positive fevers that were predicted to be causally due to malaria rises in Angola, Madagascar, Senegal (with the exception of 2010-2011), and Tanzania between the first and last surveys, consistent with a decrease in $Pf\text{PR}_{0\text{-}5}$ over the survey

time period [6], reflecting the predicted relationship between MAF and *Pf*PR_{0-5} shown in Figure 4.1. Uganda showed a rise in the proportion of malaria-positive fevers that were predicted to be causally due to malaria between the first and second survey, but this proportion dropped again slightly between the second and third survey. Liberia showed a relatively constant proportion of malaria-positive fevers that were predicted to be causally due to malaria across all three surveys (Figure 4.4a).

Fourteen of the 41 country-years had a higher proportion of malaria-positive fevers presenting at clinics than malaria-negative fevers, with, on average for all countries, 35.1% of fevers presenting at public clinics being accompanied by a malaria infection (Figure 4.4b, Table 4.2).

Amongst children with NMFI (i.e. fevers where malaria was not the underlying cause of the fever), across all surveyed country-years, 26.8% (25.5 – 27.9, 95% CrI) were accompanied by an RDT-patent malaria infection. This fraction varied significantly between country years, from 1.0% (0.4 – 1.4%, 95% CrI) in Senegal in 2015, to 66.4% (65.7 – 66.9, 95% CrI) in Burkina Faso in 2014 (Figure 4.4b, Table 4.2).

Table 4.2. Proportion of each type of fever presenting at public health clinics in each survey. MAF= malaria-attributable fever; NMFI = non-malarial febrile illness; Pf+/Pf- = *P. falciparum* RDT positive or negative (at time of seeking treatment). "MAF and NMFI" indicates febrile children with co-symptomatic MAF and NMFI.

Table 4.2. Proportion of each type of fever presenting at public health clinics in each survey, with associated 95% credible intervals. MAF= malaria-attributable fever; NMFI = non-malarial febrile illness; Pf+/Pf- = *P. falciparum* RDT positive or negative (at time of seeking treatment). "MAF and NMFI" indicates febrile children with co-symptomatic MAF and NMFI.

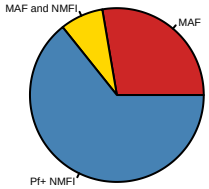
Survey	MAF Lower CrI	MAF Median	MAF Upper CrI	MAF and NMFI Lower CrI	MAF and NMFI Median	MAF and NMFI Upper CrI	NMFI Pf+ Lower CrI	NMFI Pf+ Median	NMFI Pf+ Upper CrI	NMFI Pf- Lower CrI	NMFI Pf- Median	NMFI Pf- Upper CrI
Angola 2006-2007	0.0037	0.0192	0.0699	0.0011	0.0094	0.0372	0.1508	0.1895	0.2095	0.7644	0.7782	0.7817
Angola 2011	0.0197	0.0340	0.0463	0.0012	0.0092	0.0212	0.0849	0.0930	0.1029	0.8619	0.8630	0.8641
Angola 2015-2016	0.0466	0.0691	0.0884	0.0027	0.0150	0.0284	0.0604	0.0699	0.0818	0.8406	0.8471	0.8518
Benin 2011-2012	0.1325	0.1654	0.2006	0.0025	0.0142	0.0258	0.0566	0.0707	0.0886	0.7331	0.7494	0.7628
Burkina Faso 2010	0.2092	0.2466	0.2883	0.0151	0.0408	0.0578	0.4392	0.4723	0.5010	0.2377	0.2406	0.2432
Burkina Faso 2014	0.1006	0.1258	0.1491	0.0404	0.0634	0.0824	0.5176	0.5391	0.5563	0.2707	0.2732	0.2751
Burundi 2012	0.0328	0.0500	0.0670	0.0280	0.0539	0.0636	0.2521	0.2649	0.2805	0.6306	0.6327	0.6347
Cameroon 2011	0.0063	0.0330	0.1166	0.0016	0.0136	0.0767	0.2334	0.3150	0.3487	0.6146	0.6291	0.6325
Cote d'Ivoire 2011-2012	0.0302	0.0554	0.0896	0.0028	0.0243	0.0522	0.2038	0.2229	0.2437	0.6912	0.6955	0.6989
DR Congo 2013-2014	0.0860	0.1020	0.1197	0.0241	0.0382	0.0504	0.2537	0.2661	0.2781	0.5909	0.5932	0.5951
Ghana 2014	0.2373	0.2699	0.3023	0.0254	0.0454	0.0542	0.2301	0.2500	0.2710	0.4268	0.4355	0.4439
Ghana 2016	0.1287	0.1816	0.2212	0.0010	0.0197	0.0504	0.2048	0.2274	0.2544	0.5630	0.5716	0.5783
Guinea 2012	0.0948	0.1353	0.1755	0.0160	0.0516	0.0852	0.2888	0.3243	0.3552	0.4844	0.4900	0.4941
Kenya 2015	0.0102	0.0233	0.0319	0.0039	0.0158	0.0239	0.0878	0.0945	0.1014	0.8652	0.8673	0.8690
Liberia 2009	0.0303	0.0453	0.0566	0.0265	0.0418	0.0482	0.2616	0.2699	0.2787	0.6427	0.6451	0.6470
Liberia 2011	0.0473	0.0626	0.0740	0.0321	0.0459	0.0575	0.3890	0.4002	0.4119	0.4914	0.4928	0.4942
Liberia 2016	0.0226	0.0474	0.0832	0.0274	0.0659	0.0814	0.3913	0.4084	0.4255	0.4796	0.4807	0.4818
Madagascar 2011	0.0221	0.0376	0.0575	0.0011	0.0095	0.0238	0.0590	0.0708	0.0830	0.8787	0.8803	0.8813
Madagascar 2013	0.0750	0.0916	0.1085	0.0017	0.0077	0.0166	0.0422	0.0517	0.0638	0.8417	0.8487	0.8535
Madagascar 2016	0.0487	0.0594	0.0704	0.0007	0.0051	0.0101	0.0251	0.0321	0.0400	0.8996	0.9036	0.9060
Malawi 2012	0.0761	0.1060	0.1379	0.0153	0.0373	0.0582	0.3685	0.3959	0.4180	0.4607	0.4625	0.4637
Malawi 2014	0.1218	0.1669	0.2021	0.0195	0.0512	0.0761	0.3956	0.4218	0.4502	0.3611	0.3628	0.3641
Mali 2012-2013	0.3929	0.4264	0.4512	0.0018	0.0141	0.0325	0.0840	0.0999	0.1192	0.4520	0.4597	0.4664
Mali 2015	0.1092	0.1393	0.1645	0.0056	0.0207	0.0514	0.2054	0.2198	0.2370	0.6120	0.6176	0.6229
Mozambique 2011	0.1591	0.1876	0.2137	0.0094	0.0268	0.0439	0.2121	0.2292	0.2484	0.5469	0.5567	0.5647
Mozambique 2015	0.1409	0.1707	0.2009	0.0183	0.0501	0.0669	0.3052	0.3269	0.3459	0.4465	0.4537	0.4591
Nigeria 2010	0.0969	0.1073	0.1159	0.0557	0.0629	0.0670	0.4051	0.4162	0.4282	0.4129	0.4140	0.4151

Table 4.2. Continued

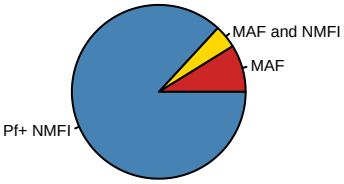
Survey	MAF Lower CrI	MAF Median	MAF Upper CrI	MAF and NMFI Lower CrI	MAF and NMFI Median	MAF and NMFI Upper CrI	NMFI Pf+ Lower CrI	NMFI Pf+ Median	NMFI Pf+ Upper CrI	NMFI Pf- Lower CrI	NMFI Pf- Median	NMFI Pf- Upper CrI
Nigeria 2015	0.0872	0.1020	0.1149	0.0225	0.0333	0.0446	0.3580	0.3693	0.3820	0.4949	0.4960	0.4970
Rwanda 2010	0.0084	0.0158	0.0198	0.0008	0.0041	0.0062	0.0206	0.0237	0.0291	0.9560	0.9569	0.9579
Rwanda 2014-2015	0.0670	0.0835	0.0958	0.0011	0.0111	0.0196	0.0807	0.0886	0.0979	0.8163	0.8177	0.8186
Senegal 2008-2009	0.0019	0.0120	0.0470	0.0006	0.0055	0.0312	0.0906	0.1218	0.1376	0.8563	0.8568	0.8570
Senegal 2010-2011	0.0241	0.0318	0.0378	0.0003	0.0040	0.0087	0.0131	0.0156	0.0192	0.9453	0.9487	0.9512
Senegal 2012-2013	0.0017	0.0104	0.0409	0.0004	0.0046	0.0270	0.0341	0.0594	0.0731	0.9201	0.9215	0.9217
Senegal 2015	0.0005	0.0033	0.0111	0.0001	0.0011	0.0069	0.0040	0.0097	0.0137	0.9838	0.9847	0.9849
Tanzania 2007-2008	0.0013	0.0055	0.0192	0.0006	0.0038	0.0162	0.1773	0.1903	0.1961	0.7971	0.7993	0.8003
Tanzania 2011-2012	0.0426	0.0539	0.0621	0.0073	0.0164	0.0201	0.0738	0.0789	0.0852	0.8490	0.8517	0.8541
Tanzania 2015-2016	0.0682	0.0765	0.0828	0.0089	0.0163	0.0185	0.0787	0.0840	0.0892	0.8210	0.8244	0.8273
Togo 2013-2014	0.1614	0.2052	0.2387	0.0051	0.0290	0.0630	0.2061	0.2314	0.2578	0.5269	0.5358	0.5440
Uganda 2009	0.0631	0.0738	0.0819	0.0457	0.0594	0.0646	0.5088	0.5187	0.5299	0.3486	0.3497	0.3510
Uganda 2014-2015	0.0705	0.0878	0.0996	0.0282	0.0523	0.0599	0.3356	0.3460	0.3588	0.5155	0.5167	0.5181
Uganda 2016	0.0485	0.0694	0.0910	0.0281	0.0625	0.0709	0.3687	0.3822	0.4011	0.4857	0.4890	0.4919

Figure 4.4.(a)

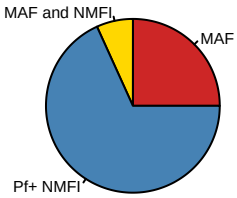
All country- years



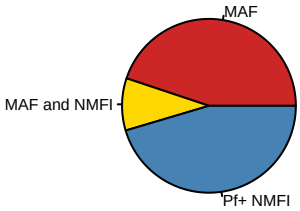
Angola 2006- 2007



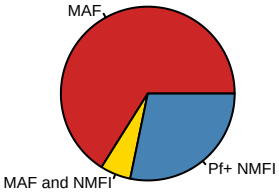
Angola 2011



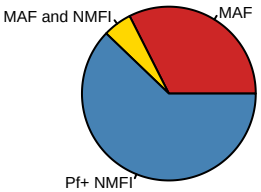
Angola 2015- 2016



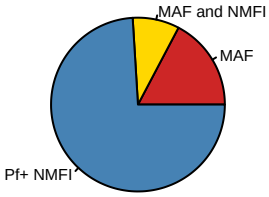
Benin 2011- 2012



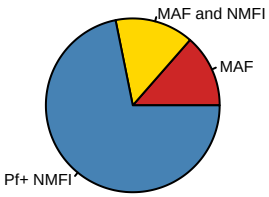
Burkina Faso 2010



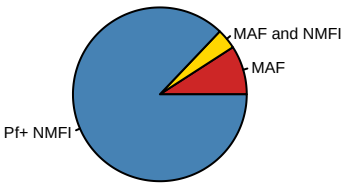
Burkina Faso 2014



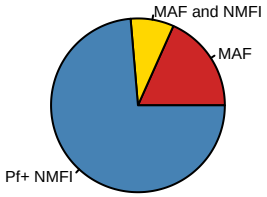
Burundi 2012



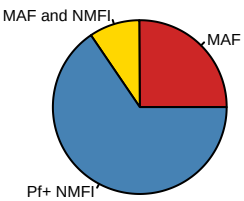
Cameroon 2011



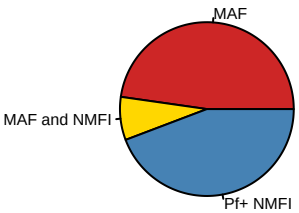
Cote d'Ivoire 2011- 2012



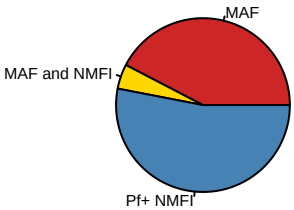
DR Congo 2013- 2014



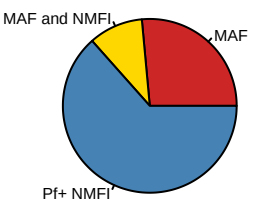
Ghana 2014



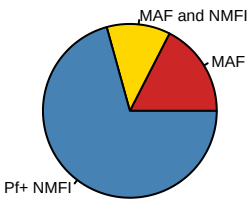
Ghana 2016



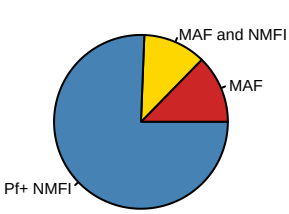
Guinea 2012



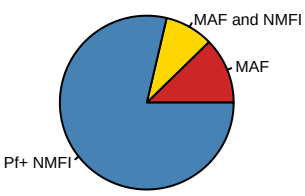
Kenya 2015



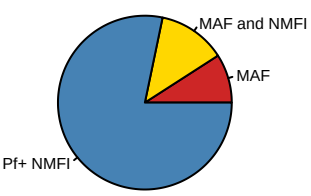
Liberia 2009



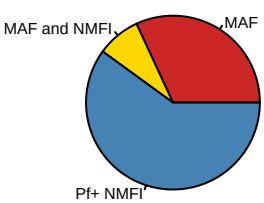
Liberia 2011



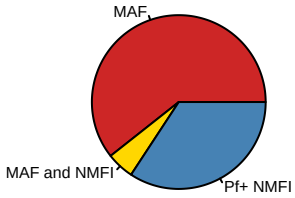
Liberia 2016



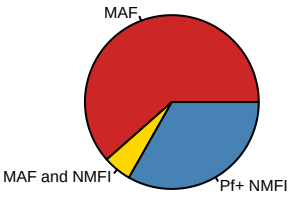
Madagascar 2011



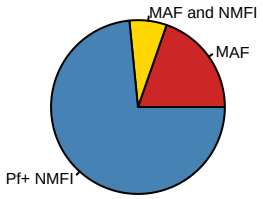
Madagascar 2013



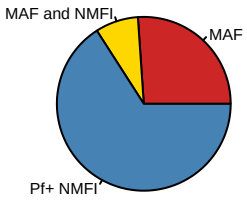
Madagascar 2016



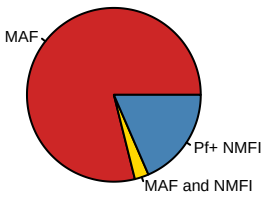
Malawi 2012



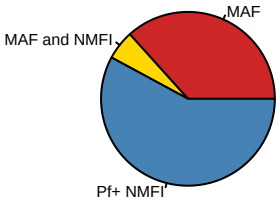
Malawi 2014



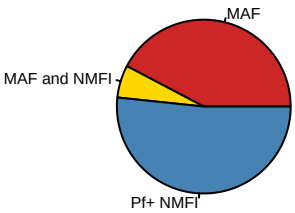
Mali 2012- 2013



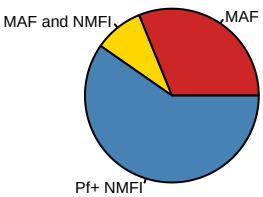
Mali 2015



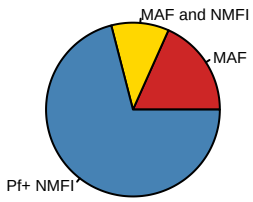
Mozambique 2011



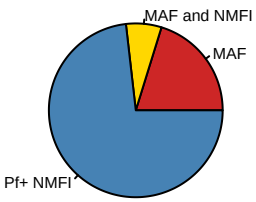
Mozambique 2015



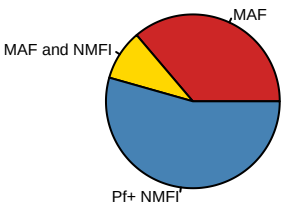
Nigeria 2010



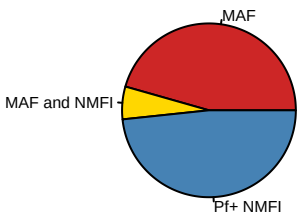
Nigeria 2015



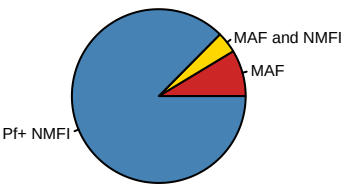
Rwanda 2010



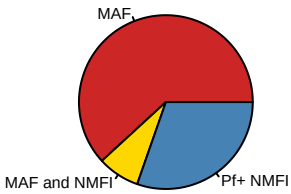
Rwanda 2014- 2015



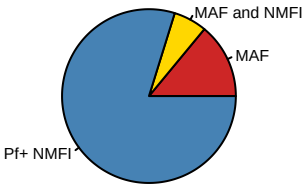
Senegal 2008- 2009



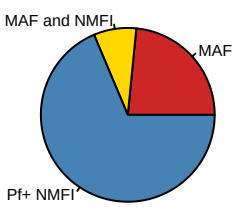
Senegal 2010- 2011



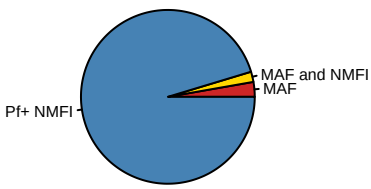
Senegal 2012- 2013



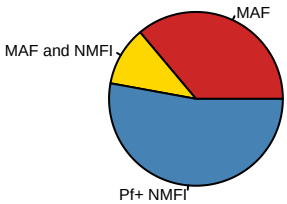
Senegal 2015



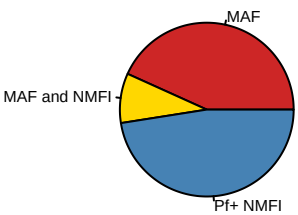
Tanzania 2007- 2008



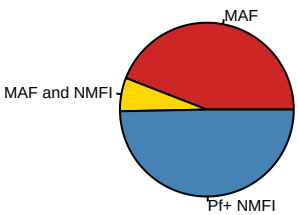
Tanzania 2011- 2012



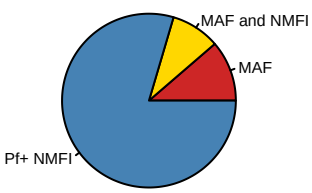
Tanzania 2015- 2016



Togo 2013- 2014



Uganda 2009



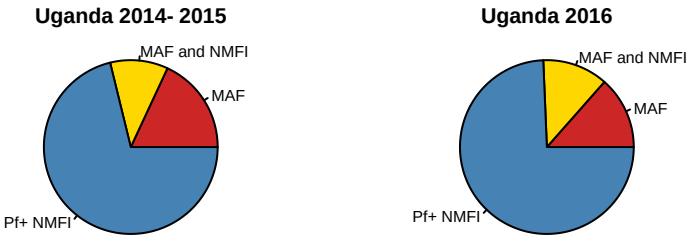
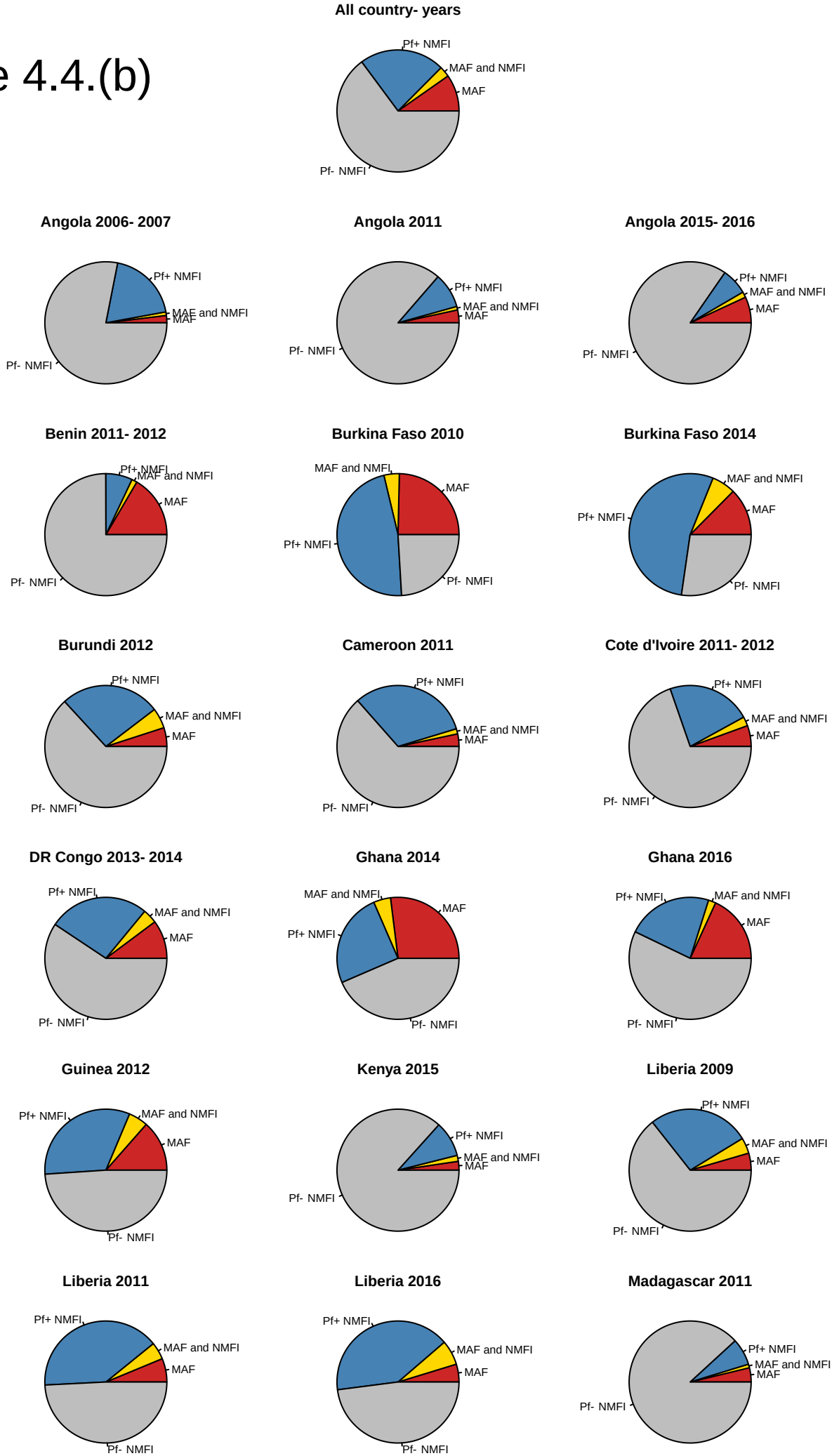
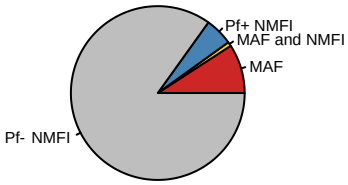

Uganda 2014- 2015
MAF and NMFI
MAF
Pf+ NMFI
Uganda 2016
MAF and NMFI
MAF
Pf+ NMFI

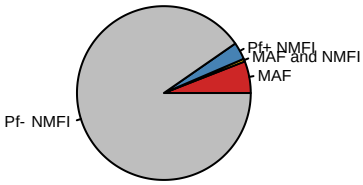
Figure 4.4.(b)


All country- years
Pf+ NMFI
MAF and NMFI
MAF
Pf- NMFI
Angola 2006- 2007
Angola 2011
Angola 2015- 2016
Benin 2011- 2012
Burkina Faso 2010
Burkina Faso 2014
Burundi 2012
Cameroon 2011
Cote d'Ivoire 2011- 2012
DR Congo 2013- 2014
Ghana 2014
Ghana 2016
Guinea 2012
Kenya 2015
Liberia 2009
Liberia 2011
Liberia 2016
Madagascar 2011

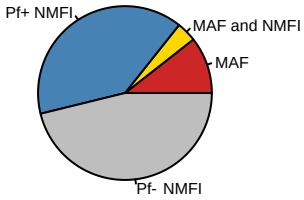
Madagascar 2013



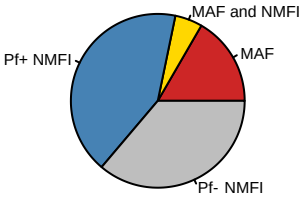
Madagascar 2016



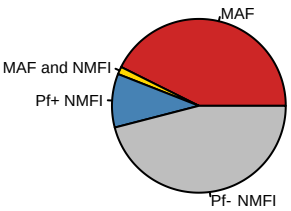
Malawi 2012



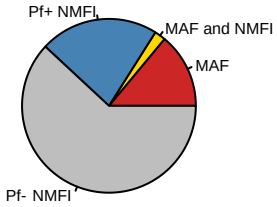
Malawi 2014



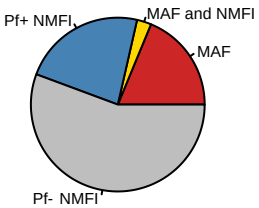
Mali 2012- 2013



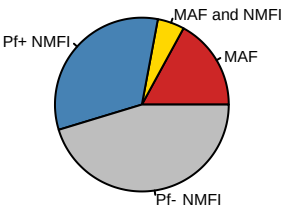
Mali 2015



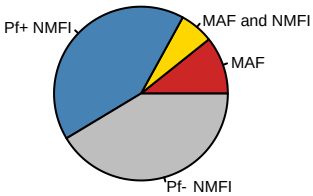
Mozambique 2011



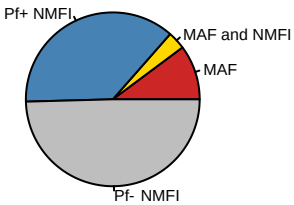
Mozambique 2015



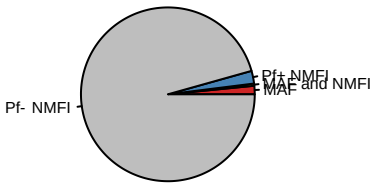
Nigeria 2010



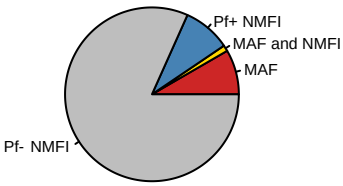
Nigeria 2015



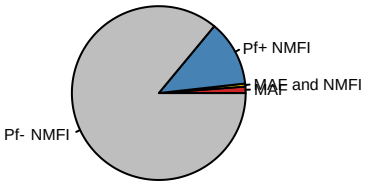
Rwanda 2010



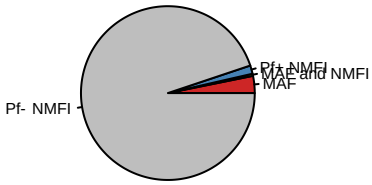
Rwanda 2014- 2015



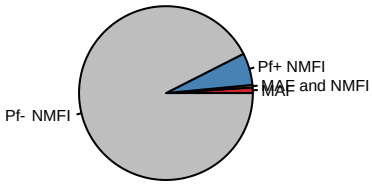
Senegal 2008- 2009



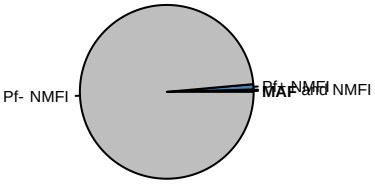
Senegal 2010- 2011



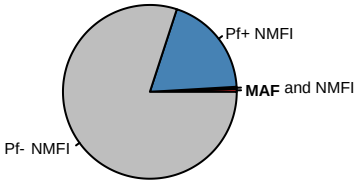
Senegal 2012- 2013



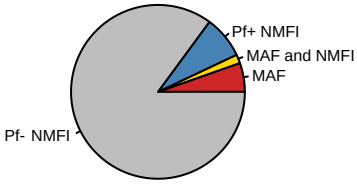
Senegal 2015



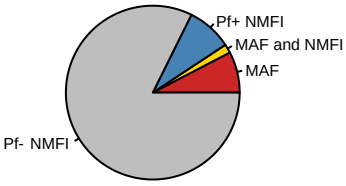
Tanzania 2007- 2008



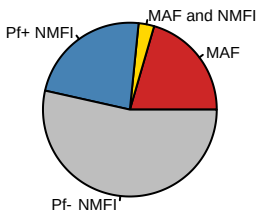
Tanzania 2011- 2012



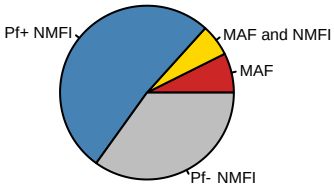
Tanzania 2015- 2016



Togo 2013- 2014



Uganda 2009



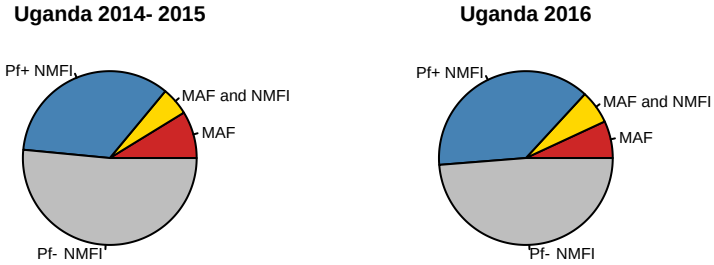

Uganda 2014- 2015
Pf+ NMFI
MAF and NMFI
MAF
Pf- NMFI
Uganda 2016
Pf+ NMFI
MAF and NMFI
MAF
Pf- NMFI

Figure 4.4. a) Estimates of proportion of fevers presenting to public health clinics that are causally due to MAF (red sections), NMFI accompanied by an asymptomatic *P. falciparum* malaria infection (blue sections) and co-symptomatic MAF and NMFI (yellow sections); and **b)** as (**a**), also including NMFI not accompanied by a *P. falciparum* malaria infection (grey sections); amongst febrile children under 5 years of age presenting to public health clinics amongst children from household surveys in 41 country-years in sub-Saharan Africa, 2006-2016.

4.5.3. Comparison with confirmed cases reported in malaria-endemic countries

Confirmed malaria cases (i.e. fever cases presenting to clinics with a positive malaria diagnosis) amongst children under 5 years of age were collated for three country-years with near-contemporaneous household surveys (Benin 2010 [46], Burundi 2012 [47], and Kenya 2015 [48]). In 2010, Benin reported 90,736 cases amongst children under 5 years of age; in 2012, Burundi reported 1,138,088 cases amongst children under 5 years of age; and in 2015, Kenya reported 1,569,892 cases amongst children under 5 years of age. Figure 4.5 displays the incidence of malaria-positive fevers presenting at clinics in the three countries, separated into malaria-attributable fevers, and malaria-positive fevers that are not caused by the malaria infection. It is estimated that 25,572 (19,487 – 33,939, 95% CrI) of malaria-positive fevers in Benin in 2010, 821,270 (777,791 – 873,594, 95% CrI) malaria-positive fevers in Burundi in 2012, and 1,116,756 (1,023,064 – 1,213,370, 95% CrI) of malaria-positive fevers in Kenya in 2015 amongst children under 5 years of age reported to the HMIS in each country were causally attributable to non-malarial causes and as such would not be resolved through effective antimalarial medication, requiring additional treatment for the non-malarial febrile illness (the underlying cause of the fever) to be resolved.

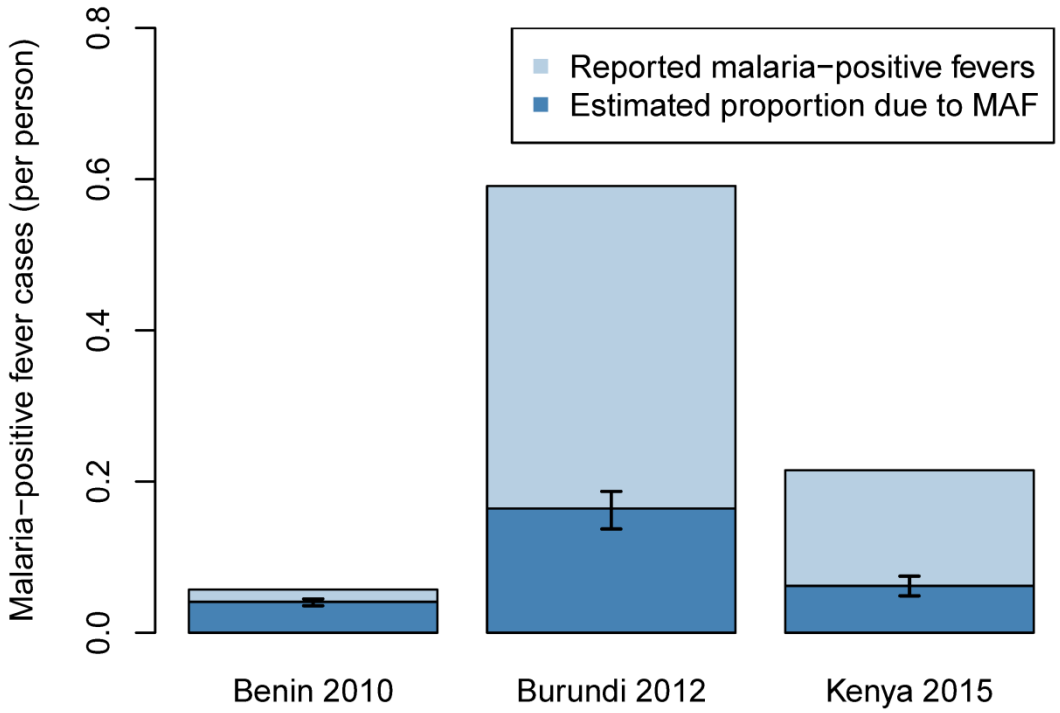


Figure 4.5. The incidence of malaria-positive fevers per child under 5 reported to HMIS in Benin 2010 (left bar), Burundi 2012 (middle bar) and Kenya 2015 (right bar) amongst children under 5 years of age in light blue bars, with the total number of malaria-attributable fevers overlain in dark blue bars. The upper and lower 95% credible intervals on the estimate of number of malaria-attributable fevers are given by black error bars. Malaria-positive fevers not causally attributable to fever were predicted to be caused by non-malarial febrile illnesses.

4.6. Discussion

The analysis presented here indicates that a significant proportion of confirmed *P. falciparum* malaria cases reported by the HMIS in malaria-endemic countries are likely to be non-malarial fevers coincident with an asymptomatic malaria infection. Across all surveyed country-years, the majority of febrile children for whom treatment was sought did not have a malaria-positive fever, and amongst the children who did have a malaria-positive fever, the malaria infection was not the underlying cause for nearly two-thirds of these fevers. These findings indicate that the adjusted case-count approach for burden estimation may significantly overestimate the clinical malaria burden by classing all fevers with a patent malaria infection as a "malaria case". Across all surveys, on average the adjusted case-count approach was predicted to overestimate malaria cases by 3.6 times, but this estimate varied significantly between surveys. The reasons for differential proportions of MAF and NMFI amongst malaria-positive fevers between countries are complex and depend on both the national prevalence of both *P. falciparum* and NMFI. Countries predicted to have the greatest overestimates for cases using the adjusted case-count approach are typically nations with a high rate of non-malarial febrile illness amongst the surveyed individuals, and are often surveys from the first half of the study decade, coinciding with higher malaria burden (and therefore higher levels of exposure-related immunity [6]) and worse sanitation and housing conditions relative to later years [49], which may increase the probability of NMFI. The application of the fractions of MAF and NMFI at clinics to contemporaneous malaria cases reported to three Ministries of Health in sub-Saharan Africa (Figure 4.5) shows the potential for malaria-positive fevers that are not causally attributable to malaria to be systematically reported as "malaria cases", leading to the potential for significant overestimations of the clinical burden of malaria.

A number of the 21 countries included in this study were surveyed multiple times between 2006 and 2016, with three surveys in Angola, Liberia, Madagascar, Tanzania and Uganda, and four surveys in Senegal. In most of these countries, a larger fraction of malaria-positive fevers were causally attributable to malaria in later surveys compared to earlier surveys within the same country (with the exception of 2016 surveys in Tanzania and Uganda). These findings may be explained by a loss of exposure-related immunity amongst children under 5 years of age as malaria prevalence decreases (all six countries showed decline in $Pf\text{PR}_{0\text{-}5}$ over the study period) [6, 50], resulting in a higher fraction of symptomatic illness amongst infected children. This increase in the proportion of MAF amongst malaria-infected febrile children could also be explained by a decrease in NMFI prevalence relative to malaria prevalence over the time period. This was not, however, observed in the current study (Figure 4.4b) [24]. In most surveyed country-years, a higher fraction of NMFI compared to MAF was observed amongst febrile children presenting at public health clinics in more recent country-years.

The findings presented here suggest that if $Pf\text{PR}_{0\text{-}5}$ continues to decline across the continent, the fraction of malaria-positive fevers presenting at clinics that are causally attributable to malaria will increase, and as such, effective antimalarial treatment will resolve a higher fraction of malaria-positive fevers presenting at public health clinics. In contrast, in countries with a higher *P. falciparum* burden, a large fraction of malaria-positive fevers will not be resolved through antimalarial treatment alone. Should this result in a loss of trust in the ability of care providers to treat perceived malaria infections, this may result in further barriers to treatment-seeking and consequently hinder prevalence reduction, if malaria-positive fevers that are not causally attributable to malaria do not receive further diagnosis and treatment of the underlying, non-malarial, cause of their fever.

Over the 41 surveyed country-years, on average approximately two-thirds of malaria-positive fevers would not be resolved with effective antimalarial treatment. If clinicians do not investigate other causes of fever given a positive RDT, non-malarial fevers may be systematically missed and remain untreated, potentially leading to missed opportunities to reduce the burden of other important non-malarial febrile illness. Evidence from literature suggests that clinicians show good adherence to integrated management of childhood illness (IMCI) guidelines when prescribing ACTs after a positive RDT [51, 52], but information is sparse on clinicians' propensity to investigate alternative causes of illness after either negative or positive RDT outcomes. Studies have shown that clinicians are more likely to prescribe antibiotics to patients with a negative RDT than malaria-positive patients in a study in Zanzibar [52], and that after IMCI training clinicians do record diagnoses of malaria co-infections with NMFI [53]. Diagnosis of common NMFIs is hampered by a lack of routine diagnostics that are cost-effective at the clinic level. Most bacterial blood-borne illnesses are only diagnosable via culture [54]. Illnesses such as brucellosis [55] and leptospirosis [56] (amongst others) are only parasitologically diagnosable via PCR. Tuberculosis is typically confirmed via microscopy (for which the equipment, staffing, and time requirements are not typically present in local clinics). Pneumonia can cause fever and is typically diagnosed via chest examination, or via X-ray or pleural fluid culture in more serious cases. Rapid diagnostic tests for tuberculosis [57] and *Streptococcus spp.* [58] have been developed but are not cost-effective for use in outpatient clinics at the current time. As such, diagnostic capacity for NMFI is severely limited in many contexts. If clinicians do not routinely investigate alternative causes for febrile illness in malaria-positive individuals, the possibility exists for systematic mismanagement of a large proportion of non-malarial febrile illnesses.

In this analysis, multiple sources of malaria-attributable fever observations were used to build a relationship between malaria-attributable fever and *Pf*PR. A number of additional factors hypothesised to affect the relationship between MAF and *Pf*PR were investigated. No effects of recent *Pf*PR declines or differential underlying treatment rates were observed on the relationship between MAF and *Pf*PR (Figures 2 and 3). It is unclear whether these effects were not observed because they do not affect the relationship, were due to insensitivity of the modelling framework, or were due to the calibration dataset being ill-adapted for measuring the effect of recent declines in *Pf*PR. Multiple sets of longitudinal cohort studies at differing levels of baseline *P. falciparum* exposure would be better-suited to measure the effect of recent *Pf*PR declines on the relationship between MAF and *Pf*PR compared to the datasets used here, as they capture the changing immunity profile of individuals over time within the same cohort. Mechanistic models suggest a loss of immunity following up-scaling of malaria interventions, and a shift towards increased levels of severe malaria-attributable fever in older children following declines in *P. falciparum* exposure [59]. Any lag between declines in *Pf*PR and this loss of exposure-related immunity would imply that the profile of the relationship between MAF and *Pf*PR may temporarily shift until exposure-related immunity reaches a new equilibrium.

The effect that high or low levels of community antimalarial treatment may have on the relationship between MAF and *Pf*PR is unclear. High levels of prompt and effective treatment may reduce the exposure-related immunity in a community, altering the relationship between MAF and *Pf*PR. Here, the treatment-seeking rate for fever was used as a proxy for the level of prompt and effective treatment, and no effect of treatment was found on the relationship between MAF and *Pf*PR. Case-control studies with prompt

treatment of fevers may increase the sensitivity of the approach used here for estimating the effect of prompt and effective treatment on the relationship between MAF and *Pf*PR. The household survey datasets used in this analysis report RDT result from the time of interview, but caregiver recall of fever episodes within the past two weeks (rather than fever measurement at the time of interview). In addition to biases in recall of recent fever [60, 61], the possibility exists that an individual with a patent malaria-attributable fever may seek and receive effective antimalarial treatment, and return to RDT-negative by the time of interview, despite having experienced a malaria infection in the two weeks preceding the survey. If left unadjusted, an overestimation of the proportion of NMFI amongst the individuals who sought and received treatment would be expected. The modelling study presented here is the first of its kind using the DHS Program dataset to adjust for the possibility of reversion from RDT-positive to RDT-negative within the two weeks preceding the survey. Amongst all RDT-negative individuals who sought and received an antimalarial, the Bayesian hierarchical model presented here accounts for the probability of reversion within the two-week time frame of the study, as determined using an adjustment model presented previously [41]. Datasets with RDT outcome at the point of care would increase the sensitivity of this approach, although diagnostic testing for all fever cases presenting at clinics is not universal; amongst febrile individuals who sought care at a public clinic in the household survey dataset only 44.3% had blood drawn at the point of care (used as a proxy for malaria diagnosis).

A key finding of this analysis is the high proportion of NMFI presenting to clinics in sub-Saharan Africa, both with and without RDT-patent malaria infections. This indicates the need for high levels of prescription of medications for NMFI amongst both RDT-positive and RDT-negative individuals for NMFIs that cannot be self-resolved. Despite household surveys documenting the type of medication received by febrile individuals who sought

care, assessing the appropriateness of non-antimalarial medications was not possible due to lack of diagnosis (or recall of diagnosis at the point of care) for NMFI for individuals in the household survey dataset.

Fever caused by *P. vivax* malaria is also, by definition, grouped within NMFI in this analysis, confounding the definition of NMFI. *P. vivax* is not widespread in Africa (in part due to widespread Duffy negativity [62]), but children in Mauritania and East Africa are at risk of *P. vivax* infection [63, 64]. Due to location of the surveyed country-years represented here (which mostly fall outside the zones of stable *P. vivax* transmission [65]), the effect of *P. vivax*-attributable fevers in the country-years represented in this analysis is presumed to be limited. Caution should, however, be taken when extending the approach presented here to areas of higher *P. vivax* burden.

The results presented here suggest a high prevalence of co-infections between malaria and NMFI amongst febrile children presenting at clinics. Here, the effects of co-morbidity (or modulating effects of co-infection on febrile illness) are not accounted for, owing to the lack of diagnosis for NMFI. Future studies may aim to investigate the effects of co-morbidity if differential diagnosis of NMFI is available.

The Ministry of Health reports used to generate the number of paediatric malaria-positive fevers that would and would not be resolved by antimalarial treatment alone in three sub-Saharan African countries (Figure 4.5) are subject to biases not adjusted for in this study. Although the reports document the total number of cases reported from health facilities, not all health facilities report to the HMIS. Biases in which facilities report to the HMIS may mean the estimates presented here are not representative on a national scale. If certain facilities (e.g. those in urban areas, typically associated with a lower *P. falciparum* burden [66], or those receiving more severe malaria cases, such as hospitals)

are not equally likely to report to the HMIS than rural facilities, the ratio of MAF to NMFI may not be nationally representative.

4.7. Conclusion

The results presented here show the potential for overestimation of the number of symptomatic malaria infections via the adjusted case-count method for malaria burden estimation. Only an estimated 37.7% (31.1 – 45.4, 95% CrI) of malaria-positive fevers amongst children under 5 years of age presenting at public clinics across the 41 surveyed country-years are causally attributable to malaria. These findings are not intended to suggest that malaria-infected individuals should not be treated with effective antimalarial medication; but rather the intention of this analysis is to increase understanding of the complex nature of the malaria burden, and to highlight the vast burden of non-malarial paediatric fever.

These findings furthermore indicate a need for standardising approaches for estimating malaria burden. Epidemiologists and public health professionals comparing burden estimates made using the adjusted case-count or cartographic approaches should be aware that these approaches estimate fundamentally different metrics. Refinement of burden estimation approaches to generate estimates of both malaria-attributable fever and malaria-positive fever would improve cross-comparability and allow assessment of the quantity of non-malarial febrile illness amongst malaria-positive fevers. Finally, we show that non-malarial febrile illness is more common than malaria-attributable fever across outpatient clinics in sub-Saharan Africa, highlighting the need for new, affordable, diagnostic tests for non-malarial febrile illnesses.

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Chapter 5 - What proportion of malaria infections receive effective antimalarial treatment?

In this chapter, estimates were produced of national community- and clinic-level coverage of artemisinin combination therapy (ACT) for children under 5 years of age residing in *P. falciparum* endemic countries surveyed between 2006 and 2016. Results were produced for 21 countries and a total of 41 unique country-years, and consisted of the total proportion of *P. falciparum* malaria-infected children who received an ACT during the two weeks preceding each household survey. For children who were malaria-infected but did not receive an ACT, the reasons why ACT was not received were quantified. Amongst febrile malaria-infected children who did receive an ACT, the Bayesian hierarchical model presented in the previous chapter was used to stratify these children by the underlying cause of their fever. This approach was selected to investigate the role of non-malarial febrile illness (NMFI) plays in bringing asymptomatic malaria infections to clinics for treatment. Additionally, the differential performance of public and private health systems was analysed for each survey to provide estimates of the proportion of individuals who were treated according to Integrated Management of Childhood Illness (IMCI) guidelines. Finally, individual-level factors such as household wealth, caregiver education, child age, and insecticide-treated bed net (ITN) usage were investigated for their effects on probability of malaria infection, treatment-seeking for fever, receiving an ACT, and experiencing NMFI. The results presented here provide insight into individual- and clinic-level coverage gaps for antimalarial medication, and assess the changing performance of public and private health systems at appropriately diagnosing and treating malaria infections over time.

This chapter has been prepared for publication, and is shown here in its pre-submission format, with figures integrated at appropriate locations within the text. There is one additional table associated with this manuscript included in the Appendix, which summarises the household survey dataset used in the analysis.

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Author contributions: UD conceived the study with PWG; assembled or digitised all datasets; conducted boosted regression tree modelling; designed basic framework for, and analysed outputs from, Bayesian hierarchical model; generated all displayed graphics and tables; wrote first draft of manuscript. EC conducted statistical analysis and implementation of Bayesian hierarchical model with input from UD. HG and DJW provided covariates. JR provided maps of *Pf*PR displayed in Figure 5.2. PWG conceived and oversaw the study.

All authors reviewed and approved the final manuscript.

5.2. Abstract

Understanding the proportion of malaria infections that receive effective antimalarial treatment with artemisinin combination therapy (ACT) is vital for measuring the effectiveness of response efforts to reduce the burden of *Plasmodium falciparum* malaria. In this analysis, a household survey dataset from 41 sub-Saharan African country-years surveyed between 2006 and 2016 was used to estimate national-level ACT coverage amongst children under 5 years of age. The analysis identified gaps in individual-, household-, clinic-, and national-level coverage. During the two weeks preceding each survey, it was estimated that only 7.9% of children with a malaria-positive fever residing in the surveyed countries received an ACT. Amongst children with a *P. falciparum* infection: *i*) 54.9% children were infected but did not have a fever, *ii)* 34.4% of children with a malaria-positive fever did not seek treatment at a formal facility, *iii)* 44.9% of children with a malaria-positive fever who sought treatment at a formal facility did not receive an antimalarial of any kind at the facility they visited, and *iv)* 51.3% of children with a malaria-positive fever who sought treatment and received an antimalarial received a non-ACT antimalarial. A Bayesian model was used to further attribute fevers in malaria-positive children to either malaria-attributable fever (MAF) or non-malarial febrile illness (NMFI) with an asymptomatic *P. falciparum* infection, it is estimated that NMFI was the underlying cause of 62.4% (56.6 – 67.6, 95% CrI) of all malaria-positive fevers treated with ACT. Further, this analysis shows that children with a malaria infection receiving treatment at a public health facility were more likely to receive an ACT compared to private facilities. Public facilities were found to have higher rates of diagnostic testing than private facilities, but also were more likely to presumptively treat malaria infections (with an antimalarial of any kind). The results

presented in this analysis are informative for measuring progress in reducing treatment coverage gaps, and for identifying inequities that remain to be addressed.

5.3. Introduction

Increased development and deployment of interventions against malaria have led to large declines in *Plasmodium falciparum* morbidity and mortality over the past two decades, with 19% of malaria prevalence reductions in sub-Saharan Africa attributed to use of artemisinin combination therapy (ACT) [1, 2]. Since 2006, the World Health Organization (WHO) has recommended ACT as the first-line treatment for *P. falciparum* malaria due to rising antimalarial resistance to all other medications [3], and this guidance has since been adopted as the official treatment strategy in all sub-Saharan African countries [4]. In 2016, the WHO reported a total of 216 million malaria cases worldwide, which represented a 5 million increase on 2015, indicating stagnation and, in some countries, reversal of gains achieved in reducing the global malaria burden [4]. Investments in malaria control programmes (from both internal and international investors) has stagnated since 2010 [5], highlighting the increased need for streamlining current intervention efforts to maximise efficiency. Identifying coverage gaps for malaria interventions has the potential to increase the impact of current intervention efforts. Given the importance of ACTs in reducing the burden of *P. falciparum* malaria in sub-Saharan Africa [1], understanding the proportion of malaria infections that receive ACT is critical for quantifying the contribution of ACT to burden reductions, and to measure the effectiveness of current intervention investments and disbursements. A multitude of barriers can prevent malaria-infected individuals from receiving ACT. Firstly, their malaria infection may be asymptomatic. The prevalence of asymptomatic

infections is a function of population exposure to *P. falciparum* infection, with older individuals in moderate to high prevalence areas acquiring protective immunity from *P. falciparum* resulting in fewer clinical attacks [6–8]. Asymptomatic malaria infections are, however, well-documented across all age groups, including children [9–11], often at parasite densities/antigen concentrations high enough to be detected by microscopy and rapid diagnostic tests (RDTs) [12–16]. If infected individuals are asymptomatic, the only opportunities for treatment lie with opportunistic treatment, for example through mass screen and treat campaigns, or mass drug administration.

Secondly, symptomatic, malaria-infected individuals may not receive an ACT because they do not seek treatment for their illness. Both socio-economic and geographical barriers to treatment-seeking for fever have been documented across literature, including affordability of medicines and transport to the treatment location [17–20], geographical distance to the treatment location [18, 21, 22], and lack of trust in the skill of clinicians and perceived ineffectiveness of treatment [21, 23]. Additionally, household-level factors affect an individual's likelihood to seek care for a fever (or for a caregiver to seek care for a febrile child) from a formal provider, including use of informal providers, household wealth, education, and birth order of the child. Propensity to try home remedies, analgesics, or leftover antimalarial medication from a previous illness before seeking treatment from a formal provider can also delay treatment-seeking [24–28].

Another barrier to full ACT coverage among malaria-infected children is the continued use of non-ACT drugs, with approximately half of *P. falciparum* infected children under five years of age who were known to have sought and received an antimalarial medication received an ACT treatment (with the remainder receiving non-ACT antimalarials) in household surveys conducted between 2014-2016 [4]. This finding is

supported by another study on ACT coverage in sub-Saharan African countries, which estimated that only 19.7% of African children under 5 years of age with a fever and a *P. falciparum* infection received an ACT in 2015 [39]. Despite a clear need for ACT treatment in an era of rising diagnostic testing and antimalarial resistance, documented supply-side barriers to provision of ACTs persist and include *i)* stock-outs in facilities [40], *ii)* patients or facilities opting for non-first-line antimalarials due to cost [41] (this issue is particularly acute in informal facilities and when travel times to formal facilities are high [42]), and *iii)* poor staff training and adherence to guidelines [34, 43–46]. Previous estimates of "effective treatment coverage" (i.e. the proportion of malaria-positive fevers that are treated and subsequently cured) in sub-Saharan Africa in 2010-2011 showed high heterogeneity between sub-Saharan African nations, ranging between 7% in Somalia to 72% in Botswana [47].

For malaria-infected, febrile individuals who do seek and receive antimalarial treatment, one reason the infection may not clear is resistance of *P. falciparum* to the prescribed antimalarial treatment. In addition to well-documented resistance to non-ACT antimalarial medications that are still commonly used (such as chloroquine [48], sulfadoxine-pyrimethamine [49], amodiaquine [50] etc.), ACT resistance has now been observed in a number of locations in Southeast Asia, and has been reported in returning travellers from Equatorial Guinea [51–54]. Another reason the infection may not clear is due to patient non-adherence to the antimalarial medication, although measuring the proportion of individuals who do not adhere to medications is challenging. Drug adherence monitoring studies are an imperfect tool for measuring patient adherence to medication, due to intrinsic biases with patients knowing their behaviour is being monitored. Nevertheless, such studies have implied that imperfect adherence to ACTs is in the range of 5 to 20% for children under 5 years of age [55, 56].

Finally, for a number of febrile *P. falciparum*-infected individuals, effective treatment with an ACT may still not resolve their fever. Approximately two-thirds of RDT-positive fevers in sub-Saharan Africa in 2014 were causally attributable to non-malarial febrile illness (NMFI) [57] due to high rates of co-infection of malaria and NMFI across the continent.

Measuring coverage of ACT is challenging, as the total number of malaria infections at community-level that receive ACT is never directly measured, and instead requires estimation from available data on related metrics. Household survey datasets have previously been used to estimate ACT coverage as they incorporate indicators on recent treatment-seeking and antimalarial usage for children under 5 years of age. In this analysis, household survey data from the DHS Program [58] on malaria positivity, fever, treatment-seeking, and antimalarial prescription for children under 5 years of age were collated from household surveys conducted between 2006 and 2016 in order to assess ACT coverage for malaria-infected children. To provide a more nuanced definition of clinical malaria-attributable illness, a Bayesian hierarchical model was used to assign the probability of febrile children experiencing one of four fever types during the two weeks preceding each survey: *i)* a malaria-attributable fever (MAF), *ii)* a fever caused by non-malarial febrile illness (NMFI) coincident with an asymptomatic *P. falciparum* malaria infection, *iii)* NMFI without a patent *P. falciparum* malaria infection, and *iv)* and co-symptomatic MAF and NMFI.

Several key metrics were estimated. First, the coverage of ACT amongst all RDT-patent malaria-infected children under 5 living in countries with a household survey during the two weeks preceding each household survey was estimated, and the associated reasons why malaria-infected children did not receive ACT were recorded. Second, the proportions of febrile children with each of the four fever types detailed above was

quantified at the community- and clinic-level, and the proportion of children with each of these fever types that receives antimalarial medication (with ACT and non-ACT antimalarials) at clinics was estimated. Next, the differential performance of public and private clinics at following Integrated Management of Childhood Illness (IMCI) guidelines and appropriate prescription of ACT was estimated. Finally, the effects of individual- and household-level factors on probability of malaria infection, experiencing NMFI, treatment-seeking, and receiving an ACT were investigated. The results presented here identify individual-, household-, clinic-, and national-level coverage gaps in ACT for malaria-infected children, and provide quantitative insights into the personal and clinical reasons why malaria infections do not receive effective antimalarial medication.

5.4. Methods

In this analysis, all estimates presented were generated through modelling household survey data. This was achieved in a number of steps. First, a dataset of fever and malaria positivity observations was extracted from 41 household surveys conducted in sub-Saharan Africa between 2006 and 2016. Next, for each febrile child in the household survey dataset, a Bayesian model was used to attribute their fever to one of four underlying causes: *i)* MAF, *ii)* co-symptomatic MAF and NMFI, *iii)* NMFI with an asymptomatic *P. falciparum* infection, and *iv)* NMFI without a *P. falciparum* infection. Finally, the subsequent treatment-seeking and treatment outcomes for each of the febrile children was used to generate the entire suite of estimated metrics presented in this analysis. The household survey data, modelling procedure, and methods for establishing nationally-representative predictions are described below.

5.4.1. Household survey dataset

To inform the effective antimalarial coverage model, 41 cross-sectional, nationally-representative surveys of malaria prevalence in children less than five years of age across 21 countries in sub-Saharan Africa, conducted between 2006 and 2016, were obtained from the Demographic and Health (DHS) Program [58]. Full details of the surveys used can be found in Additional Table 1.

For each child, the following information was recorded: *i)* their geo-referenced location, *ii)* RDT outcome (measured at the time of interview), *iii)* fever history in the past two weeks as recalled by the caregiver, *iv)* if recalled to have been febrile, whether they sought treatment, *v)* if reported to have been febrile and to have sought treatment, where they sought treatment (public or private clinics were included; informal clinics such as pharmacies, shops, markets, traditional healers, drug peddlers, and friends and relatives were not included), *vi)* what treatment they received (if any), *vii)* whether blood was taken for a parasite-based malaria diagnosis at the treatment location, and *viii)* individual-level factors (child's age, household wealth, maternal education, child's use of ITN the night preceding the survey). Observations for a total of 156,670 children were collated from the 41 surveys (Additional Table 1).

5.4.2. ACT coverage amongst malaria-positive individuals

In addition to the modelled metrics described below, ACT coverage metrics for all malaria-positive individuals (regardless of fever status) were measured directly from the household survey data. A population-weighting was applied to generate overall estimates for all children residing in all surveyed country-years during the two weeks preceding each survey. Population-weighted ACT coverage for all surveyed country-

years in the two weeks preceding each survey (and the reasons why malaria-positive individuals did not receive an ACT) was derived by multiplying indicators from each household survey dataset by the total population of children under 5 years of age in that country-year. Populations of children under 5 years of age for each country-year were extracted from United Nations (UN) population estimates [59]. For surveys that spanned two years, the national population from the survey start year was used. Population estimates for 2016 were unavailable; for the four surveys exclusively conducted during 2016, 2015 population estimates were used.

From each survey, the number of RDT-positive children was extracted, and amongst these children the following proportions were determined: *i)* the proportion who were recalled to have had a fever within the two weeks preceding the survey, *ii)* the proportion of febrile children who sought treatment at a formal treatment location, *iii)* the proportion who received an antimalarial (of any type), and *iv)* the proportion who received an ACT. These proportions were weighted by the individual weights documented in the household survey dataset (in order to obtain nationally-representative estimates) and were further multiplied by the population of children under 5 in that country-year in order to derive population-weighted estimates. The UN population dataset was also used to generate population-weighted estimates of the modelled metrics described below.

5.4.3. Covariates

Three covariates were used as covariates within the final model, which is described below, and in previous publications [56, Chapter 4 of this Thesis]. Briefly, the covariates were: *i) P. falciparum* prevalence amongst children under 5 years of age

(*Pf*PR_{0-5}), *ii)* suitability for fever without a malaria infection in children under 5 years of age, and *iii)* caregivers' propensity to seek treatment for fever of any cause for children less than 5 years of age. All covariates were available from 2006 to 2016 at a 5km x 5km spatial resolution across sub-Saharan Africa. The rationale behind the selection of these three variables, and more detailed methods for generating each variable, has been documented in previous publications [56, Chapter 4 of this Thesis].

Estimates of malaria prevalence in children 2-10 years of age (*Pf*PR_{2-10}) in Africa [1] measured via microscopy were used to generate estimates of the first covariate, *Pf*PR_{0-5}, The *Pf*PR_{2-10} estimates were converted to prevalence for children <5 years of age using the age-standardisation procedure for *Pf*PR described by Smith *et al* [60], and further standardised to RDT-based prevalence estimates of malaria using the methods described by Mappin *et al* [61].

The remaining two covariates were generated using a boosted regression tree (BRT) approach. These covariates were *i)* suitability for fever without a malaria infection (henceforth "BRT_{bg}"), and *ii)* probability of seeking treatment for a fever of any cause (henceforth "BRT_{treat}"). The two BRT variables were generated using the "gbm.step" function from the "dismo" package in the R programming language [62], with the household survey data described above used as response data within the BRTs. A total of 157 predictor variables were used, which were derived from continuous remotely-sensed environmental and sociodemographic covariates for sub-Saharan Africa at a 5km x 5km resolution, and national-level socioeconomic variables from the World Bank [63]. All variables were available between 2006 and 2016, at varying temporal resolutions (monthly, annual, synoptic, and stationary), and predictor variable values were matched to spatially and temporally contemporaneous household survey data points. The response variable for BRT_{bg} was the prevalence of fever without a malaria

infection within each geolocated cluster, as recorded in the household survey dataset. The response variable for BRT_{treat} was the proportion of febrile children within the household survey dataset who sought treatment during the past two weeks for each geolocated cluster. The BRT approach constructs regression models between responses and the 157 predictor variables, and generates continuous surfaces of both BRT_{bg} and BRT_{treat} covariates at a 5km x 5km resolution across sub-Saharan Africa for each year. The resulting BRT surfaces are subsequently utilised as predictor variables in the Bayesian hierarchical model presented below.

5.4.4. Fever attribution model

The model used in this analysis was a Bayesian hierarchical model for individual-level attribution of MAF or NMFI (or both, via co-symptomatic malaria and NMFI infections) within the 14 days preceding the survey to febrile children within the household survey dataset, and has been described elsewhere [Chapter 4 of this Thesis]. The model used additional indicators from the household survey dataset to further compute probabilities of seeking treatment for fever, receiving parasite-based diagnosis for malaria at the point of care, and of receiving ACT or non-ACT antimalarials. The RDT outcome of malaria diagnosis at the household survey interview was used to derive malaria positivity, but fever positivity was derived via two-week recall of fever by caregivers for children under 5. Under this framework, the possibility exists that a child with a malaria-positive fever during the two weeks preceding the survey may have sought and received antimalarial treatment, and the medication may have cleared the

antigens associated with the infection sufficiently to appear negative by the time of RDT diagnosis at the survey interview. In order to account for this, the model was further adapted via an adjustment procedure [64] that computes the probability of reverting from RDT positive to RDT negative between the time of treatment and the interview. The probability of successful treatment was estimated using the World Health Organization database on antimalarial efficiency, matched to the closest available contemporaneous year and location of the treatment received [65, 66].

The Bayesian hierarchical model assigned probabilities to febrile individuals falling into each of the four fever categories: MAF only, NMFI with an RDT-patent *P. falciparum* infection, NMFI without an RDT-patent *P. falciparum* infection, or co-symptomatic MAF and NMFI. These probabilities were estimated from individual-level covariates (household wealth, child's age, maternal education, and ITN usage), spatial random fields, and the three fully-spatial covariates ($Pf\mathrm{PR}_{0\text{-}5}$, $\mathrm{BRT}_{\mathrm{bg}}$ and $\mathrm{BRT}_{\mathrm{treat}}$) as described in the previous sub-sections. Survey-level random effects were applied to each treatment-based probability. The Bayesian hierarchical notation and parametrisations are given in a previous publication [Chapter 4 of this Thesis]. In brief, the hierarchical model assigned probabilities of an individual experiencing a MAF or NMFI (or both) in the two weeks preceding the survey by enumerating every possible scenario by which an individual may have received the parasitaemia, fever, and treatment outcomes documented in the household survey. The parasitaemia and treatment outcomes categorised were: RDT test result (positive/negative), treatment sought (yes/no; stratified by public and private treatment), blood drawn at point of care for parasite-based diagnosis of malaria (yes/no), and antimalarials received (yes/no; segregated by ACT and non-ACT antimalarials). Individual weights, as documented by the original household surveys, were used to generate nationally-representative estimates of MAF

and NMFI. The algorithm by which the probability of each individual experiencing MAF, NMFI, or both, based on these categorical criteria, was demonstrated in the previous publication [Chapter 4 of this Thesis].

5.5. Results

The observed proportion of children without fever (with and without an asymptomatic *P. falciparum* infection), and estimates for the proportion of children with each of the four fever types (MAF, NMFI with and without an asymptomatic *P. falciparum* infection, and co-symptomatic MAF and NMFI) in the two weeks preceding each of the 41 household surveys are given in Table 1, with the median of all posterior draws presented with associated 95% credible intervals for estimated metrics.

By attributing two-week positivity of MAF and NMFI at an individual-level to children within the complete household survey dataset, an array of household survey indicators can be assessed for their effect on MAF and NMFI positivity. Here, analysis was focused on indicators of ACT coverage and health systems performance, but a multitude of combinations of indicators are possible for the full household survey dataset (with individual-level attributions of MAF and NMFI). A sample of further tabulations are appended to the model code (Additional File 1) and can be adapted by users to produce any set of statistical summaries from the household survey dataset. All mean percentages reported for the 41 surveyed countries were valid for all children residing in the 41 surveyed countries during the two weeks preceding each household survey, and are population-weighted values derived using annual UN population estimates, as described above.

Table 5.1. Modelled estimates of the proportion of children in each survey falling into each fever type category. *P. falciparum* positivity was derived through RDT diagnosis at the time of interview; infections below the sensitivity threshold of RDTs used in the survey would be reported as "no infection". For each proportion, the median (50%) and lower (2.50%) and upper (97.50%) credible intervals are reported.

Table 5.1. Modelled estimates of the proportion of children in each survey falling into each fever type category. *P. falciparum* infections are derived through RDT outcomes; infections below the sensitivity threshold of RDTs used in the survey would be reported as "no infection". For each proportion, the median (50%) and lower (2.50%) and upper (97.50%) credible intervals are reported.

		Proportion of children with no fever and an asymptomatic *P. falciparum* infection	**Proportion of children with no fever and no *P. falciparum* infection**	**Proportion of children with a malaria-attributable fever (MAF) only**		
Country	**Survey Year(s)**	**Observed**	**Observed**	**Lower CrI**	**Median**	**Upper CrI**
Angola	2006/2007	0.1583	0.6311	0.0192	0.0220	0.0269
Angola	2011	0.0663	0.5663	0.0121	0.0134	0.0151
Angola	2015/2016	0.0915	0.7380	0.0130	0.0140	0.0151
Benin	2011/2012	0.2040	0.6824	0.0221	0.0235	0.0249
Burkina Faso	2010	0.5879	0.1882	0.0537	0.0581	0.0632
Burkina Faso	2014	0.3014	0.2621	0.0454	0.0494	0.0531
Burundi	2012	0.0672	0.4872	0.0193	0.0208	0.0225
Cameroon	2011	0.1517	0.5314	0.0319	0.0373	0.0515
Cote d'Ivoire	2011/2012	0.2986	0.4251	0.0312	0.0339	0.0369
Democratic Republic of the Congo	2013/2014	0.1772	0.5068	0.0264	0.0280	0.0299
Ghana	2014	0.2843	0.5616	0.0330	0.0357	0.0382
Ghana	2016	0.1711	0.5305	0.0355	0.0393	0.0424
Guinea	2012	0.2490	0.4022	0.0431	0.0474	0.0524
Kenya	2015	0.0280	0.5816	0.0069	0.0078	0.0088
Liberia	2009	0.1655	0.3309	0.0213	0.0235	0.0255
Liberia	2011	0.1841	0.2577	0.0277	0.0296	0.0322
Liberia	2016	0.2134	0.3580	0.0328	0.0364	0.0396
Madagascar	2011	0.0573	0.7891	0.0107	0.0117	0.0125
Madagascar	2013	0.0605	0.8147	0.0110	0.0118	0.0125
Madagascar	2016	0.0352	0.7938	0.0068	0.0077	0.0086
Malawi	2012	0.2134	0.4378	0.0526	0.0571	0.0622
Malawi	2014	0.1761	0.4938	0.0381	0.0420	0.0461
Mali	2013	0.4033	0.4946	0.0462	0.0476	0.0488
Mali	2015	0.1866	0.5186	0.0264	0.0284	0.0302
Mozambique	2011	0.3106	0.5419	0.0272	0.0294	0.0315

Table 5.1. (continued)

		Proportion of children with no fever and an asymptomatic P. falciparum infection	Proportion of children with no fever and no *P. falciparum* infection	Proportion of children with a malaria-attributable fever		
Country	**Survey Year(s)**	**Observed**	**Observed**	**Lower CrI**	**Median**	**Upper CrI**
Mozambique	2015	0.2322	0.4500	0.0498	0.0540	0.0594
Nigeria	2010	0.2777	0.3255	0.0374	0.0403	0.0433
Nigeria	2015	0.1884	0.3749	0.0346	0.0369	0.0395
Rwanda	2010	0.0171	0.8117	0.0020	0.0023	0.0025
Rwanda	2014/2015	0.0420	0.7508	0.0132	0.0143	0.0152
Senegal	2008/2009	0.0710	0.5724	0.0112	0.0128	0.0172
Senegal	2010/2011	0.0203	0.7324	0.0040	0.0045	0.0049
Senegal	2012/2013	0.0215	0.8019	0.0028	0.0034	0.0054
Senegal	2015	0.0044	0.8365	0.0005	0.0008	0.0014
Tanzania	2007/2008	0.1113	0.6820	0.0129	0.0139	0.0159
Tanzania	2011/2012	0.0476	0.7244	0.0133	0.0143	0.0152
Tanzania	2015/2016	0.0895	0.7138	0.0192	0.0203	0.0215
Togo	2013/2014	0.2435	0.5125	0.0296	0.0326	0.0355
Uganda	2009	0.1989	0.3175	0.0322	0.0346	0.0372
Uganda	2014/2015	0.1446	0.5278	0.0233	0.0252	0.0272
Uganda	2016	0.0978	0.5165	0.0334	0.0356	0.0381

Table 5.1. (continued)

		Proportion of children with co-symptomatic malaria-attributable fever (MAF) and non-malarial febrile illness (NMFI)			Proportion of children with non-malarial febrile illness (NMFI) and an asymptomatic *P. falciparum* infection			Proportion of children with non-malarial febrile illness (NMFI) and no *P. falciparum* infection		
Country	**Survey Year(s)**	**Lower CrI**	**Median**	**Upper CrI**	**Lower CrI**	**Median**	**Upper CrI**	**Lower CrI**	**Median**	**Upper CrI**
Angola	2006/2007	0.0027	0.0033	0.0052	0.0339	0.0380	0.0409	0.1457	0.1469	0.1472
Angola	2011	0.0055	0.0058	0.0061	0.0441	0.0457	0.0469	0.3024	0.3026	0.3028
Angola	2015/2016	0.0022	0.0024	0.0027	0.0174	0.0185	0.0194	0.1351	0.1356	0.1359
Benin	2011/2012	0.0014	0.0015	0.0017	0.0110	0.0120	0.0130	0.0759	0.0766	0.0771
Burkina Faso	2010	0.0082	0.0086	0.0091	0.1027	0.1080	0.1123	0.0487	0.0491	0.0494
Burkina Faso	2014	0.0241	0.0252	0.0262	0.2388	0.2429	0.2470	0.1184	0.1191	0.1195
Burundi	2012	0.0140	0.0149	0.0159	0.1133	0.1151	0.1166	0.2943	0.2948	0.2952
Cameroon	2011	0.0047	0.0066	0.0173	0.0762	0.0904	0.0969	0.1799	0.1815	0.1819
Cote d'Ivoire	2011/2012	0.0080	0.0085	0.0089	0.0737	0.0762	0.0789	0.1572	0.1576	0.1580
Democratic Republic of the Congo	2013/2014	0.0097	0.0100	0.0104	0.0853	0.0872	0.0888	0.1904	0.1908	0.1910
Ghana	2014	0.0047	0.0054	0.0059	0.0392	0.0413	0.0435	0.0710	0.0717	0.0724
Ghana	2016	0.0068	0.0074	0.0083	0.0583	0.0611	0.0639	0.1895	0.1908	0.1919
Guinea	2012	0.0137	0.0144	0.0153	0.1301	0.1346	0.1387	0.1516	0.1523	0.1528
Kenya	2015	0.0053	0.0057	0.0063	0.0396	0.0405	0.0412	0.3359	0.3365	0.3369
Liberia	2009	0.0164	0.0182	0.0195	0.1451	0.1471	0.1488	0.3139	0.3148	0.3155
Liberia	2011	0.0239	0.0249	0.0259	0.2145	0.2172	0.2193	0.2859	0.2863	0.2867
Liberia	2016	0.0178	0.0190	0.0213	0.1596	0.1624	0.1654	0.2104	0.2107	0.2109
Madagascar	2011	0.0016	0.0018	0.0020	0.0135	0.0143	0.0151	0.1258	0.1258	0.1259
Madagascar	2013	0.0011	0.0012	0.0013	0.0088	0.0093	0.0100	0.1021	0.1024	0.1026
Madagascar	2016	0.0007	0.0009	0.0010	0.0057	0.0065	0.0074	0.1556	0.1559	0.1561
Malawi	2012	0.0151	0.0163	0.0177	0.1358	0.1405	0.1449	0.1345	0.1348	0.1350
Malawi	2014	0.0141	0.0156	0.0169	0.1248	0.1289	0.1320	0.1433	0.1437	0.1439
Mali	2013	0.0013	0.0015	0.0016	0.0130	0.0141	0.0154	0.0386	0.0389	0.0391
Mali	2015	0.0091	0.0095	0.0098	0.0805	0.0821	0.0840	0.1742	0.1748	0.1754
Mozambique	2011	0.0041	0.0043	0.0045	0.0402	0.0421	0.0439	0.0709	0.0717	0.0724

Table 5.1. (continued)

		Proportion of children with co-symptomatic malaria-attributable fever and non-malarial febrile illness			Proportion of children with non-malarial febrile illness and an asymptomatic *P. falciparum* infection			Proportion of children with non-malarial febrile illness and no *P. falciparum* infection		
Country	**Survey Year(s)**	**Lower CrI**	**Median**	**Upper CrI**	**Lower CrI**	**Median**	**Upper CrI**	**Lower CrI**	**Median**	**Upper CrI**
Mozambique	2015	0.0128	0.0135	0.0144	0.1122	0.1162	0.1205	0.1325	0.1339	0.1350
Nigeria	2010	0.0201	0.0215	0.0228	0.1718	0.1753	0.1787	0.1594	0.1596	0.1599
Nigeria	2015	0.0186	0.0194	0.0202	0.1781	0.1808	0.1835	0.1993	0.1995	0.1997
Rwanda	2010	0.0004	0.0005	0.0006	0.0034	0.0036	0.0038	0.1647	0.1648	0.1648
Rwanda	2014/2015	0.0021	0.0025	0.0029	0.0187	0.0196	0.0205	0.1707	0.1709	0.1709
Senegal	2008/2009	0.0020	0.0027	0.0060	0.0274	0.0318	0.0340	0.3087	0.3088	0.3088
Senegal	2010/2011	0.0002	0.0005	0.0009	0.0026	0.0029	0.0031	0.2392	0.2395	0.2397
Senegal	2012/2013	0.0005	0.0007	0.0022	0.0056	0.0073	0.0082	0.1648	0.1649	0.1649
Senegal	2015	0.0001	0.0002	0.0006	0.0008	0.0013	0.0016	0.1568	0.1568	0.1568
Tanzania	2007/2008	0.0028	0.0032	0.0043	0.0399	0.0419	0.0429	0.1474	0.1477	0.1479
Tanzania	2011/2012	0.0033	0.0035	0.0037	0.0233	0.0240	0.0248	0.1857	0.1861	0.1865
Tanzania	2015/2016	0.0035	0.0039	0.0041	0.0259	0.0269	0.0279	0.1452	0.1456	0.1459
Togo	2013/2014	0.0076	0.0080	0.0084	0.0719	0.0746	0.0774	0.1280	0.1287	0.1294
Uganda	2009	0.0227	0.0241	0.0258	0.2566	0.2603	0.2633	0.1641	0.1645	0.1650
Uganda	2014/2015	0.0125	0.0145	0.0155	0.1122	0.1138	0.1156	0.1738	0.1741	0.1745
Uganda	2016	0.0165	0.0172	0.0179	0.1346	0.1372	0.1392	0.1949	0.1957	0.1964

5.5.1. Prevalence of fever types and ACT coverage at community and clinic level

Population-weighted estimates were generated for all surveyed country-years to account for each country's contribution to the total coverage of ACT across all surveyed country-years. Population estimates from the UN database approximate that 211,960,303 children under 5 years of age lived in the 41 surveyed country years during the two weeks preceding each survey. Of these children, 64,805,318 (30.6%) were estimated to have had an RDT-patent *P. falciparum* infection in the two weeks preceding each household survey. Amongst malaria-infected children, 45.1% were estimated to have had a fever (of any underlying cause) in the two weeks preceding each household survey. Amongst the malaria-infected febrile children, 65.6% (and 29.6% of all malaria-infected children) were predicted to have sought treatment at a formal care provider (public or private) in the two weeks preceding each household survey. Amongst malaria-infected febrile children who sought treatment, 55.1% (and 16.3% of all malaria-positive children) received an antimalarial of any kind. Amongst malaria-infected febrile children who sought treatment and received an antimalarial, 48.7% (and 7.9% of malaria-infected children) received an ACT. A Sankey diagram of the population-weighted estimates across all surveyed country-years of the proportion of malaria-positive children who received an ACT is displayed in Figure 5.1.
Table 5.2 shows the number and proportion of individuals fulfilling each of the above criteria for each of the 41 household surveys.

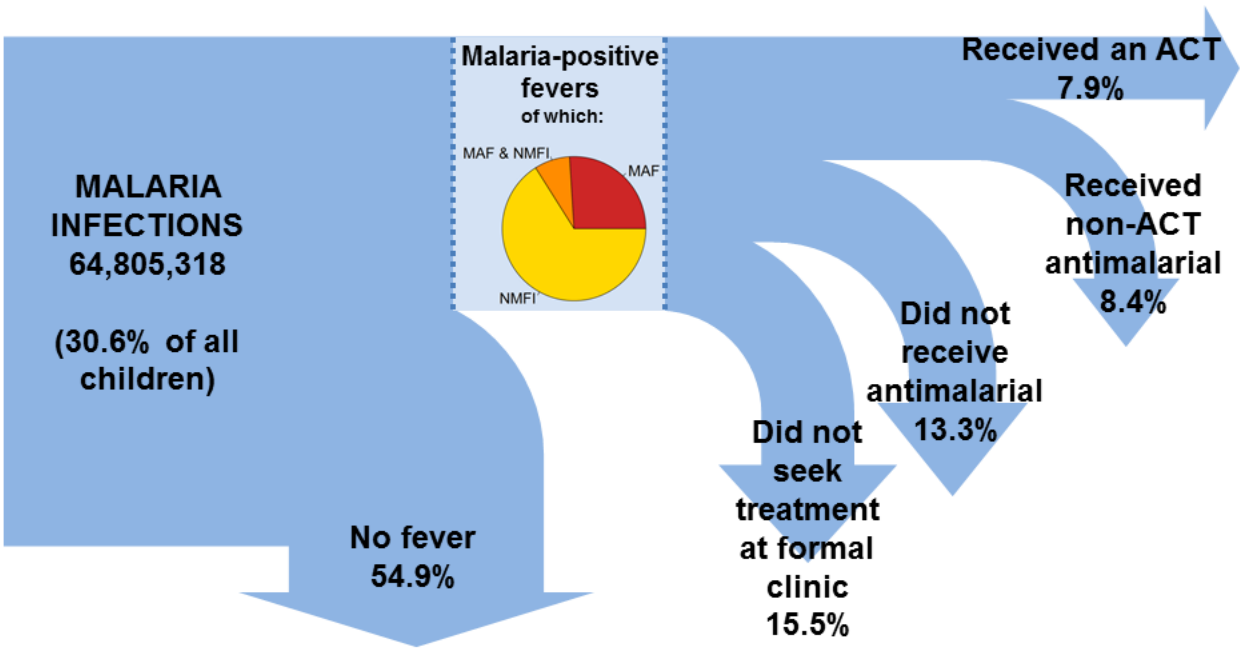


Figure 5.1. ACT coverage amongst *P. falciparum*-infected children, and quantified reasons why *P. falciparum* malaria-infected in children under 5 did not receive ACT across all 41 surveyed country-years in sub-Saharan Africa, 2006-2016. Proportions are population-weighted and representative of all the surveyed country-years during the two weeks preceding each survey. Of 64,805,318 malaria-infected children across all surveyed country-years, 30.6% were RDT-positive. Amongst malaria-positive febrile children, the overlain pie chart shows the population-weighted proportion of fevers where the underlying cause was: *i)* MAF (red; 23.7% of malaria-positive febrile children), *ii)* co-symptomatic MAF and NMFI (orange; 7.7%), and *iii)* NMFI (yellow; 68.4%).

Table 5.2. Raw number of children under 5 in each survey who: *i)* had an RDT patent malaria infection (P+), *ii)* had a malaria infection and a fever (P+F+), *iii)* of those who had a malaria infection and a fever, estimated proportions of those that were malaria-attributable fevers (MAF) and those that were non-malarial fevers (NMFI) with associated 2.5%, 50% and 97.5% credible intervals, *iv)* had a malaria infection, a fever, and sought treatment at a formal public or private facility (P+F+T+), *v)* had a malaria infection, a fever, and sought treatment at a formal public or private facility and received an antimalarial of any kind (P+F+T+A+), and *vi)* had a malaria infection, a fever, and sought treatment at a formal public or private facility and received an ACT (P+F+T+A+ACT+). Co-symptomatic MAF and NMFI is included within MAF (and excluded from NMFI). UN population estimates for each country-year are also included; these were used to generate the population-weighted estimates.

Table 5.2. Raw number of children under 5 in each survey who: i) had an RDT patent malaria infection (P+), ii) had a malaria infection and a fever (P+F+), iii) of those who had a malaria infection and a fever, estimated proportions of those that were malaria-attributable fevers (MAF) and those that were non-malarial fevers (NMFI) with associated 2.5%, 50% and 97.5% credible intervals, iv) had a malaria infection, a fever, and sought treatment at a formal public or private facility (P+F+T+), v) had a malaria infection, a fever, and sought treatment at a formal public or private facility and received an antimalarial of any kind (P+F+T+A+), and vi) had a malaria infection, a fever, and sought treatment at a formal public or private facility and received an ACT (P+F+T+A+ACT+). Co-symptomatic MAF and NMFI is included within MAF (and excluded from NMFI). UN population estimates for each country-year are also included; these were used to generate the population-weighted estimates. All tabulated numbers are derived directly from the DHS Program surveys, with the exception of the "MAF" and "NMFI" columns, which are modelled estimates.

		Total	P+	P+F+	MAF			NMFI			P+F+T+	P+F+T+A+	P+F+T+A+ACT+	UN Population
Country	**Year of Survey**	**N**	**N**	**N**	**Lower CrI**	**Median**	**Upper CrI**	**Lower CrI**	**Median**	**Upper CrI**	**N**	**N**	**N**	**N**
Angola	**2006/2007**	1147	279	71	25	29	34	37	42	46	28	11	2	**3693471**
Angola	**2011**	2900	354	173	48	51	55	118	122	125	70	25	22	**4290563**
Angola	**2015/2016**	2996	458	114	51	53	57	57	61	63	55	14	13	**4717892**
Benin	**2011/2012**	3103	804	125	81	84	88	37	41	44	41	13	2	**1603612**
Burkina Faso	**2010**	5629	4246	1018	363	389	421	597	629	655	541	323	91	**2856990**
Burkina Faso	**2014**	5430	3513	1761	389	413	437	1324	1348	1372	1046	769	228	**3088687**
Burundi	**2012**	3462	698	472	106	112	118	354	360	366	283	176	132	**1879212**
Cameroon	**2011**	4493	1375	628	178	208	279	349	420	450	310	119	30	**3503784**
Cote d'Ivoire	**2011/2012**	2621	1164	343	115	123	130	213	220	228	98	15	6	**3356337**
DR Congo	**2013/2014**	6985	2426	1027	298	312	328	699	715	729	521	233	51	**13222905**
Ghana	**2014**	2332	940	210	99	105	111	99	105	111	154	93	81	**3980451**
Ghana	**2016**	1417	474	167	67	72	77	90	95	100	95	48	42	**4055985**
Guinea	**2012**	2734	1174	503	148	159	170	333	344	355	181	86	6	**1918815**
Kenya	**2015**	2817	233	150	35	37	40	110	113	115	97	64	59	**7166489**
Liberia	**2009**	3013	1032	523	110	115	122	401	408	413	350	289	125	**640675**
Liberia	**2011**	2320	1170	704	136	141	149	555	563	568	466	333	254	**667559**
Liberia	**2016**	2097	1014	496	120	126	133	363	370	376	275	231	210	**701125**
Madagascar	**2011**	5181	322	112	51	54	57	55	58	61	33	13	3	**3453578**
Madagascar	**2013**	4440	276	79	43	46	48	31	33	36	33	7	4	**3605675**
Madagascar	**2016**	3108	105	34	18	19	21	13	15	16	20	3	0	**3770130**
Malawi	**2012**	1881	714	363	117	125	133	230	238	246	181	113	102	**2795556**
Malawi	**2014**	1712	496	259	76	80	86	173	179	183	175	131	123	**2895270**
Mali	**2012/2013**	4093	1773	230	174	179	183	47	51	56	79	31	3	**3086369**
Mali	**2015**	6590	1912	782	233	247	259	523	535	549	330	192	56	**3271256**
Mozambique	**2011**	4273	1458	276	115	123	130	146	153	161	144	89	63	**4444951**

Table 5.2 (continued)

		Total	P+	P+F+	MAF			NMFI			P+F+T+	P+F+T+A+	P+F+T+A+ACT+	UN Population
Country	**Year of Survey**	**N**	**N**	**N**	**Lower CrI**	**Median**	**Upper CrI**	**Lower CrI**	**Median**	**Upper CrI**	**N**	**N**	**N**	**N**
Mozambique	**2015**	3698	1203	491	169	181	193	298	310	322	292	204	197	**4816063**
Nigeria	**2010**	4278	2006	899	221	235	248	651	664	678	760	359	42	**27699315**
Nigeria	**2015**	4900	2013	1155	261	275	288	867	880	894	735	310	124	**31109162**
Rwanda	**2010**	3603	79	21	8	9	10	11	12	13	13	4	4	**1682697**
Rwanda	**2014/2015**	3101	230	105	46	48	51	54	57	59	72	22	22	**1699270**
Senegal	**2008/2009**	3514	423	176	51	59	75	101	117	125	74	17	13	**2073872**
Senegal	**2010/2011**	3269	107	27	16	17	18	9	10	11	12	3	3	**2196990**
Senegal	**2012/2013**	5262	217	82	24	31	43	39	51	58	35	6	4	**2353609**
Senegal	**2015**	5428	57	20	6	9	13	7	11	14	10	2	1	**2601312**
Tanzania	**2007/2008**	5567	696	240	65	70	78	162	170	175	146	102	43	**7501235**
Tanzania	**2011/2012**	6358	580	249	101	106	111	138	143	148	154	110	79	**8376715**
Tanzania	**2015/2016**	7344	855	291	132	137	144	147	154	159	227	172	163	**9398450**
Togo	**2013/2014**	2838	1039	309	101	109	117	192	200	208	121	53	28	**1125359**
Uganda	**2009**	3353	1745	1036	180	191	204	832	845	856	826	582	245	**6275788**
Uganda	**2014/2015**	3986	1283	639	158	165	173	466	474	481	488	406	364	**7105209**
Uganda	**2016**	2733	868	579	155	161	169	410	418	424	384	340	312	**7277920**
TOTAL (All surveys)		156006	41811	16939	4891	5206	5599	11340	11733	12048	9955	6113	3352	**211960303**

Figure 5.2 summarises the proportion of each fever type at the community and clinic-level, and treatment-seeking and antimalarial treatment outcomes for each survey. The proportion of RDT-patent malaria infections documented in the household survey datasets that were accompanied by a fever (of any cause) in the two weeks preceding the survey ranged from 12.9% in Mali 2012-2013 to 67.3% in Burundi 2012. Amongst only febrile malaria-infected individuals documented in the household survey datasets, the proportion who sought treatment at a formal treatment location in the two weeks preceding the survey ranged from 28.7% in Cote d'Ivoire 2011-2012 to 84.5% in Nigeria in 2010. Amongst malaria-infected febrile children who sought treatment, antimalarial prescription was lowest in Madagascar 2016 (15.0% received antimalarials of any kind) and highest in Uganda 2016 (88.6% received antimalarials of any kind). Amongst those documented in the household survey datasets who sought treatment, ACT prescription was lowest in Madagascar 2016 (0%) and highest in Uganda 2016 (81.3%). Amongst antimalarials prescribed to malaria-infected febrile children who sought treatment at formal facilities in the two weeks preceding the survey, the proportion of those that were ACTs was lowest in Madagascar 2016 (0%) and highest in Senegal 2010/2011, Rwanda 2014/2015, and Rwanda 2010 (all 100%). Amongst all malaria-infected individuals in the two weeks preceding the household survey (regardless of fever status or treatment-seeking), the fraction that received an ACT ranged from 0% in Madagascar 2016 to 35.9% in Uganda 2016.

The population-weighted proportion of children across all surveyed country-years for whom no fever was recalled in the two weeks preceding each household survey was 68.5%. This proportion varied substantially between surveys, from 44.2% in Liberia 2011 to 89.8% in Mali 2013. On average, 25.0% of children who were not febrile in the

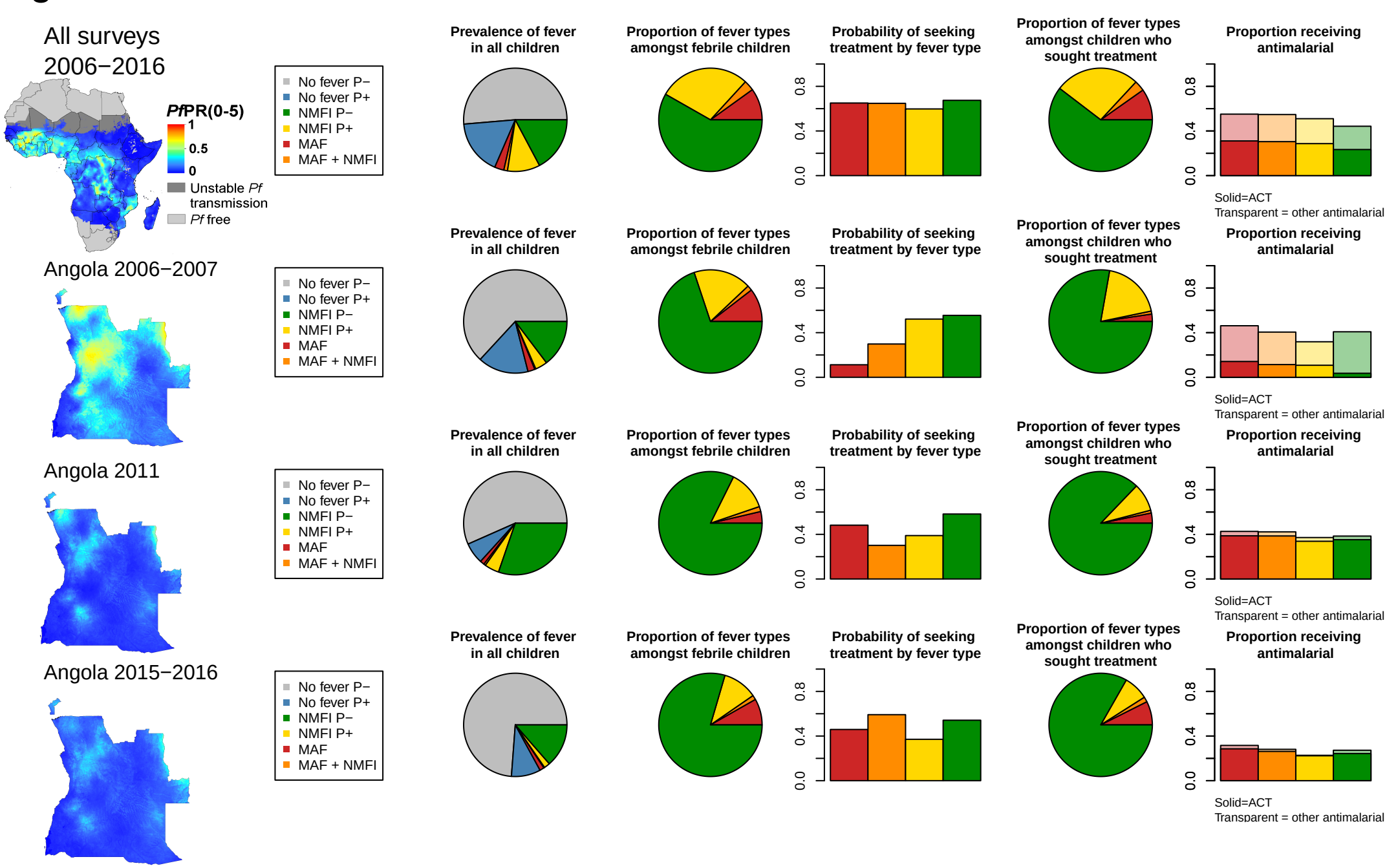
two weeks preceding each household survey (and 17.2% of all children) had an asymptomatic malaria infection, ranging from 0.5% of non-febrile children in Senegal 2015 (0.4% of all children) to 75.7% of non-febrile children in Burkina Faso 2010 (58.8% of all children).

Febrile children were sub-divided by the underlying cause of their fever; the proportion of children with each fever type can be found in Table 5.1. Amongst febrile children at the community-level, population-weighted estimates for all surveyed country-years reveal that 9.9% (9.2-10.8, 95% CrI) of fevers in the two weeks preceding each household survey were due to MAF, 3.2% (3.0-3.5, 95% CrI) of fevers were due to co-symptomatic MAF and NMFI, 28.6% (27.8-29.3, 95% CrI) of fevers were due to NMFI coincident with an RDT-patent asymptomatic *P. falciparum* infection, and 58.2% (58.1-58.3, 95% CrI) were due to NMFI without an RDT-patent *P. falciparum* infection. These fractions are displayed for each survey in the second panel of Figure 5.2 (and third panel for proportion of fever types amongst febrile children), and varied significantly by country and through time.

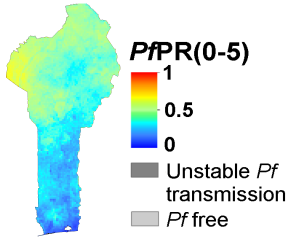
Across all surveys, the probability of febrile children seeking treatment differed minimally by fever type; however, treatment-seeking rates for different fever types were more variable in individual country-years. The proportion of each fever type presenting at clinics directly relates to the treatment-seeking rate and community fever type prevalence (Figure 5.2).

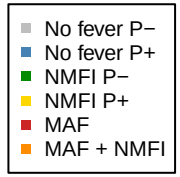
Table 5.3 shows the population-weighted probability across all surveyed country-years of receiving an antimalarial (of any type) and probability of receiving an ACT amongst febrile children with each fever type who sought treatment at a formal clinic (public or private). Probability of receiving an antimalarial (of any kind) and probability of receiving an ACT differed between fever types.

Figure 5.2.

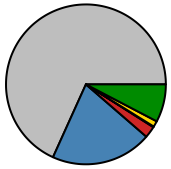

All surveys 2006−2016
PfPR(0-5)
1
0.5
0
Unstable Pf transmission
Pf free
Angola 2006−2007
Angola 2011
Angola 2015−2016
No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI
Prevalence of fever in all children
Proportion of fever types amongst febrile children
Probability of seeking treatment by fever type
Proportion of fever types amongst children who sought treatment
Proportion receiving antimalarial
0.0
0.4
0.8
Solid=ACT
Transparent = other antimalarial

Benin 2011−2012

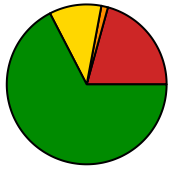




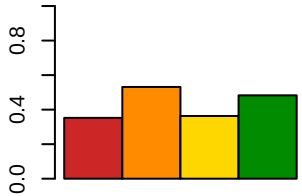
Prevalence of fever in all children



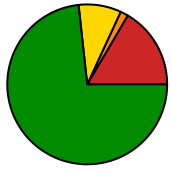
Proportion of fever types amongst febrile children



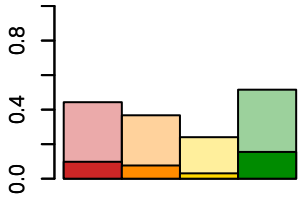
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

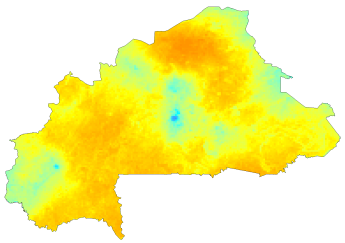


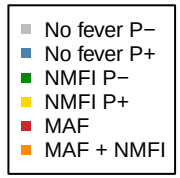
Proportion receiving antimalarial



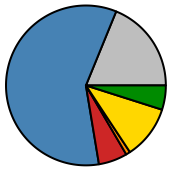
Solid=ACT
Transparent = other antimalarial

Burkina Faso 2010

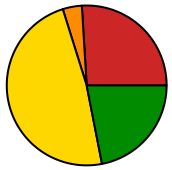




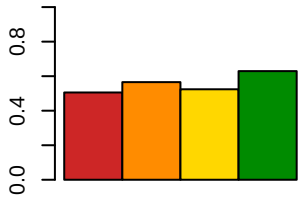
Prevalence of fever in all children



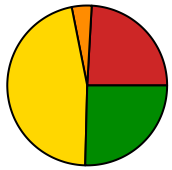
Proportion of fever types amongst febrile children



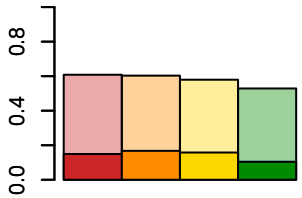
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

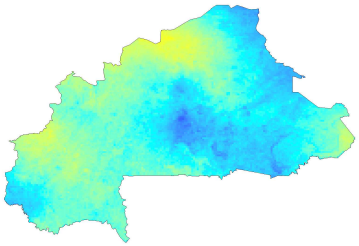


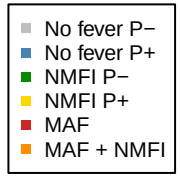
Proportion receiving antimalarial



Solid=ACT
Transparent = other antimalarial

Burkina Faso 2014





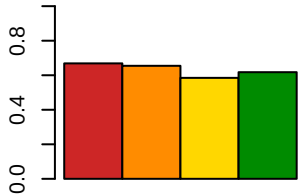
Prevalence of fever in all children



Proportion of fever types amongst febrile children



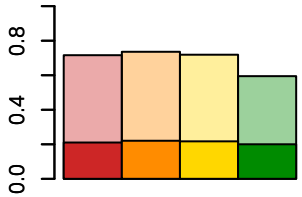
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

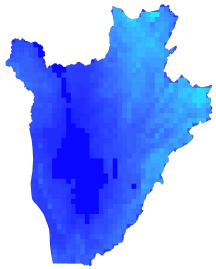


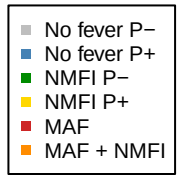
Proportion receiving antimalarial



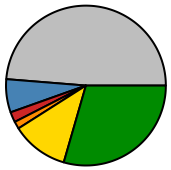
Solid=ACT
Transparent = other antimalarial

Burundi 2012

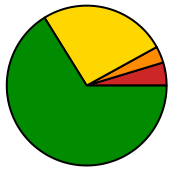




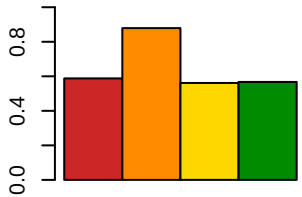
Prevalence of fever in all children



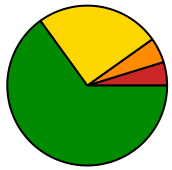
Proportion of fever types amongst febrile children



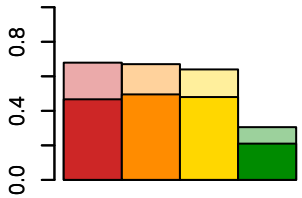
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

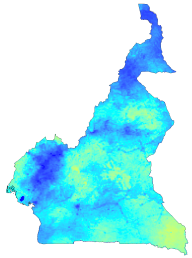


Proportion receiving antimalarial



Solid=ACT
Transparent = other antimalarial

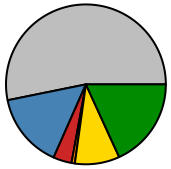
Cameroon 2011



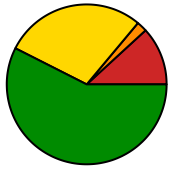
*Pf*PR(0-5)
1
0.5
0
Unstable *Pf* transmission
Pf free

No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI

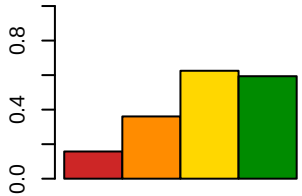
Prevalence of fever in all children



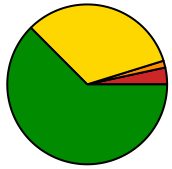
Proportion of fever types amongst febrile children



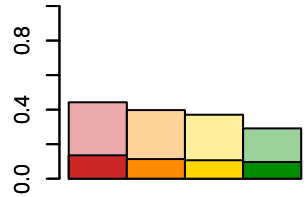
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

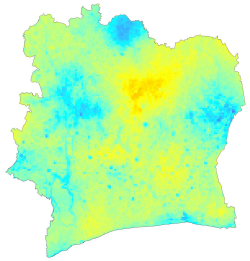


Proportion receiving antimalarial



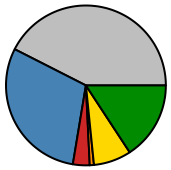
Solid=ACT
Transparent = other antimalarial

Cote d'Ivoire 2011−2012

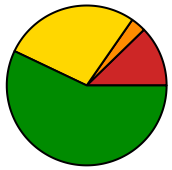


No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI

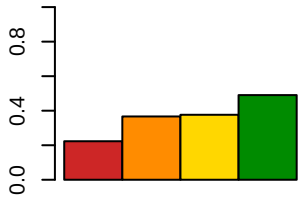
Prevalence of fever in all children



Proportion of fever types amongst febrile children



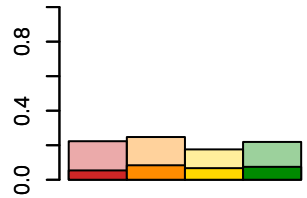
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

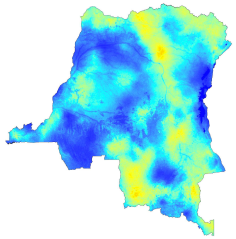


Proportion receiving antimalarial



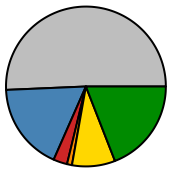
Solid=ACT
Transparent = other antimalarial

DR Congo 2013−2014



No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI

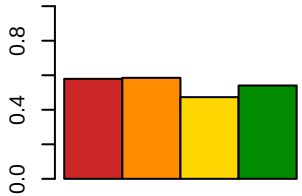
Prevalence of fever in all children



Proportion of fever types amongst febrile children



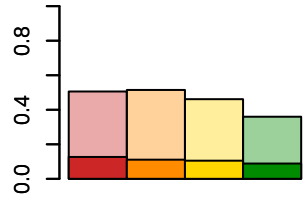
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

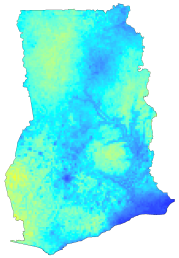


Proportion receiving antimalarial



Solid=ACT
Transparent = other antimalarial

Ghana 2014

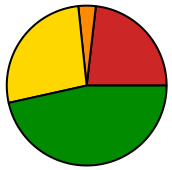


No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI

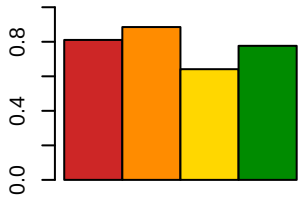
Prevalence of fever in all children



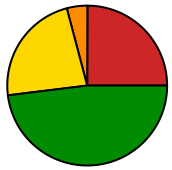
Proportion of fever types amongst febrile children



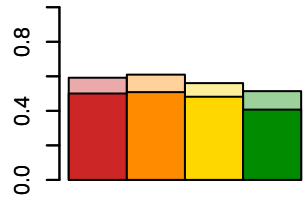
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

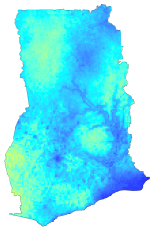


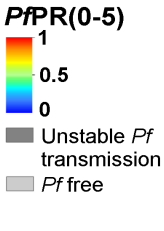
Proportion receiving antimalarial

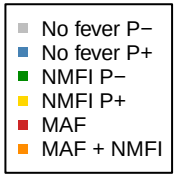


Solid=ACT
Transparent = other antimalarial

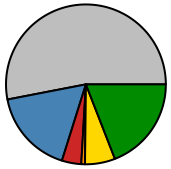
Ghana 2016



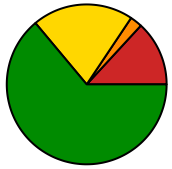




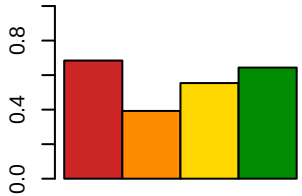
Prevalence of fever in all children



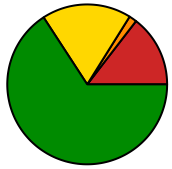
Proportion of fever types amongst febrile children



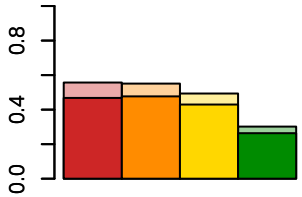
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

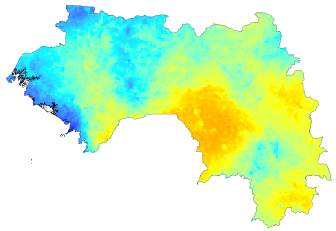


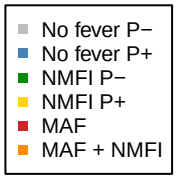
Proportion receiving antimalarial



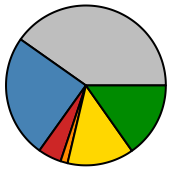
Solid=ACT
Transparent = other antimalarial

Guinea 2012

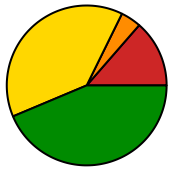




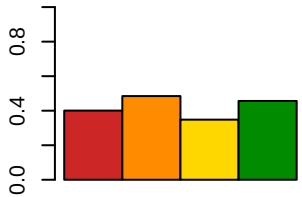
Prevalence of fever in all children



Proportion of fever types amongst febrile children



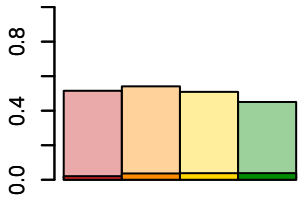
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

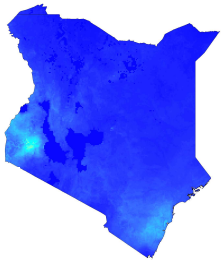


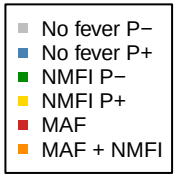
Proportion receiving antimalarial



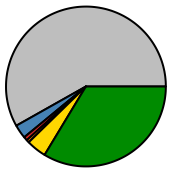
Solid=ACT
Transparent = other antimalarial

Kenya 2015

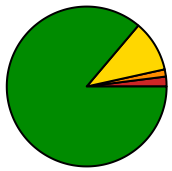




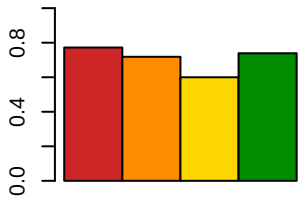
Prevalence of fever in all children



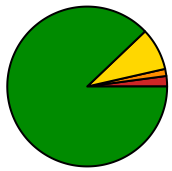
Proportion of fever types amongst febrile children



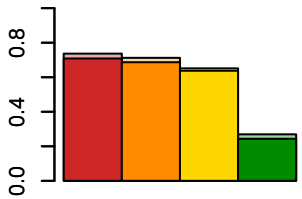
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

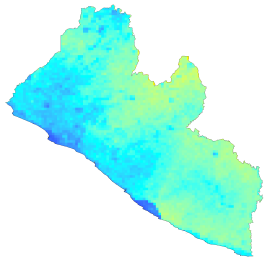


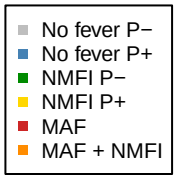
Proportion receiving antimalarial



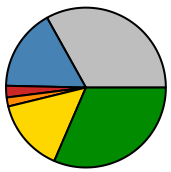
Solid=ACT
Transparent = other antimalarial

Liberia 2009

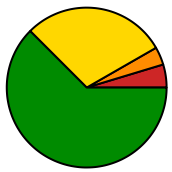




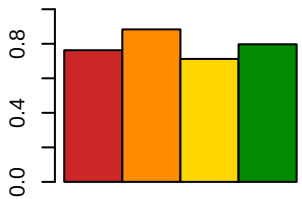
Prevalence of fever in all children



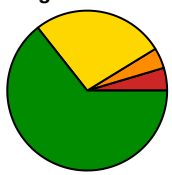
Proportion of fever types amongst febrile children



Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

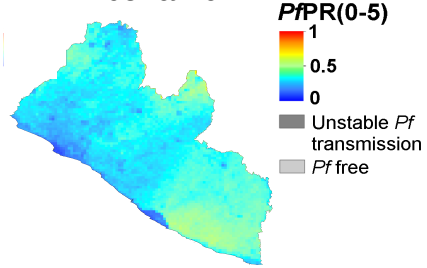


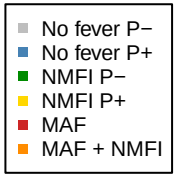
Proportion receiving antimalarial

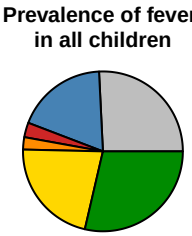


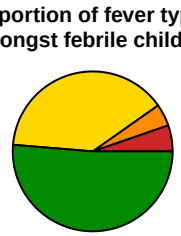
Solid=ACT
Transparent = other antimalarial

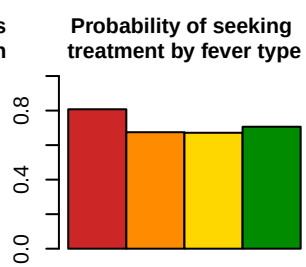
Liberia 2011

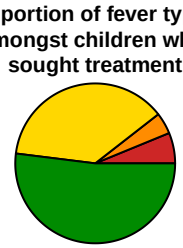


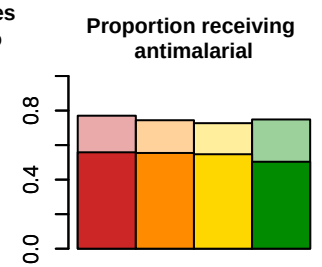






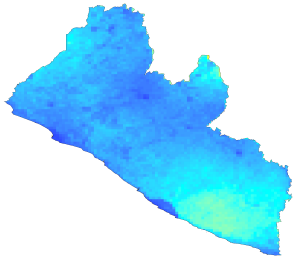


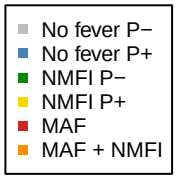


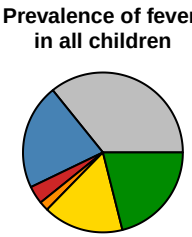


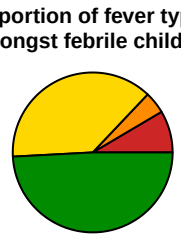
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Transparent = other antimalarial

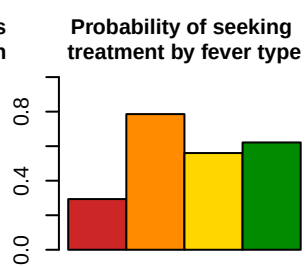
Liberia 2016

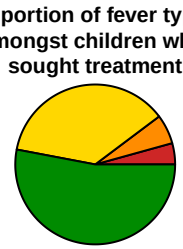


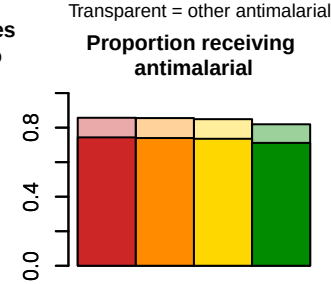








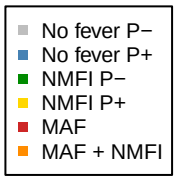


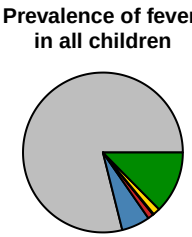


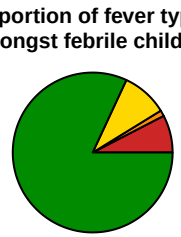
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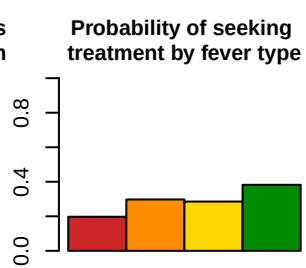
Madagascar 2011

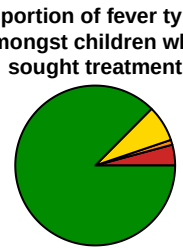


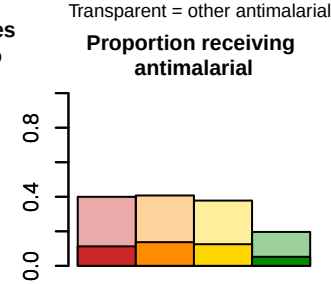








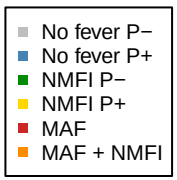


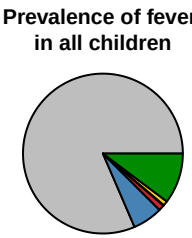


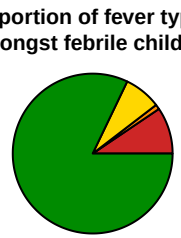
Solid=ACT
Transparent = other antimalarial

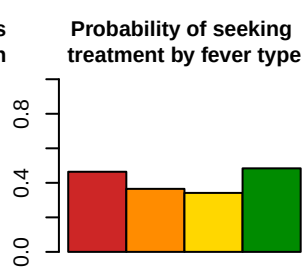
Madagascar 2013

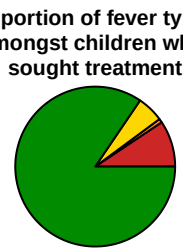


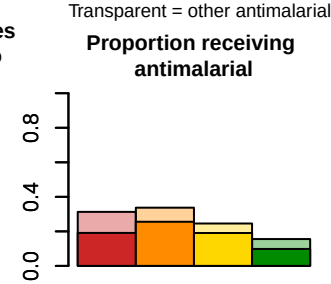




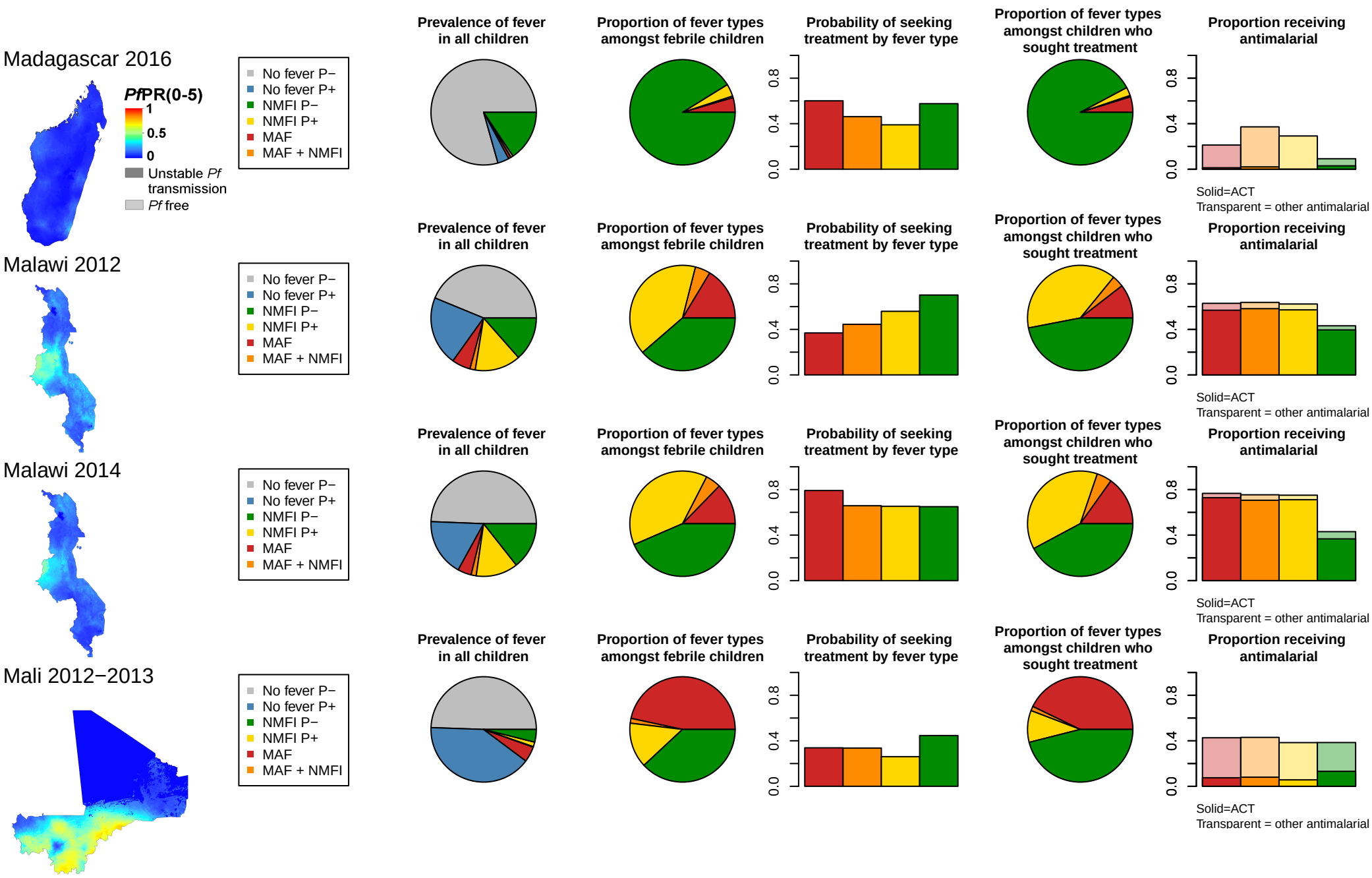




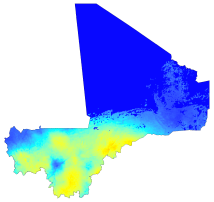


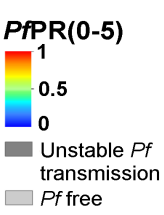


Solid=ACT
Transparent = other antimalarial


Madagascar 2016
PfPR(0-5)
1
0.5
0
Unstable Pf transmission
Pf free
Malawi 2012
Malawi 2014
Mali 2012−2013
No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI
Prevalence of fever in all children
Proportion of fever types amongst febrile children
Probability of seeking treatment by fever type
Proportion of fever types amongst children who sought treatment
Proportion receiving antimalarial
0.0
0.4
0.8
Solid=ACT
Transparent = other antimalarial

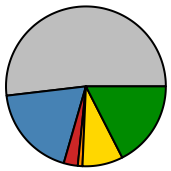
Mali 2015



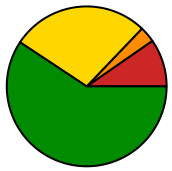


No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI

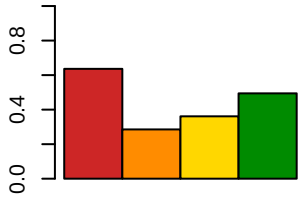
Prevalence of fever in all children



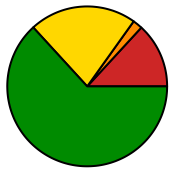
Proportion of fever types amongst febrile children



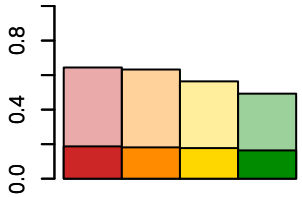
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

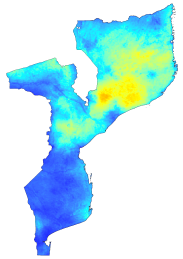


Proportion receiving antimalarial



Solid=ACT
Transparent = other antimalarial

Mozambique 2011

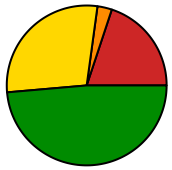


No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI

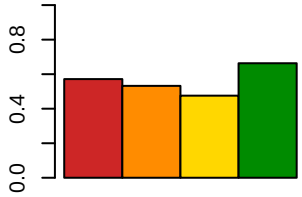
Prevalence of fever in all children



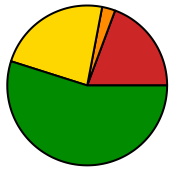
Proportion of fever types amongst febrile children



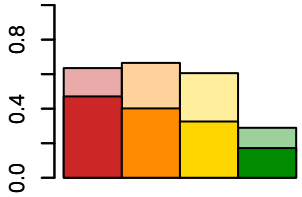
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

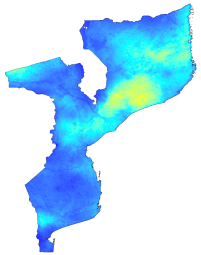


Proportion receiving antimalarial



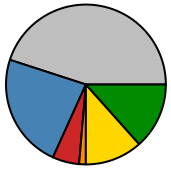
Solid=ACT
Transparent = other antimalarial

Mozambique 2015

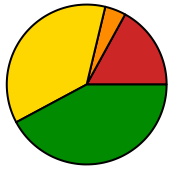


No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI

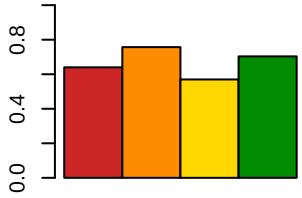
Prevalence of fever in all children



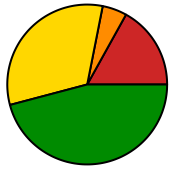
Proportion of fever types amongst febrile children



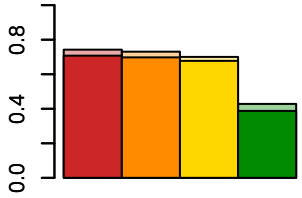
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

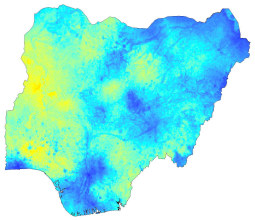


Proportion receiving antimalarial



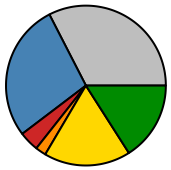
Solid=ACT
Transparent = other antimalarial

Nigeria 2010

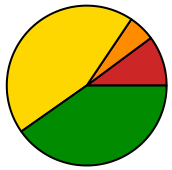


No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI

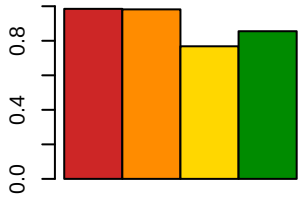
Prevalence of fever in all children



Proportion of fever types amongst febrile children



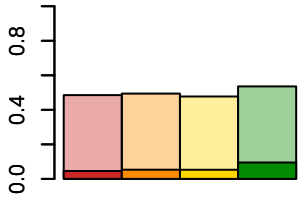
Probability of seeking treatment by fever type



Proportion of fever types amongst children who sought treatment

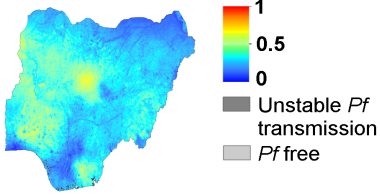


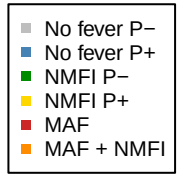
Proportion receiving antimalarial

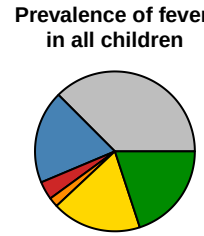


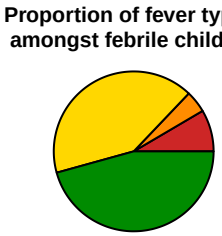
Solid=ACT
Transparent = other antimalarial

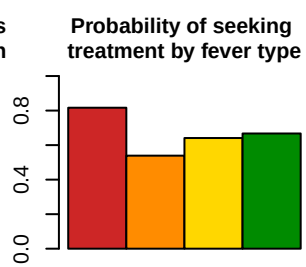
Nigeria 2015

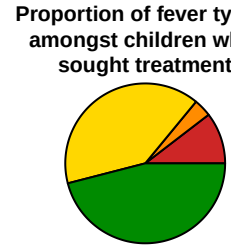


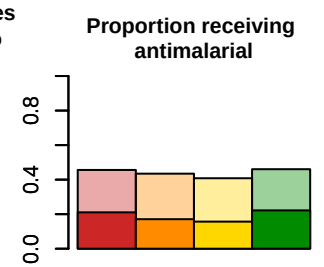






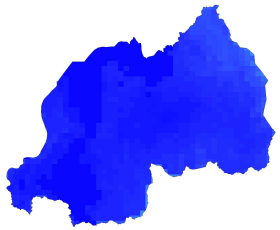


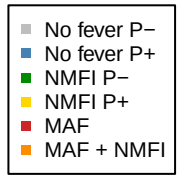


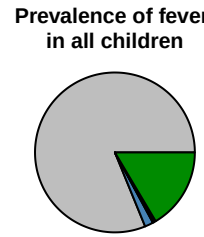


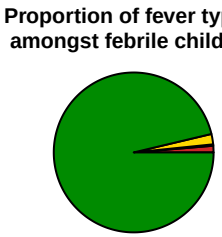
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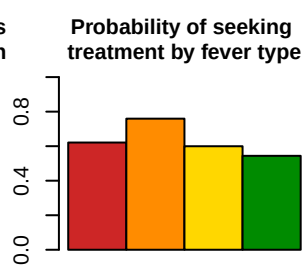
Rwanda 2010

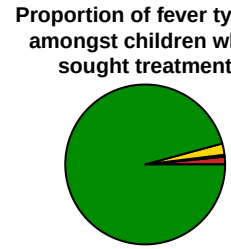


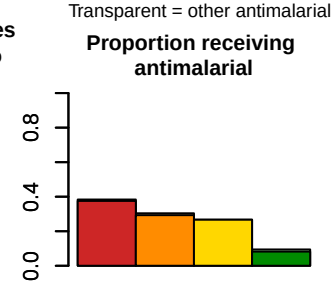






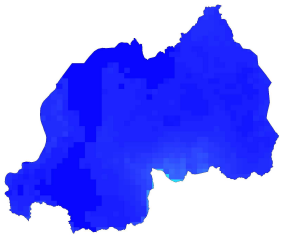


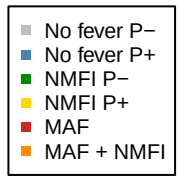


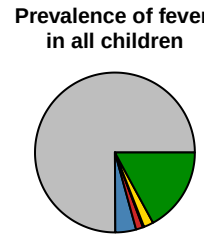


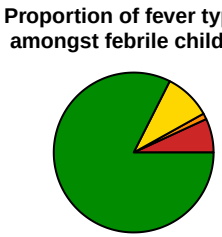
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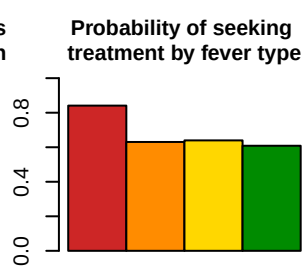
Rwanda 2014−2015

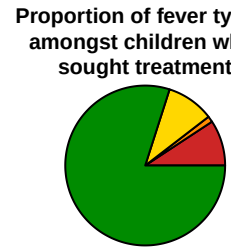


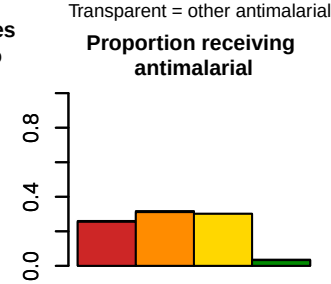






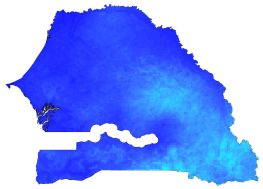


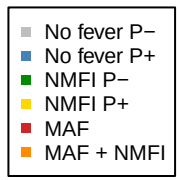


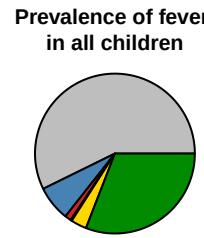


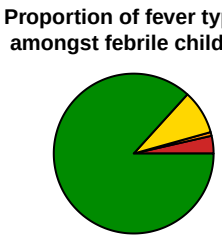
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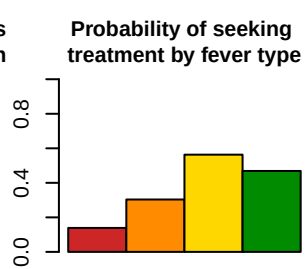
Senegal 2008−2009

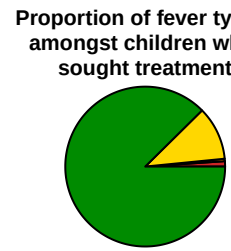


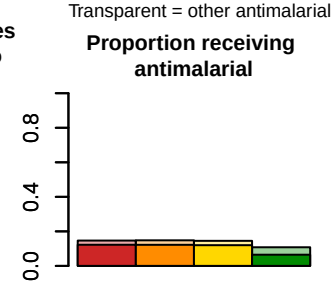




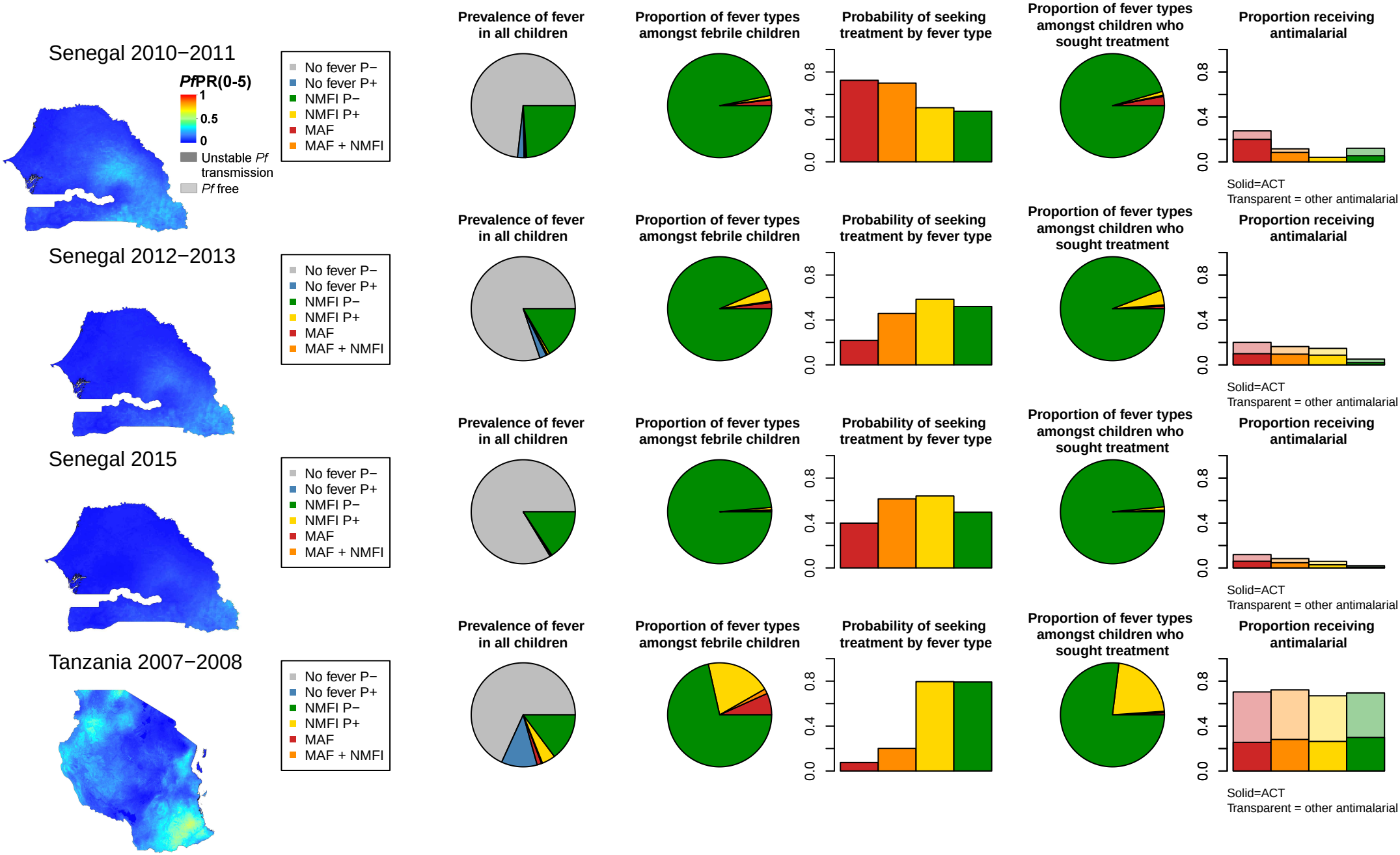




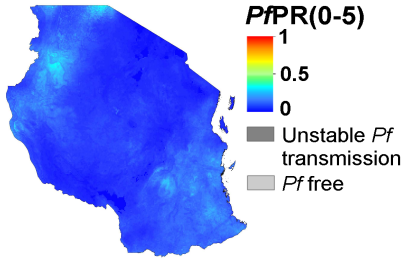


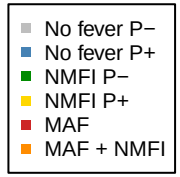


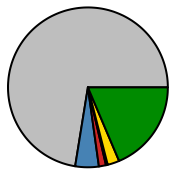
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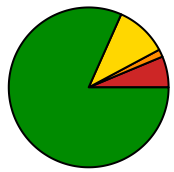

Senegal 2010−2011
PfPR(0-5)
1
0.5
0
Unstable Pf transmission
Pf free
No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI
Prevalence of fever in all children
Proportion of fever types amongst febrile children
Probability of seeking treatment by fever type
Proportion of fever types amongst children who sought treatment
Proportion receiving antimalarial
0.0
0.4
0.8
Solid=ACT
Transparent = other antimalarial
Senegal 2012−2013
Senegal 2015
Tanzania 2007−2008

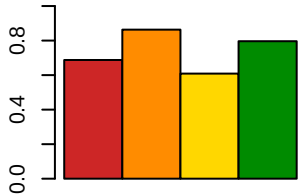
Tanzania 2011−2012

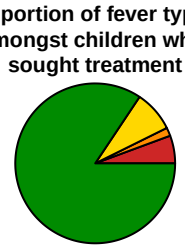


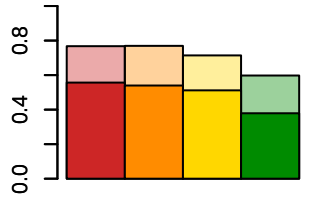






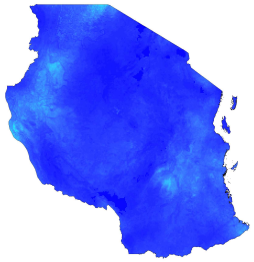


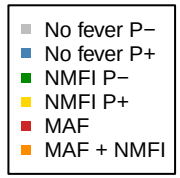


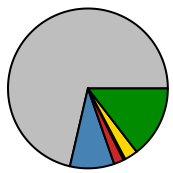


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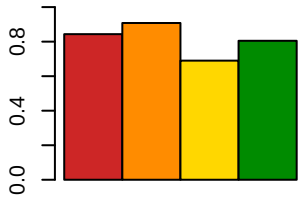
Tanzania 2015−2016

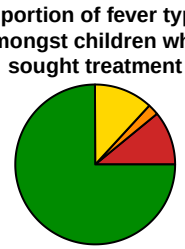


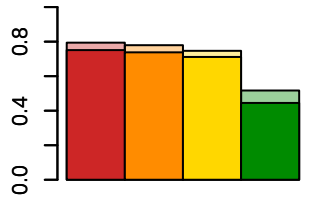






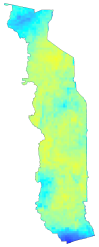


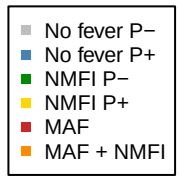


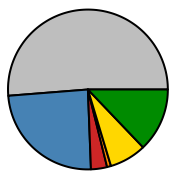


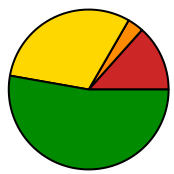
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Transparent = other antimalarial

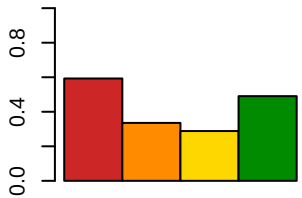
Togo 2013−2014

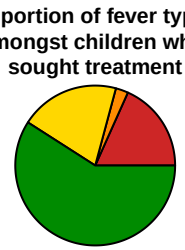


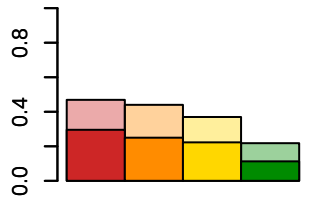






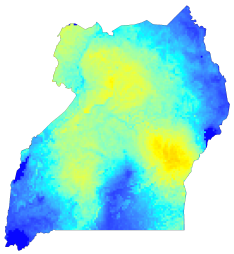


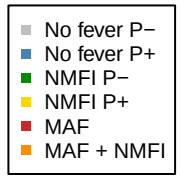




Solid=ACT
Transparent = other antimalarial

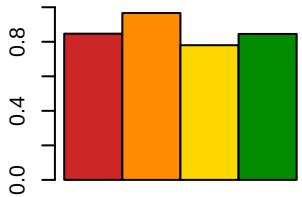
Uganda 2009

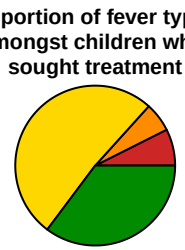


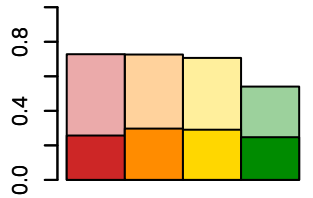












Solid=ACT
Transparent = other antimalarial

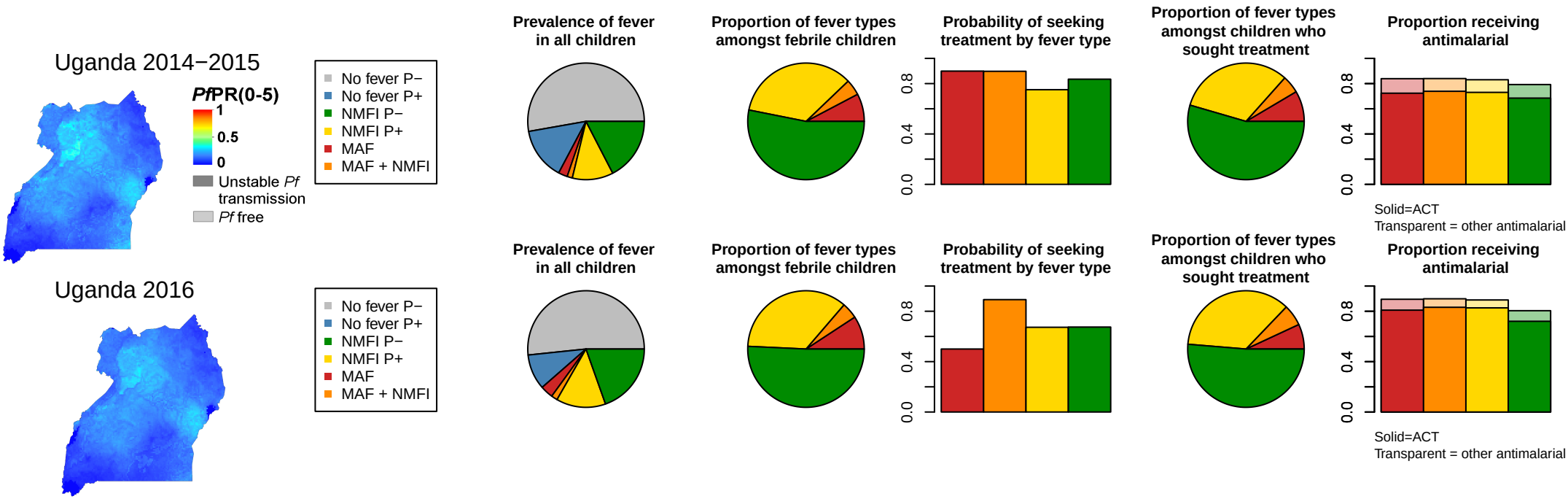

Uganda 2014−2015
PfPR(0-5)
1
0.5
0
Unstable Pf transmission
Pf free
No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI
Prevalence of fever in all children
Proportion of fever types amongst febrile children
Probability of seeking treatment by fever type
Proportion of fever types amongst children who sought treatment
Proportion receiving antimalarial
0.0
0.4
0.8
Solid=ACT
Transparent = other antimalarial
Uganda 2016
No fever P−
No fever P+
NMFI P−
NMFI P+
MAF
MAF + NMFI
Prevalence of fever in all children
Proportion of fever types amongst febrile children
Probability of seeking treatment by fever type
Proportion of fever types amongst children who sought treatment
Proportion receiving antimalarial
0.0
0.4
0.8
Solid=ACT
Transparent = other antimalarial

Figure 5.2. For each survey, six panels are presented from left to right. First panel: the contemporaneous country *Pf*$PR_{0\text{-}5}$ [1, 60] (for 2016 surveys, the 2015 *P. falciparum* prevalence is shown). Second panel: prevalence of each fever type in all children in the two weeks preceding each survey. Third panel: proportion of each fever type amongst febrile children. Fourth panel: the probability of each fever type seeking treatment from a formal provider (public or private) in the two weeks preceding each survey. Fifth panel: the proportion of fever types amongst children who sought treatment at a formal provider in the two weeks preceding each survey. Sixth panel: the proportion of children within each fever type who received antimalarials at the formal provider, segregated into any antimalarial (transparent bars), and overlain with the proportion of children who received an ACT (opaque bars). The first row shows the results for all surveyed country-years; these are population-weighted proportions of all metrics, valid for the two weeks preceding each household survey.
The six categories of febrile illness/malaria infection status for children under 5 were as follows: *i)* no fever without a *P. falciparum* infection (No fever P-; grey), *ii)* no fever and an asymptomatic *P. falciparum* infection (No fever P+; blue), *iii)* a non-malarial febrile illness without a malaria infection (NMFI P-; green), *iv)* a non-malarial febrile illness with a *P. falciparum* infection (NMFI P+; yellow), *v)* malaria-attributable fever (MAF; red), and *vi)* co-symptomatic malaria-attributable fever and non-malarial febrile illness (MAF + NMFI; orange). Malaria positivity is derived through RDT outcomes; *P. falciparum* infections sub-patent for RDT would be considered malaria-negative.

The probability of receiving an antimalarial of any kind amongst children with a fever who sought treatment was weakly correlated with national-level *Pf*$PR_{0\text{-}5}$. Children with fever who sought treatment who were living in countries with higher national malaria prevalence were more likely to be prescribed antimalarials of any kind, particularly amongst individuals with a fever without a patent *P. falciparum* infection (r= 0.33 for

MAF, r = 0.55 for NMFI without a *P. falciparum* infection). Conversely, probability of receiving an ACT, specifically, was not positively correlated with *Pf*PR_{0-5} (r = -0.18 for MAF, r = 0.01 for NMFI without a *P. falciparum* infection). The heterogeneity between countries in the rate of antimalarial and ACT prescription amongst fever types presenting at formal public and private clinics can be found in the final panel of Figure 5.2.

Table 5.3. Population-weighted probabilities across all 41 surveyed country-years of receiving an antimalarial (of any type) and of receiving an ACT, amongst febrile children who sought treatment at a formal clinic (public or private) in the two weeks preceding each survey. Estimates were stratified by probability of receiving an antimalarial/ACT amongst febrile children with each of the four fever types: MAF, co-symptomatic MAF and NMFI, NMFI with an asymptomatic RDT-patent *P. falciparum* infection, and NMFI without an RDT-patent *P. falciparum* infection. Probabilities are given as percentages with associated 95% credible intervals in brackets.

		Amongst children who sought treatment	
		% Probability of receiving an antimalarial (of any type)	**% Probability of receiving an ACT**
Fever type	**MAF**	55.1 (53.3-57.0)	31.1 (29.8-32.4)
	Co-symptomatic MAF and NMFI	54.7 (53.3-56.4)	30.4 (29.4-31.6)
	NMFI with asymptomatic *P. falciparum*	51.0 (50.3-51.7)	28.7 (28.2-29.1)
	NMFI without *P. falciparum* infection	44.2 (44.0-44.4)	23.4 (23.2-23.5)

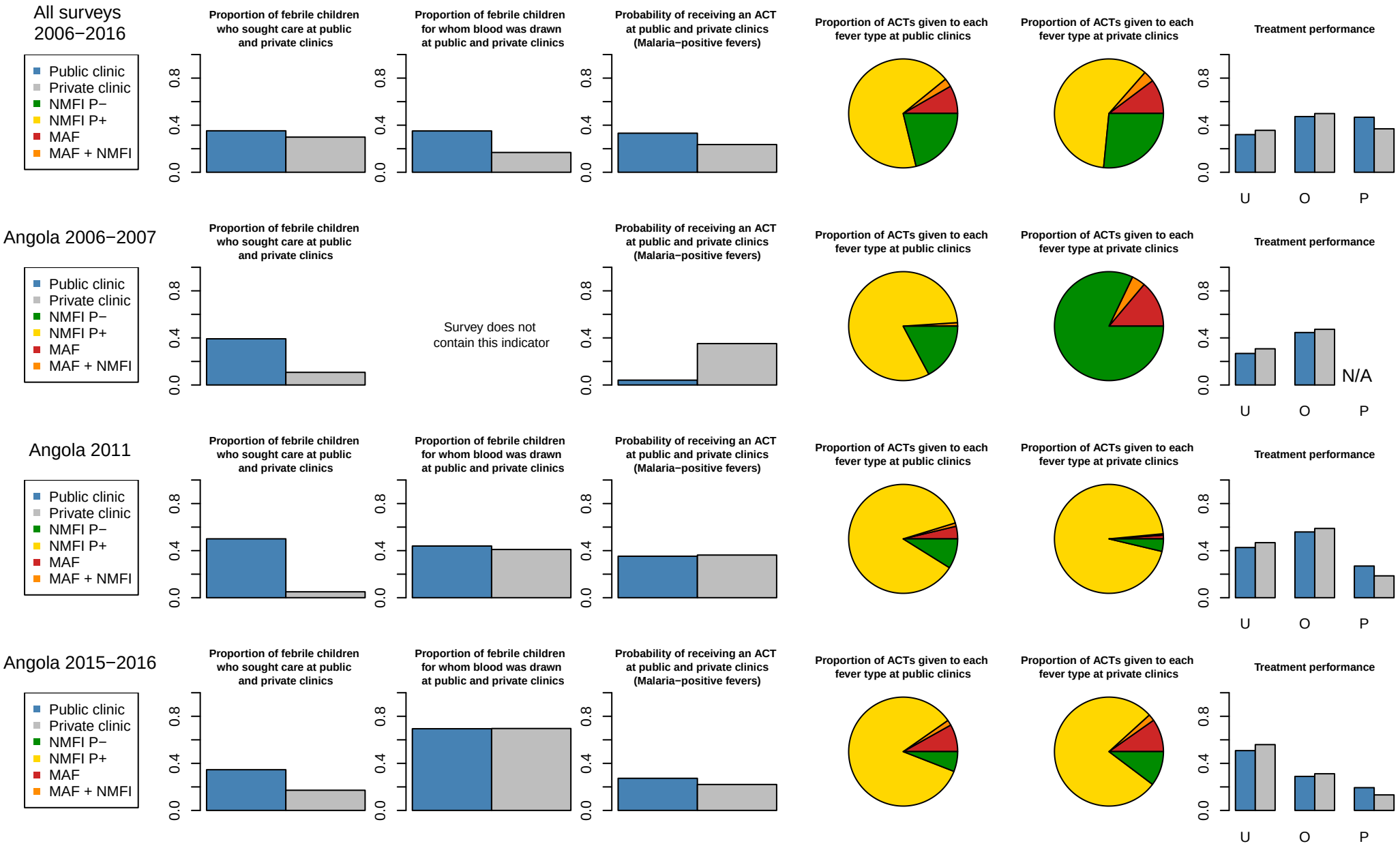
5.5.2. Performance of public and private health centres

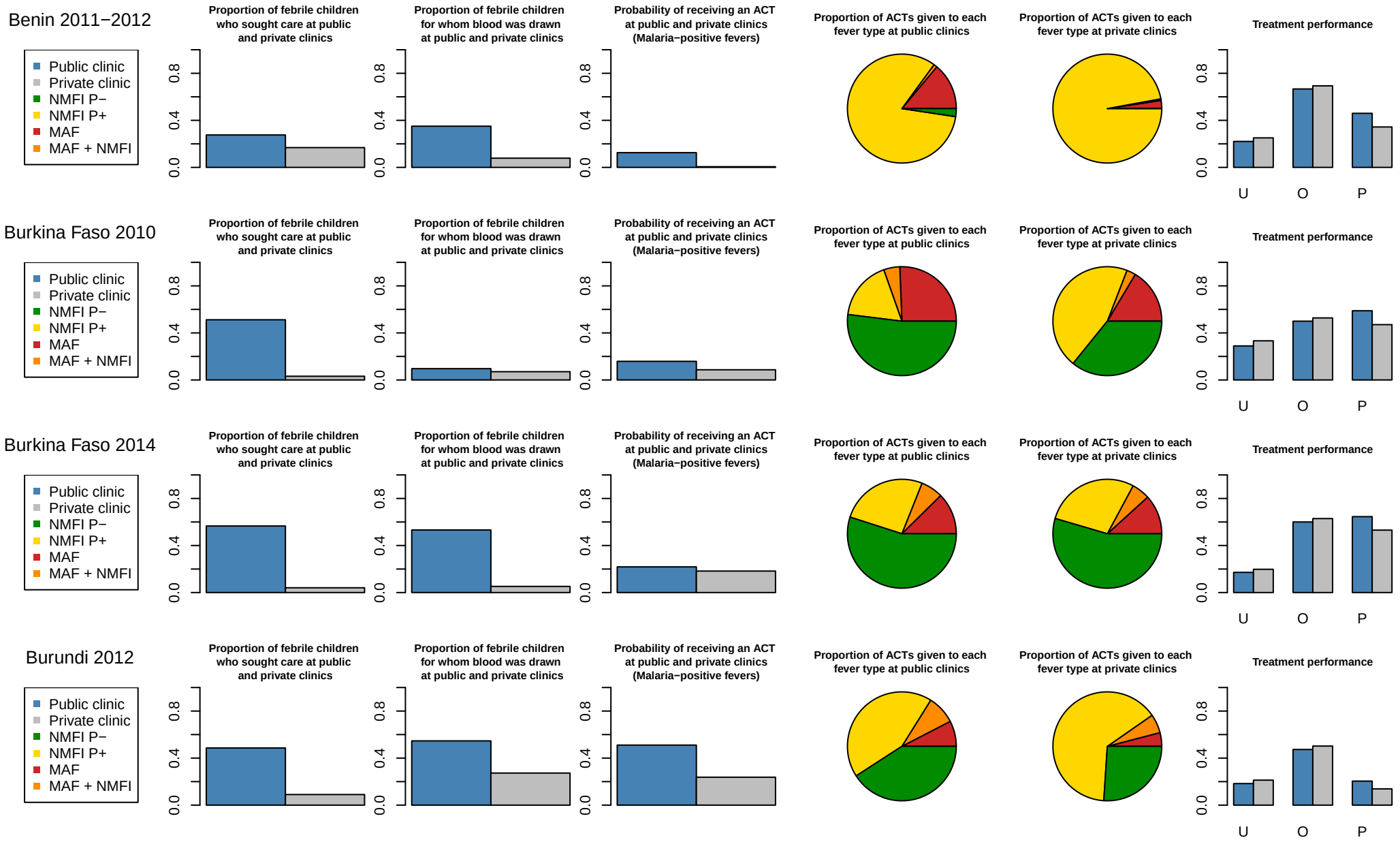
Figure 5.3 shows the differential performance of public and private health centres across all surveys at adhering to diagnosis and treatment guidelines for febrile children. Caregivers of febrile children preferentially sought treatment at public clinics across all surveys, with 35.2% of febrile children seeking treatment at a public clinic, and 29.9% of children seeking treatment at a private clinic (population-weighted estimate). Most surveyed countries showed a preference for public clinics, with the exception of Cameroon 2011, Liberia 2009, Nigeria 2010 and 2015, Tanzania 2015-2016, and Uganda 2009 and 2015-2015 (Figure 5.3, first panel).

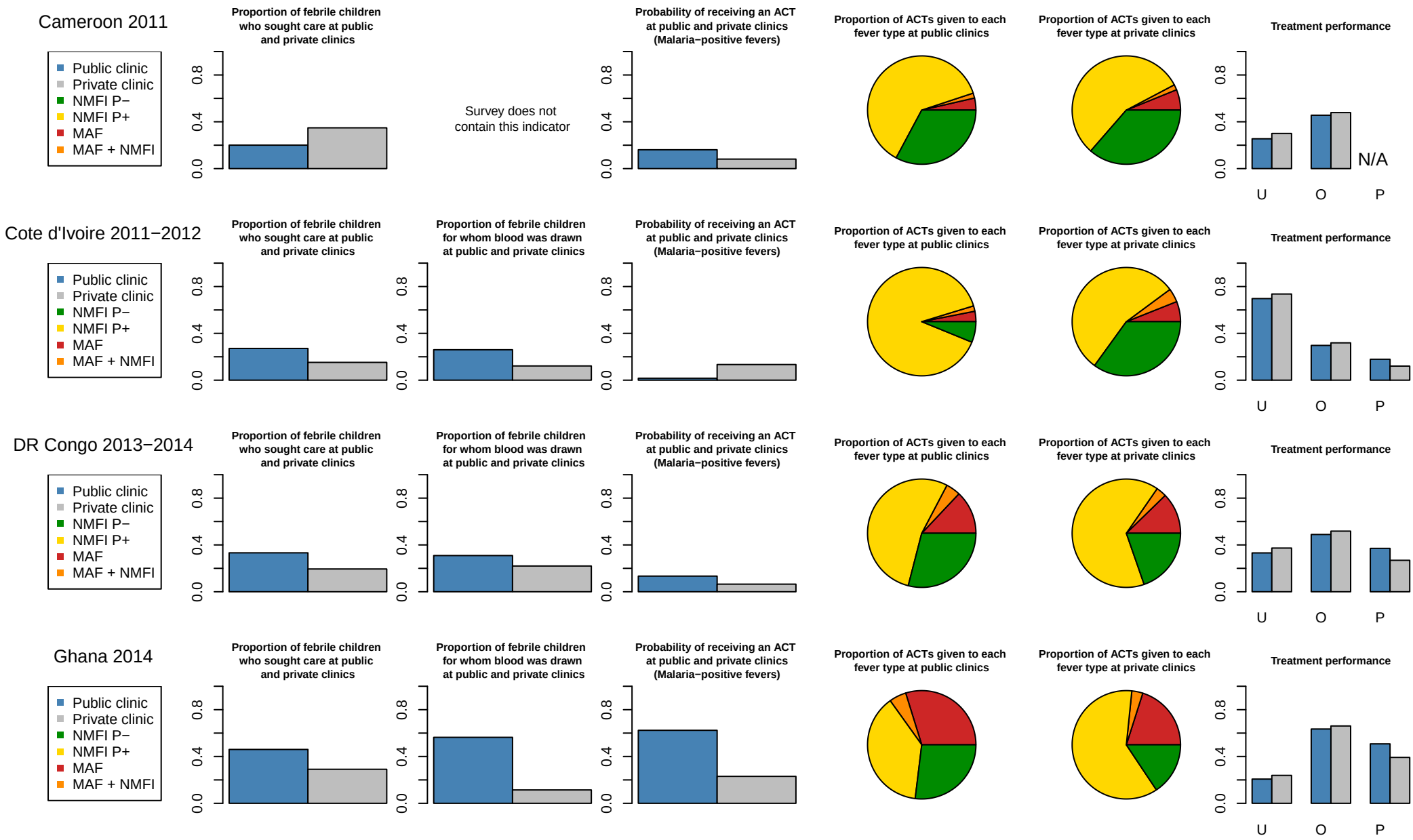
IMCI protocols direct that a parasite-based diagnosis of malaria via RDT or microscopy should be made before prescription of an antimalarial [67]. To do this, the clinician must take a blood sample from the child. The DHS Program datasets do not provide an indicator of RDT or microscopy usage at the point of care, but do ask the caregiver whether blood was drawn using a finger- or heel-prick. In this analysis, the result of this indicator is used as a proxy for diagnostic usage at the point of care. Public clinics were more likely to draw blood from a febrile child at the point of care (35.1% of febrile children, population-weighted estimate) compared to private clinics (16.8%, population-weighted estimate; Figure 5.3, second panel). Surveys conducted later in the study period had a higher proportion of febrile children receiving a blood draw than earlier surveys (r= 0.67 for public clinics, r= 0.35 for private clinics). Malaria-positive fevers were more likely to receive an ACT at public clinics than private clinics (Figure 5.3, third panel), with a 33.2% and 23.5% probability, respectively. This differed by country-year, but in many surveys (particularly those with few malaria-positive individuals) the total number of malaria-positive individuals receiving an ACT was very

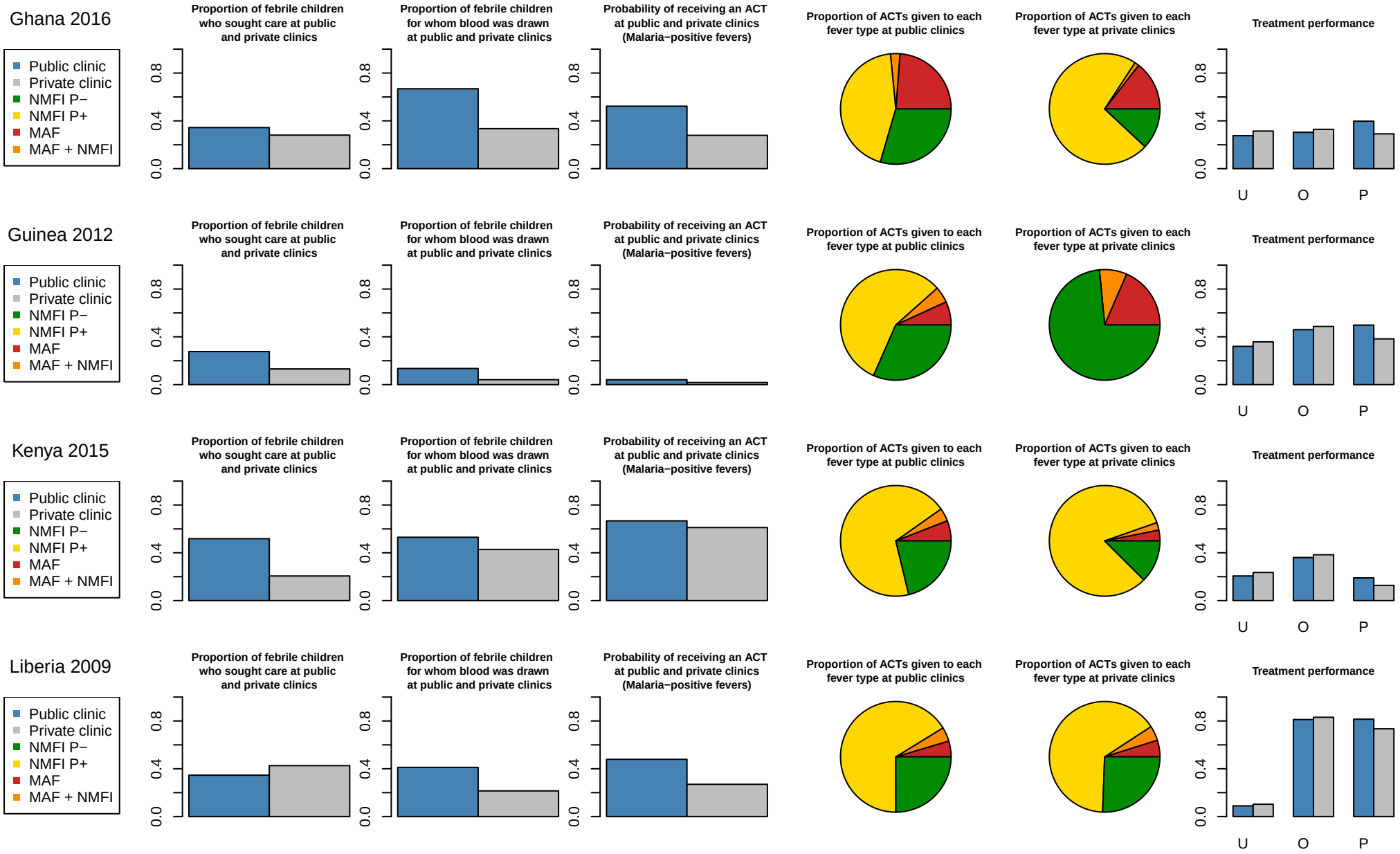
low (Table 5.2). Amongst febrile individuals who received an ACT, the fraction of ACTs given to febrile children without a *P. falciparum* infection was slightly higher at private clinics compared to public clinics (Figure 5.3, fourth and fifth panels). Approximately one-third of febrile malaria-infected children that presented at the clinic did not receive an antimalarial of any kind (i.e. under-treatment) at both public and private clinics, but public clinics were slightly less likely to under-treat malaria infections than private clinics. Almost half of malaria-negative children with NMFI received antimalarials (of any kind) in both public and private clinics (i.e. over-treatment), but public clinics were slightly less likely to over-treat than private clinics. Public clinics were, however, more likely to presumptively treat febrile children for malaria (i.e. prescribe antimalarials without drawing blood for malaria diagnosis) than private clinics, despite a higher level of diagnostic testing at public clinics. 46.7% and 36.9% of febrile individuals were given antimalarials (of any kind) without a diagnostic test at public and private clinics, respectively. The rates of under-treatment, over-treatment and presumptive treatment for each survey are shown in the final panel of Figure 5.3.

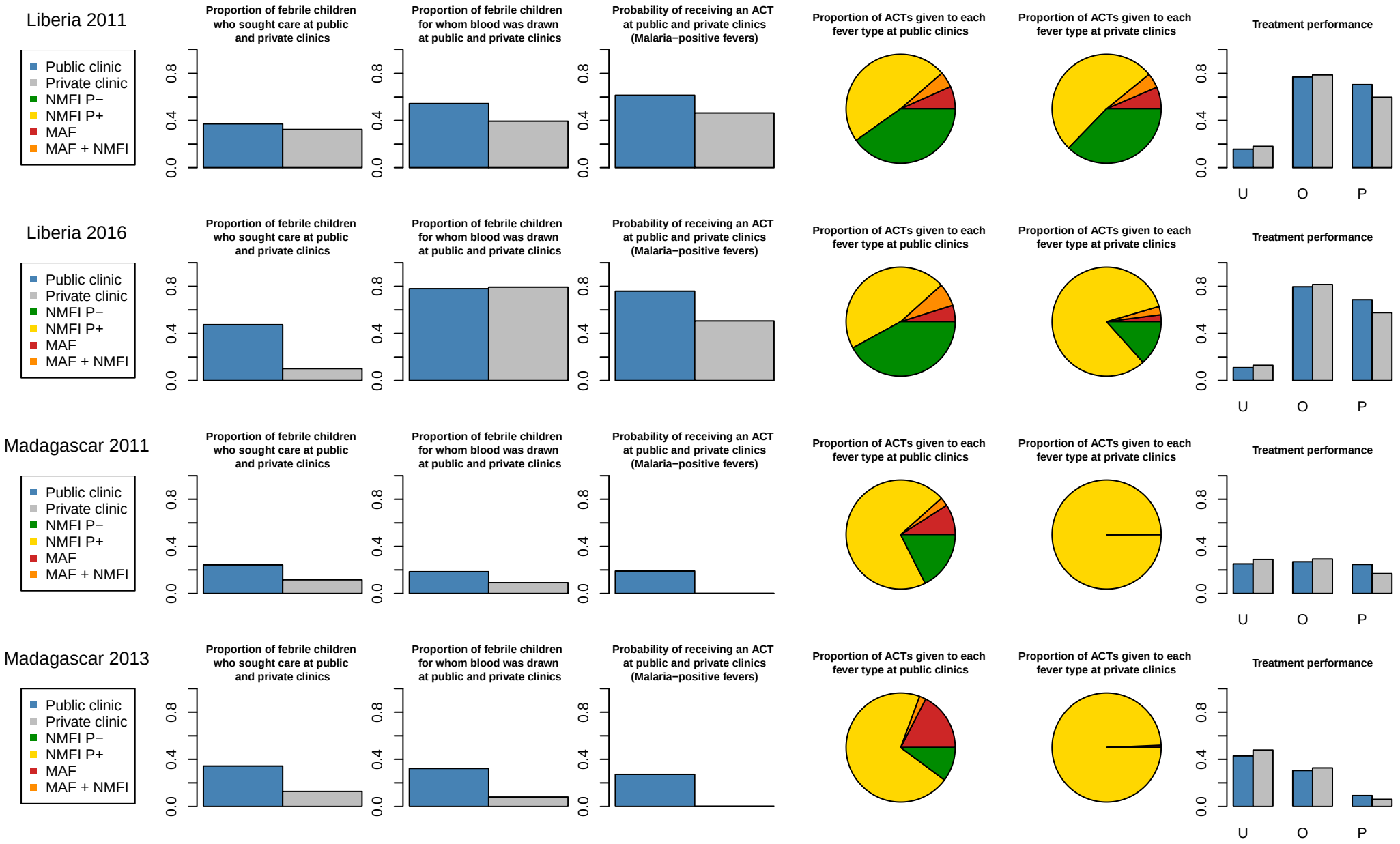
Figure 5.3.

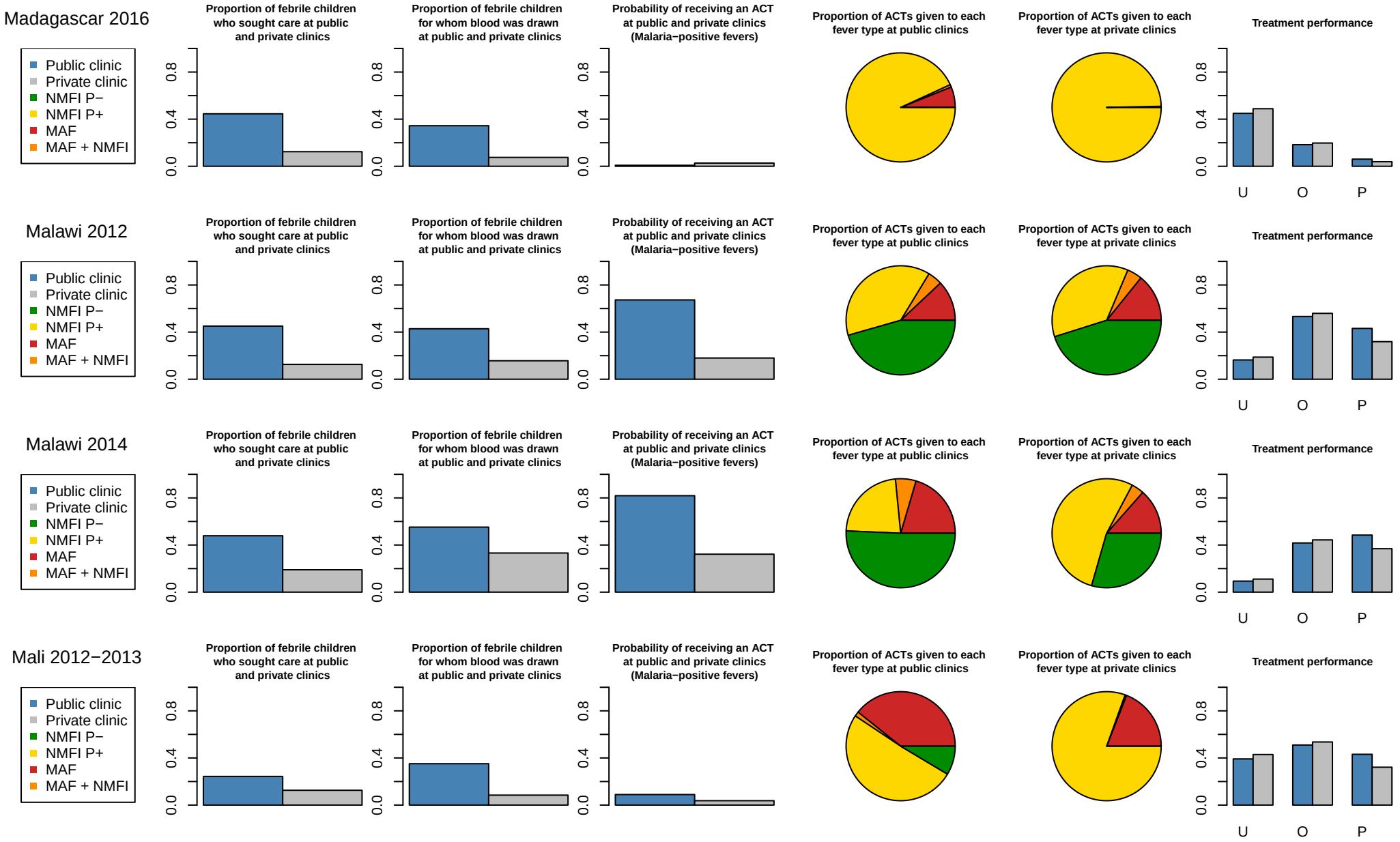

All surveys 2006−2016
Angola 2006−2007
Angola 2011
Angola 2015−2016
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Survey does not contain this indicator
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P
N/A

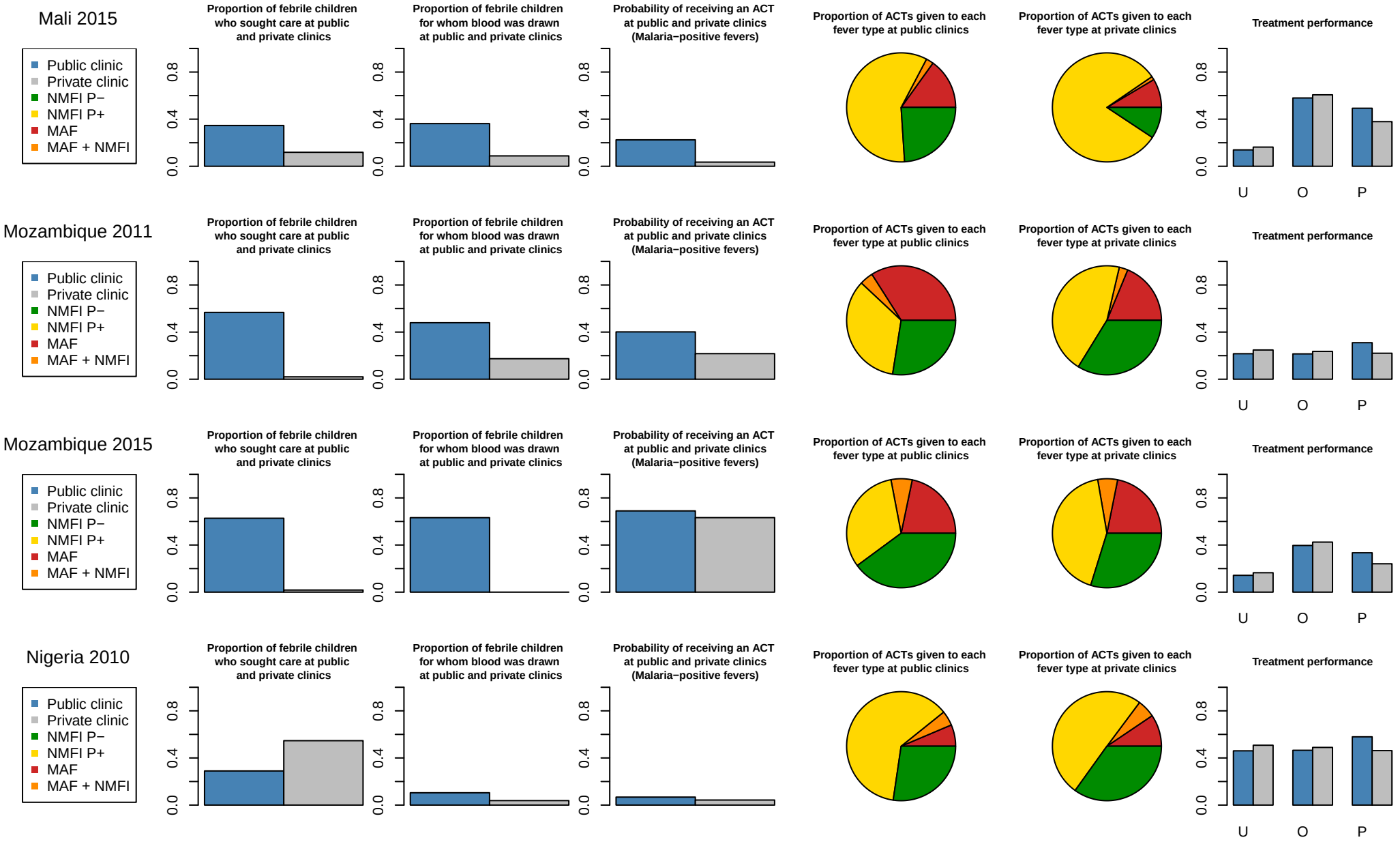

Benin 2011−2012
Burkina Faso 2010
Burkina Faso 2014
Burundi 2012
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P

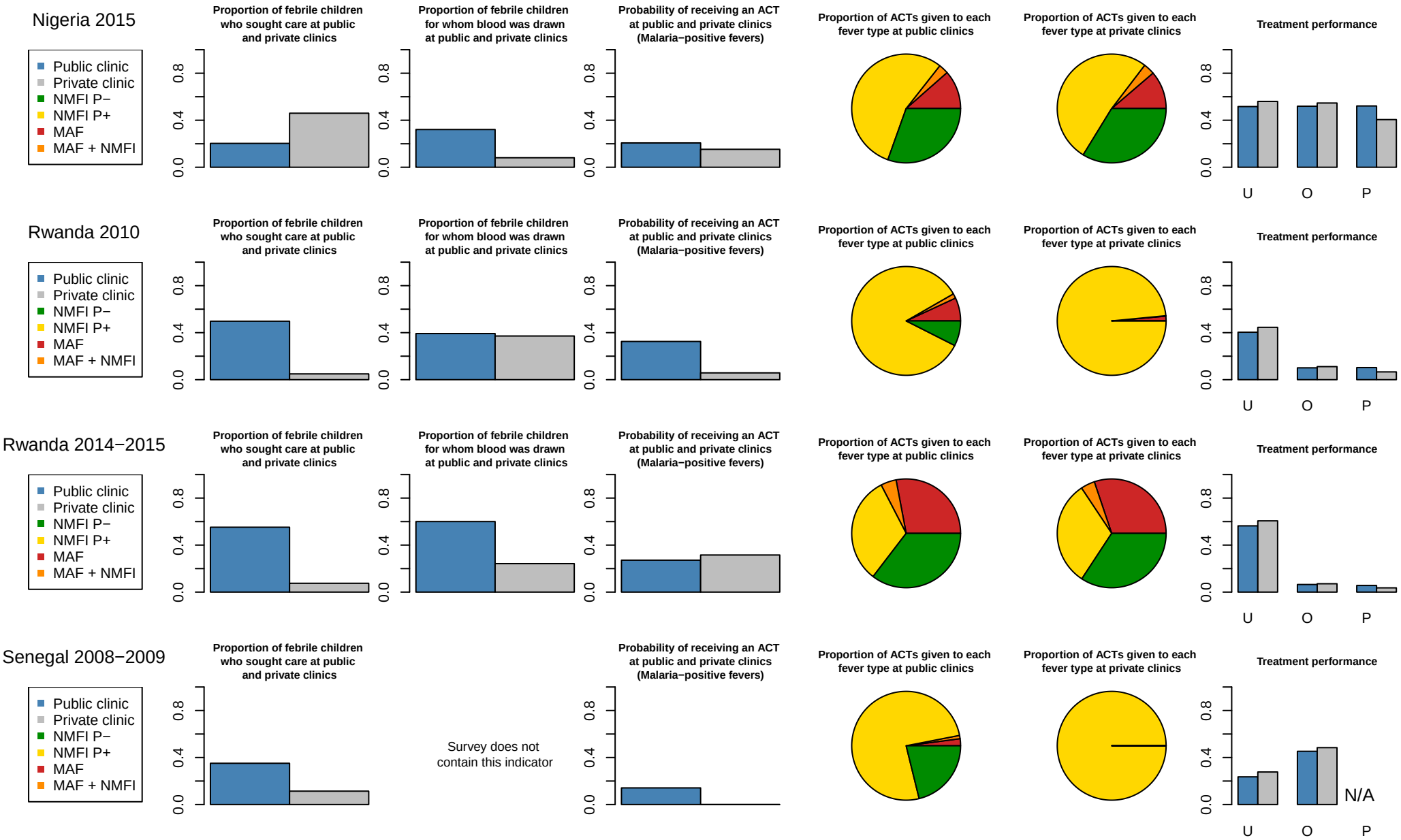

Cameroon 2011
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Survey does not contain this indicator
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
N/A
U
O
P
Cote d'Ivoire 2011−2012
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
DR Congo 2013−2014
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
Ghana 2014
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P

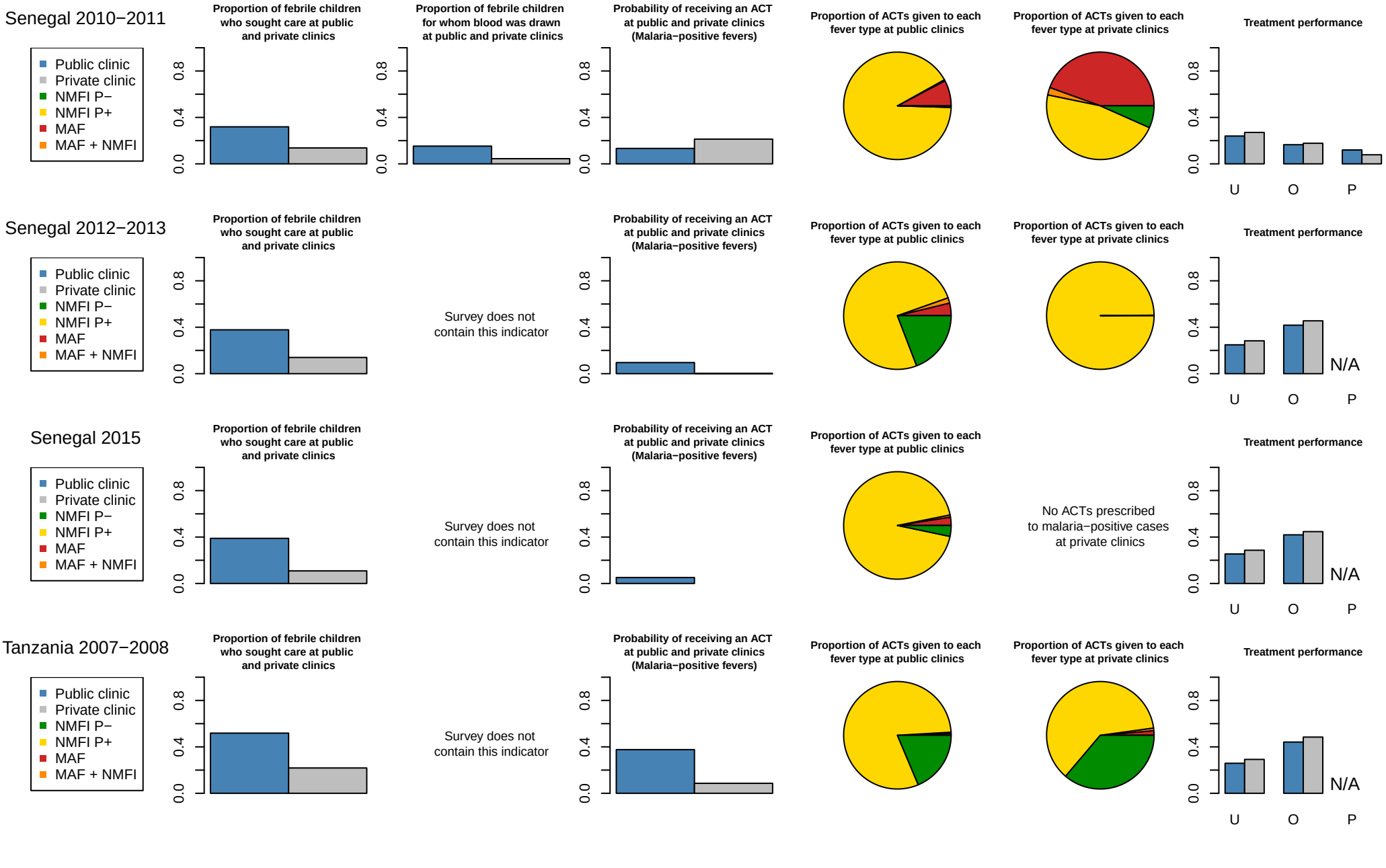

Ghana 2016
Guinea 2012
Kenya 2015
Liberia 2009
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P

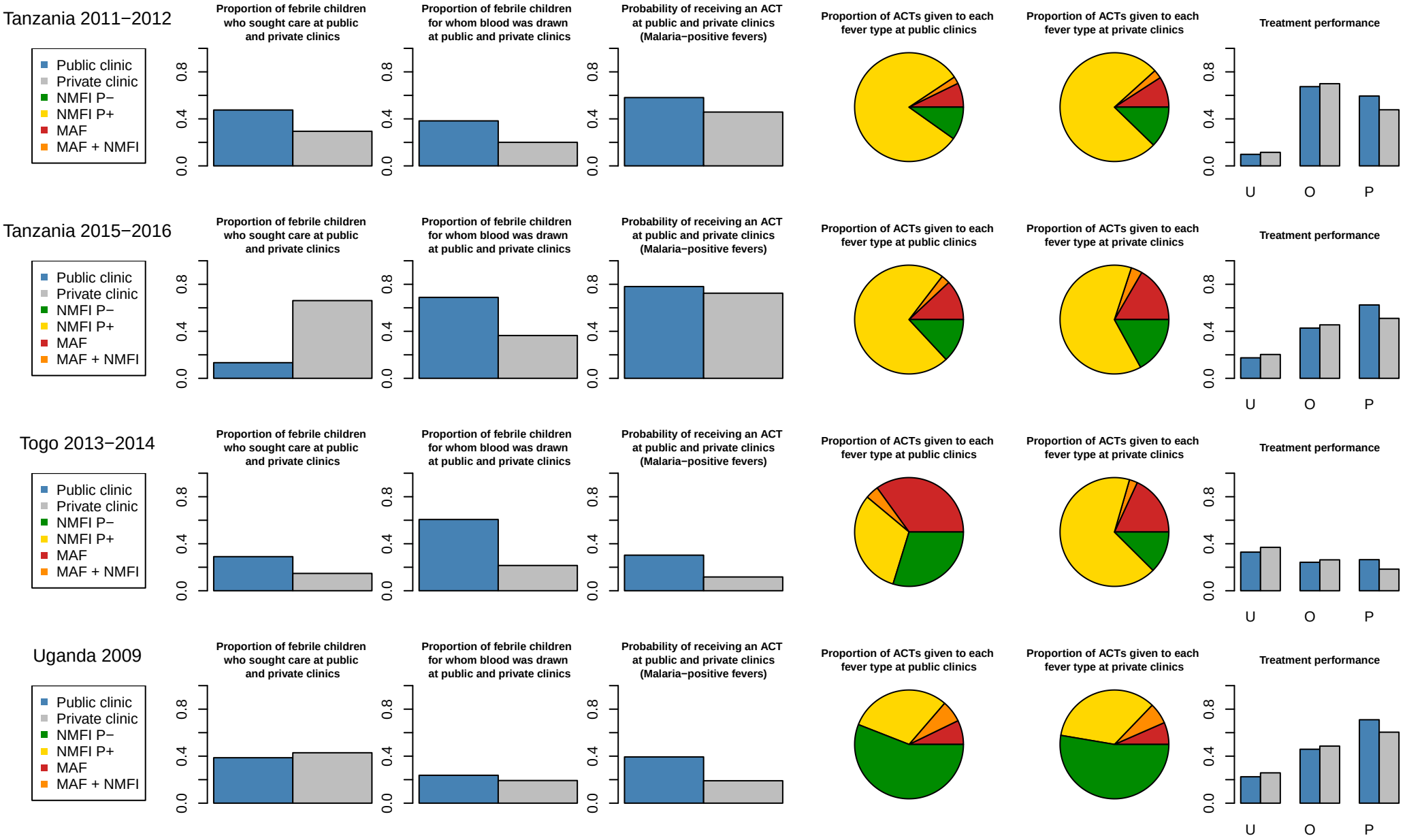

Liberia 2011
Liberia 2016
Madagascar 2011
Madagascar 2013
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P


Madagascar 2016
Malawi 2012
Malawi 2014
Mali 2012−2013
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P


Mali 2015
Mozambique 2011
Mozambique 2015
Nigeria 2010
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P


Nigeria 2015
Rwanda 2010
Rwanda 2014−2015
Senegal 2008−2009
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P
Survey does not contain this indicator
N/A


Senegal 2010−2011
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P
Senegal 2012−2013
Survey does not contain this indicator
N/A
Senegal 2015
No ACTs prescribed to malaria−positive cases at private clinics
Tanzania 2007−2008


Tanzania 2011−2012
Tanzania 2015−2016
Togo 2013−2014
Uganda 2009
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P

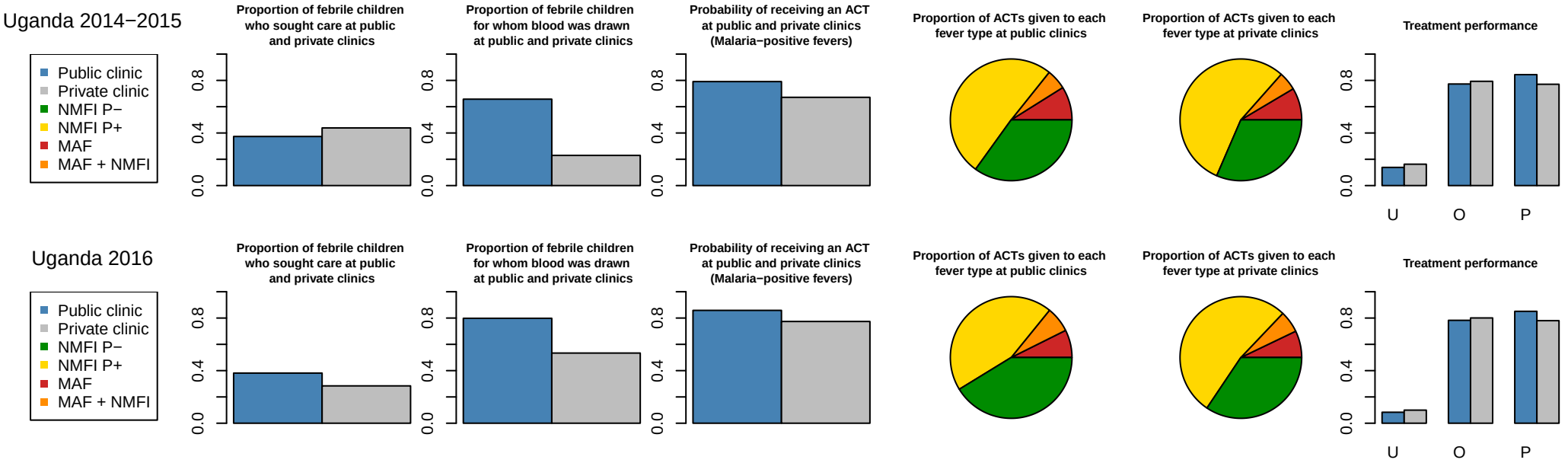

Uganda 2014−2015
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P
Uganda 2016
Public clinic
Private clinic
NMFI P−
NMFI P+
MAF
MAF + NMFI
Proportion of febrile children who sought care at public and private clinics
Proportion of febrile children for whom blood was drawn at public and private clinics
Probability of receiving an ACT at public and private clinics (Malaria−positive fevers)
Proportion of ACTs given to each fever type at public clinics
Proportion of ACTs given to each fever type at private clinics
Treatment performance
0.0
0.4
0.8
U
O
P

Figure 5.3. Comparison of utilisation and performance of public and private clinics for treatment of febrile children under 5 years of age across all 41 surveys in sub-Saharan Africa, 2006-2016. For each survey, six panels are shown, from left to right. First panel: amongst febrile children who sought treatment, the proportion who sought treatment at formal public clinics (blue) vs formal private clinics (grey). Second panel: the proportion of febrile children who received a blood draw via a heel- or finger-prick (used as a proxy for malaria diagnostic testing) at public (blue) and private (grey) clinics. Third panel: the proportion of malaria-positive fevers at public (blue) and private (grey) clinics that received an ACT. Fourth and fifth panel: the proportion of all prescribed ACTs that were given to each of the four fever types (malaria-attributable fever (red), non-malarial fever with an asymptomatic *P. falciparum* infection (yellow), non-malarial fever without a *P. falciparum* infection (green), and co-symptomatic malaria-attributable fever and non-malarial febrile illness (orange)) in public (fourth panel) and private (fifth panel) clinics. Sixth panel: the proportion of under-treatment ("U"; malaria infections that were not treated), over-treatment ("O"; fevers without a malaria infection that received antimalarial medication) and presumptive treatment ("P"; fevers that received antimalarial medication without blood being drawn at the point of care) for formal public (blue) and private (grey) clinics. "Treatment" is defined as receiving an antimalarial of any kind. The first row shows the results for all surveyed country-years; these are population-weighted proportions of all metrics, valid for the two weeks preceding each household survey.

5.5.3. Effect of individual factors on febrile illness and treatment outcomes

The effect of household wealth, maternal education levels, and age of child was investigated on four metrics: *i)* the probability of seeking treatment for a fever in the two weeks preceding the household survey, *ii)* the probability of experiencing NMFI in the two weeks preceding the household survey, *iii)* the probability of being RDT-

positive at the time of interview, and *iv)* the probability of receiving an ACT for MAF at the point of treatment.

Figure 5.4 shows the effects of household wealth, maternal education levels, and age of child on the metrics described above. The top row shows the effect of household wealth, maternal education levels, and age of child on the relative probability of seeking treatment for a fever of any underlying cause in the two weeks preceding the household survey. Caregivers in richer households were more likely to seek treatment for febrile children. Younger febrile children were more likely to be taken for treatment than older children. Maternal education did not have a strong effect on the probability of a febrile child being taken for treatment.

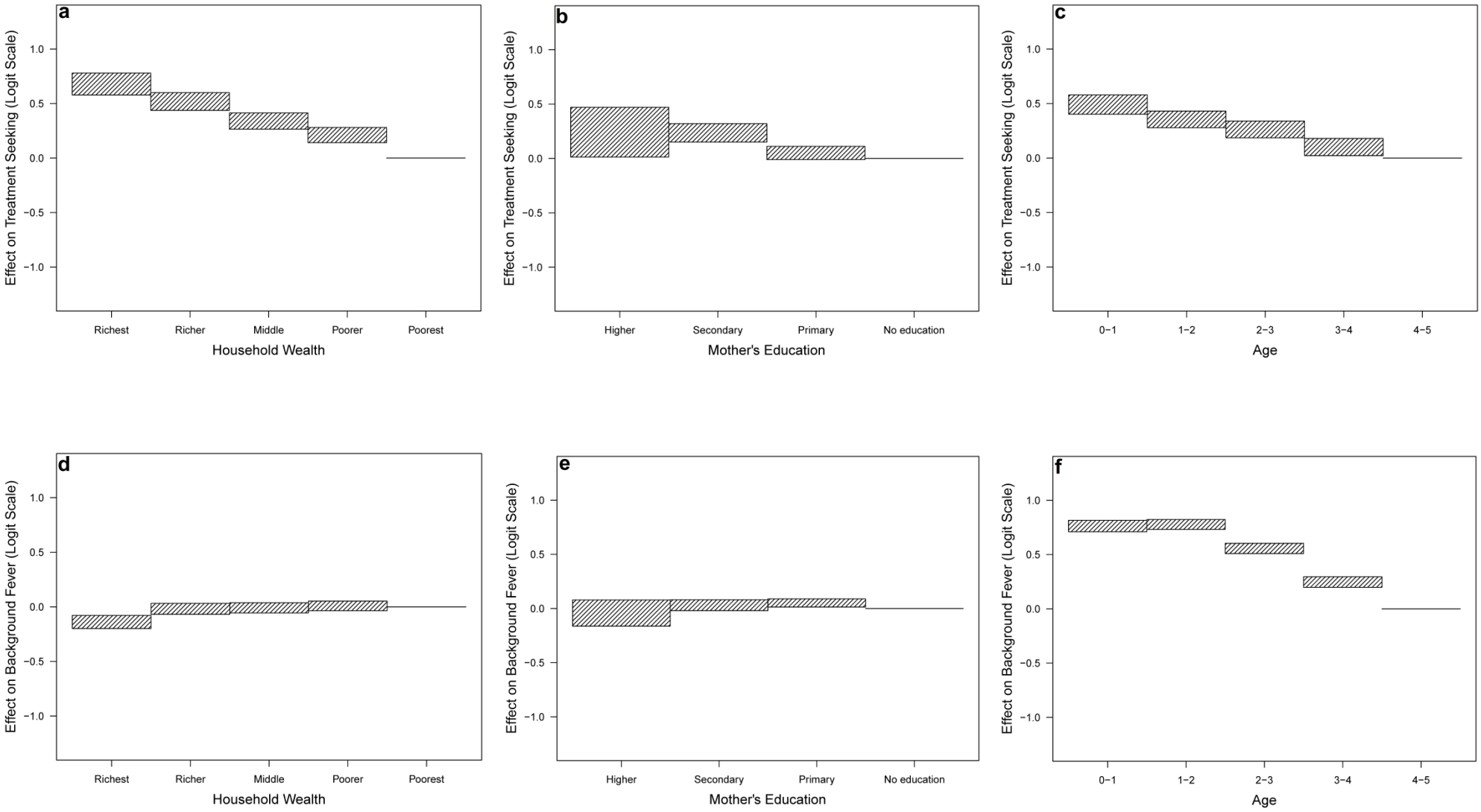
The second row of Figure 5.4 shows the effect of household wealth, maternal education levels, and age of child on the relative probability of experiencing NMFI (background fever) in the two weeks preceding the survey. The background fevers can, by definition, be accompanied by an asymptomatic, RDT-patent, *P. falciparum* infection. Small effects of household wealth were observed, with children from the richest households having a relatively lower probability of experiencing a non-malarial fever in the two weeks preceding the survey. Mother's education was not found to have a significant effect on the probability of experiencing a non-malarial fever. Younger children (0-2 years of age) were significantly more likely to experience a non-malarial fever in the two weeks preceding the survey compared to older children (3-4 years of age).

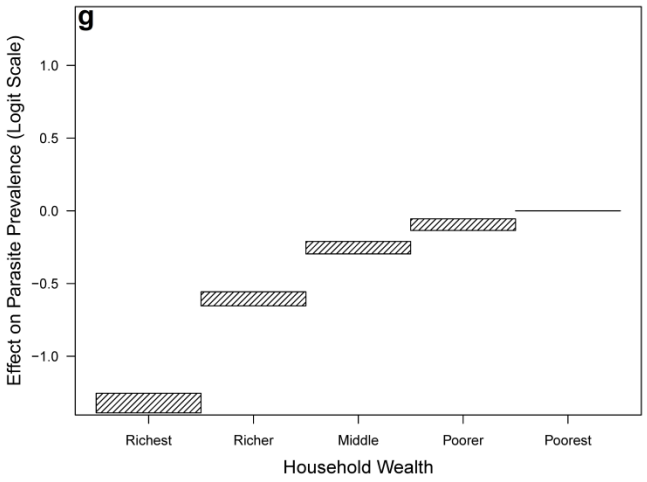
The third row of Figure 5.4 shows the effect of household wealth, maternal education levels, and age of child on the relative probability of a child being RDT-positive at the household survey interview. All three individual-level factors have strong effects: younger children, children from richer households, and children with well-educated caregivers were less likely to be RDT positive compared to children from poorer

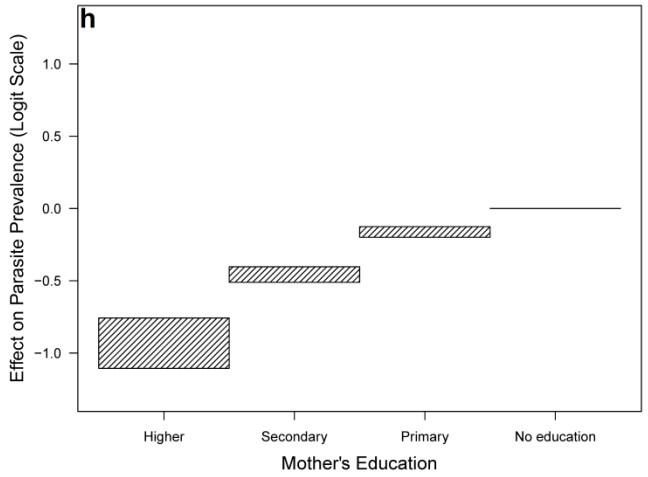
households, older children, and children that had caregivers with no or primary-level education.

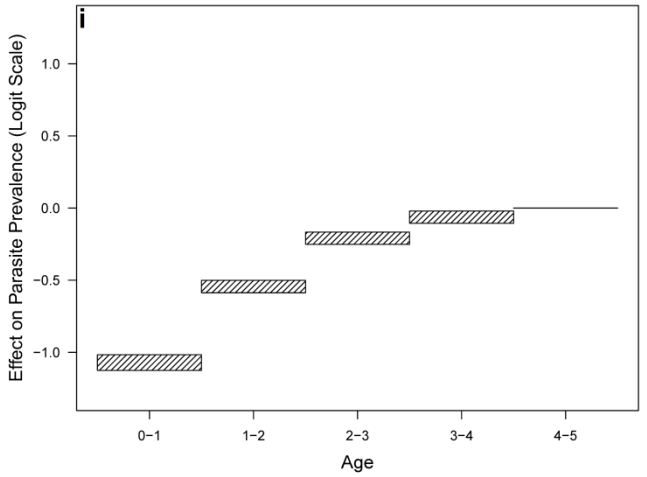
The final row of Figure 5.4 shows the effect of household wealth, maternal education levels, and age of child on the probability that a child with a malaria-attributable fever who sought treatment received an ACT, amongst all those with malaria-attributable fevers who sought treatment. Children from richer households with a malaria-attributable fever were more likely to receive an ACT than children from poorer households. Children with caregivers with secondary education were more likely to receive and ACT than children with less-educated caregivers, but children with mothers with higher education were least likely to receive an ACT; this is likely to be due to the small sample size of children with a malaria-attributable fever who sought treatment and had a mother with higher education. Age did not affect the probability of a child receiving an ACT with the exception of children aged over 4 years; these children were less likely to receive an ACT. The dashed line associated with each hatched bar shows the proportion of malaria-positive febrile children (regardless of the underlying cause of the fever) who for whom treatment was sought and an ACT was received, as a proportion of all malaria-positive febrile children for whom treatment was sought.

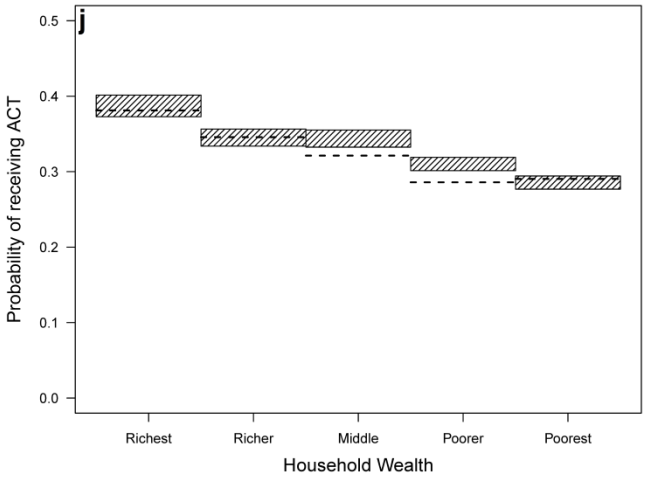
An additional effect of children sleeping under an ITN during the night preceding the survey on the probability of *P. falciparum* malaria infection was investigated. A negligible effect was found with those children who were reported to have slept under an ITN had a relative probability of -0.04 ± 0.01 (logit scale) of being infected with *P. falciparum* compared to those that did not sleep under an ITN.

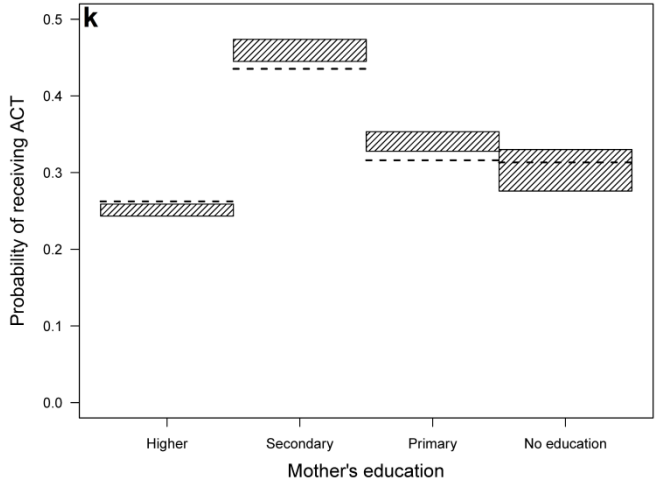

a
Effect on Treatment Seeking (Logit Scale)
1.0
0.5
0.0
−0.5
−1.0
Richest
Richer
Middle
Poorer
Poorest
Household Wealth
b
Effect on Treatment Seeking (Logit Scale)
Higher
Secondary
Primary
No education
Mother's Education
c
Effect on Treatment Seeking (Logit Scale)
0−1
1−2
2−3
3−4
4−5
Age
d
Effect on Background Fever (Logit Scale)
Household Wealth
e
Effect on Background Fever (Logit Scale)
Mother's Education
f
Effect on Background Fever (Logit Scale)
Age


g
Effect on Parasite Prevalence (Logit Scale)
1.0
0.5
0.0
−0.5
−1.0
Richest
Richer
Middle
Poorer
Poorest
Household Wealth


h
Effect on Parasite Prevalence (Logit Scale)
1.0
0.5
0.0
−0.5
−1.0
Higher
Secondary
Primary
No education
Mother's Education


i
Effect on Parasite Prevalence (Logit Scale)
1.0
0.5
0.0
−0.5
−1.0
0−1
1−2
2−3
3−4
4−5
Age


j
Probability of receiving ACT
0.5
0.4
0.3
0.2
0.1
0.0
Richest
Richer
Middle
Poorer
Poorest
Household Wealth


k
Probability of receiving ACT
0.5
0.4
0.3
0.2
0.1
0.0
Higher
Secondary
Primary
No education
Mother's education

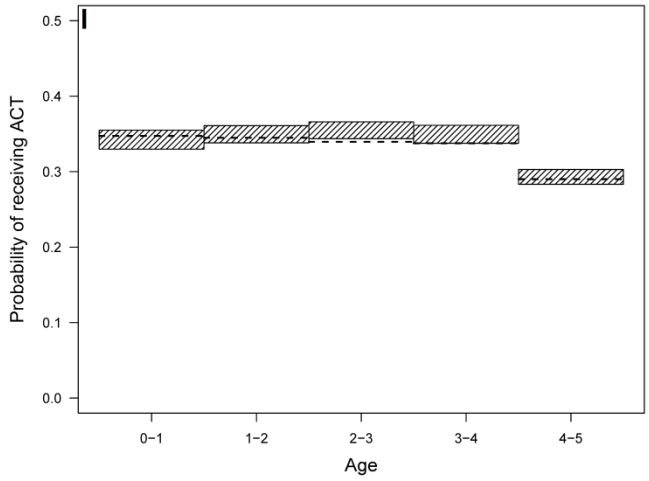

l
Probability of receiving ACT
0.5
0.4
0.3
0.2
0.1
0.0
0−1
1−2
2−3
3−4
4−5
Age

Figure 5.4. ***a-c)*** Relative effects of household wealth (**a**), maternal education (**b**), and age of child (**c**) on the probability of the caregiver seeking treatment for their febrile child. ***d-f)*** Effects of household wealth (**d**), maternal education (**e**), and age of child (**f**) on the child experiencing NMFI in the two weeks preceding the survey. Background fevers can, by definition, be coincident with an asymptomatic *P. falciparum* infection. ***g-i)*** Relative effects of household wealth (**g**), maternal education (**h**), and age of child (**i**) on the probability of a child being *P. falciparum* positive at the time of interview. For plots ***a-i,*** relative effects are defined as the relative probability of each "event" (i.e. treatment-seeking, experiencing NMFI, etc) occurring, when compared to a benchmark category for each indicator. The benchmark categories used are: "poorest" for household wealth, "No education" for maternal education, and "Age 4-5" for age of child. The 95% credible intervals for all effects relative to the benchmark are shown within the hatched boxes***. j-l)*** Modelled probability of receiving an ACT amongst children with malaria-attributable fevers who sought treatment, separated by household wealth (**j**), maternal education (**k**), and age of child (**l**). The 95% credible intervals for children with malaria-attributable fevers are shown in hatched boxes, and the raw proportion of children with a malaria-positive fever (regardless of underlying cause) who received an ACT amongst those who sought treatment is shown with a dashed line for reference.

5.6. Discussion

The population-weighted estimates presented here show that, amongst malaria-infected children residing in the 41 surveyed country-years in the two weeks preceding each survey, only 7.9% received an ACT. The primary reason for non-receipt of ACT was that most infections were not accompanied by a fever in the two weeks preceding the survey. Across all children in surveyed country-years, approximately a quarter of healthy children had an RDT-patent *P. falciparum* infection, suggesting strong potential for continuing transmission of malaria even if all febrile children received effective

antimalarial treatment. Additionally, the analysis presented here also shows that for nearly two-thirds of malaria-positive fevers that received ACT, NMFI was the underlying cause of the fever (and the malaria infection was asymptomatic). The high prevalence of asymptomatic malaria infections in both children without a fever and children with NMFI indicates the magnitude of the asymptomatic *P. falciparum* reservoir, and the significant role of NMFI in bringing asymptomatic malaria infections to clinics for antimalarial treatment.

5.6.1. Treatment-seeking

The most common reason for febrile malaria-infected children not receiving an antimalarial is that they did not seek treatment during the two weeks preceding the survey (34.4% of all febrile malaria-infected individuals, and 15.5% including non-febrile malaria-infected individuals). Individuals with MAF who do not seek treatment pose a particular problem for malaria prevalence reduction efforts. Symptomatic malaria infections are typically accompanied by a higher parasite density than asymptomatic malaria infections, increasing the probability of infecting a mosquito if bitten [68]. In this study, caregivers from poorer households and caregivers with lower education levels were less likely to take their febrile children for treatment than caregivers from richer, better educated households (Figure 5.4). Affordability of medicines and transport to the health facility has been found to provide a barrier to treatment-seeking for poorer households in previous studies [17–20]. The results presented here imply that education intervention campaigns, or subsidies for medicines or transport to health facilities in deprived, low-education areas may help close the treatment-seeking coverage gap and increase the number of children receiving effective treatment.

Poor perceptions of the effectiveness of treatment received have been cited as reasons for not seeking treatment [69, 70]. In this study, it was estimated that the probability of *P. falciparum* infection was higher in households with lower maternal education levels and poorer households. As a result, a higher proportion of children with a fever caused by NMFI were also co-infected with asymptomatic *P. falciparum* in these households. Effective antimalarial medication, though able to resolve the asymptomatic *P. falciparum* infection, would not resolve these fevers. High rates of unresolved fevers despite antimalarial treatment in areas with high concentrations of poor households with less well-educated caregivers may exacerbate poor perceptions of the effectiveness of treatment and health services, particularly if a diagnostic test is used (and returns a positive result) prior to antimalarial prescription.

5.6.2. Antimalarial prescription

Febrile, malaria-infected children for whom treatment is sought but who do not receive an ACT represent the largest source of "missed opportunities" for ACT coverage. Whilst treating malaria-infected children who do not have a fever or who do not seek treatment is challenging, increasing access to ACT for children who do seek treatment may be more readily addressed by national malaria control programmes. The results presented here show that the scale of "missed opportunities" is vast across the continent, with only 55.1% of malaria-infected febrile children for whom treatment was sought in the two weeks preceding the survey receiving an antimalarial drug of any kind. Further, only 26.8% of malaria-infected febrile children for whom treatment was sought received an ACT. The lack of antimalarial prescription indicates either that clinicians may be misdiagnosing malaria infections, or that antimalarial stock-outs are common, with some evidence existing for the latter [71, 72]. Although the DHS Program surveys are

intended to be nationally-representative, they are typically conducted only over 2-4 months (Additional Table 1). Levels of ACT provision in the DHS Program surveys may not be representative of the annual average for each country-year, depending on the frequency and seasonality of ACT stock-outs (as well as seasonal patterns of *P. falciparum* prevalence) within the studied countries.

In low *P. falciparum* burden countries, malaria-positive fevers were generally less likely to be treated with an antimalarial of any kind compared to higher burden countries (Figure 5.2), suggesting clinicians in countries with a low *P. falciparum* burden may presume fevers are not causally attributable to malaria. In countries with a higher *P. falciparum* burden, overall treatment rates with any antimalarial for malaria-positive fevers were higher, but the fraction of antimalarials that were ACTs was lower than the corresponding fraction in low burden countries. Across all surveyed country-years, amongst febrile, malaria-infected children who received an antimalarial drug, only half of antimalarials received were ACTs (population-weighted estimate). In countries with multiple surveys over the study period, the fraction of antimalarials that were ACTs increased with each survey, with the exception of Madagascar where a decline in the fraction of prescribed antimalarials that were ACTs was observed between 2013 and 2016. This decrease may be an artefact of the low sample size of malaria-positive individuals who sought treatment in Madagascar, rather than a real change in ACT treatment rate or treatment policy change. Analysing treatment rates for malaria-positive fevers in low endemicity countries is challenging as the total number of malaria-positive fevers who seek treatment is small, and may not be informative for measuring change in ACT vs non-ACT prescription. For example, in the Madagascar 2016 survey, only 20 malaria-positive children sought treatment, none of whom received an ACT. Similarly,

in Senegal 2015, only 10 malaria-positive children sought treatment, one of whom received an ACT (Table 5.2).

An additional limitation of measuring treatment-seeking rate within two weeks preceding the survey is that some febrile children who became febrile close to the time of interview may have, had the interview not intervened, sought treatment for fever at a later date. These children are included as "not having sought treatment" in the dataset. This analysis does not adjust for the likelihood of seeking treatment after the survey interview. A subset of the surveys included in this analysis asked caregivers of febrile children who sought treatment "how many days after the onset of fever did you seek treatment?", for which the mean number of days was 1.73 (±2.4) days, and as such the effect was presumed to be small. If this indicator was included for a higher proportion of surveys, future modelling efforts may seek to address this limitation.

5.6.3. Performance of public and private clinics

Amongst all febrile children who sought treatment in all surveyed country years, most were taken to public clinics, although some countries did not adhere to this trend. The most prominent exception was Nigeria, where 69% of children across both the 2010 and 2015 surveys who sought treatment did so at a private clinic. A potential limitation of the data categorisation used in this analysis is that public facility treatment-seeking was prioritised such that children who sought care at both public and private clinics were recorded as seeking care only at a public clinic. The effect of this data categorisation approach was assumed to be limited, as only 3.8% of febrile children who sought treatment visited both public and private clinics.

In addition to inadequate prescription of effective antimalarial medications to malaria-infected children, this study found evidence of other non-adherence to IMCI guidelines,

particularly by private health clinics. IMCI guidelines state that suspected malaria cases (i.e. fevers) should receive a parasite-based diagnostic test prior to treatment [67]. Presumptive diagnosis is commonplace across health facilities in sub-Saharan Africa [30–33], and numerous studies show that over 50% of individuals who receive a negative parasite-based diagnosis still received antimalarial medication [34–37]. As well as promoting resistance, ACT over-prescription reduces the cost-effectiveness of ACT use. Given the increased cost-per-dose of ACTs compared to other antimalarials [38], reducing over-prescription may help increase access to ACTs to those who are genuinely infected with *P. falciparum*. The results presented in this analysis show that fewer than half of febrile children received a diagnostic test at the clinic they visited, and that private clinics were half as likely as public clinics to use diagnostic tests on febrile children. In later surveys, febrile children who sought treatment were more likely to receive a diagnostic test compared to earlier surveys, which correlates with evidence that RDT disbursements in Africa have increased over time, although since 2013 they have plateaued [4]. Across all surveyed country-years, public clinics were more likely to provide diagnostic testing to febrile children, but also more likely to presumptively treat febrile children with antimalarials of any kind (Figure 3). This somewhat counterintuitive finding was due to higher overall rates of antimalarial prescription in public clinics compared to private.

Both private and public health centres prescribed close to a quarter of ACTs to children with an NMFI and no malaria infection. Ensuring ACTs are prescribed only to malaria-infected individuals (through use of diagnostic tests, and adherence to test results) could potentially improve access to ACTs for malaria-infected individuals, particularly in locations where stock-outs are common.

5.6.4. Effects of household wealth, caregiver education, child age, and insecticide-treated bed net use

Amongst children with MAF who sought and received antimalarial treatment, children from poor and less-educated households were less likely to receive an ACT (and thus received a non-ACT antimalarial) compared to richer households with caregivers educated to secondary level. This finding indicates a coverage gap in the stock and/or prescription of ACTs at facilities attended by poorer, less well-educated demographics. Addressing this coverage gap would reduce inequity in ACT prescription amongst children from different socio-economic backgrounds.

This study found that infants aged 0-1 years were more likely to experience non-malarial fevers than children aged 2-4. This suggests that a higher proportion of malaria infections in the younger age group are likely to be accompanied by a non-malarial fever. Only limited effects of household wealth or maternal education were found on probability of NMFI, suggesting fevers caused by NMFI are more cross-sectional through socio-economic status than MAF.

Sleeping under an ITN the night preceding the survey was not found to have an effect on probability of malaria infection in children under 5 years of age. ITNs have been credited with the majority of malaria prevalence declines over the past 20 years and their use in malaria prevention is undisputed [1, 73]. In this study ITN use did not produce a significant effect, but the model assessed for correlative effects rather than causative effects and as such may not distinguish between the effects of net use amongst individuals at differing levels of underlying malaria infection risk.

5.6.5. Comparison to previous estimates of ACT coverage

Despite fundamentally different modelling approaches, this study shares some overlap of aims and data sources to a previous analysis by Galactionova and colleagues of "effective coverage" of antimalarials amongst children under 5 in sub-Saharan Africa in 2010-2011, defined as the proportion of malaria-positive fevers cured by antimalarial medication [47]. As with this study, the analysis by Galactionova and colleagues showed significant variability between countries in the proportion of malaria-positive fevers that were effectively treated, and variation in the key "missed opportunities" for treatment at the clinical level between different countries.

The study presented here is distinct from [47] in both modelling approach and key outputs. Most notably, the study presented here assesses the coverage of ACT (and other antimalarials) across all malaria infections, rather than just malaria infections associated with a fever. The modelling approach used in this analysis further stratifies malaria-positive fevers by underlying cause, and uses subsequent survey information to assess whether the individual received an ACT in order to calculate national-level ACT coverage, while simultaneously identifying individual-level and household-level factors that affect the probability of receiving an ACT. The study presented by Galactionova and colleagues uses survey-level presumptive treatment rates as a proxy for malaria infections, and then scales these by survey-level rates for treatment-seeking, healthcare facility usage, drug compliance, adherence, resistance and efficacy in order to obtain national-level estimates of effective antimalarial coverage. The survey-level approach taken in [47] limits the analysis to only assess national-level factors affecting antimalarial coverage. Galactionova and colleagues generated estimates of effective antimalarial coverage for all sub-Saharan African countries in 2010-2011, imputing data from other sources for countries without a household survey. The approach used by

Galactionova and colleagues is not, therefore, restricted to surveys with geo-positioned individual locations and malaria RDT testing, greatly increasing the number of available surveys. The study by Galactionova and colleagues also takes antimalarial coverage a step further by also estimating the cure rate, by incorporating information on drug adherence, clinical efficacy and resistance. Cure rate was not estimated in this analysis. Adherence was not included as only a subset of the included DHS Program surveys contained indicators on the number of days for which antimalarial medications were taken. In [47], DHS Program data on adherence is augmented by imputing adherence from field studies of adherence reported in literature; however these studies are subject to inherent bias when the study subjects are aware their adherence is being monitored, and for that reason was not included in this analysis.

Galactionova and colleagues additionally incorporate informal routes to treatment in their modelling approach (e.g. obtaining medications from markets, shops and friends and family). Informal facilities were not included in this analysis due to the high prevalence of counterfeit medications in this sector [74]. Proportion of counterfeit drugs was incorporated as a constant for informal facilities (and assumed no counterfeit drugs were obtained from formal facilities) in the modelling approach used by Galactionova and colleagues [47]. The analysis presented here only measured coverage of ACTs obtained from formal facilities, and therefore the number of counterfeit medications was assumed to be negligible.

The analysis presented here is the first to utilise a complete set of RDT outcomes within the response data when estimating ACT coverage; previous multi-national ACT coverage estimates for sub-Saharan Africa have imputed RDT outcomes for all (through using presumptive treatment as a proxy for malaria infection) [47] or the majority [39] of individuals. By using confirmed RDT outcomes, ACT coverage can be framed as the

proportion of all malaria infections, regardless of febrile illness, that receive effective treatment. This study finds differences in treatment-seeking rates between fevers of different underlying causes; in previous studies assumptions that treatment-seeking rates are the same across febrile conditions underpins estimates of ACT coverage and effective treatment rates [47].

The study presented here estimates coverage of ACT in the past 14 days, and does not attempt to measure the coverage of ACT provided promptly (i.e. within 24 hours of the onset of fever). Future ACT coverage studies may wish to adopt a holistic approach that incorporates all the strengths of both this analysis and previous analyses, and estimates both overall ACT coverage, and the coverage of prompt and effective antimalarial treatment. This may be accomplished by enumerating malaria infections (febrile or otherwise) that are subsequently cured via ACT, by including data on time between onset of symptoms and receipt of medications, efficacy and adherence to medication, informal routes for obtaining ACT, and full records of RDT status to ensure that ACT coverage is only being measured amongst confirmed malaria-infected individuals.

5.7. Conclusion

This study assessed ACT coverage in 41 country-years over a decade time period, and quantified the reasons why malaria-infected children did not receive ACTs. The primary reason for malaria-infected children not receiving ACT was that their malaria infections were not accompanied by a fever. Amongst malaria-infected febrile children, fevers were further stratified by the underlying cause of the fever (i.e. attributable to malaria, or NMFI coincident with an asymptomatic malaria infection). Through use of this

stratification, the role of NMFI in bringing asymptomatic malaria infections to clinics for treatment was highlighted.

To improve access to ACTs for malaria-infected children, several coverage gaps were identified by this analysis. The finding with the most programmatic relevance was that almost half of malaria-infected febrile children who sought treatment at a formal health clinic did not receive an antimalarial of any kind, and only a quarter received an ACT. Amongst children who do seek treatment, poorer children and children from less educated households are also less likely to receive an ACT; up-scaling of ACT supplies in clinics in deprived areas may help address this. The level of diagnostic testing available in all clinic types was low and would benefit from increased access to (or encouragement to increase usage of) RDTs, particularly in private clinics. To improve treatment-seeking rates for malaria-infected febrile children, poorer households, and those with low caregiver education levels should be targeted with intervention campaigns, as these demographics are shown to be less likely to seek treatment.

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Chapter 6 - Discussion

6.1. Summary and aim

This thesis aimed to provide insight into the burden of *Plasmodium falciparum* malaria amongst children in sub-Saharan Africa, and generate estimates for the proportion of *P. falciparum* malaria infections and clinical illness cases that receive effective antimalarial treatment. To accomplish this, a modelling approach was devised where malaria-positive fevers in the household survey datasets were stratified into those that were truly symptomatic malaria-attributable illnesses (malaria-attributable fever; MAF), and malaria-positive fevers where the underlying cause of the fever was non-malarial (non-malarial febrile illness; NMFI). For malaria-positive NMFI cases, the malaria infection was asymptomatic; therefore by treating the malaria infection, the fever may still not be resolved. For the underlying response data, household survey records on over 150,000 children under 5 years of age were collated, primarily from the Demographic and Health Surveys (DHS) Program [1]. The household survey dataset, in its raw form, provides information on *i)* the prevalence of malaria amongst the surveyed children, *ii)* the prevalence of fever amongst the surveyed children, as determined by caregiver recall, during the two weeks preceding the survey, and *iii)* information on the treatment-seeking outcomes and medications received by febrile children. In this thesis, this household survey data is manipulated to provide new insights into the prevalence and treatment rates of MAF and NMFI in surveyed countries in sub-Saharan Africa. In Chapter 2, cartographic estimates of the prevalence of MAF and NMFI amongst children under 5 in sub-Saharan Africa were presented. Chapter 3 presented an essential adjustment to household survey datasets to improve accuracy of paired two-week malaria and fever outcomes. In Chapters 4 and 5, febrile children in the household survey datasets were

assigned a probabilistic individual-level estimate of two-week history of MAF or NMFI in order to derive a set of nationally-representative metrics. Amongst malaria-positive febrile children presenting at public health clinics, the fever attribution model was used to predict the proportion of malaria-positive fevers that were causally due to malaria versus NMFI amongst who presented to public health clinics in Chapter 4. These proportions were then used to assess the potential for overestimation of malaria burden using conventional burden estimation approaches. In Chapter 5, using information on the subsequent treatment-seeking behaviour and medications received by children with MAF and NMFI, nationally-representative estimates of artemisinin combination therapy (ACT) coverage amongst malaria-infected children under 5 years of age were presented in 41 country-years across 21 sub-Saharan African countries. Further, national-level estimates were produced of: *i)* the proportion of all malaria infections in children under 5 that were accompanied by a fever in the two weeks preceding each household survey, *ii)* the proportion of those malaria-positive fevers that were due to MAF and/or due to NMFI, *iii)* the proportion of children with MAF and NMFI that sought treatment, and *iv)* the proportion of children with MAF and NMFI that received antimalarial treatment (segregated by ACT and non-ACT medications).

The results provided here can be utilised by epidemiologists and public health officials to aid in more accurate understanding of the *P. falciparum* malaria burden across sub-Saharan Africa, to evaluate the proportion of paediatric febrile illnesses that receive effective antimalarial treatment, and to identify coverage gaps for effective antimalarial treatment. Further, through use of the use of the MAF/NMFI attribution model for febrile children, the proportion of malaria-positive fevers amongst children in the household surveys that were not resolved through antimalarial treatment (as the underlying cause of the fever was non-malarial) was estimated.

In this Discussion chapter, a more detailed summary of each chapter of this thesis is given, followed by a critique of the methodologies and datasets used for analysis. Finally, the interpretation and implications of the key outputs from this thesis are discussed.

6.2. Chapter summary

In the introductory chapter (Chapter 1), a literature review of the topics covered by this thesis was presented. The current state of knowledge of malaria epidemiology and endemicity was outlined, focusing on the role of effective antimalarial treatment with ACTs in reducing the burden of *P. falciparum* malaria. ACTs were responsible for 19% of malaria prevalence reductions in sub-Saharan Africa between 2000 and 2015 [2, 3]. The use of treatment-seeking rates for all-cause fever in *P. falciparum* burden estimates was discussed, identifying potential differences between treatment-seeking rates for MAF and NMFI, and the effect this may have on burden estimates. Finally, methods for estimating malaria-attributable fever rates amongst malaria-positive fevers were outlined, and previous attempts to measure the coverage of effective antimalarial medication were discussed, identifying shortcomings of these approaches and the motivation for renewed efforts in estimating effective antimalarial coverage.

Chapter 2 outlined the principals on which the rest of the thesis relies: not all malaria-positive fevers are malaria-attributable. The analysis presented in Chapter 2 estimated that, in 2014, only 28% of malaria-positive fevers in children under 5 years of age across sub-Saharan Africa were causally attributable to malaria. By using a Bayesian hierarchical model to predict the prevalence of MAF and NMFI with and without an asymptomatic *P. falciparum* malaria infection, the spatial heterogeneity in prevalence of each of the fever types was outlined, and the interpretation of the causative agents of

malaria-positive febrile illness amongst malaria-positive children was refined. In addition, Chapter 2 provided the first continuous cartographic estimates of NMFI and all-cause fever amongst children in sub-Saharan Africa.

Chapter 3 provided a critical adjustment to household survey datasets for accurate contemporaneous analysis of paired fever recall and rapid diagnostic test (RDT)-derived malaria diagnostic outcomes. In the household survey datasets, caregivers recall the child's fever history over the past 14 days, but RDTs are administered at the point of interview. As such, a febrile child who sought treatment may have been RDT-positive at the point of treatment, received antimalarial medication, and the antigens from the malaria infection may have cleared sufficiently for the RDT to present a negative outcome by the time of interview. In the household survey dataset, that child would then be recorded as a malaria-negative fever, which was incorrect for the purposes of the analysis documented in this thesis. In Chapters 4 and 5, RDT outcomes were adjusted probabilistically for interview-RDT-negative children who received antimalarial medication in the two weeks preceding the interview, allowing for the possibility of some of these children to revert from RDT-positive at the time of treatment to RDT-negative by the time of interview. Chapter 3 presented the development of this adjustment, based on observations of the duration of persistent RDT positivity after antimalarial treatment from literature, to which a Bayesian survival model was fit to provide estimates for the likelihood of a recently-treated individual presenting a negative RDT within two weeks of treatment.

Chapter 4 built on the results presented in Chapter 2, and refined and extended the Bayesian hierarchical model in order to predict the proportion of malaria-attributable and non-malarial fevers (whether accompanied by an asymptomatic *P. falciparum* infection or not) that present at public outpatient health clinics in sub-Saharan Africa. The

proportion of malaria-positive fevers that are/are not causally attributable to malaria was then used to estimate the potential magnitude of overestimation of the symptomatic malaria burden when using conventional burden estimation techniques that involve adjusting reported cases of malaria in clinics (i.e. malaria-positive fevers). The methodology for generating these estimates began with a re-calibration of the relationship between MAF and *P. falciparum* malaria prevalence in children under 5 years of age ($Pf\text{PR}_{0\text{-}5}$), which was fundamental to the modelling approach used to generate estimates of MAF and NMFI prevalence. In Chapter 2, the relationship between $Pf\text{PR}_{0\text{-}5}$ and MAF in children under 5 was estimated using an assumed relationship driven by simulations from the OpenMalaria transmission model [4–7] and fit directly to the household survey dataset. Little information on how this relationship changes depending on differing fever definitions (e.g. fever recall, measured fever, or different definitions of malaria-attributable fevers) is documented in existing literature. In Chapter 4, datasets encompassing numerous fever definitions were used to estimate the underlying relationship between MAF and $Pf\text{PR}_{0\text{-}5}$, with any biases introduced by fitting the model to only household survey data removed. The relationship was found to decline exponentially until $Pf\text{PR}_{0\text{-}5}$ reaches approximately 40%. When $Pf\text{PR}_{0\text{-}5} > 40\%$, approximately half of all malaria-positive fevers were found to be causally attributable to malaria. The relationship between MAF and $Pf\text{PR}_{0\text{-}5}$ used in the Bayesian hierarchical model in Chapter 2 was replaced with this more robust estimate of the relationship in Chapters 4 and 5.

In Chapter 4, the Bayesian hierarchical model was further strengthened to produce individual-level probabilistic estimations of MAF and NMFI (which can either be accompanied by an asymptomatic RDT-positive malaria infection, or be RDT-negative) for febrile children in the household survey datasets. These individual-level attributions

of underlying fever cause were estimated using a wider variety of predictor variables than the Bayesian hierarchical model presented in Chapter 2. In addition to the remotely sensed environmental and sociodemographic variables, individual- and household-level variables that affect the likelihood of a child having MAF or NMFI were also incorporated, such as household wealth, child age, mother's education, and use of insecticide-treated bed nets (ITNs). In Chapter 4, the treatment-seeking behaviour of children with MAF or NMFI (as documented in the household survey dataset) in the two weeks preceding the survey was followed to produce estimates of the proportion of each of these types of fever that would be observed in public-sector outpatient clinics for each country-year. The proportion of malaria-positive fevers that were not causally attributable to the malaria infection can be used to assess the potential magnitude of overestimation of the malaria burden if calculated using the adjusted-case-count approach for burden estimation. These results were applied to national Ministry of Health reports of outpatient malaria cases amongst children under 5 years of age in three sub-Saharan African countries, in order to estimate the proportion of these confirmed malaria-positive fevers that were causally attributable to NMFI (and as such would not be resolved by effective antimalarial treatment).

In Chapter 5, the Bayesian hierarchical model was further refined to produce nationally-representative estimates of the proportion of malaria infections in country-years with a household survey that received effective antimalarial medication (during the two weeks preceding each survey). The results presented showed significant spatial and temporal variation in the proportion of malaria infections that received ACT treatment. A number of countries (Liberia, Mali, Tanzania, Uganda) with multiple surveys between 2006 and 2016 showed gains in the proportion of malaria-positive febrile individuals who received effective antimalarial treatment, indicating narrowing coverage gaps for ACT.

Individual- and clinic-level factors were investigated, and wealth, age, and maternal education were found to significantly affect the likelihood of a caregiver seeking treatment for their febrile child. Effective antimalarial treatment was more likely to be prescribed at public clinics than private clinics. Further, public clinics were significantly more likely to diagnose malaria infections parasitologically before prescribing treatment.

6.3. Methodological discussion

In this section, the data sources and statistical analyses used to generate the key outputs in this thesis will be discussed, and the strengths and limitations of each approach will be assessed. The statistical frameworks used in this thesis were designed to maximise the use of all available information from each dataset in order to produce robust estimations of all of the key outputs in a manner that would be nationally-representative and broadly informative across the continent. Table 6.1 summarises the sources of data and statistical frameworks employed throughout this thesis. For a number of the key outputs of this thesis, alternative promising statistical frameworks were investigated during exploratory analysis; in this chapter the strengths and limitations of these alternative methods and the reasons for selecting the methods presented in Chapters 2-5 will be discussed.

Table 6.1. Key thesis outputs with data sources and statistical frameworks used.

Key outputs	**Presented in**	**Data sources**	**Statistical framework**
Estimating MAF/NMFI/all-cause fever prevalence across sub-Saharan Africa, 2006-2014	Chapter 2	Household survey dataset Remotely sensed covariates	Boosted regression trees Spatiotemporal Bayesian geostatistical model (for *Pf*PR_{0-5}) Bayesian hierarchical model
Estimating time-to-negativity for RDTs after treatment	Chapter 3	Literature review of RDT time-to-negativity after antimalarial treatment	Bayesian survival model
Refining estimates for the relationship between MAF and *Pf*PR for children under 5 years of age	Chapter 4	Literature review of parasite-density threshold-based estimations of MAF Literature review of paired fever and malaria observations PRISM dataset Household survey dataset	Bayesian model for re-calibrating MAF vs *Pf*PR_{0-5} relationship
Estimates for the proportion of MAF and NMFI amongst febrile children presenting at public-sector outpatient clinics Estimates of ACT coverage	Chapter 4 Chapter 5	Household survey dataset Previous model outputs Remotely sensed covariates National-level World Bank variables World Health Organization (WHO) treatment effectiveness dataset	Bayesian hierarchical model

6.3.1. Household survey data

In subsequent sub-sections, datasets and statistical frameworks will be discussed alongside each other in the context in which they were used. The household survey dataset, however, was used extensively throughout this thesis. The strengths and shortcomings of the household survey dataset for use in estimation of all key thesis outputs will be discussed separately in this sub-section.

Nationally-representative, cross-sectional household survey datasets on demographic and health indicators have been produced by a number of initiatives for nearly four decades, providing standardised and consistent questionnaires in each survey, allowing cross-comparability between countries [8]. In this thesis, the DHS Program represented the primary data source in Chapter 2 and only data source in Chapters 4 and 5 for household surveys. Many surveys are designed to assess national-level population access and utilisation of malaria interventions (such as diagnostic use, or treatment-seeking and prescription), but DHS Program surveys are the only suite of data that provide three key continuous and consistent factors across multiple surveys for each surveyed individual which were crucial for generating the outputs of this thesis. These key factors are: *i)* a parasitological diagnosis of malaria, *ii)* documentation of recent recalled fever history, and *iii)* GPS coordinates for surveyed individuals. DHS Program data are well-suited for estimating the primary outputs of this thesis, but the reliance upon geo-referenced surveys with parasitaemia testing limited the continental-scale analysis presented in this thesis to only the last 12 years (with the majority of surveys conducted only within the last 7-8 years). Critically, the household survey dataset utilised in this thesis contained consistent indicators between country-years and was designed to produce nationally-representative samples. Paired observations of fever and malaria positivity can also be extracted from literature (e.g. the literature review presented in Chapter 4), but

inconsistent methodologies and gaps in spatial coverage precluded their inclusion in this research.

The household survey dataset is not, however, without limitations. Paediatric fevers are not measured at the time of interview, instead relying on the caregiver recalling whether their child had a fever in the past two weeks. This limitation may introduce the caregiver's bias in defining a fever, and thus affect the accuracy of fever outcomes, compared to measured fever via a set axillary temperature criterion on the day of interview. Caregivers have shown sub-optimal accuracy in reporting fevers experienced over 14 day periods [9, 10]. Caregiver recall of treatment-seeking is also an imperfect metric. For example, if the primary caregiver does not report taking the febrile child for treatment, a secondary caregiver may take the child, which may not be reflected in the household survey dataset. Caregiver recall of blood draws (for diagnostic purposes) and antimalarial medication prescribed are also used within this thesis, although studies in Zambia suggest that caregivers give imperfect recall for these factors [11]. This factor may be mitigated, however, by the interview procedure in the DHS Program surveys, whereby the interviewer typically requests to see any prescribed medications. Additionally, caregivers may recall the type of facility visited (public or private) erroneously. Finally, for children who do receive treatment, the caregiver is not typically asked about the duration the child took the medication in DHS Program surveys (although this indicator is available in select surveys), so measurement of antimalarial adherence is not consistently possible.

In this thesis, the RDT-derived malaria diagnosis was used rather than microscopic diagnosis, which is also often included in household surveys. This decision was made because RDTs give a better indication of malaria positivity over the past two weeks, due to antigen persistence after successful antimalarial treatment [12, Chapter 3]. RDTs are,

however, an imperfect tool for diagnosing malaria. The WHO/FIND Product Testing Program (PTP) regularly assesses RDTs available on the market. In order to be approved by the WHO/FIND PTP, an RDT needs to be sensitive against a blood sample inoculated with *P. falciparum* at 200 parasites/µl, although this threshold has changed over the study period covered by thesis (2006-2016) [13]. All RDTs used in the DHS Program datasets were approved by the WHO/FIND PTP at the time of survey. Evidence suggests, however, that 20-50% of all human-to-mosquito transmissions are from infections at parasite densities lower than those detected by RDTs or microscopy at low endemicity levels [14]. This indicates that the RDTs used in household surveys may systematically miss low-density infections (typically asymptomatic) that would otherwise be detected by more sensitive diagnostics such as polymerase chain reaction (PCR). Higher-sensitivity RDTs would go some way to address this problem. For example, theoretical studies show that RDTs with a detection limit of 200 parasites/µl would detect 55% of the infectious reservoir of *P. falciparum* infections, whereas prospective high-sensitivity RDTs with a detection threshold of 20 parasites/µl or 2 parasites/µl would detect 83% and 95% of the reservoir, respectively [15]. In addition to RDT-derived outcomes, microscopic diagnosis is available from the DHS Program datasets. Microscopic analysis of infected blood samples from febrile individuals can be used to directly diagnose MAF if blood parasite density is recorded during diagnosis using a pyrogenic parasite blood density threshold, over which a fever is deemed to be causally attributable to the malaria infection [16–19]. However, the DHS Program datasets do not record blood parasite density, making observed distinctions between clinical malaria cases and malaria-positive fevers where NMFI is the underlying cause of the fever impossible from these datasets.

The DHS Program surveys are typically conducted over 2-4 months in a year, and typically coincide with the high malaria transmission season for Malaria Indicator Surveys (MIS; a subset of the DHS Program surveys used in this thesis). The short study period of the DHS Program surveys prevents the malaria prevalence data from reflecting the underlying seasonality of malaria transmission over the course of a year. DHS Program observations were matched both spatially and temporally with contemporaneous environmental covariates available at monthly intervals to produce predictor variables during the boosted regression tree (BRT) modelling. The metrics presented in this thesis, however, do not capture the monthly seasonal fluctuations in the prevalence of MAF and NMFI and as such are accurate only as yearly averages [20].

Individual-level factors from the DHS Program datasets are also used in Chapters 4 and 5; included in these indicators is usage of ITNs the night preceding the survey. National distribution campaigns of ITNs or seasonal usage in malaria-endemic countries may lead to rapid and effective reductions in malaria transmission that may only be short-lived if individuals stop using the intervention after a period of time. Seasonal differences in ITN usage have been observed in Kenya during the dry and rainy seasons [21], and reduced usage over the course of a year after ITN distribution campaigns have been observed in Burkina Faso [22]. In the household surveys, no information was available on whether intervention usage was at baseline levels, or at elevated levels due to recent distributions or seasonal effects, and was not accounted for in the modelling approaches presented in this thesis.

6.3.2. Duration of RDT positivity after successful antimalarial treatment

This sub-section describes the strengths and limitations of the datasets and modelling approaches detailed in Chapter 3. To estimate the duration for which RDTs remain positive after successful antimalarial treatment, a systematic literature review of observations of persistent RDT positivity for up to 60 days after treatment was conducted. While the collated literature review dataset represented the largest assembled set of observations of persistent RDT positivity, each study varied in the protocols used to collate observations. Future lab-based analysis aiming to estimate the duration of persistent positivity would benefit from adopting a consistent diagnostic approach across multiple age groups, especially given the lack of available data for adults in the collated dataset in Chapter 3.

A Bayesian survival model was fit to the literature review dataset. Issues with fitting frequentist models to the literature dataset motivated the Bayesian approach. As well as the fixed effects of interest (age, RDT type, treatment type), adjustments for random effects (such as intrinsic study-level biases, or year of study) needed to be learnt by the model. While fitting random effects is possible using frequentist approaches, generating outputs with confidence/credible intervals that account for the random effects was only possible within a Bayesian framework. In exploratory analyses for Chapter 3, frequentist approaches for estimating the decline in proportion of positive RDTs with increasing number of days after treatment were explored. During exploratory analysis, Kaplan-Meier survival estimates and Cox proportional hazard models were fit to the dataset to estimate the proportion of RDTs still positive between 0 and 60 days after treatment. Fixed effects of age, RDT type, and treatment were used to allow for comparative analysis (as per the final model presented in Chapter 3). Both these methodologies produced survival curves comparable to the model presented in Chapter 3, but were

superseded by the more sophisticated Bayesian survival model for a number of reasons. Firstly, the frequentist approaches were unable to generate survival model estimates with confidence intervals when incorporating random effects. Confidence intervals were necessary to include the effects of the year of studies (to account for changes in RDT sensitivity over time) and intrinsic biases of individual study procedures. Both the Kaplan-Meier and Cox proportional hazard approaches generated stepped estimates rather than curves (which represent the shape of the true underlying relationship), as they do not incorporate a regularisation penalty against non-smooth functions. Additionally, the probability of treatment failure, which cannot be incorporated in Kaplan-Meier or Cox proportional hazard models, was learnt in the final Bayesian survival model. Without the treatment failure adjustment, the frequentist approaches overestimated the proportion of RDTs that remain positive for malaria at each time point solely due to persistent antigenicity from a successfully treated malaria infection, as individuals in the literature review dataset whose treatment had failed were not removed. Figure 6.1 shows a comparison of the final Bayesian survival model estimate (as shown in Chapter 3) and the Cox proportional hazard model estimate for the proportion of RDTs that were still positive 0-60 days after treatment.

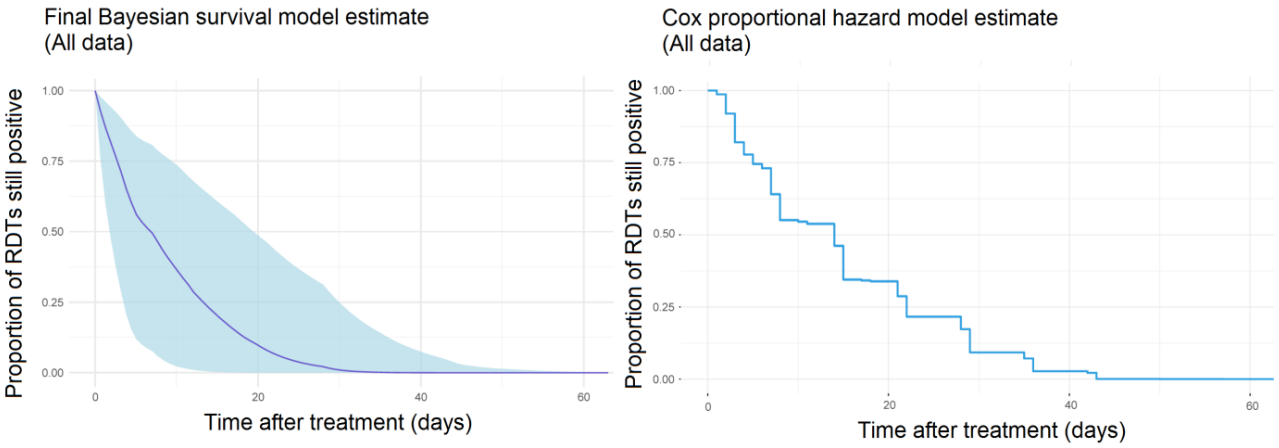


Figure 6.1. Comparison of the final Bayesian model estimate (left panel) and Cox proportional hazard model (right panel) of proportion of RDTs still positive 0-60 days after antimalarial treatment. The Bayesian model estimate was described and presented in Chapter 3; the Cox proportional hazard model was generated during exploratory analysis for Chapter 3.

6.3.3. Environmental and sociodemographic correlates of MAF, NMFI, and treatment-seeking

The three covariates used in the Bayesian hierarchical model for MAF and NMFI included: *i)* *Pf*$PR_{0\text{-}5}$, (in Chapters 2, 4, and 5); *ii)* suitability for a malaria-negative ("background") fever (in Chapters 2, 4, and 5; referred to as "BRT_{bg}" from Chapter 4 onwards), and *iii)* probability of seeking treatment for all-cause fever (in Chapters 4 and 5; referred to as "BRT_{treat}"). The motivation for using these three covariates was to minimise the total set of covariates to maximise computational efficiency, while still retaining information from the entire suite of remotely-sensed variables held within the Malaria Atlas Project (MAP) repository.

The challenge of developing a set of covariates for predicting MAF and NMFI prevalence shares similarities with the process of selecting covariates for *Pf*PR, as

detailed in Weiss *et al.* [20] and Bhatt *et al.* [2]. In these publications, a set of remotely-sensed environmental and socioeconomic variables was used as covariates for predicting *Pf*PR, following a covariate selection procedure. Covariates were selected from the entire set of available variables by initially leveraging variables through transformations and pairwise combinations, and iteratively selecting univariate and subsequently multivariate models with the strongest in- and out-of-sample predictive accuracy for *Pf*PR. The final set of variables used to predict *Pf*PR consisted of the 20 best predictor variables (that each were, in themselves, transformations and interactions of the original set of variables) [20].

In line with the Bayesian geostatistical model for *Pf*PR, the Bayesian hierarchical model presented in Chapters 2, 4 and 5 of this thesis required a slim set of covariates in order to remain computationally feasible. As such, the number of covariates used for prediction of MAF and NMFI needed to be as reduced as possible while still retaining the maximum amount of predictive information from all available variables. The full set of potential covariates was reduced to just three for use in the Bayesian hierarchical model presented in this thesis (and only two in Chapter 2).

The first covariate was the cartographic estimates of *Pf*PR presented Bhatt *et al.* [2], used with age [23] and diagnostic test [24] transformations. The estimates of *Pf*PR presented in [2] were generated using a dataset of geo-located observations of community malaria prevalence, which were then paired with 20 spatially and temporally contemporaneous environmental variables (as described above), and used in a Bayesian geostatistical model to produce estimates of *P. falciparum* prevalence in children aged 2-10 years of age ($PfPR_{2\text{-}10}$) continuously across Africa from 2000-2015. The strengths and limitations of this modelling approach are described in full in the associated publication.

A boosted regression tree (BRT) approach was used to generate the two non-*Pf*PR covariates. These were: *i)* suitability for a malaria-negative fever, and *ii)* probability of seeking treatment for all-cause fever. BRTs represent a flexible regression approach that allows large sets of covariates to be combined into a single predictive model. BRTs are advantageous because they combine the strength of regression trees, which relate and measure the predictive performance of each covariate to the response, and boosting, which allows models to be combined to improve the overall model's predictive performance [25]. Additionally, the transformation and interaction steps (described in full in Weiss *et al.* [20]) for covariate selection in the Bayesian geostatistical model for *Pf*PR [2] can be bypassed, as BRTs consider non-linear relationships between the variable and response, and can identify and model interactions [25]. A limitation of the BRT approach, however, is that BRT models are non-spatial and do not account for spatial autocorrelative effects, which may result in overfitting. The issue of overfitting is particularly problematic with household survey data, where data points from a dataset of multiple household surveys are clustered in space and time. Furthermore, the surveys are spatially and temporally sparse, with large swaths of the continent having no surveys. Lastly, despite being nationally-representative, the locations of measured household survey clusters within surveyed countries are not random (due to, for example, uninhabited areas of countries) which is an underlying assumption of some spatial modelling techniques.

During exploratory analysis for Chapter 2, a similar variable selection approach to the approach detailed by Weiss et al [20] for *Pf*PR was attempted for MAF and NMFI prevalence, to generate a reduced set of variables from the entire suite that most accurately predicted the prevalence of malaria-negative fever (for use in conjunction with *Pf*PR for prediction of MAF and NMFI prevalence). This approach was eventually

superseded by the BRT model for fever without a malaria infection, as detailed in Chapters 2, 4, and 5. The variable selection mechanism detailed by Weiss *et al*. [20] is computationally demanding, so during exploratory analysis for Chapter 2 a spatial leave-one-out cross-validation (SLOOCV) procedure (inspired by Le Rest and colleagues [26]) was attempted on the cluster-level household survey data points to select a set of 20 or fewer spatiotemporally dynamic geographical and socioeconomic covariates that best predict fever without a malaria infection, in a multi-phase covariate selection procedure.

For the SLOOCV procedure, one data point was removed at random from the household survey data points (which were aggregated to geo-located cluster level). All other points within an 1100km threshold distance of this data point were also removed to avoid any spatially autocorrelative effects of these points. This threshold was chosen based on the empirical variogram of malaria-negative fever prevalence at each cluster point, where the threshold distance was defined as the distance where the semivariance between points approached to the maximum (calculated using *variog* function from the *geoR* package in the R programming language). With one data point (and any points within the threshold distance) removed, generalised linear models (GLMs) were constructed, testing the relationship between each of the baseline set of covariates and prevalence of fever without a malaria infection in the remaining clusters. Using these single-covariate models, the prevalence fever without a malaria infection at the removed point was estimated. This process was iterated 100 times with different points, using an identical sampling seed to ensure comparability between covariates. Each covariate was then ranked by their log-likelihood score, calculated as follows:

$$sum((n_{obs,i} * \log(p_{predicted,i}) + (n_{tot,i} + n_{obs,i}) * \log(1 - p_{predicted,i}))$$

Where $n_{obs,i}$ is the observed number fever cases without an RDT-patent malaria infection at each removed cluster site, i, $n_{tot,i}$ is the total number of individuals tested for malaria and fever at each removed cluster site, and $p_{predicted,i}$ is the proportion of individuals predicted to have a fever without an RDT-patent malaria infection at the removed cluster site, as predicted by the fitted GLM. A less-negative (higher) score indicates a better model. Average log-likelihood scores for each covariate type group (e.g. within all vegetation index covariates, within all precipitation covariates) were calculated, and covariates were then weighted jointly and equally by their individual performance within their covariate type group, and by the performance of their covariate type group as a whole.

In the second phase of the covariate selection procedure, 2000 individual covariates from the complete set were selected using a sampling procedure where chance of an individual covariate being selected was proportional to the sum of each covariate's within-type weight, and the weight of the covariate type group (e.g. vegetation indices, temperature indices, elevation, etc.) that each covariate falls within. These 2000 covariates were then paired randomly. Each pair was then used as two explanatory variables in a second round of 100 GLMs at different removed points, and the strength of each set of paired covariates for predicting prevalence of fever without a patent malaria infection was measured using the log-likelihood score.

The third phase of the covariate selection procedure used log-likelihood scores from each of the previous rounds to construct 1000 4-covariate models, where 500 of these models contained four explanatory variables composed of two 2-covariate models from the second phase; and 500 contained four explanatory variables composed of one two-

covariate model from the second phase, and two single-covariate models from the first phase, where covariates with higher (better) log-likelihood scored in previous phases were more likely to be matched together. Despite iteratively pairing the most robust predictor variables together, the third phase groups of predictor variables returned lower (worse) log-likelihood scores than the models in the first and second phase. For this reason, a reduced suite of fewer than 10 covariates that predicted the prevalence of fever without a patent malaria infection in combination could not be identified using the SLOOCV approach.

6.3.4. Bayesian hierarchical model for estimating MAF and NMFI

The Bayesian hierarchical model used throughout this thesis (Chapters 2, 4, and 5) allowed a flexible framework for estimating desired metrics, such as the spatiotemporal prevalence of MAF, NMFI, and all-cause fever across sub-Saharan Africa (Chapter 2), and individual-level attribution of MAF and NMFI to each febrile child throughout the household survey dataset, which allowed for further derivations of nationally-representative estimates of *P. falciparum* burden (Chapter 4) and ACT coverage (Chapter 5).

The modelling approach presented in Chapter 2 allowed cartographic estimates of MAF and NMFI prevalence to be generated across the continent, but did not incorporate the influence of individual-level factors (such as household wealth, education, child age, and ITN usage) on the prevalence of MAF or NMFI. In practise, and as estimated in Chapter 5, these factors do have an effect on MAF and NMFI prevalence. In addition to incorporating these individual-level and household-level factors, the final model presented in Chapters 4 and 5 also used the adjustment for recently-treated individuals

presented in Chapter 3, and presented a re-calibration of the assumed relationship between *Pf*PR and MAF used in the model, which removed bias introduced through only using DHS Program data to learn the relationship. The model used in Chapters 4 and 5 also includes an updated set of remotely-sensed environmental variables in order provide contemporaneous BRT estimates for household survey observations in 2015 and 2016 (as the model presented in Chapter 2 uses BRT estimates up to 2014 only). Due to the paucity of continuous data on the individual-level and household-level factors, the final model presented in Chapters 4 and 5 was restricted only to provide probabilistic attributions of MAF and NMFI to febrile individuals in the household survey dataset, rather than producing updated continuous cartographic estimates of MAF and NMFI prevalence at pixel-level across the continent. This final approach did, however, provide a flexible framework for analysing the effects of indicators from the household survey datasets on the probability of MAF and NMFI. The model presented in Chapters 2, 4, and 5 was well-suited for estimation of the desired metrics and key outputs presented in each chapter, but some retrospective comments on potential improvements to the model are discussed below.

A shortcoming of the modelling approach used here was the reliance on other modelled estimates as predictor variables, namely $Pf\text{PR}_{0\text{-}5}$, $\text{BRT}_{\text{treat}}$, and BRT_{bg}. These three modelled variables were used as covariates instead of a larger set of raw remotely-sensed variables (for example, vegetation indices, road networks, elevation, aridity, and temperature variables) as the hierarchical Bayesian modelling approach was not computationally efficient with larger sets of covariates. Each of the three modelled variables used as covariates were produced with some underlying uncertainty. The uncertainties for $Pf\text{PR}_{0\text{-}5}$ are detailed in Bhatt et al. [2], although additional uncertainty was introduced via the age-standardisation procedure [23] and microscopy-to-RDT

prevalence conversion [24] prior to use in the final model presented in this thesis. For the two BRT variables, measurements of uncertainty were not generated. No associated uncertainty from any of the three covariates was propagated within the final Bayesian hierarchical model, nor would it have been computationally feasible to do so; however, propagating uncertainties would improve the coverage of the final predicted posterior credible intervals.

Other, more flexible approaches to incorporating raw remotely-sensed variables while retaining computational feasibility could be considered. The Bayesian hierarchical model presented in this analysis learnt a slope and random effect for each of the three predictor variables in order to compute a "mean function" which was used to estimate MAF and NMFI probability/prevalence. Using the 150+ remotely-sensed variables stored in the MAP repository (which were used in the analysis presented in this thesis to generate the three modelled variables used as covariates in the final model) as individual covariates would provide more flexibility to the model but would require learning a slope and random field for each, which was computationally infeasible for this analysis. Using alternative, more flexible methods such as the "stacked generalisation" approach recently presented by Bhatt and colleagues [27], where multiple non-linear mean functions are embedded within the modelling framework, would allow a far larger suite of predictor variables to be used without significant extra computational cost.

The modelling approach used in this analysis was only able to produce spatially-predictive estimates for some of the modelled metrics. Treatment-seeking probability for each fever type, for example, was learnt using the modelled predictor variables and a spatially continuous random field, and thus accounts for spatial heterogeneities in treatment-seeking. However, for other variables, such as the probability of receiving a heel- or finger-prick, or being over/under/presumptively treated, only a survey-level

effect was learnt. Learning a fully spatial effect for these variables would be useful to better understand heterogeneity in these metrics within-countries. For example, the probability of a febrile child presenting at a public health clinic receiving a parasite-based diagnosis for malaria in the Democratic Republic of the Congo in 2013-2014 was found to be 30.9%, but this is likely to vary spatially in such a vast country with a large proportion of remote habitations. By allowing all terms to learn spatial effects, modelled outputs could be more informative for identification of spatial coverage gaps for treatment and diagnostic usage in clinics. While this was not considered computationally feasible for simultaneous analysis of all 41 surveys featured in this thesis, it may be possible to adapt the approach presented here to produce a fully spatial model for a single survey.

The hierarchical Bayesian model presented in this thesis does not consider effects of co-infection of *P. falciparum* and other febrile illnesses on the probability of morbidity. Other established models, such as OpenMalaria, have identified that their simulations produce higher levels of severe disease due to *P. falciparum* than rates recorded by the World Malaria Report. A posited reason for this overestimate is that the model was calibrated on historical data, which was collated when co-infections were more common than they are now [28]. Modulating effects of co-infections were not included in the approach presented in this thesis due to the varying (and often unknown) effects of co-infection of other diseases, as well as the lack of diagnosis of co-infections within the household dataset. Future modelling efforts may seek to learn the effect of co-infection on the probability of developing febrile illness.

The analysis of the proportion of infected individuals who receive antimalarial treatment presented in Chapter 5 was not the first to attempt to do so using household survey data. Estimates of effective coverage and health systems effectiveness by Galactionova and

colleagues [29] attempted to document similar outcomes to those presented within this thesis. The analysis presented in this thesis used a fundamentally different methodology than those of Galactionova and colleagues in order to achieve similar goals. The analysis presented in this thesis used RDT-derived outcomes for estimating malaria infection prevalence (rather than using antimalarial prescriptions at the point of care as a proxy for malaria infections, as in [29]), and distinguishes between antimalarials prescribed presumptively and after a parasite-based diagnostic. Additionally, the analysis presented in this thesis assessed the contribution of household- and individual-level factors to the likelihood of receiving effective antimalarial medication, aiding identification, and targeting of coverage gaps.

Other modelling techniques for estimating the prevalence of MAF were considered alongside the final Bayesian hierarchical model during exploratory analysis for Chapter 2. Computational simulations of malaria transmission can also be adapted to estimate the proportion of individuals within populations with a symptomatic infection (i.e. a malaria-attributable fever). Mathematical models of malaria provide a framework for understanding the transmission dynamics of malaria infection [30]. Models have been widely developed to simulate the changes in the number of symptomatic malaria infections under different hypothetical intervention scenarios, such as the introduction of malaria vaccines [6, 31], possible introduction of a high-sensitivity routine diagnostic [15], and increased ITN usage [32], amongst others. The effect of these interventions is assessed by simulating the proportion of the population with a patent malaria infection under different transmission intensity and intervention scenarios. During exploratory analysis for Chapter 2, a transmission model was adapted to attempt to measure the rate of malaria-attributable fever within a four-week window with increasing *Pf*PR, with the rationale that the resulting relationship could be applied to transform cartographic

estimates of *Pf*PR produced by Bhatt *et al* [2] in order to produce estimates of the prevalence of MAF.

Using the OpenMalaria transmission model developed by researchers at the Swiss Tropical and Public Health Institute [4–7], the relationship between transmission intensity and prevalence of symptomatic infections (synonymous with malaria-attributable fevers in the context of a transmission model) in children under five years of age was simulated. A series of simulations under 30 different transmission intensities were used to estimate the proportion of children at each transmission intensity with symptomatic infections. Simulations were run under a total of 1000 parameterisations corresponding to draws from the posterior distribution, resulting from fitting of matched age-structured prevalence and clinical incidence data from 30 unique active case detection sites across *P. falciparum* endemic Africa, as described in Cameron *et al.* (2015) [33]. After a 90-year warm-up period to allow exposure-based immunity to reach equilibrium levels, the number of symptomatic infections (where probability of a symptomatic infection was a function of simulated blood parasite density as defined in [7]) within the cohort of children under 5 years of age was recorded. Figure 6.2 shows the fitted relationship from OpenMalaria between *Pf*PR in children under 5 years of age, and the proportion of all individuals under 5 years of age who experienced a symptomatic malaria infection within any given two week window. Overlain is the proportion of children under 5 within the DHS Program dataset (used throughout this thesis) who experienced a malaria-attributable fever (calculated using the empirical method described in Chapter 4) in the two weeks preceding the survey, segregated by community $PfPR_{0\text{-}5}$.

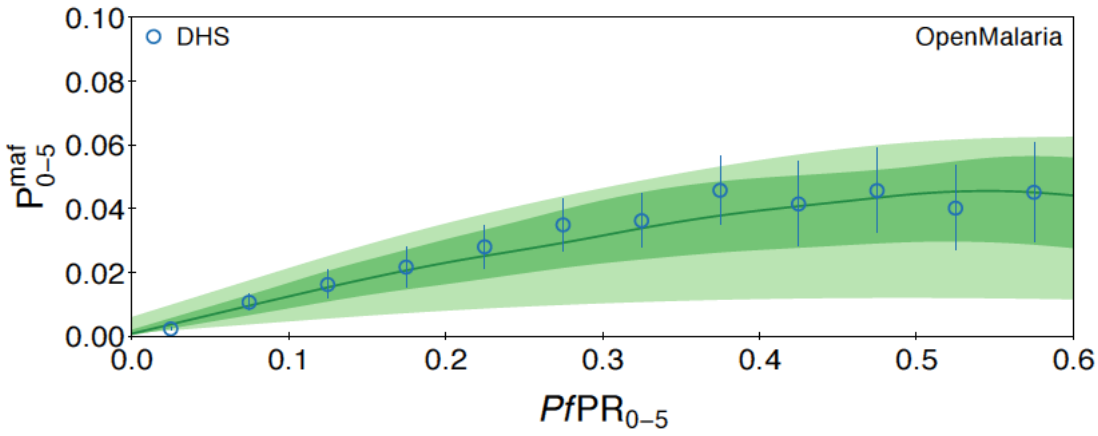


Figure 6.2. The proportion of individuals <5 years old who experienced a malaria-attributable fever within the two weeks preceding the survey, stratified by *Pf*PR$_{0-5}$, as inferred from the household survey data (median represented by blue points, and 95% credible intervals by intersecting lines), and as predicted by OpenMalaria under the parametrisation defined in Cameron *et al*. (2015) [33] (median represented by dark green line, 95% and 68% credible intervals by dark and light green bands respectively). This graphic was produced by Ewan Cameron.

This approach was useful for estimating the relationship between MAF and *Pf*PR, and showed remarkable similarity in modelled MAF estimates compared to MAF calculated empirically from the DHS Program data. This approach did not, however, allow for estimation of the prevalence malaria-positive fevers where malaria was not the underlying cause of the fever, nor did it allow for estimation of NMFI prevalence. For this reason, the Bayesian hierarchical model was implemented, and the OpenMalaria simulations were used to fit the relationship between MAF and *Pf*PR in the Bayesian hierarchical model (Chapter 2).

6.4. Interpretation and implications

A multitude of outputs are presented in this thesis, but the key intentions were to: *i)* provide new insights into the contribution of malaria to the burden of paediatric fever, and *ii)* assess the coverage of effective antimalarial treatment for malaria infections. The implications of individual chapters, and the key outputs as a whole, are discussed in this sub-section.

6.4.1. Cartographic estimates of MAF and NMFI

The maps presented in Chapter 2 represent the first quantitative cartographic estimates of all-cause fever and NMFI, and can be used by epidemiologists to identify hotspots of paediatric febrile illness, and can be used in conjunction with qualitative databases of neglected febrile illnesses, such as the database collated by the Worldwide Antimalarial Resistance Network (WWARN) [34]. Although the maps presented here do not attribute NMFI to individual diseases, the maps can be used as an indicator for public health officials on paediatric fever burden; this is particularly important given fever, as a syndrome, is not currently quantified by the ongoing Global Burden of Disease (GBD) studies, unlike other common syndromes such as diarrhoea and anaemia [35, 36]. Estimates of the burden of diseases are intended to provide a benchmark across which the relative contributions of each disease to ill-health can be assessed [37]. While the global burden of *P. falciparum* malaria is quantified annually for the WHO's World Malaria Report [38], and the Institute for Health Metrics and Evaluation's (IHME) GBD study [39], less is known about the prevalence and burden of other individual diseases that contribute to the overall burden of paediatric fever. Future research should focus on providing cartographic estimates of neglected NMFI, to compliment the results presented

here and those from other mapping studies such as those for dengue virus transmission [40, 41], *P. vivax* malaria [42], *P. knowlesi* malaria [43], Zika virus [44], soil-transmitted helminths [45], lymphatic fileriasis [46], leishmaniasis [47], Lassa fever [48], and trachoma [49]. Increasing the availability of maps for neglected tropical diseases (NTDs) will aid in expanding the information available to health professionals seeking to understand the prevalent febrile illnesses in their local area, as well as providing valuable data for spatially-specific targeting of inventions that reduce local transmission [50].

The results of this research demonstrate the need for multi-analyte routine diagnostics for NMFI in Africa capable of differentiating causes of NMFI. The WHO, the Foundation for Innovative New Diagnostics (FIND) and Médecins Sans Frontières (MSF) are in preliminary stages are attempting to develop a multiplex diagnostic for acute febrile illness, and these projects are presently identifying the most appropriate suite of disease analytes to screen in a clinical setting [51]. Due to anticipated costs, such a diagnostic would initially be deployed only in inpatient settings and as such would not provide diagnoses of NMFI in forthcoming DHS Program surveys. However, increasing availability of routine diagnostics for NMFIs in outpatient consultations would aid effective fever management, as well as provide parasite-based diagnostic information which can be used for mapping NMFIs.

By establishing the framework of modelling treatment effectiveness for MAF and malaria-coincident fevers separately, the estimates provided here can be used to advise clinicians on the proportion of malaria-positive fevers presenting at outpatient clinics that may not be resolved due to undiagnosed co-infection with NMFI. The results presented here are not intended to dissuade clinicians from giving antimalarials, but highlight the need for adherence to Integrated Management of Childhood Illness (IMCI) guidelines for investigation of alternative causes of fever, regardless of RDT outcome.

6.4.2. Duration of RDT positivity after successful antimalarial treatment

The estimates presented in Chapter 3 showed that RDTs remain positive for a highly variable amount of time after successful antimalarial treatment, depending on the age, medication received, and RDT used to diagnose the patient. The results presented here are intended to be of use to epidemiologists for essential adjustments of parasitaemia data with paired recalled fever history, as described for the household survey data in Chapters 4 and 5 of this thesis. The results are also intended to be of use for clinicians to assess the probability of a febrile illness in a recently-treated RDT-positive individual being due to either NMFI with persistent antigenicity from the recently cleared malaria infection, or due to malaria re-infection or recrudescence. The results may also be of use for contextualising *P. falciparum* burden estimates given these are often based on reported incidence, which in turn is increasingly based on RDT diagnoses. This thesis also represents the first published collation of uncoordinated literature on this topic, providing estimates for duration of persistence of RDT positivity after antimalarial treatment, with robust uncertainties.

6.4.3. Individual-level attribution of MAF and NMFI to febrile individuals in household survey datasets and overestimation of the malaria burden

In Chapters 4 and 5, attribution of MAF and NMFI (which can affect individuals with either positive or negative RDTs at the time of interview) for each febrile individual in the household survey dataset provides new insights into the factors that affect the likelihood of a malaria-infected individual receiving effective antimalarial treatment. The

attribution of MAF and NMFI to febrile individuals within the household survey data adds value to the DHS Program dataset, by enabling distinction between fevers that are simply coincident with a malaria infection, and those that are causally attributable to malaria. The final Bayesian hierarchical model presented in Chapter 4 was the first of its kind to incorporate a calibration of the relationship between MAF and $Pf\text{PR}_{0\text{-}5}$ from such a wide variety of sources and MAF estimation techniques. Future work should focus on extending this calibration to be valid for children and adults over 5 years of age. Older age groups may show different relationship profiles due to exposure-related immunity in highly endemic areas [52], which would fundamentally alter the ratios of MAF and NMFI attributed to febrile individuals amongst surveys of older age groups. Extending this work to cover all age groups would allow the methods presented in this thesis to be adapted meaningfully to estimate prevalence of MAF and malaria-positive fevers for all ages. If the outputs produced by the modelling approach used in this thesis can be adapted to produce estimates of incidence (i.e. the number of expected cases in a year) of MAF and malaria-positive fevers, the mismatch between adjusted-case-count methods and cartographic methods (as described in Chapter 4) can be appropriately addressed. This may, however, be fundamentally impossible to estimate at a continental scale; estimating disease incidence from prevalence data requires knowledge of the duration of symptomatic illness [33]. This factor is well-characterised within transmission models for malaria-attributable fever, but for estimating incidence of malaria-positive fevers (regardless of the fever's underlying cause), information on the duration of symptomatic NMFI is also required. Such information is impossible to measure in practise due to the heterogeneity of underlying causes of NMFI across the continent [34], and the lack of diagnosis of NMFI in survey data.

6.4.4. ACT coverage

The population-weighted analysis of household survey data in Chapter 5 showed that, across 41 surveyed country-years in sub-Saharan Africa, only 7.9% of malaria-infected children received an ACT in the two weeks preceding the household survey. The primary reason why children did not receive an ACT was because their infections were not accompanied by a fever during the two weeks preceding the survey, highlighting the importance of asymptomatic malaria infections as a potential reservoir of onwards transmission. Conversely, the majority of successfully treated malaria infections were asymptomatic malaria infections, for which care was sought and antimalarial treatment was received only because they were co-incident with NMFI (Chapter 4, Figure 4.3). These highlight the role of NMFI in bringing asymptomatic malaria infections to clinics for treatment. Programmatically, the most worrying statistic was that, amongst febrile malaria-infected children who sought treatment at a formal facility, only slightly over half received an antimalarial of any kind at the facility they visited.

Chapter 5 identified numerous coverage gaps for treatment-seeking and ACT coverage. Febrile children from poorer households were less likely to be taken for treatment. Amongst children who were taken for treatment, children with MAF from poorer and less-educated households were also less likely to receive an ACT (with the exception of children from households where the caregiver had higher education; the potential reasons for this are discussed in Chapter 5). Fewer than half of febrile children received a diagnostic test prior to treatment, although the fraction receiving a diagnostic test increased in later studies relative to earlier studies. Countries with low malaria burden typically also had low levels of antimalarial prescription for malaria-positive fevers, suggesting that clinicians in these countries either did not presume that febrile illnesses were due to malaria, or that antimalarial drugs were not readily available. This outcome

has potentially serious implications for eliminating *P. falciparum* in low-burden settings despite the substantial resources being allocated to reduce malaria in such locations. In high malaria burden countries, although the prescription rate for antimalarials of any type was high, the proportion of those that were ACTs was low, in spite of WHO recommendations that ACTs be used as first-line treatment in all sub-Saharan countries. The results presented in Chapter 5 suggest that closing coverage gaps in treatment-seeking and ACT coverage for low-income, poorly educated, deprived areas would be the most effective way to increase the number of malaria infections and MAF cases that receive effective antimalarial treatment.

6.4.5. Broader outcomes and implications of the results

Given the flexibility of the modelling approach used in this thesis, a priority for disseminating the outcomes of this thesis is to make the code and datasets publicly available for other users to adapt. At the time of writing (September 2018), the code for the Bayesian hierarchical model and BRT model, as presented in Chapter 2, are currently available to the public on the MAF-NMFI GitHub designed for this project [53], and the code for generating the probabilistic attributions of MAF and NMFI and revised BRT code will be made publicly available on the GitHub after Chapters 4 and 5 are published in peer-reviewed journals. The R and C++ code used in Chapters 4 and 5 for the Bayesian hierarchical model is included in the Appendix for Chapter 4. DHS Program data must be requested and downloaded via the DHS Program website [1], but users of these datasets can adapt the models presented in this thesis to attribute MAF and NMFI to individuals within the household survey datasets. The flexibility of the modelling approach used in this thesis allows users to investigate the effect of any indicator within

the household survey dataset on MAF and NMFI, in addition to the indicators assessed within the scope of this thesis (treatment-seeking and medication coverage, public and private facility performance, and effects of factors such as age, education, wealth, and ITN use).

The key outputs from Chapters 2, 4, and 5 from this thesis represent a synthesis of the best available data and, within the expertise of the co-authors of each chapter, the most appropriate modelling methodologies and outputs. There is potential, however, for the results presented here to be extended beyond the scope of this thesis to provide meaningful and useful metrics for malaria burden estimations and measurements of antimalarial coverage across the African continent.

Should the prevalence of *P. falciparum* malaria continue to decrease across sub-Saharan Africa, the proportion of paediatric febrile illnesses that are attributable to *P. falciparum* is predicted to also decrease. Progress in reducing malaria prevalence is strongly tied to funding for malaria interventions and research, which has remained stagnant for the past half-decade and is provided inequitably between malaria-endemic nations [37, 54]. This is concerning as previous research suggests *P. falciparum* elimination without elevated levels of domestic funding is unlikely [55]. With the direction of the changing burden of *P. falciparum* malaria uncertain, the future burden of MAF (compared to other causes of febrile illness) also remains uncertain. Future efforts to assess the relationship between MAF and *Pf*PR would benefit from providing a focus on assessing changes in the relationship profile with recent declines in *Pf*PR, usage and effectiveness of antimalarial treatment and prophylaxis in the local community, and assessing the relationship profile amongst different age groups. Among these factors, the effect of age was not explored within the scope of this thesis due to limited data availability for older age groups. A broader analysis of the relationship between MAF and *Pf*PR will allow targeting of

interventions to most at-risk groups (i.e. groups most likely to develop MAF within a community with a certain *Pf*PR). The models and code provided by this thesis establish a framework to do so, but at the present time no appropriate datasets are publicly available to support this analysis. Researchers may opt instead to use established transmission models to estimate the effects of changing *Pf*PR and treatment rates on MAF [33], although these preclude estimation of the prevalence of malaria-positive fevers not causally attributable to *P. falciparum* infection.

6.5. Conclusions

This thesis had two major aims: to estimate the proportion of *P. falciparum* malaria-positive fevers that are causally due to malaria in children under 5, and to estimate the proportion of *P. falciparum* infections in children under 5 that receive effective antimalarial treatment. In Chapter 2, cartographic estimates of the proportion of all-cause fevers experienced by children in sub-Saharan Africa between 2006-2014 that were malaria-positive and malaria-attributable were presented. These results highlighted the large proportion of malaria-positive fevers that were causally attributable to NMFI at community-level. At the clinic-level, where malaria-positive fevers were typically recorded as "malaria cases" and subsequently used for burden estimation, Chapter 4 showed that the majority of these malaria-positive fevers were causally attributable to NMFI. Finally, in Chapter 5, the coverage of ACT and non-ACT antimalarials for 41 surveyed country-years was presented, and coverage gaps for access to antimalarials and treatment-seeking were identified at individual-level, household-level, community-level, clinic-level, and nationally. By using a modelling approach that segregated malaria-positive fevers by underlying cause (i.e. MAF or NMFI), the role that NMFI has in bringing asymptomatic malaria infections to clinics for treatment was highlighted.

The research presented in this thesis represents a synthesis of the best-available datasets and modelling approaches for estimating the metrics of interest. The analytical framework used can be continually updated and improved as new data becomes available. The framework used is also highly flexible, allowing for the effects of multiple factors on MAF and NMFI probability to be assessed; the model code has been made publicly available [53] for that purpose.

It is the hope that this thesis can be informative for a wide audience. For epidemiologists measuring the burden of *P. falciparum* malaria, this thesis can provide quantitative insights into the difference between burden estimation methods (i.e. the adjusted case-count approach and the cartographic approach, detailed in Chapter 4). For researchers and public health officials aiming to improve ACT coverage or treatment-seeking rates at formal facilities, or identify countries where clinics are failing to adhere to guidelines for treatment of paediatric fevers, this thesis provides estimates of these metrics between 2006 and 2016 and an analytical framework for measuring future changes. Finally, for researchers investigating the prevalence of causative agents of NMFI, this thesis provides maps of the prevalence of NMFI to guide and target future research.

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Symptomatic illness and treatment of *Plasmodium falciparum* malaria in African children

Appendix

Appendix to Chapter 2 - Quantifying the contribution of *Plasmodium falciparum* malaria to febrile illness amongst African children

This appendix includes:

1. Figure 1 – Figure Supplement 1: The histogram of the probability integral transform diagnostic.
2. Figure 5 – Figure Supplement 1: Model fits and validation.
3. Supplementary File 1: Yearly population-weighted percentages for all-cause fever prevalence, and malaria-attributable fever, malaria-positive fever, and non-malarial febrile illness within all-cause fever amongst population at risk in children under 5 years of age in malaria-endemic Africa, 2006–2014.
4. Supplementary File 2: Household survey data used in analysis.
5. Supplementary File 3: Covariates used in BRT, listed by contribution to the final model.
6. Supplementary File 4: Model parameters and credible intervals of the final multinomial model; final model coefficients.

An additional household survey for Sudan 2012 was used in analysis but not reported in the published manuscript due to confidentiality restrictions.

All supplementary materials for this chapter are available online at:
https://elifesciences.org/articles/29198/figures

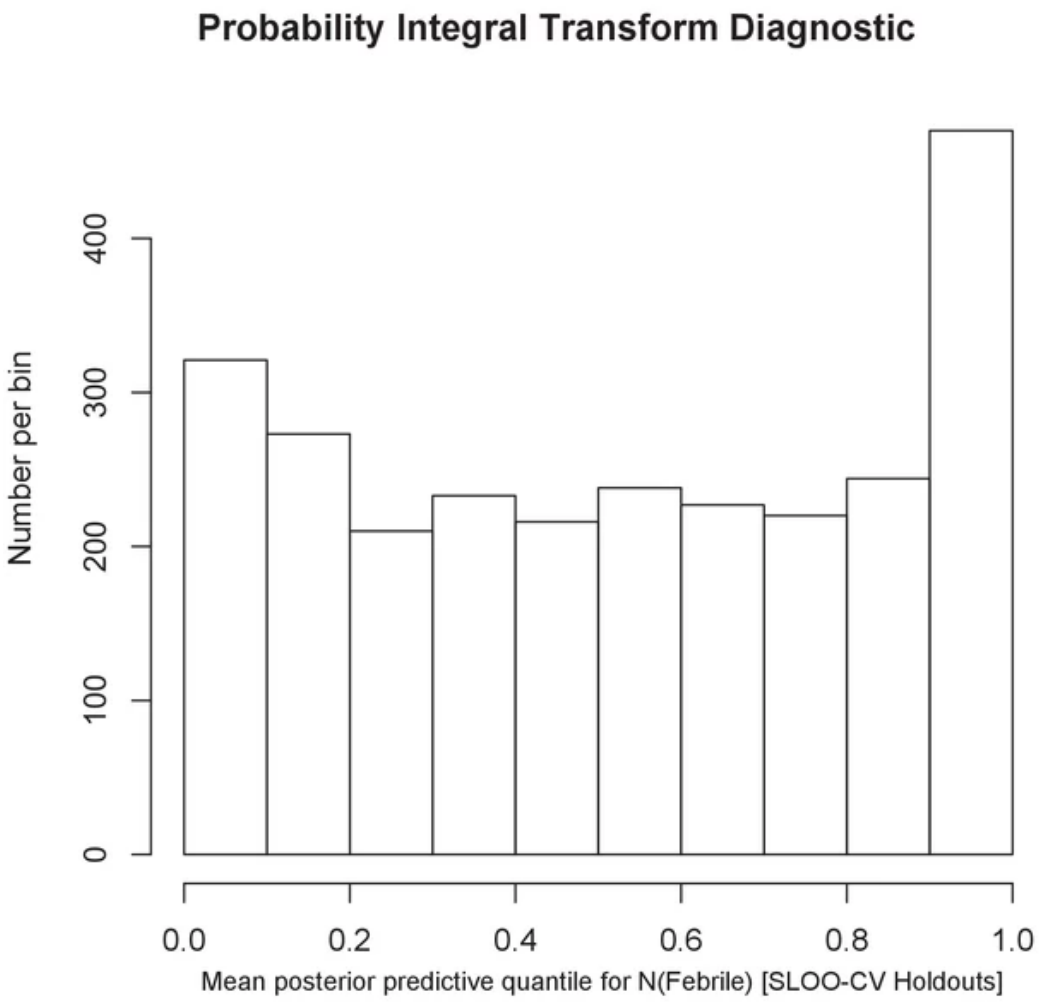


Figure 1 - figure supplement 1. The histogram of the probability integral transform diagnostic.

The uniform shape of the histogram shows that predictions at sites held out from the initial model drawn from the predicted posterior distribution for the prevalence of febrile illness matched well.

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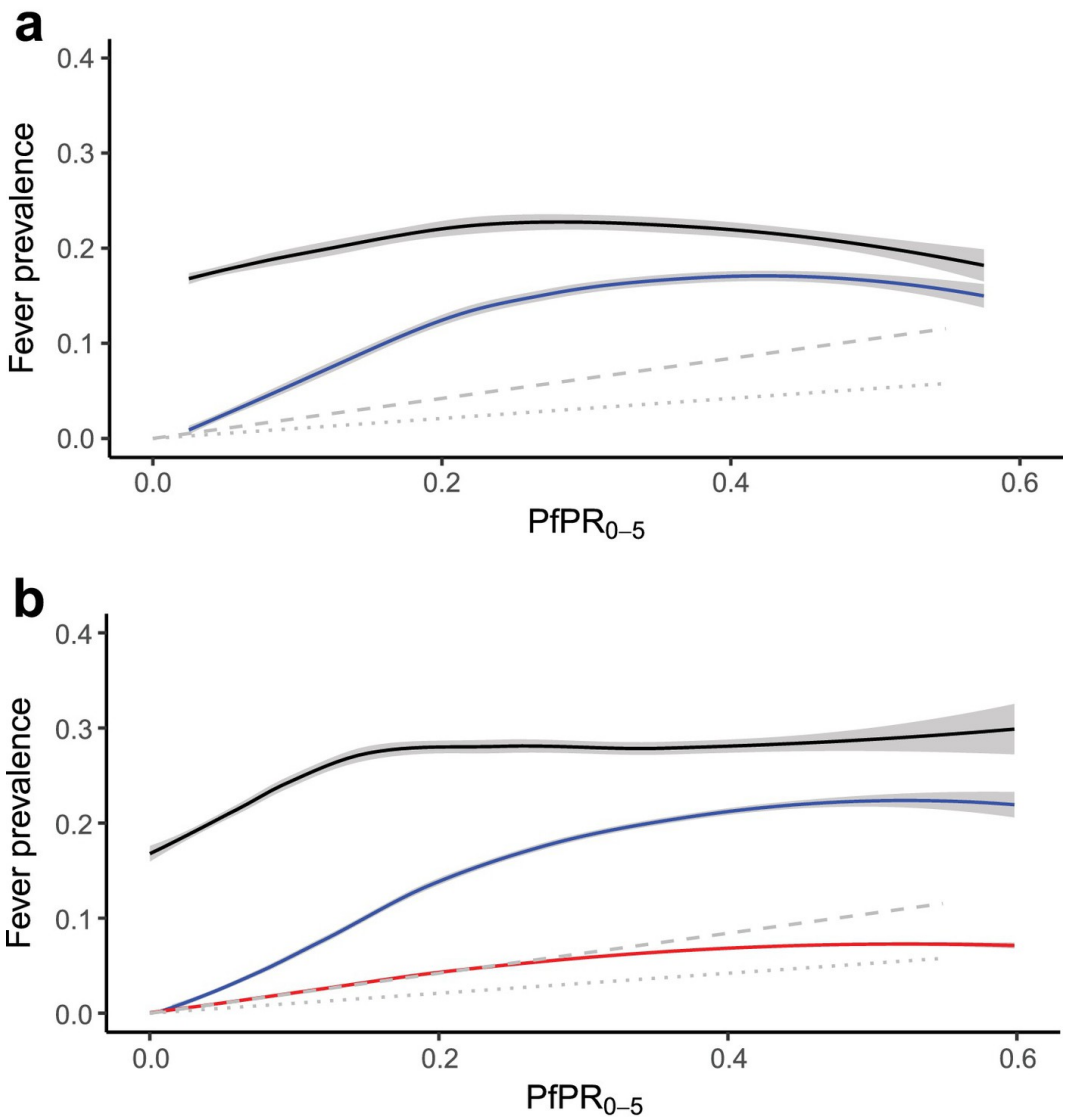


Figure 5 - figure supplement 1: Model fits and validation.
(a) Response data relationship between all-cause fever (black line) and malaria-positive fevers (blue line), and predicted incidence (symptomatic illness) for the duration of the past zero to four weeks (grey dashed line) and past zero to two weeks (grey dotted line)* with *Pf*PR0-5 from household survey datasets; and **(b)** the modelled relationship between all-cause fever (black line), malaria-positive fevers (blue line), and malaria attributable fevers (red line), and predicted incidence in the past zero to four weeks (grey dashed line) and past zero to two weeks (grey dotted line)* with *Pf*PR0-5 sampled from 10,000 pixels in predicted raster layers. Mean lines were fitted using locally-weighted regression, and shaded with 95% confidence intervals.
*In both plots, the predicted incidence lines are generated from an ensemble of transmission models estimating the relationship between *P. falciparum* prevalence and incidence, standardised to ages 0 to 4 years old (Cameron *et al.*, 2015). The grey dashed line depicts the

estimated proportion of children in the past zero to four weeks who had a clinical episode of malaria, and the grey dotted line depicts the estimated proportion of children in the past zero to two weeks who had a clinical episode of malaria, each with increasing *P. falciparum* malaria prevalence. A good fit between predicted MAF and transmission model estimations of clinical incidence indicates our model has strong predictive performance.

Supplementary File 1: Yearly population-weighted percentages for all-cause fever prevalence, and malaria-attributable fever, malaria-positive fever, and non-malarial febrile illness within all-cause fever amongst population at risk in children under 5 years of age in malaria-endemic Africa, 2006-2014.

2006

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	3386167	19.83	44.83	53.52	76.01
Benin	1454960	31.48	51.65	32.99	82.96
Botswana	123844	12.80	2.73	61.30	98.33
Burkina Faso	2546073	25.70	80.08	45.99	63.17
Burundi	1279756	25.10	48.02	43.57	79.08
Cameroon	3160350	22.62	64.69	51.21	66.87
Central African Republic	621620	30.32	81.50	36.39	70.34
Chad	1994888	29.90	31.94	34.27	89.06
Congo	600786	29.93	51.64	35.16	81.84
Cote d'Ivoire	2799296	19.49	81.06	60.25	51.16
Democratic Republic of the Congo	9976559	24.67	79.12	44.81	64.54
Djibouti	13802	8.43	10.41	74.49	92.25
Equatorial Guinea	92547	36.72	78.16	17.97	85.95
Eritrea	841322	6.49	6.02	77.78	95.32
Ethiopia	11658963	22.85	7.56	41.68	96.85
Gabon	207182	30.22	21.04	35.01	92.63
Gambia	269213	20.57	12.25	47.00	94.24
Ghana	3279539	30.60	58.56	34.09	80.04
Guinea	1643448	37.87	51.53	26.48	86.36
Guinea-Bissau	238089	9.15	28.29	69.48	80.35
Kenya	5262909	26.51	11.49	34.82	96.00
Liberia	585744	50.67	54.60	17.70	90.34
Madagascar	3096560	26.70	26.47	39.70	89.49
Malawi	2371328	29.12	58.32	36.72	78.58
Mali	2301398	33.61	45.64	32.04	85.37
Mauritania	404505	16.48	7.88	55.37	95.64
Mozambique	3965700	18.72	67.94	57.55	60.90
Namibia	199589	28.87	10.48	38.48	95.97
Niger	2784610	55.08	43.31	14.77	93.60
Nigeria	25009397	38.11	59.36	25.87	84.65
Rwanda	1283519	11.16	19.48	68.73	86.61
Senegal	1964809	12.98	20.91	64.06	86.61
Sierra Leone	879657	34.25	57.36	31.53	81.91
Somalia	1647691	10.94	15.75	67.05	89.44
South Africa	724213	13.48	12.91	59.53	92.31
South Sudan	1363828	21.94	47.66	39.25	81.29
Sudan	5066206	18.46	10.44	44.35	95.37
Swaziland	3159	15.39	0.49	65.04	99.68
Togo	915710	30.33	69.81	36.15	74.76
Uganda	5739776	21.74	71.51	49.55	64.57
United Republic of Tanzania	6962126	20.81	35.83	44.74	83.97
Zambia	2197577	20.67	33.08	49.66	83.57
Zimbabwe	1842439	17.50	6.01	51.35	96.91

2007

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	3497368	19.43	38.47	52.73	79.72
Benin	1486989	32.70	49.22	31.66	84.42
Botswana	124635	14.45	2.42	59.31	98.56
Burkina Faso	2610544	26.73	80.94	43.93	64.44
Burundi	1339422	19.40	50.81	53.98	72.58
Cameroon	3228558	22.30	61.68	51.63	68.15
Central African Republic	625125	29.96	78.18	37.03	71.05
Chad	2049821	17.24	34.67	54.47	81.12
Congo	619377	27.63	47.67	38.34	81.72
Cote d'Ivoire	2823457	19.13	80.01	61.10	51.12
Democratic Republic of the Congo	10208555	25.73	78.07	42.30	66.98
Djibouti	13809	8.38	7.88	73.30	94.22
Equatorial Guinea	95115	27.82	76.03	28.14	78.60
Eritrea	871449	5.98	5.76	79.34	95.43
Ethiopia	11739530	24.23	5.93	39.65	97.65
Gabon	212039	41.80	14.44	23.69	96.58
Gambia	276874	22.97	9.33	44.36	95.86
Ghana	3350110	28.86	58.51	36.29	78.76
Guinea	1676402	29.05	53.97	36.72	80.18
Guinea-Bissau	242171	28.50	12.90	31.57	95.93
Kenya	5393059	26.99	9.31	33.61	96.87
Liberia	604904	50.12	51.56	18.15	90.64
Madagascar	3147920	26.59	23.15	39.70	90.81
Malawi	2463307	37.91	57.36	26.33	84.90
Mali	2379716	30.59	42.87	35.26	84.88
Mauritania	413187	18.97	6.37	50.68	96.77
Mozambique	4047797	18.43	64.62	56.71	63.35
Namibia	199036	27.16	8.85	40.41	96.42
Niger	2888182	56.96	45.11	13.64	93.85
Nigeria	25733491	41.43	58.32	22.56	86.84
Rwanda	1328505	12.22	15.50	65.85	89.79
Senegal	2018925	12.20	18.39	66.09	87.85
Sierra Leone	891570	34.78	57.16	30.97	82.29
Somalia	1686312	9.84	10.85	68.09	92.61
South Africa	735976	12.66	9.44	61.75	94.17
South Sudan	1410885	21.43	46.14	39.24	81.89
Sudan	5132096	17.34	9.47	45.82	95.66
Swaziland	3198	11.88	0.44	70.98	99.69
Togo	937633	28.58	70.68	38.77	72.60
Uganda	5912545	23.74	67.39	44.42	70.07
United Republic of Tanzania	7200272	22.00	31.64	42.20	86.65
Zambia	2248015	18.55	29.31	53.12	84.43
Zimbabwe	1863460	16.11	6.72	54.35	96.35

2008

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	3606293	16.85	30.05	57.23	82.80
Benin	1518332	33.02	45.17	31.72	85.67
Botswana	125522	18.44	1.81	52.23	99.06
Burkina Faso	2674710	25.94	84.02	45.45	61.82
Burundi	1403381	24.66	43.90	43.66	80.83
Cameroon	3296136	31.43	49.86	36.09	82.00
Central African Republic	628567	23.08	79.70	50.66	59.63
Chad	2103405	18.13	33.23	51.98	82.73
Congo	638329	29.43	42.52	35.23	85.02
Cote d'Ivoire	2851809	22.25	74.34	53.05	60.56
Democratic Republic of the Congo	10441556	36.51	72.06	26.94	80.58
Djibouti	13830	6.44	6.59	79.68	94.75
Equatorial Guinea	97798	27.85	63.30	28.91	81.70
Eritrea	900880	6.22	5.31	78.92	95.81
Ethiopia	11810520	24.10	3.25	41.86	98.64
Gabon	217064	38.74	14.15	26.22	96.29
Gambia	284740	23.01	8.15	44.58	96.37
Ghana	3419110	27.81	58.34	37.80	77.95
Guinea	1710916	22.88	59.29	47.40	71.90
Guinea-Bissau	246315	29.32	12.41	30.76	96.18
Kenya	5517235	26.52	8.63	34.12	97.06
Liberia	624125	52.51	47.43	16.81	92.03
Madagascar	3201004	22.31	19.12	45.85	91.23
Malawi	2557239	28.69	66.25	37.81	74.95
Mali	2460173	29.59	37.90	36.29	86.24
Mauritania	421759	17.11	7.15	54.42	96.11
Mozambique	4120796	28.37	53.68	37.16	80.05
Namibia	198531	31.36	6.62	36.27	97.60
Niger	2995883	53.37	49.49	15.39	92.38
Nigeria	26476056	38.72	58.66	24.85	85.42
Rwanda	1381127	11.47	14.44	67.65	90.23
Senegal	2074713	26.55	11.44	39.64	95.47
Sierra Leone	900354	37.73	59.87	27.90	83.30
Somalia	1726066	9.47	5.65	71.85	95.94
South Africa	747053	14.95	4.82	57.50	97.23
South Sudan	1460052	21.98	45.11	36.95	83.33
Sudan	5192323	21.02	7.38	40.62	97.00
Swaziland	3241	12.24	0.38	69.47	99.74
Togo	959846	32.89	67.56	32.98	77.72
Uganda	6085969	39.61	60.88	23.29	85.82
United Republic of Tanzania	7441541	21.30	27.64	43.25	88.04
Zambia	2300095	17.35	26.33	54.39	85.68
Zimbabwe	1887588	16.76	6.31	53.53	96.62

2009

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	3710362	36.67	16.39	27.92	95.42330232
Benin	1548917	27.70	43.67	38.39	83.23663081
Botswana	126366	16.67	2.16	55.82	98.7961605
Burkina Faso	2738009	27.16	85.01	42.21	64.11521501
Burundi	1468973	22.53	45.45	47.00	78.63969121
Cameroon	3362776	27.58	46.50	40.72	81.06544285
Central African Republic	632589	23.87	76.45	48.73	62.74648168
Chad	2156113	17.53	32.92	53.14	82.50582264
Congo	657226	29.83	39.55	34.22	86.46861526
Cote d'Ivoire	2888243	22.27	70.78	52.87	62.58006995
Democratic Republic of the Congo	10674930	36.61	68.73	26.59	81.72177784
Djibouti	13873	4.93	5.03	84.25	95.76464704
Equatorial Guinea	100502	23.38	50.45	35.60	82.0386842
Eritrea	929358	6.61	4.88	77.48	96.21742942
Ethiopia	11881679	24.50	1.74	42.03	99.2689042
Gabon	222166	38.00	18.87	26.57	94.98624423
Gambia	292905	16.50	6.20	56.68	96.48763543
Ghana	3484718	26.92	61.56	38.52	76.28732247
Guinea	1746002	30.10	53.64	35.60	80.90354532
Guinea-Bissau	250535	31.74	12.63	28.65	96.38153401
Kenya	5633447	26.84	9.90	32.34	96.79837115
Liberia	642423	53.41	44.29	16.37	92.7517001
Madagascar	3257193	18.14	16.35	53.37	91.27700329
Malawi	2646651	28.81	70.18	37.75	73.50779308
Mali	2542579	16.34	45.97	59.71	72.55220484
Mauritania	430172	15.94	7.01	56.64	96.03019195
Mozambique	4187847	17.93	64.48	57.50	62.92648608
Namibia	198126	26.84	5.74	42.29	97.57222487
Niger	3108686	49.19	52.88	18.02	90.46822147
Nigeria	27236424	43.73	52.56	20.30	89.33211962
Rwanda	1435054	22.46	9.10	46.52	95.76799958
Senegal	2131847	26.80	11.26	39.85	95.51349362
Sierra Leone	907356	36.44	61.59	29.36	81.91764208
Somalia	1766517	8.50	4.19	76.14	96.81132658
South Africa	755874	11.92	7.41	63.52	95.29214915
South Sudan	1510829	27.22	40.46	29.83	87.93017424
Sudan	5248904	21.34	6.85	40.59	97.21833994
Swaziland	3284	12.59	0.83	67.32	99.44334694
Togo	982224	38.28	64.33	26.38	83.03218517
Uganda	6259787	41.30	62.37	21.37	86.67232895
United Republic of Tanzania	7679036	21.76	26.67	42.05	88.78739113
Zambia	2356104	18.42	26.94	52.32	85.90360879
Zimbabwe	1914175	22.02	5.48	45.29	97.51877919

2010

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	3806800	36.36	15.23	28.20	95.71
Benin	1578644	25.35	42.43	41.78	82.27
Botswana	127026	15.60	1.89	57.95	98.90
Burkina Faso	2799846	24.40	85.46	48.04	58.95
Burundi	1533600	22.78	41.04	45.84	81.19
Cameroon	3428132	29.60	41.52	36.63	84.79
Central African Republic	637857	29.69	71.24	38.12	72.84
Chad	2208386	33.55	24.22	28.35	93.13
Congo	675646	25.91	39.44	39.47	84.43
Cote d'Ivoire	2936976	19.15	71.23	60.22	57.10
Democratic Republic of the Congo	10908065	38.12	64.55	24.80	83.99
Djibouti	13943	6.50	3.64	79.93	97.09
Equatorial Guinea	103132	27.75	44.30	38.13	83.11
Eritrea	956585	4.42	6.53	85.02	94.45
Ethiopia	11962762	24.23	1.53	42.09	99.35
Gabon	227259	29.04	25.40	35.05	91.10
Gambia	301476	15.60	5.57	58.29	96.75
Ghana	3544975	22.67	67.60	46.62	68.48
Guinea	1780695	29.55	53.68	36.32	80.50
Guinea-Bissau	254847	33.15	13.73	27.59	96.21
Kenya	5739385	28.70	10.69	30.30	96.76
Liberia	658777	51.34	40.02	17.74	92.90
Madagascar	3317997	15.16	14.70	58.36	91.42
Malawi	2724888	35.67	63.97	28.59	81.71
Mali	2626823	29.85	37.73	35.08	86.76
Mauritania	438375	15.44	4.60	56.67	97.39
Mozambique	4251863	29.51	54.71	34.79	80.96
Namibia	197881	27.96	4.50	40.43	98.18
Niger	3227770	56.81	54.49	12.96	92.94
Nigeria	28014645	43.03	50.11	20.63	89.66
Rwanda	1484010	18.39	9.91	52.92	94.75
Senegal	2190056	25.72	11.01	40.84	95.50
Sierra Leone	913852	40.22	62.35	25.31	84.22
Somalia	1807259	9.13	3.35	75.04	97.48
South Africa	760775	13.32	6.28	59.60	96.26
South Sudan	1562778	26.10	41.45	30.92	87.19
Sudan	5303709	21.12	6.49	40.82	97.35
Swaziland	3322	11.43	1.57	69.13	98.91
Togo	1004646	31.75	65.09	33.49	78.20
Uganda	6433758	40.98	58.85	21.23	87.51
United Republic of Tanzania	7905709	20.01	25.13	45.32	88.61
Zambia	2418492	15.65	30.61	57.58	82.38
Zimbabwe	1942672	18.39	4.69	51.31	97.59

2011

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	3893356	37.66	16.02	26.85	95.70
Benin	1607422	26.96	38.87	39.23	84.75
Botswana	127391	17.33	1.64	54.38	99.11
Burkina Faso	2859740	26.53	81.22	43.84	64.39
Burundi	1595255	37.99	30.64	26.34	91.93
Cameroon	3491918	29.78	37.21	35.44	86.81
Central African Republic	644900	28.50	70.09	39.91	72.02
Chad	2260552	27.23	23.83	37.10	91.16
Congo	693261	27.06	38.15	38.11	85.46
Cote d'Ivoire	3001444	29.22	58.57	39.02	77.15
Democratic Republic of the Congo	11140484	35.43	59.34	27.63	83.61
Djibouti	14045	6.37	5.99	79.69	95.23
Equatorial Guinea	105616	16.54	62.55	61.29	61.66
Eritrea	982313	7.02	3.75	77.53	97.10
Ethiopia	12061418	23.69	1.36	43.07	99.41
Gabon	232275	41.24	24.73	23.24	94.25
Gambia	310540	19.94	4.75	49.96	97.63
Ghana	3598290	18.07	70.23	58.79	58.71
Guinea	1814248	34.96	52.28	29.66	84.49
Guinea-Bissau	259266	27.88	15.87	33.45	94.69
Kenya	5833110	27.76	11.36	31.06	96.47
Liberia	672372	52.98	39.37	16.68	93.43
Madagascar	3384646	16.11	10.87	58.16	93.68
Malawi	2786662	26.40	63.04	41.25	73.99
Mali	2712848	29.02	39.79	36.20	85.60
Mauritania	446322	15.76	4.20	56.19	97.64
Mozambique	4315033	17.41	63.33	58.68	62.84
Namibia	197842	27.36	4.53	41.78	98.11
Niger	3354137	29.43	59.89	35.94	78.48
Nigeria	28811037	40.71	48.91	22.45	89.02
Rwanda	1523094	15.49	10.87	58.42	93.65
Senegal	2249147	22.19	10.27	45.34	95.34
Sierra Leone	920814	40.51	60.39	25.11	84.84
Somalia	1847984	9.49	3.88	74.05	97.13
South Africa	760421	12.39	5.97	63.02	96.24
South Sudan	1615581	21.18	41.40	37.93	84.30
Sudan	5358148	16.79	6.88	48.14	96.69
Swaziland	3354	10.33	1.65	71.33	98.82
Togo	1027022	36.68	59.00	27.85	83.57
Uganda	6607697	35.22	52.88	26.63	85.92
United Republic of Tanzania	8115973	22.31	18.37	41.38	92.40
Zambia	2489238	20.51	24.15	47.90	88.43
Zimbabwe	1972688	17.92	4.52	52.52	97.62

2012

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	3970700	36.51	17.46	27.77	95.15
Benin	1635299	11.30	59.68	73.59	56.08
Botswana	127486	15.08	1.58	56.97	99.10
Burkina Faso	2917829	34.38	73.62	31.71	76.66
Burundi	1654316	44.15	26.10	21.22	94.46
Cameroon	3554232	30.63	35.73	33.66	87.97
Central African Republic	653583	28.65	68.97	39.90	72.48
Chad	2312573	34.85	21.43	27.04	94.21
Congo	710145	20.77	40.46	47.94	80.61
Cote d'Ivoire	3080596	29.33	54.71	38.63	78.87
Democratic Republic of the Congo	11372278	29.67	53.67	34.17	81.66
Djibouti	14177	8.38	7.25	73.90	94.64
Equatorial Guinea	107968	18.24	56.97	56.71	67.69
Eritrea	1006631	7.69	3.75	75.13	97.18
Ethiopia	12175969	25.56	1.49	39.94	99.40
Gabon	237225	39.53	30.21	24.44	92.62
Gambia	320066	16.19	4.25	56.68	97.59
Ghana	3645136	25.78	58.40	41.63	75.69
Guinea	1846803	34.76	53.11	30.03	84.05
Guinea-Bissau	263784	28.41	15.61	33.41	94.79
Kenya	5915342	33.21	12.41	26.40	96.72
Liberia	683421	54.11	41.73	15.94	93.35
Madagascar	3456757	19.06	10.47	51.59	94.60
Malawi	2833295	29.43	52.27	35.89	81.24
Mali	2800594	13.28	62.85	71.05	55.34
Mauritania	454028	17.45	3.91	52.63	97.94
Mozambique	4377099	18.08	64.41	57.93	62.68
Namibia	197995	25.18	5.45	43.57	97.62
Niger	3487381	29.76	56.89	35.53	79.79
Nigeria	29624871	40.64	48.52	22.52	89.07
Rwanda	1553329	14.94	11.48	58.39	93.30
Senegal	2309113	25.02	7.90	40.63	96.79
Sierra Leone	928097	31.30	60.43	35.24	78.71
Somalia	1888733	10.80	4.91	68.92	96.61
South Africa	755185	11.08	6.67	65.42	95.64
South Sudan	1669249	23.56	39.06	36.43	85.77
Sudan	5412047	18.37	6.80	44.86	96.95
Swaziland	3379	10.33	1.43	71.09	98.98
Togo	1049365	31.52	57.39	33.32	80.88
Uganda	6781629	37.09	43.18	24.84	89.27
United Republic of Tanzania	8311188	22.65	16.90	40.31	93.19
Zambia	2567766	17.14	32.65	52.72	82.79
Zimbabwe	2004218	14.12	5.56	60.38	96.64

2013

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	4039964	30.03	21.55	35.39	92.37
Benin	1662330	24.26	39.04	42.39	83.45
Botswana	127364	12.51	2.24	63.39	98.58
Burkina Faso	2974350	41.95	63.97	23.81	84.77
Burundi	1711681	41.12	22.98	23.66	94.56
Cameroon	3615223	29.86	37.56	34.70	86.97
Central African Republic	663647	15.64	82.76	72.05	40.37
Chad	2364311	37.58	20.55	24.96	94.87
Congo	726451	20.00	40.07	48.06	80.74
Cote d'Ivoire	3172697	28.58	54.85	39.15	78.53
Democratic Republic of the Congo	11603660	33.23	48.33	29.36	85.81
Djibouti	14336	6.58	14.64	78.90	88.45
Equatorial Guinea	110222	15.23	62.38	64.54	59.74
Eritrea	1029671	7.19	4.23	76.32	96.77
Ethiopia	12302873	24.39	1.52	41.35	99.37
Gabon	242140	30.37	36.87	33.92	87.50
Gambia	330010	15.75	4.07	57.83	97.65
Ghana	3686312	23.56	55.58	45.77	74.56
Guinea	1878694	27.68	55.17	38.84	78.57
Guinea-Bissau	268394	26.18	17.07	36.92	93.70
Kenya	5987122	37.06	13.73	23.22	96.81
Liberia	692316	49.30	47.88	18.80	91.00
Madagascar	3533702	12.95	15.75	63.88	89.94
Malawi	2867316	31.14	40.09	33.48	86.58
Mali	2890052	12.80	67.98	73.95	49.73
Mauritania	461517	16.02	4.11	54.80	97.75
Mozambique	4437156	17.76	60.34	58.49	64.71
Namibia	198316	21.87	6.30	47.58	97.00
Niger	3626942	31.24	49.08	33.15	83.73
Nigeria	30455676	42.67	48.31	21.06	89.83
Rwanda	1576958	18.52	11.10	51.37	94.30
Senegal	2370019	23.28	7.55	41.91	96.84
Sierra Leone	935283	29.46	56.74	37.35	78.81
Somalia	1929636	9.70	8.43	70.31	94.08
South Africa	745730	11.63	10.62	63.17	93.29
South Sudan	1723899	25.03	35.44	34.02	87.94
Sudan	5464823	20.51	6.83	41.32	97.18
Swaziland	3400	5.64	2.39	83.47	98.00
Togo	1071715	29.88	54.89	34.53	81.05
Uganda	6955633	37.59	34.05	24.43	91.68
United Republic of Tanzania	8494008	20.69	16.45	43.88	92.78
Zambia	2653085	18.32	38.47	52.01	79.99
Zimbabwe	2037398	16.99	5.65	55.25	96.88

2014

Country	Population at risk (<5 years old)	All-cause fever prevalence (%)	Fevers with a malaria infection prevalence within all-cause fever (%)	MAF prevalence within malaria-positive fever (%)	NMFI prevalence within all-cause fever (%)
Angola	4101953	35.55	19.79	29.08	94.24
Benin	1688538	25.52	35.77	40.00	85.69
Botswana	127068	18.27	1.56	52.31	99.18
Burkina Faso	3029479	42.09	61.43	23.63	85.49
Burundi	1768185	34.32	24.08	29.86	92.81
Cameroon	3674987	30.04	36.26	34.29	87.57
Central African Republic	674893	23.15	71.03	49.77	64.65
Chad	2415619	35.93	20.19	26.67	94.61
Congo	742310	22.28	36.05	43.46	84.33
Cote d'Ivoire	3276529	31.08	49.83	35.20	82.46
Democratic Republic of the Congo	11834826	33.44	45.18	28.81	86.98
Djibouti	14521	16.31	6.56	54.63	96.42
Equatorial Guinea	112407	13.82	66.23	59.67	60.48
Eritrea	1051515	5.27	4.68	81.88	96.17
Ethiopia	12439084	25.75	1.39	39.93	99.45
Gabon	247048	44.94	35.62	20.87	92.57
Gambia	340340	20.93	3.05	48.25	98.53
Ghana	3722385	21.89	51.82	48.78	74.72
Guinea	1910232	15.98	65.70	63.59	58.23
Guinea-Bissau	273092	16.23	19.26	53.56	89.68
Kenya	6049072	39.46	13.46	21.49	97.11
Liberia	699366	42.55	45.10	23.84	89.25
Madagascar	3615050	17.84	11.46	54.38	93.77
Malawi	2890749	30.74	39.22	33.71	86.78
Mali	2981281	34.24	44.79	30.84	86.19
Mauritania	468805	18.09	3.76	51.57	98.06
Mozambique	4494219	17.87	55.42	56.97	68.43
Namibia	198789	26.24	5.64	41.66	97.65
Niger	3772518	53.37	43.76	14.68	93.58
Nigeria	31303659	42.79	47.58	20.88	90.07
Rwanda	1595960	18.80	10.89	51.04	94.44
Senegal	2431965	25.48	6.74	38.99	97.37
Sierra Leone	941950	34.83	50.38	30.79	84.49
Somalia	1970830	10.11	7.84	69.89	94.52
South Africa	732545	12.87	9.80	59.85	94.14
South Sudan	1779688	25.38	38.41	34.19	86.87
Sudan	5515843	20.10	7.10	41.73	97.04
Swaziland	3416	4.60	2.94	86.92	97.45
Togo	1094111	26.63	53.08	39.27	79.16
Uganda	7129790	36.46	36.13	25.37	90.83
United Republic of Tanzania	8666588	14.80	17.20	55.16	90.51
Zambia	2744482	19.98	35.41	49.07	82.63
Zimbabwe	2072430	17.33	5.26	53.35	97.20

Supplementary File 2: Household survey data used in analysis.

Country	Survey years	Source	Tested	R+F+	R+F-	R-F+	R-F-
Angola	2006-2007	DHS Program	1156	73	210	170	703
Angola	2011	DHS Program	2828	170	171	875	1612
Benin	2011-2012	DHS Program	3095	125	681	238	2051
Burkina Faso	2010	DHS Program	5300	941	3048	291	1020
Burkina Faso	2014	DHS Program	5354	1742	1728	607	1277
Burundi	2012	DHS Program	3465	473	226	1024	1742
Cameroon	2011	DHS Program	4511	633	747	759	2372
Cote d'Ivoire	2011-2012	DHS Program	2557	340	790	356	1071
DR Congo	2013-2014	DHS Program	6430	921	1272	1194	3043
Ghana	2011	UNICEF MICS	4352	828	1707	281	1536
Ghana	2014	DHS Program	2311	205	719	175	1212
Guinea	2012	DHS Program	2741	503	671	445	1122
Kenya	2015	DHS Program	2844	153	85	982	1624
Liberia	2009	DHS Program	3024	523	511	933	1057
Liberia	2011	DHS Program	2333	710	468	654	501
Madagascar	2011	DHS Program	5204	113	210	747	4134
Madagascar	2013	DHS Program	4476	79	199	537	3661
Madagascar	2016	DHS Program	3139	34	71	459	2575
Malawi	2012	DHS Program	1890	366	352	267	905
Malawi	2014	DHS Program	1717	262	238	271	946
Mali	2010	DHS Program	1716	344	293	337	742
Mali	2012-2013	DHS Program	4108	231	1547	183	2147
Mali	2015	DHS Program	6618	788	1132	1225	3473
Mozambique	2011	DHS Program	4320	279	1188	330	2523
Namibia	2009	Namibian Ministry of Health*	1142	9	22	332	779
Nigeria	2015	DHS Program	4814	1127	830	1038	1819
Rwanda	2010	DHS Program	3619	21	58	595	2945
Rwanda	2014-2015	DHS Program	3110	105	125	521	2359
Senegal	2008-2009	DHS Program	3508	175	248	1001	2084
Senegal	2010-2011	DHS Program	3209	27	78	688	2416
Senegal	2012-2013	DHS Program	5274	82	135	898	4159
Swaziland	2010	Swaziland NMCP †	257	1	0	32	224
Tanzania	2007-2008	DHS Program	5496	234	450	781	4031
Tanzania	2011-2012	DHS Program	6230	254	338	1141	4497
Togo	2013-2014	DHS Program	2844	309	731	367	1437
Uganda	2009	DHS Program	3361	1037	710	570	1044
Uganda	2014-2015	DHS Program	3983	640	654	670	2019

R+/- = RDT positive/negative; F+/- = Fever positive/negative

*Reference: National Vector-Borne Diseases Control Programme of the Ministry of Health and Social Services, the National Planning Commission/Central Bureau of Statistics, the Namibia Defense Force (NDF), the National Institute of Pathology (NIP),and WHO. Namibia Malaria Incidator Survey 2009. Windhoek, Namibia, 2009.

† Reference: National Malaria Control Programme (NMCP) of the Ministry of Health and Social Welfare and the Central Statistical Office of the Ministry of Economic Planning, the Clinton Health Access Initiative, the Global Health Group of the University of California, WHO. Swaziland Malaria Indicator Survey 2010.

Overall 2x2 table of survey data and predictions:

Household survey data

Total number (*N* = 155,369)

	RDT +	RDT -
Fever +	15177	26111
Fever -	23052	91029

Proportion

	RDT +	RDT -
Fever +	0.098	0.168
Fever -	0.148	0.586

Predictions*

Total number (*N* = 206,178,365)

	RDT +	RDT -
Fever +	24425776	37088228
Fever -	34151725	110512636

	RDT +	RDT -
Fever +	0.118	0.180
Fever -	0.166	0.536

*Predicted values are the total population within stable *P. falciparum* transmission zones of all children under five years of age in surveyed country-years detailed above (e.g. Mozambique was surveyed in 2011, so predicted values include all children at risk of *P. falciparum* in Mozambique in 2011. For surveys spanning two years, both years were included in predicted values.)

Supplementary File 3: Covariates used in BRT, listed by contribution to the final model. EVI: Enhanced Vegetation Index; GUF: Global Urban Footprint; LST: Land Surface Temperature; PET - potential evapotranspiration; TCB - Tassled Cap Brightness; TCW - Tassled Cap Wetness; TMI - Topographic Moisture Index; TSI - Temperature Suitability Index; WB - World Bank Variable.
"Product" definitions for EVI, LST, TSI, TCW and TCB: Monthly - average value over study month; All-years synoptic - mean EVI for all years 2000-2015; Delta dynamic - difference between monthly value and synoptic product; Monthly synoptic - mean of study month across all years; Delta monthly - difference between study month and monthly synoptic product; Delta annual - difference between study month and study year (e.g. July 2008 - Mean 2008). "Lag" defines the number of months that the covariate dataset lags behind the month of each household survey dataset point (e.g. if a household survey data point is recorded in July 2008, a covariate with a lag of 2 months will be taken from May 2008).

Contribution to final model (%)	Variable Type	Product type	Spatial summary	Temporal resolution	Lag
7.203	Proportion of children in primary school (WB National)	-	N/A	Yearly	N/A
5.880	Percentage of pregnant women who receive prenatal care (WB National)	-	N/A	Yearly	N/A
4.373	DPT immunisation coverage (WB annual)	-	N/A	Yearly	N/A
2.656	Public expenditure on health system (WB national)	-	N/A	Yearly	N/A
2.604	Annual GDP growth (WB national)	-	N/A	Yearly	N/A
1.704	Precipitation	-	N/A	Stationary	N/A
1.618	Precipitation	-	N/A	Stationary	N/A
1.252	LST night	Delta dynamic	Mean	Fully dynamic	1
1.237	EVI	Delta annual	Minimum	Fully dynamic	0
1.102	LST night	Delta monthly	Range	Fully dynamic	4
1.002	EVI	Delta monthly	Standard deviation	Fully dynamic	4
1.002	LST delta	Delta annual	Mean	Fully dynamic	0
0.977	EVI	Delta dynamic	Mean	Fully dynamic	1
0.972	LST day	Delta annual	Maximum	Fully dynamic	1
0.970	TSI	Monthly synoptic	Mean	Month only	2
0.924	Precipitation	-	N/A	Stationary	N/A
0.893	LST day	Monthly synoptic	Standard deviation	Month only	2
0.892	LST day	Delta dynamic	Range	Fully dynamic	2
0.875	LST delta	Monthly synoptic	Mean	Month only	0
0.870	LST day	Delta monthly	Minimum	Fully dynamic	1

0.853	TSI	Delta monthly	Maximum	Fully dynamic	0
0.838	LST night	Delta monthly	Minimum	Fully dynamic	0
0.822	Precipitation	-	N/A	Stationary	N/A
0.821	EVI	Monthly synoptic	Minimum	Month only	4
0.811	TSI	Monthly synoptic	Range	Month only	3
0.774	TSI	Delta monthly	Minimum	Fully dynamic	4
0.757	EVI	Delta monthly	Minimum	Fully dynamic	1
0.755	TCB	Delta annual	Standard deviation	Fully dynamic	4
0.749	TCB	Delta annual	Maximum	Fully dynamic	3
0.748	TMI	-	Maximum	Stationary	N/A
0.737	Accessibility	-	Standard deviation	Stationary	N/A
0.735	Land cover	Fraction	N/A	Yearly	N/A
0.732	TSI	Monthly synoptic	Mean	Month only	3
0.689	TCB	Delta monthly	Mean	Fully dynamic	1
0.678	LST night	Delta dynamic	Minimum	Fully dynamic	0
0.672	LST delta	Delta monthly	Mean	Fully dynamic	0
0.663	TCB	Monthly synoptic	Mean	Month only	4
0.643	LST delta	Monthly synoptic	Mean	Month only	1
0.640	EVI	Monthly synoptic	Range	Month only	2
0.633	LST night	Delta dynamic	Mean	Fully dynamic	3
0.615	EVI	Delta monthly	Minimum	Fully dynamic	0
0.606	TCW	Delta monthly	Mean	Fully dynamic	1
0.599	LST day	Delta monthly	Standard deviation	Fully dynamic	4
0.592	TMI	-	Minimum	Stationary	N/A
0.576	LST night	Monthly synoptic	Standard deviation	Month only	3
0.557	EVI	Delta monthly	Range	Fully dynamic	2
0.552	LST night	Monthly synoptic	Minimum	Month only	2
0.545	Land cover	Fraction	N/A	Yearly	N/A
0.543	TSI	Delta annual	Minimum	Fully dynamic	4
0.542	LST night	Monthly synoptic	Range	Month only	1
0.540	TSI	Delta monthly	Maximum	Fully dynamic	2
0.539	TSI	Monthly synoptic	Minimum	Month only	4
0.538	TCB	Delta annual	Standard deviation	Fully dynamic	2

0.516	LST night	Monthly synoptic	Mean	Month only	0
0.510	LST delta	Monthly synoptic	Maximum	Month only	2
0.508	Precipitation	-	N/A	Stationary	N/A
0.507	TSI	Delta monthly	Standard deviation	Fully dynamic	4
0.501	TCB	Monthly	Minimum	Fully dynamic	1
0.498	LST night	Delta dynamic	Maximum	Fully dynamic	2
0.497	LST day	Monthly synoptic	Standard deviation	Month only	1
0.493	TSI	Monthly synoptic	Standard deviation	Month only	2
0.488	LST night	Delta monthly	Maximum	Fully dynamic	3
0.487	LST night	Monthly synoptic	Standard deviation	Month only	0
0.481	LST night	Delta monthly	Mean	Fully dynamic	4
0.478	LST night	Delta monthly	Maximum	Fully dynamic	2
0.477	LST night	Delta annual	Maximum	Fully dynamic	2
0.474	TSI	Delta monthly	Range	Fully dynamic	3
0.454	TCB	Delta annual	Range	Fully dynamic	1
0.449	LST night	Monthly synoptic	Standard deviation	Month only	2
0.444	LST day	Monthly synoptic	Standard deviation	Month only	3
0.444	TSI	Delta monthly	Mean	Fully dynamic	1
0.439	LST day	Delta monthly	Maximum	Fully dynamic	4
0.436	TCW	Delta annual	Standard deviation	Fully dynamic	0
0.435	LST day	Delta dynamic	Standard deviation	Fully dynamic	0
0.435	EVI	Monthly synoptic	Standard deviation	Month only	2
0.431	EVI	All-years synoptic	Minimum	Stationary	N/A
0.429	EVI	Monthly synoptic	Standard deviation	Month only	4
0.427	EVI	Delta dynamic	Minimum	Fully dynamic	4
0.423	EVI	Delta monthly	Standard deviation	Fully dynamic	0
0.415	LST night	Monthly synoptic	Mean	Month only	1
0.413	LST night	Monthly synoptic	Maximum	Month only	4
0.413	TCW	Delta monthly	Mean	Fully dynamic	4
0.412	Population density	-	N/A	Yearly	N/A
0.410	LST night	Delta dynamic	Standard deviation	Fully dynamic	0
0.409	Elevation	Flow accumulation	Mean	Stationary	N/A
0.408	TCW	Monthly	Standard deviation	Fully dynamic	3

0.407	TSI	Monthly synoptic	Maximum	Month only	4
0.403	EVI	Delta monthly	Minimum	Fully dynamic	2
0.403	LST day	Delta monthly	Range	Fully dynamic	1
0.400	EVI	Delta monthly	Standard deviation	Fully dynamic	1
0.398	Land cover	Adjacencies	N/A	Yearly	N/A
0.395	LST day	Monthly synoptic	Minimum	Month only	2
0.394	TCW	Delta monthly	Mean	Fully dynamic	0
0.389	TSI	Delta monthly	Maximum	Fully dynamic	4
0.388	PET	-	Standard deviation	Stationary	N/A
0.385	Nighttime lights	-	Mean	Stationary	N/A
0.380	EVI	Monthly synoptic	Range	Month only	0
0.379	LST day	Delta annual	Standard deviation	Fully dynamic	3
0.379	Proportion urban in cell (GUF)	-	N/A	Stationary	N/A
0.375	LST night	Monthly synoptic	Range	Month only	1
0.369	Land cover	Fraction	N/A	Yearly	N/A
0.358	TCW	Delta annual	Standard deviation	Fully dynamic	3
0.356	LST night	Delta annual	Range	Fully dynamic	1
0.355	Population density	-	Minimum	Stationary	N/A
0.350	LST day	Delta monthly	Minimum	Fully dynamic	3
0.348	LST day	Delta monthly	Range	Fully dynamic	0
0.346	EVI	Delta dynamic	Standard deviation	Fully dynamic	1
0.341	LST day	Monthly synoptic	Standard deviation	Month only	4
0.341	TCW	Delta monthly	Mean	Fully dynamic	2
0.340	TSI	Delta monthly	Standard deviation	Fully dynamic	2
0.339	TCB	Delta monthly	Mean	Fully dynamic	0
0.337	TCB	Delta monthly	Mean	Fully dynamic	4
0.335	Precipitation	-	N/A	Stationary	N/A
0.332	TCW	Delta monthly	Mean	Fully dynamic	3
0.330	TCB	Delta monthly	Mean	Fully dynamic	4
0.329	TSI	Monthly synoptic	Minimum	Month only	0
0.325	LST day	Monthly synoptic	Mean	Month only	3
0.320	EVI	Delta dynamic	Range	Fully dynamic	0
0.320	TCB	Monthly	Maximum	Fully dynamic	4

0.320	TSI	Delta monthly	Maximum	Fully dynamic	3
0.318	LST night	Delta monthly	Maximum	Fully dynamic	1
0.316	LST delta	Delta monthly	Mean	Fully dynamic	2
0.312	TCB	Delta monthly	Mean	Fully dynamic	2
0.312	TSI	Delta monthly	Minimum	Fully dynamic	2
0.311	LST delta	All-years synoptic	Maximum	Stationary	N/A
0.311	LST night	Monthly synoptic	Standard deviation	Month only	4
0.310	LST night	Delta dynamic	Maximum	Fully dynamic	4
0.307	EVI	Delta monthly	Mean	Fully dynamic	3
0.295	LST night	Delta monthly	Range	Fully dynamic	0
0.293	EVI	Delta monthly	Range	Fully dynamic	3
0.281	LST night	Delta annual	Standard deviation	Fully dynamic	3
0.281	LST night	Delta dynamic	Standard deviation	Fully dynamic	4
0.277	TSI	Monthly	Standard deviation	Fully dynamic	1
0.276	EVI	Delta dynamic	Range	Fully dynamic	4
0.275	EVI	Monthly synoptic	Mean	Month only	0
0.269	LST day	Delta monthly	Standard deviation	Fully dynamic	3
0.268	Land cover	Fraction	N/A	Yearly	N/A
0.260	Precipitation	-	N/A	Stationary	N/A
0.256	LST night	Delta monthly	Standard deviation	Fully dynamic	2
0.253	TCW	Delta annual	Standard deviation	Fully dynamic	1
0.247	TCB	Delta annual	Range	Fully dynamic	3
0.247	TCW	Delta annual	Standard deviation	Fully dynamic	4
0.244	EVI	Delta monthly	Maximum	Fully dynamic	2
0.241	TSI	Monthly synoptic	Mean	Month only	1
0.239	TSI	Delta monthly	Minimum	Fully dynamic	3
0.238	LST night	Delta annual	Standard deviation	Fully dynamic	2
0.231	LST day	Monthly synoptic	Range	Month only	4
0.229	EVI	All-years synoptic	Range	Stationary	N/A
0.226	LST day	Delta annual	Range	Fully dynamic	4
0.226	LST day	Monthly synoptic	Range	Month only	0
0.226	TSI	Delta monthly	Range	Fully dynamic	0
0.223	LST delta	Delta annual	Maximum	Fully dynamic	2

0.223	TCW	Delta annual	Standard deviation	Fully dynamic	2
0.222	Accessibility	-	Range	Stationary	N/A
0.214	TMI	-	Standard deviation	Stationary	N/A
0.206	EVI	Delta annual	Standard deviation	Fully dynamic	2
0.206	Land cover	Fraction	N/A	Yearly	N/A
0.200	TCW	Delta dynamic	Mean	Fully dynamic	2
0.199	Land cover	Fraction	N/A	Yearly	N/A
0.197	LST night	Monthly synoptic	Minimum	Month only	3
0.188	TSI	Monthly	Standard deviation	Fully dynamic	2
0.171	EVI	Delta monthly	Mean	Fully dynamic	4
0.164	LST night	Monthly synoptic	Standard deviation	Month only	4
0.163	EVI	Delta dynamic	Standard deviation	Fully dynamic	3
0.156	TSI	Monthly synoptic	Standard deviation	Month only	1
0.145	Population density	-	Standard deviation	Stationary	N/A
0.113	Nighttime lights	-	Maximum	Stationary	N/A
0.069	Land cover	Fraction	N/A	Yearly	N/A
0.065	Land cover	Fraction	N/A	Yearly	N/A
0.064	Land cover	Majority class	N/A	Yearly	N/A
0.026	Elevation	Slope angle	Minimum	Stationary	N/A
0.005	TCW	Delta annual	Maximum	Fully dynamic	2
0.000	Any urban in cell (GUF)	-	N/A	Stationary	N/A
0.000	Significant urban in cell (GUF)	-	N/A	Stationary	N/A
0.000	Land cover	Adjacencies	N/A	Yearly	N/A

Supplementary File 4:

a) Model parameters and credible intervals of the final multinomial model.

(Hyper-)Parameter	Posterior Mode	Approx. SE
$\log \kappa_{\mathrm{bg}}$	0.02	0.06
$\log \tau_{\mathrm{bg}}$	-1.50	0.05
$\log \kappa_{\mathrm{pr}}$	1.28	0.05
$\log \tau_{\mathrm{pr}}$	-2.67	0.06
δ	-1.82	0.04
ψ	-0.35	0.04
ξ	-0.07	0.02

b) Final model coefficients

	log_kappa_pbg	log_tau_pbg	log_kappa_pr	log_tau_pr	logit_prop_maf	slope_maf	sqslope_maf
Mean	-1.21954	-0.16566	-0.58738	-0.66011	-1.51823	-0.13105	-0.0047416
Standard deviation	0.114707	0.072582893	0.131519330	0.097987524	0.026756679	0.021337289	0.005256507

Appendix to Chapter 3 - How long do rapid diagnostic tests remain positive after anti-malarial treatment?

This appendix includes:

1. Additional file 1: Details of the publications used in analysis.
2. Additional file 2: Bayesian survival model priors and likelihoods.

All appendices for this chapter are available online at:

https://malariajournal.biomedcentral.com/articles/10.1186/s12936-018-2371-9

Additional File 1. Details of the publications used in analysis.

ID	Author	Country	Month Start	Year Start	Month End	Year End	RDT brand	RDT model/lot number	RDT type †	Lines on same test ^	LowAge	UpAge	Selection of participants
1	Kyabinze	Uganda	10	2006	9	2007	ICT & Paracheck	Unknown	HRP2	No	0.5	4	Febrile
2	Mbabazi	Uganda	11	2011	1	2012	Carestart	D21MO (September 2013)	HRP2	No	0	1	Febrile
3	Mbabazi	Uganda	11	2011	1	2012	Carestart	H11MY (July 2013)	pLDH (Pf)	No	0	1	Febrile
4	Kattenburg	Burkina Faso	11	2010	12	2010	SD Bioline	Unknown	HRP2	No	?	?	Pregnant women antenatal care
5	Swarthout	DRC	3	2004	6	2004	Paracheck	Unknown	HRP2	No	0.5	4	Febrile
6	Swarthout	DRC	3	2004	6	2004	Paracheck	Unknown	HRP2	No	0.5	4	Febrile
7	Swarthout	DRC	3	2004	6	2004	Paracheck	Unknown	HRP2	No	0.5	4	Febrile
8	Swarthout	DRC	3	2004	6	2004	Paracheck	Unknown	HRP2	No	0.5	4	Febrile
9	Swarthout	DRC	3	2004	6	2004	Paracheck	Unknown	HRP2	No	0.5	4	Febrile
10	Ly	Senegal	10	2008	1	2009	Paracheck	Unknown	HRP2	No	0**	99**	Febrile
11	Houze	Benin	4	2007	11	2007	Immunoquick	Unknown	HRP2	No	0.5	4	Febrile
12	Houze	Benin	4	2007	11	2007	Optimal	Unknown	pLDH (Pan & Pf)	No	0.5	4	Febrile
13	Houze	Benin	4	2007	11	2007	Immunoquick	Unknown	HRP2	No	0.5	4	Febrile
14	Houze	Benin	4	2007	11	2007	Optimal	Unknown	pLDH (Pan & Pf)	No	0.5	4	Febrile
15	Houze	Benin	4	2007	11	2007	Immunoquick	Unknown	HRP2	No	0.5	4	Febrile
16	Houze	Benin	4	2007	11	2007	Optimal	Unknown	pLDH (Pan & Pf)	No	0.5	4	Febrile
17	Mohammed	Ethiopia	10	2008	1	2009	Paracheck	Unknown	HRP2	No	1	20	Febrile
18	Aydin-Schmidt	Tanzania	6 (1) 7 (2)*	2009 (1) 2010 (2)*	9 (1) 10 (2)*	2009 (1) 2010 (2)*	ParaHit	Unknown	HRP2	No	0.5	5	Febrile
19	Aydin-Schmidt	Tanzania	6 (1) 7 (2)*	2009 (1) 2010 (2)*	9 (1) 10 (2)*	2009 (1) 2010 (2)*	CareStart	G0151	pLDH (Pf)	No	0.5	5	Febrile
20	Huong	Vietnam	7	2000	9	2000	ICT	Unknown	HRP2/pLDH (Pan)	No	4	60	Febrile
21	Huong	Vietnam	7	2000	9	2000	Paracheck	Unknown	HRP2	No	4	60	Febrile
22	Tjitra	Indonesia	3	1999	4	1999	ICT	Unknown	HRP2	No	0**	99**	Febrile
23	Tjitra	Indonesia	3	1999	4	1999	ICT	Unknown	HRP2/pLDH (Pan)	No	0**	99**	Febrile
24	Tjitra	Indonesia	3	1999	4	1999	ICT	Unknown	HRP2	No	0**	99**	Febrile
25	Tjitra	Indonesia	3	1999	4	1999	ICT	Unknown	HRP2/pLDH (Pan)	No	0**	99**	Febrile
26	Tjitra	Indonesia	3	1999	4	1999	ICT	Unknown	HRP2	No	0**	99**	Febrile
27	Tjitra	Indonesia	3	1999	4	1999	ICT	Unknown	HRP2/pLDH (Pan)	No	0**	99**	Febrile
28	Iqbal	Kuwait	9	1999	8	2001	ICT	Unknown	HRP2	Yes	9	46	Febrile
29	Iqbal	Kuwait	9	1999	8	2001	ICT	Unknown	HRP2/pLDH (Pan)	Yes	9	46	Febrile
30	Iqbal	Kuwait	9	1999	8	2001	OptiMal	Unknown	pLDH (Pan)	No	9	46	Febrile
31	Rubio	Returned travellers	?	1998	?	1999	ParaSight-F	Unknown	HRP2	No	1	72	Returned travellers
32	Rubio	Returned travellers	?	1998	?	1999	OptiMal	Unknown	pLDH (Pan)	No	1	72	Returned travellers
33	Grandesso	Uganda	9	2011	1	2013	SD Bioline	05FK50-02-4	HRP2	No	0	5	Febrile
34	Grandesso	Uganda	9	2011	1	2013	SD Bioline	05FK50-02-4	HRP2	No	0	5	Febrile
35	Grandesso	Uganda	9	2011	1	2013	SD Bioline	05FK50-02-4	HRP2	No	0	5	Febrile
36	Grandesso	Uganda	9	2011	1	2013	Carestart	G0111	HRP2	No	0	5	Febrile
37	Grandesso	Uganda	9	2011	1	2013	Carestart	G0111	HRP2	No	0	5	Febrile
38	Grandesso	Uganda	9	2011	1	2013	Carestart	G0111	HRP2	No	0	5	Febrile
39	Grandesso	Uganda	9	2011	1	2013	Carestart	G0111	pLDH (Pan)	No	0	5	Febrile
40	Grandesso	Uganda	9	2011	1	2013	Carestart	G0111	pLDH (Pan)	No	0	5	Febrile
41	Grandesso	Uganda	9	2011	1	2013	Carestart	G0111	pLDH (Pan)	No	0	5	Febrile
42	Singh	India	4	2004	8	2004	ParaHit	25977	HRP2	No	0**	99**	Febrile
43	Mayxay	Thailand	11	1998	5	2000	Parasight-F	Unknown	HRP2	No	0**	99**	Severe and uncomplicated malaria cases
44	Humar	Returned travelers	1	1994	7	1995	Parasight-F	Unknown	HRP2	No	0**	99**	Returned travellers
45	Schiff	Tanzania	?	?	?	?	Parasight-F	Unknown	HRP2	No	14	60	Febrile
46	Karbwang	Thailand/Myanmar	?	?	?	?	Parasight-F	Unknown	HRP2	No	0**	99**	Febrile [excluded if parasitemia > 5%]
47	Fogg	Uganda	4	2005	6	2005	Paracheck	Unknown	HRP2	No	0**	99**	Febrile
48	Fogg	Uganda	4	2005	6	2005	Vistapan	Unknown	pLDH (Pan)	No	0**	99**	Febrile
49	Fogg	Uganda	4	2005	6	2005	Carestart	Unknown	pLDH (Pan)	No	0**	99**	Febrile
50	Fogg	Uganda	4	2005	6	2005	Parabank	Unknown	pLDH (Pan)	No	0**	99**	Febrile
51	Yadav	India	5	2011	4	2013	ParaHit	Unknown	HRP2	No	0.25	12	Febrile
52	Nyunt	Myanmar	10	2010	12	2010	SD Bioline	Cat No 05FK60, Lot No 090007	HRP2	Yes	6	99**	Febrile
53	Nyunt	Myanmar	10	2010	12	2010	SD Bioline	Cat No 05FK60, Lot No 090007	pLDH (Pan)	Yes	6	99**	Febrile
54	Mharakurwa	Zimbabwe	5	<1997	6	<1997	ParaSight-F	Unknown	HRP2	No	0**	99**	Febrile
55	Mueller	PNG	4	2000	1	2003	Optimal	Unknown	pLDH (Pan)	No	1.4	45	Febrile
56	Kilauzi	DRC	10	2012	12	2012	SD Bioline	Unknown	HRP2	Yes	0.25	4	Febrile
57	Kilauzi	DRC	10	2012	12	2012	SD Bioline	Unknown	pLDH (Pan)	Yes	0.25	4	Febrile
58	Gerstl	Sierra Leone	3	2008	7	2008	Carestart	G0121	pLDH (Pan)	No	0	4	Febrile
59	Nour	Sudan	9	2003	3	2004	Paracheck	Unknown	HRP2	No	0**	99**	Febrile
60	Nour	Sudan	9	2003	3	2004	Optimal	Unknown	pLDH (Pan)	No	0**	99**	Febrile
61	Kocharekar	India	5	2010	11	2011	Advantage MalCard	ACM15101	pLDH (Pan)	No	18	70	Febrile
62	Kocharekar	India	5	2010	11	2011	ParaHit	4000006623	HRP2	No	18	70	Febrile
63	Moody	Returned travellers	?	<2000	?	<2000	Optimal	Unknown	pLDH (Pan)	No	0**	99**	Returned travellers
64	Miller	Thailand	?	<2001	?	<2001	Optimal	Unknown	pLDH (Pan)	No	0**	99**	Febrile
65	Wongsrichanalai	Thailand	1	1997	7	1997	ICT	Unknown	HRP2	No	0**	99**	Microscopy-confirmed *P. falciparum* patients
66	Djimde	Mali	10	2009	12	2009	SD Bioline	05FK50	HRP2	No	0**	99**	Febrile
67	Djimde	Mali	10	2009	12	2009	SD Bioline	05FK60	HRP2/pLDH (Pan)	No	0**	99**	Febrile

"?" Represents unknown values; not reported in text

* Two different surveying periods were used, but only one aggregated pool of data was reported. The start and end dates of the two surveying periods are listed here with (1) and (2) as the first and second surveying period, respectively.

** Studies with ages listed as 0-99 did not report specific ages of subjects but confirmed that subjects of all ages were included.

† For the purposes of analysis, RDTs labelled "HRP2" are grouped as HRP2-only RDTs, and all other RDTs (including those in combination with HRP2) are grouped as other RDTs.

^ "Lines on same test" refers to study groups where combination RDTs were used but the result for the individual lines on each RDT were reported. Study groups from these publications feature twice with each result reported separately.

*** "Points omitted?" column refers to whether points were omitted due to increases in positive proportions. If labelled "None", all points were used in the analysis. If labelled "Some", one or more points were omitted from analysis due to small increases. If labelled "All", the entire row was omitted from analysis due to large increases.

ID	Treatment type	Drug variety	Parasite density (per µL)	N	Days after treatment - percentage of individuals still RDT positive																Points omitted? ***
					1	2	3	4	5	6	7	10	14	17	21	28	35	42	49	56	63	
1	National treatment guidelines	ACT	?	162	-	-	100	-	-	-	97	-	88	-	63	41	18	9	3	1	0	None
2	ACT (artemether-lumefantrine or dihydroartemisinin–piperaquine)	ACT	?	131	-	94	-	-	-	-	91	-	79	-	68	51	-	-	-	-	-	None
3	ACT (artemether-lumefantrine or dihydroartemisinin–piperaquine)	ACT	?	131	-	5	-	-	-	-	1	-	0	-	0	0	-	-	-	-	-	None
4	ACT (artesunate-amodiaquine, arthemeter-lumefantrine or artesunate-mefloquine)	ACT	?	32	78	66	59	-	-	-	41	-	25	-	9	6	-	-	-	-	-	None
5	ACT (artesunate-amodiaquine or artesunate + sulphadoxine-pyrimethamine)	ACT	50 to 200,000	30	-	-	-	-	-	-	100	-	100	-	100	100	77.3	-	-	-	-	None
6	ACT (artesunate-amodiaquine or artesunate + sulphadoxine-pyrimethamine)	ACT	20 to 50,000	42	-	-	-	-	-	-	100	-	100	-	97.6	97.6	79.2	-	-	-	-	None
7	ACT (artesunate-amodiaquine or artesunate + sulphadoxine-pyrimethamine)	ACT	10 to 20,000	22	-	-	-	-	-	-	100	-	100	-	100	90.9	71.4	-	-	-	-	None
8	ACT (artesunate-amodiaquine or artesunate + sulphadoxine-pyrimethamine)	ACT	2 to 10,000	18	-	-	-	-	-	-	94.4	-	88.9	-	72.2	66.7	50	-	-	-	-	None
9	ACT (artesunate-amodiaquine or artesunate + sulphadoxine-pyrimethamine)	ACT	2 to 200,000	112	-	-	-	-	-	-	99.1	-	98.2	-	94.6	92	73.5	-	-	-	-	None
10	ACT (combination unknown)	ACT	?	10	-	-	-	60	-	-	40	-	-	-	-	-	-	-	-	-	-	None
11	ACT (artesunate-amodiaquine)	ACT	?	80	-	-	80.9	-	-	-	72.8	-	43.4	-	26.4	24.3	2.6	2.6	-	-	-	None
12	ACT (artesunate-amodiaquine)	ACT	?	80	-	-	12.3	-	-	-	3.8	-	2.6	-	3	1.7	2.6	0	-	-	-	Some
13	Sulfadoxine-pyrimethamine	Non-ACT	?	44	-	-	76.2	-	-	-	60.9	-	35.7	-	17.9	50	19.6	0	-	-	-	All
14	Sulfadoxine-pyrimethamine	Non-ACT	?	44	-	-	46.8	-	-	-	38.7	-	21.3	-	17.9	12.3	0	0	-	-	-	None
15	ACT (artemether-lumefantrine)	ACT	?	81	-	-	86	-	-	-	69.8	-	46.4	-	30.2	25.1	4.7	7.2	-	-	-	Some
16	ACT (artemether-lumefantrine)	ACT	?	81	-	-	5.1	-	-	-	2.6	-	1.3	-	1.3	1.3	2.6	0	-	-	-	Some
17	ACT (artemether-lumefantrine)	ACT	?	80	-	-	-	-	-	-	98.7	-	60	-	48.1	44.6	-	-	-	-	-	None
18	ACT (artemether-lumefantrine)	ACT	2000 to 250,000	43	100	100	100	-	-	-	97	-	80	-	64	43	10	7	-	-	-	None
19	ACT (artemether-lumefantrine)	ACT	2000 to 250,000	43	100	77	60	-	-	-	22	-	1	-	0	0	0	0	-	-	-	None
20	ACT (artesunate-mefloquine)	ACT	?	87	-	-	-	-	-	-	50	-	0	-	0	0	-	-	-	-	-	None
21	ACT (artesunate-mefloquine)	ACT	?	87	-	-	-	-	-	-	80	-	40	-	20	0	-	-	-	-	-	None
22	Chloroquine	Non-ACT	?	66	66	78	83	-	-	-	59	-	37	-	-	10	-	-	-	-	-	Some
23	Chloroquine	Non-ACT	?	66	33	55	55	-	-	-	50	-	37	-	-	5	-	-	-	-	-	All
24	Sulfadoxine-pyrimethamine	Non-ACT	?	36	50	43	39	-	-	-	30	-	10	-	-	8	-	-	-	-	-	None
25	Sulfadoxine-pyrimethamine	Non-ACT	?	36	40	55	50	-	-	-	42	-	19	-	-	0	-	-	-	-	-	All
26	ACT (artesunate + sulphadoxine-pyrimethamine)	ACT	?	15	86	86	91	-	-	-	91	-	67	-	-	45	-	-	-	-	-	Some
27	ACT (artesunate + sulphadoxine-pyrimethamine)	ACT	?	15	24	14	8	-	-	-	0	-	0	-	-	21	-	-	-	-	-	All
28	Chloroquine or quinine	Non-ACT	?	240	-	-	82.1	-	-	-	62.4	-	34.9	-	-	-	-	-	-	-	-	None
29	Chloroquine or quinine	Non-ACT	?	240	-	-	32.8	-	-	-	30.1	-	19.7	-	-	-	-	-	-	-	-	None
30	Chloroquine or quinine	Non-ACT	?	240	-	-	38.4	-	-	-	14.8	-	-	-	-	-	-	-	-	-	-	None
31	Chloroquine	Non-ACT	?	169	-	-	-	-	-	-	-	50	-	-	-	-	-	-	-	-	-	None
32	Chloroquine	Non-ACT	?	169	-	-	-	-	-	-	-	-	-	50	-	-	-	-	-	-	-	None
33	ACT (artesunate-amodiaquine)	ACT	1 to 1,999	73	-	92	88	-	75	-	71	-	58	-	37	23	16	7	-	-	-	None
34	ACT (artesunate-amodiaquine)	ACT	2000 to 199,999	386	-	100	95	-	95	-	86	-	84	-	65	50	34	-	-	-	-	None
35	ACT (artesunate-amodiaquine)	ACT	>200,000	59	-	100	100	-	100	-	96	-	91	-	80	80	43	-	-	-	-	None
36	ACT (artesunate-amodiaquine)	ACT	1 to 1,999	73	-	94	92	-	92	-	85	-	85	-	66	52	30	22	-	-	-	None
37	ACT (artesunate-amodiaquine)	ACT	2000 to 199,999	386	-	100	98	-	95	-	95	-	92	-	92	75	63	45	-	-	-	None
38	ACT (artesunate-amodiaquine)	ACT	>200,000	59	-	100	100	-	100	-	98	-	95	-	90	86	75	74	-	-	-	None
39	ACT (artesunate-amodiaquine)	ACT	1 to 1,999	73	-	100	100	-	13	-	13	-	7	-	1	1	1	0	-	-	-	None
40	ACT (artesunate-amodiaquine)	ACT	2000 to 199,999	386	-	100	100	-	26	-	26	-	0	-	0	0	0	0	-	-	-	None
41	ACT (artesunate-amodiaquine)	ACT	>200,000	59	-	100	100	-	46	-	46	-	26	-	19	19	19	1	-	-	-	None
42	Chloroquine or primaquine	Non-ACT	?	94	-	-	-	-	-	-	-	41.5	-	-	-	-	-	-	-	-	-	None
43	Artesunate (monotherapy or with azithromucine or lumefantrine)	Non-ACT	?	52	-	-	-	-	-	-	-	-	67	-	-	-	-	-	-	-	-	None
44	?	Non-ACT	?	19	-	-	95	-	-	-	68	-	-	-	-	27	-	-	-	-	-	None
45	Sulfadoxine-pyrimethamine	Non-ACT	?	40	-	97.5	50	30	25	20	20	10	10	-	-	-	-	-	-	-	-	None
46	Artemether	Non-ACT	?	72	55.6	69.4	-	-	-	-	52.1	-	25.4	-	-	-	-	-	-	-	-	Some
47	ACT (artemether-lumefantrine)	ACT	<250,000	226	-	-	86.2	-	-	-	80.8	-	69.7	-	-	-	-	-	-	-	-	None
48	ACT (artemether-lumefantrine)	ACT	<250,000	221	-	-	36.1	-	-	-	23.4	-	8.9	-	-	-	-	-	-	-	-	None
49	ACT (artemether-lumefantrine)	ACT	<250,000	230	-	-	42.5	-	-	-	27.6	-	9.5	-	-	-	-	-	-	-	-	None
50	ACT (artemether-lumefantrine)	ACT	<250,000	204	-	-	17.8	-	-	-	8.9	-	4.6	-	-	-	-	-	-	-	-	None
51	Chroroquine & primaquine	Non-ACT	?	270	-	-	-	-	-	-	-	24.4	-	-	-	-	-	-	-	-	-	None
52	ACT (artemether-lumefantrine)	ACT	500 to 100,000	63	-	-	100	-	-	-	98.4	-	90.5	-	71.4	60.32	-	-	-	-	-	None
53	ACT (artemether-lumefantrine)	ACT	500 to 100,000	63	-	-	28.6	-	-	-	12.7	-	4.8	-	4.8	3.17	-	-	-	-	-	None
54	Chloroquine	Non-ACT	?	55	78	92	82	90	92	64	67	60	60	-	-	-	-	-	-	-	-	Some
55	Cotrimoxazole-rifampin-isoniazid or mefloquine or sulfadoxine-pyrimethamine	Non-ACT	?	255	-	31.4	-	-	-	-	20.8	-	2.5	-	-	-	-	-	-	-	-	None
56	ACT (artesunate-amodiaquine)	ACT	?	103	-	-	100	-	-	-	100	-	95	-	86.2	84.1	-	-	-	-	-	None
57	ACT (artesunate-amodiaquine)	ACT	?	103	-	-	7.8	-	-	-	1.9	-	1	-	0	11.4	-	-	-	-	-	Some
58	ACT (artesunate-amodiaquine)	ACT	?	155	-	63.9	-	-	-	-	5.8	-	-	-	0.6	-	-	-	-	-	-	None
59	Chloroquine	Non-ACT	?	52	94.2	93.9	86	-	-	-	35	-	9.4	-	0	0	-	-	-	-	-	None
60	Chloroquine	Non-ACT	?	52	92.3	75.5	41.9	-	-	-	20	-	9.4	-	0	0	-	-	-	-	-	None
61	?	ACT	?	101	-	-	-	-	-	-	14.9	-	7.92	-	-	-	-	-	-	-	-	None
62	?	ACT	?	101	-	-	-	-	-	-	37.3	-	58.41	-	-	-	-	-	-	-	-	All
63	?	Non-ACT	?	58	76	61	62	68	38	-	-	-	-	-	-	-	-	-	-	-	-	Some
64	?	Non-ACT	?	12	100	75	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	None
65	ACT (artesunate-mefloquine-primaquine)	ACT	?	35	-	70	-	-	-	-	47	-	44	-	-	-	-	-	-	-	-	None
66	ACT (artemether-lumefantrine)	ACT	?	25	-	-	-	-	-	-	100	-	100	-	-	-	-	-	-	-	-	None
67	ACT (artemether-lumefantrine)	ACT	?	25	-	-	-	-	-	-	100	-	100	-	-	-	-	-	-	-	-	None
	Total number of study groups reporting observations for each day:				15	30	43	4	12	2	60	5	57	1	36	42	23	16	1	1	1	

"?" Represents unknown values; not reported in text

* Two different surveying periods were used, but only one aggregated pool of data was reported. The start and end dates of the two surveying periods are listed here with (1) and (2) as the first and second surveying period, respectively.

** Studies with ages listed as 0-99 did not report specific ages of subjects but confirmed that subjects of all ages were included.

† For the purposes of analysis, RDTs labelled "HRP2" are grouped as HRP2-only RDTs, and all other RDTs (including those in combination with HRP2) are grouped as other RDTs.

^ "Lines on same test" refers to study groups where combination RDTs were used but the result for the individual lines on each RDT were reported. Study groups from these publications feature twice with each result reported separately.

*** "Points omitted?" column refers to whether points were omitted due to increases in positive proportions. If labelled "None", all points were used in the analysis. If labelled "Some", one or more points were omitted from analysis due to small increases. If labelled "All", the entire row was omitted from analysis due to large increases.

ID	Reference
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"?" Represents unknown values; not reported in text

* Two different surveying periods were used, but only one aggregated pool of data was reported. The start and end dates of the two surveying periods are listed here with (1) and (2) as the first and second surveying period, respectively.

** Studies with ages listed as 0-99 did not report specific ages of subjects but confirmed that subjects of all ages were included.

† For the purposes of analysis, RDTs labelled "HRP2" are grouped as HRP2-only RDTs, and all other RDTs (including those in combination with HRP2) are grouped as other RDTs.

^ "Lines on same test" refers to study groups where combination RDTs were used but the result for the individual lines on each RDT were reported. Study groups from these publications feature twice with each result reported separately.

*** "Points omitted?" column refers to whether points were omitted due to increases in positive proportions. If labelled "None", all points were used in the analysis. If labelled "Some", one or more points were omitted from analysis due to small increases. If labelled "All", the entire row was omitted from analysis due to large increases.

Additional File 2: Bayesian survival model priors and likelihoods

Priors

$\boldsymbol{\beta_i} \sim \boldsymbol{N}(\mathbf{0}, \boldsymbol{\sigma_\beta})$ for $\boldsymbol{i} = \mathbf{1}, \mathbf{2}, \dots, \mathbf{12}$

$\boldsymbol{Z_j} \sim \boldsymbol{N}(\mathbf{0}, \boldsymbol{\sigma_Z})$ for $\boldsymbol{j} = \mathbf{1}, \mathbf{2}, \dots, \mathbf{62}$

$\boldsymbol{\sigma_\beta} \sim \boldsymbol{Exp}(\mathbf{1})$

$\boldsymbol{\sigma_Z} \sim \boldsymbol{Exp}(\mathbf{1})$

$\boldsymbol{log\ c_k} \sim \boldsymbol{N}(\boldsymbol{log\ c_{k-1}}, \frac{\mathbf{1}}{\mathbf{10}}(\boldsymbol{t_k} - \boldsymbol{t_{k-1}}))$

Likelihoods

Given a survival curve $S(t)$, the likelihood of an individual being RDT positive at time t_{lower} and RDT negative at t_{upper} is

$$\mathrm{P}\big(t_{lower} < t < t_{upper}\big) = S(t_{lower}) - S\big(t_{upper}\big)$$

For individuals who are still RDT positive at time of the end of study, t_{max} , is

$$P(t > t_{max}) = S(t_{max})$$

Appendix to Chapter 4 - Overestimation of the *Plasmodium falciparum* malaria burden in African children due to coincident infections with non-malarial febrile illnesses

This appendix includes:

1. Additional Table 1: Studies and data used for parasite density threshold dataset. For each study, the *Pf* PR_{0-5}, parasite density threshold used, upper and lower age bounds, and the number or proportion of malaria-positive febrile individuals over and under the parasite density threshold is given.
2. Additional Table 2: Household survey data utilised for (*i*) modelling relationship between MAF and *Pf*PR, and (*ii*) modelling proportion of MAF and NMFI cases seeking treatment in clinics.
3. Additional Table 3: Literature review and PRISM datasets utilised for modelling relationship between MAF and *Pf*PR. For each study, the fever and parasite positivity status for each individual was extracted. Not all datapoints listed here were used in the final model; analysis was restricted to children under 5 years of age.
4. Additional Table 4: Predictor variables for BRT model for BRT_{bg} listed by contribution to the final model.
5. Additional Table 5: Predictor variables for BRT model for BRT_{treat} listed by contribution to the final model.
6. Additional File 1: R code for generating individual-level attributions of MAF and NMFI to febrile children in household survey dataset.
7. TMB code for generating individual-level attributions of MAF and NMFI to febrile children in household survey dataset.

Additional Table 1. Studies and data used for parasite density threshold dataset. For each study, the study *P. falciparum* prevalence in children under 5 years of age (*Pf* PR_{0-5}), parasite density threshold used, upper and lower age bounds, and the number or proportion of malaria-positive febrile individuals over and under the parasite density threshold is given.

ID	Reference	Study	Site	Country	Publication Year	Year(s) studied	*Pf* PR_{0-5}	Parasite density threshold	AgeLow	AgeUp	*Pf* Pos under threshold	*Pf* Pos over threshold	Numeric or Proportion	Proportion over threshold
1	1	Bloland	Asembo Bay	Kenya	1999	1992	0.7049	1500	0	0.4	222	320	N	0.59
2	1	Bloland	Asembo Bay	Kenya	1999	1992	0.7049	6000	0.5	0.9	221	307	N	0.58
3	1	Bloland	Asembo Bay	Kenya	1999	1992	0.7049	7000	1	2	118	179	N	0.60
4	1	Bloland	Asembo Bay	Kenya	1999	1992	0.7049	7000	2	3	96	57	N	0.37
5	1	Bloland	Asembo Bay	Kenya	1999	1992	0.7049	3500	3	4	191	98	N	0.34
6	2	Lusingu	Mgome	Tanzania	2004	2001	0.8120	5000	0	0.9	9.33	16.57	N	0.64
7	2	Lusingu	Mgome	Tanzania	2004	2001	0.8120	5000	1	1	7.25	17.13	N	0.70
8	2	Lusingu	Mgome	Tanzania	2004	2001	0.8120	5000	2	2	3.15	17.00	N	0.84
9	2	Lusingu	Mgome	Tanzania	2004	2001	0.8120	5000	3	3	1.95	1.95	N	0.50
10	2	Lusingu	Mgome	Tanzania	2004	2001	0.8120	5000	4	4	5.40	2.40	N	0.31
11	2	Lusingu	Ubiri	Tanzania	2004	2001	0.2409	1000	2	2	1.52	3.03	N	0.67
12	2	Lusingu	Ubiri	Tanzania	2004	2001	0.2409	1000	4	4	2.73	1.17	N	0.30
13	3	Molez	Barkedji	Senegal	2006	1994–1995	0.0874	2500	0	4	11	12	N	0.52
14	4,5	Mwangi	Ngerenya	Kenya	2003;2005	1999–2001	0.2231	10000	0	0.9	34	41	N	0.55
15	4,5	Mwangi	Chonyi	Kenya	2003;2005	1999–2001	0.3658	10000	0	0.9	50	76	N	0.60
16	4,5	Mwangi	Ngerenya	Kenya	2003;2005	1999–2001	0.2231	10000	1	5	188	546	N	0.74
17	4,5	Mwangi	Chonyi	Kenya	2003;2005	1999–2001	0.3658	10000	1	5	155	371	N	0.71
18	6	Owusu-Agyei	Kintampo	Ghana	2009	2004	0.6424	20000	0	0.9	100	45	N	0.31
19	6	Owusu-Agyei	Kintampo	Ghana	2009	2004	0.6424	20000	1	1.9	164	146	N	0.47
20	6	Owusu-Agyei	Kintampo	Ghana	2009	2004	0.6424	20000	2	2.9	138	108	N	0.44
21	6	Owusu-Agyei	Kintampo	Ghana	2009	2004	0.6424	20000	3	3.9	144	80	N	0.36
22	6	Owusu-Agyei	Kintampo	Ghana	2009	2004	0.6424	20000	4	4.9	87	46	N	0.35
23	7	Velema	Pahou	Benin	1991	1989	0.4551	20000	0	3	295	30	N	0.09
24	8	PRISM	Nagongera	Uganda	NA	2011	0.4740	5000	0	4	4	11	N	0.73
25	8	PRISM	Walukuba	Uganda	NA	2011	0.2488	5000	0	4	1	3	N	0.75
26	9	Afrane	Iguhu	Kenya	2014	2007-2009	0.0856	500	0	4	0.35	0.65	P	0.65

Additional Table 1 (Continued)

ID	Reference	Study	Site	Country	Publication Year	Year(s) studied	*Pf* PR_{0-5}	Parasite density threshold	AgeLow	AgeUp	*Pf* Pos under threshold	*Pf* Pos over threshold	Numeric or Proportion	Proportion over threshold
27	10	Cherif	Sapone	Burkina Faso	2017	2007	0.5566	5000	0.5	5	1301	1138	N	0.47
28	11	Mugyenyi	Ngerenya	Kenya	2017	2002	0.1220	2500	1	5	22	22	N	0.50
29	11	Mugyenyi	Ngerenya	Kenya	2017	2002-2003	0.1017	2500	1	5	34	99	N	0.74
30	11	Mugyenyi	Ngerenya	Kenya	2017	2003	0.1360	2500	1	5	36	61	N	0.63
31	12	Tiono	Banfora	Burkina Faso	2014	2009-2010	0.4776	5000	0	5	101	468	N	0.82

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Additional Table 2. Household survey data utilised for *(i)* modelling relationship between MAF and *Pf* PR, and *(ii)* modelling proportion of MAF and NMFI cases seeking treatment in clinics. P+/- refers to the number of children *P. falciparum* positive/negative at time of interview. F+/- refers to the number of children for whom fever was/was not recalled in the two weeks preceding the survey.

Country	Survey start year	Survey start month	Survey end year	Survey end month	N	P+F+	P+F-	P-F+	P-F-	Sought treatment (public)	Sought treatment (any)
Angola	2006	12	2007	1	1156	73	210	170	703	93	119
Angola	2011	1	2011	6	2914	173	181	903	1657	554	610
Angola	2015	12	2016	1	3012	114	344	368	2186	146	258
Benin	2011	12	2012	1	3119	125	682	240	2072	99	158
Burkina Faso	2010	5	2010	12	5640	1020	3235	317	1068	699	744
Burkina Faso	2014	9	2014	12	5448	1768	1756	616	1308	1385	1468
Burundi	2012	12	2013	1	3465	473	226	1024	1742	730	870
Cameroon	2011	1	2011	8	4511	633	747	759	2372	310	777
Cote d'Ivoire	2011	12	2012	1	2638	345	828	359	1106	178	260
Democratic Republic of the Congo	2013	12	2014	1	6996	1029	1401	1288	3278	794	1194
Ghana	2014	9	2014	12	2341	210	734	178	1219	204	297
Ghana	2016	10	2016	11	1423	168	308	253	694	165	256
Guinea	2012	6	2012	10	2741	503	671	445	1122	267	383
Kenya	2015	7	2015	8	2845	153	85	982	1625	583	796
Liberia	2008	12	2009	1	3024	523	511	933	1057	548	1056
Liberia	2011	9	2011	12	2333	710	468	654	501	564	930
Liberia	2016	9	2016	11	2108	501	519	431	657	480	560
Madagascar	2011	3	2011	5	5212	113	210	748	4141	235	358
Madagascar	2013	4	2013	6	4476	79	199	537	3661	219	313
Madagascar	2016	4	2016	7	3139	34	71	459	2575	224	281
Malawi	2012	3	2012	4	1890	366	352	267	905	283	376
Malawi	2014	5	2014	6	1717	262	238	271	946	279	366
Mali	2012	12	2013	1	4108	231	1547	183	2147	111	168
Mali	2015	9	2015	11	6618	788	1132	1225	3473	688	928
Mozambique	2011	5	2011	12	4323	279	1188	330	2526	355	367
Mozambique	2015	6	2015	9	3709	493	715	580	1921	690	710
Nigeria	2010	10	2010	12	4302	905	1115	724	1558	447	1391

Additional Table 2 (Continued)

Country	Survey start year	Survey start month	Survey end year	Survey end month	N	P+F+	P+F-	P-F+	P-F-	Sought treatment (public)	Sought treatment (any)
Nigeria	2015	10	2015	11	4920	1158	861	1048	1853	429	1427
Rwanda	2010	12	2011	1	3619	21	58	595	2945	302	338
Rwanda	2014	12	2015	1	3110	105	125	521	2359	338	386
Senegal	2008	12	2009	1	3519	176	248	1007	2088	408	518
Senegal	2010	12	2011	1	3278	27	81	695	2475	249	321
Senegal	2012	12	2013	1	5274	82	135	898	4159	391	489
Senegal	2015	2	2015	11	5441	21	37	928	4455	418	508
Tanzania	2007	12	2008	1	5576	240	456	792	4088	584	764
Tanzania	2011	12	2012	1	6379	249	331	1184	4615	685	1070
Tanzania	2015	12	2016	1	7366	291	564	1087	5424	209	1110
Togo	2013	12	2014	1	2844	309	731	367	1437	219	312
Uganda	2009	12	2010	2	3361	1037	710	570	1044	699	1319
Uganda	2014	12	2015	1	4022	642	655	682	2043	541	1037
Uganda	2016	6	2016	12	2753	583	291	532	1347	444	743

All surveys can be obtained with permission from the DHS Program: https://dhsprogram.com/

Additional Table 3. Literature review and PRISM datasets utilised for modelling relationship between MAF and *Pf* PR. For each study, the fever and parasite positivity status for each individual was extracted. Not all datapoints listed here were used in the final model; analysis was restricted to children under 5 years of age. *Search methodology for datapoint, as documented in Methods. ** PRISM Data can be downloaded from the ClinEpiDb website: https://clinepidb.org/

ID	Reference	Point used in model?	Source *	Author	Publication Year	Study Year	AgeLow	AgeUp	Method for P+	Fever recall or measured?	Fever period
1	1	No	MAP PfPR database	Erhardt	2006	2002	0	4	PCR	Measured	-
2	1	No	MAP PfPR database	Erhardt	2006	2002	5	9	PCR	Measured	-
3	1	No	MAP PfPR database	Erhardt	2006	2002	0	4	PCR	Measured	-
4	1	No	MAP PfPR database	Erhardt	2006	2002	5	9	PCR	Measured	-
5	2	No	MAP PfPR database	Schellenberg	1994	1989	1	5	Microscopy	Measured	-
6	3	No	MAP PfPR database	Bisoffi	2010	2006	0	99	Microscopy	Measured	-
7	3	Yes	MAP PfPR database	Bisoffi	2010	2006	0	1.00	Microscopy	Measured	-
8	3	Yes	MAP PfPR database	Bisoffi	2010	2006	1	4	Microscopy	Measured	-
9	3	No	MAP PfPR database	Bisoffi	2010	2006	5	14	Microscopy	Measured	-
10	3	No	MAP PfPR database	Bisoffi	2010	2006	15	99	Microscopy	Measured	-
11	4	Yes	MAP PfPR database	Mabunda	2009	2002-2003	0	1.00	Microscopy	Measured	-
12	4	Yes	MAP PfPR database	Mabunda	2009	2002-2003	1	1	Microscopy	Measured	-
13	4	Yes	MAP PfPR database	Mabunda	2009	2002-2003	2	4	Microscopy	Measured	-
14	4	No	MAP PfPR database	Mabunda	2009	2002-2003	5	6	Microscopy	Measured	-
15	4	No	MAP PfPR database	Mabunda	2009	2002-2003	7	9	Microscopy	Measured	-
16	5	No	MAP PfPR database	Mayor	2007	1999	15	83	Microscopy	Recall	24 hours
17	6	No	MAP PfPR database	Moukandja	2016	2013 (April)	3	85	Microscopy	Measured	-
18	6	No	MAP PfPR database	Moukandja	2016	2013 (June)	3	85	Microscopy	Measured	-
19	6	No	MAP PfPR database	Moukandja	2016	2013 (July)	3	85	Microscopy	Measured	-
20	6	No	MAP PfPR database	Moukandja	2016	2013 (October)	3	85	Microscopy	Measured	-
21	6	No	MAP PfPR database	Moukandja	2016	2014 (March)	3	85	Microscopy	Measured	-
22	6	No	MAP PfPR database	Moukandja	2016	2014 (June)	3	85	Microscopy	Measured	-
23	7	No	MAP PfPR database	Barbosa	2014	2010 (March - May)	0.25	99	Microscopy	Recall	7 days
24	7	No	MAP PfPR database	Barbosa	2014	2010 (May - July)	0.25	99	Microscopy	Recall	7 days
25	7	No	MAP PfPR database	Barbosa	2014	2010 (October - Nov)	0.25	99	Microscopy	Recall	7 days
26	7	No	MAP PfPR database	Barbosa	2014	2011 (March - April)	0.25	99	Microscopy	Recall	7 days
27	7	No	MAP PfPR database	Barbosa	2014	2011 (October - Nov)	0.25	99	Microscopy	Recall	7 days
28	7	No	MAP PfPR database	Barbosa	2014	2012 (April - May)	0.25	99	Microscopy	Recall	7 days
29	7	No	MAP PfPR database	Barbosa	2014	2012 (October Nov)	0.25	99	Microscopy	Recall	7 days

Additional Table 3 (Continued)

ID	Reference	Point used in model?	Source *	Author	Publication Year	Study Year	AgeLow	AgeUp	Method for P+	Fever recall or measured?	Fever period
30	7	No	MAP PfPR database	Barbosa	2014	2013 (April - May)	0.25	99	Microscopy	Recall	7 days
31	7	No	MAP PfPR database	Barbosa	2014	2010 (March - May)	0.25	99	PCR	Recall	7 days
32	7	No	MAP PfPR database	Barbosa	2014	2010 (May - July)	0.25	99	PCR	Recall	7 days
33	7	No	MAP PfPR database	Barbosa	2014	2010 (October - Nov)	0.25	99	PCR	Recall	7 days
34	7	No	MAP PfPR database	Barbosa	2014	2011 (March - April)	0.25	99	PCR	Recall	7 days
35	7	No	MAP PfPR database	Barbosa	2014	2011 (October - Nov)	0.25	99	PCR	Recall	7 days
36	7	No	MAP PfPR database	Barbosa	2014	2012 (April - May)	0.25	99	PCR	Recall	7 days
37	7	No	MAP PfPR database	Barbosa	2014	2012 (October-Nov)	0.25	99	PCR	Recall	7 days
38	7	No	MAP PfPR database	Barbosa	2014	2013 (April - May)	0.25	99	PCR	Recall	7 days
39	8	Yes	MAP PfPR database	Burdam	2016	2013	1	4	Microscopy	Recall	24 hours
40	9	No	MAP PfPR database	Imwong	2015	2013	0	99	PCR	Recall	Unknown
41	10	No	MAP PfPR database	Phommasone	2016	2015	15	80	PCR	Recall	2 days
42	11	No	MAP PfPR database	Geiger	2013	2009-2012	0.5	90	Microscopy	Measured	-
43	12	No	MAP PfPR database	Mboera	2015	2012	4	16	Microscopy	Measured	-
44	13	No	MAP PfPR database	Mwesigwa	2015	2012	0	99	PCR	Recall	24 hours
45	13	No	MAP PfPR database	Mwesigwa	2015	2012	0	99	PCR	Measured	-
46	14	No	MAP PfPR database	Ouattara	2014	2010-2012	0	15	RDT	Measured	-
47	14	No	MAP PfPR database	Ouattara	2014	2010-2012	0	15	Microscopy	Measured	-
48	15	No	MAP PfPR database	Charlwood	2015	2007	0	75	Microscopy	Measured	-
49	15	No	MAP PfPR database	Charlwood	2015	2009	0	75	Microscopy	Measured	-
50	15	No	MAP PfPR database	Charlwood	2015	2010	0	75	Microscopy	Measured	-
51	15	No	MAP PfPR database	Charlwood	2015	2011	0	75	Microscopy	Measured	-
52	16	No	MAP PfPR database	Kimbi	2013	2011	4	15	Microscopy	Measured	-
53	17	No	MAP PfPR database	Mathanga	2015	2011	5	21	Microscopy	Recall	14 days
54	17	No	MAP PfPR database	Mathanga	2015	2011	5	21	Microscopy	Measured	-
55	18	No	MAP PfPR database	Gneme	2013	2007-2010	3	15	Microscopy	Measured	-
56	19	No	MAP PfPR database	Proietti	2011	2009	0	9	Microscopy	Measured	-
57	20	No	MAP PfPR database	Sutcliffe	2011	2007-2009	0	99	RDT	Measured	-
58	20	No	MAP PfPR database	Sutcliffe	2011	2007-2009	0	99	RDT	Recall	2 days
59	21	No	MAP PfPR database	Gitonga	2010	2008-2010	5	20	RDT	Measured	-
60	22	No	MAP PfPR database	Damien	2010	2007-2008	0	5	Microscopy	Measured	-

Additional Table 3 (Continued)

ID	Reference	Point used in model?	Source *	Author	Publication Year	Study Year	AgeLow	AgeUp	Method for P+	Fever recall or measured?	Fever period
61	23	No	MAP PfPR database	Eisele	2007	2006	0	92	PCR	Measured	-
62	24	No	MAP PfPR database	Mustafa	2009	2005-2006	1	70	Microscopy	Measured	-
63	24	No	MAP PfPR database	Mustafa	2009	2005-2006	1	73	Microscopy	Measured	-
64	24	No	MAP PfPR database	Mustafa	2009	2005-2006	1	99	Microscopy	Measured	-
65	24	No	MAP PfPR database	Mustafa	2009	2005-2006	1	90	Microscopy	Measured	-
66	25	Yes	MAP PfPR database	Ouédraogo	2008	2006	0.5	1	Microscopy	Measured	-
67	26	No	MAP PfPR database	Pluess	2009	2006	0	99	Microscopy	Measured	-
68	26	No	MAP PfPR database	Pluess	2009	2006	0	99	Microscopy	Recall	14 days
69	27	No	PubMed search	Tchuinkam	2015	Unknown	0	99	Microscopy	Measured	-
70	27	No	PubMed search	Tchuinkam	2015	Unknown	0	99	Microscopy	Measured	-
71	28	No	PubMed search	Incardona	2007	2001	0	99	Microscopy	Measured	-
72	28	No	PubMed search	Incardona	2007	2002	0	99	Microscopy	Measured	-
73	28	No	PubMed search	Incardona	2007	2003	0	99	Microscopy	Measured	-
74	29	Yes	PubMed search	Dicko	2005	1993	0.5	0.99	Microscopy	Measured	-
75	29	Yes	PubMed search	Dicko	2005	1993	1	1	Microscopy	Measured	-
76	29	Yes	PubMed search	Dicko	2005	1993	2	4	Microscopy	Measured	-
77	29	No	PubMed search	Dicko	2005	1993	5	9	Microscopy	Measured	-
78	29	Yes	PubMed search	Dicko	2005	1993	0.5	0.99	Microscopy	Measured	-
79	29	Yes	PubMed search	Dicko	2005	1993	1	1	Microscopy	Measured	-
80	29	Yes	PubMed search	Dicko	2005	1993	2	4	Microscopy	Measured	-
81	29	No	PubMed search	Dicko	2005	1993	5	9	Microscopy	Measured	-
82	30	Yes	PubMed search	Vounatsou	1999	1992-1993	0	0.17	Microscopy	Measured OR recall	Measured/24h recall
83	30	Yes	PubMed search	Vounatsou	1999	1992-1993	0.25	0.42	Microscopy	Measured OR recall	Measured/24h recall
84	30	Yes	PubMed search	Vounatsou	1999	1992-1993	0.5	0.67	Microscopy	Measured OR recall	Measured/24h recall
85	30	Yes	PubMed search	Vounatsou	1999	1992-1993	0.75	0.92	Microscopy	Measured OR recall	Measured/24h recall
86	30	Yes	PubMed search	Vounatsou	1999	1992-1993	0	0.17	Microscopy	Measured OR recall	Measured/24h recall
87	30	Yes	PubMed search	Vounatsou	1999	1992-1993	0.25	0.42	Microscopy	Measured OR recall	Measured/24h recall
88	30	Yes	PubMed search	Vounatsou	1999	1992-1993	0.5	0.67	Microscopy	Measured OR recall	Measured/24h recall
89	30	Yes	PubMed search	Vounatsou	1999	1992-1993	0.75	0.92	Microscopy	Measured OR recall	Measured/24h recall
90	31	No	PubMed search	Charchuk	2016	2013	0	2	RDT	Recall	2 weeks
91	31	No	PubMed search	Charchuk	2016	2013	3	5	RDT	Recall	2 weeks

Additional Table 3 (Continued)

ID	Reference	Point used in model?	Source *	Author	Publication Year	Study Year	AgeLow	AgeUp	Method for P+	Fever recall or measured?	Fever period
92	31	No	MAP PfPR database	Charchuk	2016	2012	5	19	RDT	Measured	NA
93	32	No	MAP PfPR database	Parr	2016	2011-2013	0	99	Microscopy and RDT	Recall	24h
94	33	No	MAP PfPR database	Pava	2016	2013	0	99	Microscopy	Recall	30 days
95	34	Yes	PRISM Data	-	-	2011	0	4	Microscopy	Measured	NA
96	34	Yes	PRISM Data	-	-	2011	0	4	Microscopy	Measured	NA
97	34	Yes	PRISM Data	-	-	2011	0	4	Microscopy	Measured	NA
98	34	Yes	PRISM Data	-	-	2011	0	4	Microscopy	Recall	24h
99	34	Yes	PRISM Data	-	-	2011	0	4	Microscopy	Recall	24h
100	34	Yes	PRISM Data	-	-	2011	0	4	Microscopy	Recall	24h
101	34	No	PRISM Data	-	-	2011	5	14	Microscopy	Measured	NA
102	34	No	PRISM Data	-	-	2011	5	14	Microscopy	Measured	NA
103	34	No	PRISM Data	-	-	2011	5	14	Microscopy	Measured	NA
104	34	No	PRISM Data	-	-	2011	5	14	Microscopy	Recall	24h
105	34	No	PRISM Data	-	-	2011	5	14	Microscopy	Recall	24h
106	34	No	PRISM Data	-	-	2011	5	14	Microscopy	Recall	24h
107	34	No	PRISM Data	-	-	2011	15	71	Microscopy	Measured	NA
108	34	No	PRISM Data	-	-	2011	15	71	Microscopy	Measured	NA
109	34	No	PRISM Data	-	-	2011	15	71	Microscopy	Measured	NA
110	34	No	PRISM Data	-	-	2011	15	71	Microscopy	Recall	24h
111	34	No	PRISM Data	-	-	2011	15	71	Microscopy	Recall	24h
112	34	No	PRISM Data	-	-	2011	15	71	Microscopy	Recall	24h

Additional Table 3 (Continued)

ID	Reference	N	P+F+	P+F-	P-F+	P-F-	P+	F+	Estimated MAF cases	Estimated MAF cases as a proportion of P+F+
1	1	1267	34	18	54	1161	52	88	31.69	0.93
2	1	842	24	6	10	802	30	34	23.63	0.98
3	1	1104	72	10	23	999	82	95	70.15	0.97
4	1	1015	32	5	8	970	37	40	31.70	0.99
5	2	407	41	86	33	247	127	74	26.03	0.63
6	3	1426	147	121	519	639	268	666	26.89	0.18
7	3	209	132	18	27	32	150	159	63.36	0.48
8	3	665	394	72	110	89	466	504	136.41	0.35
9	3	412	198	72	77	65	270	275	51.59	0.26
10	3	969	117	153	262	437	270	379	15.80	0.14
11	4	1517	161	479	68	809	640	229	111.38	0.69
12	4	1609	166	725	46	672	891	212	108.92	0.66
13	4	3515	162	1641	88	1624	1803	250	69.32	0.43
14	4	1244	40	558	33	613	598	73	9.45	0.24
15	4	951	31	343	19	558	374	50	18.68	0.60
16	5	249	6	30	33	180	36	39	0.42	0.07
17	6	370	8	153	1	208	161	9	7.23	0.90
18	6	267	1	108	0	158	109	1	1.00	1.00
19	6	218	2	113	2	101	115	4	0.00	0.00
20	6	255	1	86	0	168	87	1	1.00	1.00
21	6	232	9	125	5	93	134	14	2.16	0.24
22	6	145	1	66	0	78	67	1	1.00	1.00
23	7	159	0	1	62	96	1	63	0.00	0.00
24	7	199	0	1	53	145	1	54	0.00	0.00
25	7	211	0	0	45	166	0	45	0.00	0.00
26	7	216	0	0	34	182	0	34	0.00	0.00
27	7	204	0	0	40	164	0	40	0.00	0.00
28	7	178	0	0	22	156	0	22	0.00	0.00
29	7	199	0	0	65	134	0	65	0.00	0.00

Additional Table 3 (Continued)

ID	Reference	N	P+F+	P+F-	P-F+	P-F-	P+	F+	Estimated MAF cases	Estimated MAF cases as a proportion of P+F+
30	7	175	0	0	46	129	0	46	0.00	0.00
31	7	150	3	7	59	81	10	62	0.00	0.00
32	7	187	1	11	51	124	12	52	0.00	0.00
33	7	198	4	20	38	136	24	42	0.00	0.00
34	7	199	1	1	30	167	2	31	0.70	0.70
35	7	197	0	0	38	159	0	38	0.00	0.00
36	7	177	0	0	21	156	0	21	0.00	0.00
37	7	199	0	0	65	134	0	65	0.00	0.00
38	7	169	0	0	43	126	0	43	0.00	0.00
39	8	533	3	19	3	508	22	6	2.87	0.96
40	9	1465	43	185	139	1098	228	182	17.38	0.40
41	10	858	21	25	249	563	46	270	6.89	0.33
42	11	1764	199	552	164	849	751	363	77.42	0.39
43	12	1019	2	44	12	961	46	14	1.43	0.72
44	13	9094	711	745	3484	4154	1456	4195	46.86	0.07
45	13	9094	209	1247	289	7349	1456	498	153.91	0.74
46	14	1482	249	698	147	388	947	396	0.00	0.00
47	14	1482	236	718	160	368	954	396	0.00	0.00
48	15	32	7	0	3	22	7	3	6.16	0.88
49	15	431	7	153	7	264	160	14	2.87	0.41
50	15	369	19	82	25	243	101	44	9.58	0.50
51	15	258	3	119	2	134	122	5	1.21	0.40
52	16	728	88	158	130	352	246	218	21.65	0.25
53	17	2645	541	1046	426	632	1587	967	0.00	0.00
54	17	2641	449	1134	287	771	1583	736	19.59	0.04
55	18	830	111	413	45	261	524	156	33.94	0.31
56	19	425	85	168	42	130	253	127	23.22	0.27
57	20	330	8	71	6	245	79	14	6.11	0.76
58	20	330	41	38	82	169	79	123	15.19	0.37
59	21	30542	55	1258	678	28551	1313	733	24.54	0.45
60	22	3074	105	618	131	2220	723	236	64.71	0.62

Additional Table 3 (Continued)

ID	Reference	N	P+F+	P+F-	P-F+	P-F-	P+	F+	Estimated MAF cases	Estimated MAF cases as a proportion of P+F+
61	23	708	9	14	52	633	23	61	7.25	0.81
62	24	421	21	4	47	349	25	68	18.03	0.86
63	24	522	68	17	45	392	85	113	59.25	0.87
64	24	1049	40	20	99	890	60	139	33.99	0.85
65	24	1636	45	2	53	1536	47	98	43.43	0.97
66	25	456	123	117	79	137	240	202	35.22	0.29
67	26	723	8	234	12	469	242	20	1.96	0.25
68	26	723	70	172	116	365	242	186	11.64	0.17
69	27	675	243	98	166	168	341	409	73.52	0.30
70	27	736	126	43	171	396	169	297	75.03	0.60
71	28	4074	35	88	166	3785	123	201	29.83	0.85
72	28	2624	42	142	373	2067	184	415	13.87	0.33
73	28	4954	199	411	404	3940	610	603	142.27	0.71
74	29	162	29	54	7	72	83	36	21.65	0.75
75	29	231	38	110	6	77	148	44	27.30	0.72
76	29	811	93	462	26	230	555	119	36.63	0.39
77	29	1230	105	692	49	384	797	154	14.81	0.14
78	29	77	3	15	4	55	18	7	1.78	0.59
79	29	313	13	93	11	196	106	24	7.37	0.57
80	29	772	35	342	25	370	377	60	11.14	0.32
81	29	1191	60	482	39	610	542	99	27.43	0.46
82	30	203	15	48	16	124	63	31	7.80	0.52
83	30	202	40	81	18	63	121	58	13.11	0.33
84	30	140	35	56	13	36	91	48	10.86	0.31
85	30	101	30	41	3	27	71	33	22.90	0.76
86	30	189	11	25	20	133	36	31	6.29	0.57
87	30	209	33	75	17	84	108	50	14.82	0.45
88	30	177	44	74	9	50	118	53	26.00	0.59
89	30	135	31	68	9	27	99	40	6.25	0.20
90	31	233	5	20	57	151	25	62	0.00	0.00
91	31	167	4	24	34	105	28	38	0.00	0.00

Additional Table 3 (Continued)

ID	Reference	N	P+F+	P+F-	P-F+	P-F-	P+	F+	Estimated MAF cases	Estimated MAF cases as a proportion of P+F+
92	31	109	5	39	7	58	44	12	0.26	0.05
93	32	800	17	63	91	629	80	108	6.89	0.41
94	33	2761	8	137	102	2514	145	2616	2.35	0.29
95	34	211	1	14	13	183	15	14	0.01	0.01
96	34	215	15	43	16	141	58	31	9.09	0.61
97	34	222	4	12	15	191	16	19	2.83	0.71
98	34	211	4	11	13	183	15	17	3.01	0.75
99	34	215	19	39	26	131	58	45	9.39	0.49
100	34	222	3	13	16	190	16	19	1.76	0.59
101	34	169	3	10	6	150	13	9	2.50	0.83
102	34	149	4	56	4	85	60	8	1.30	0.33
103	34	118	0	5	7	106	5	7	-0.31	0.00
104	34	169	5	8	5	151	13	10	4.58	0.92
105	34	149	5	55	7	82	60	12	0.28	0.06
106	34	118	0	5	6	107	5	6	-0.27	0.00
107	34	98	0	0	5	93	0	5	0.00	0.00
108	34	106	1	4	4	97	5	5	0.80	0.80
109	34	114	1	4	6	103	5	7	0.72	0.72
110	34	98	0	0	2	96	0	2	0.00	0.00
111	34	106	1	4	7	94	5	8	0.65	0.65
112	34	114	1	4	3	106	5	4	0.86	0.86

Additional Table 3 (Continued)

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Additional Table 3 (Continued)

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Additional Table 4. Predictor variables for BRT model for BRT[bg] listed by contribution to the final model. EVI: Enhanced Vegetation Index; GUF: Global Urban Footprint; LST: Land Surface Temperature; PET - potential evapotranspiration; TCB - Tassled Cap Brightness; TCW - Tassled Cap Wetness; TMI - Topographic Moisture Index; TSI - Temperature Suitability Index; WB - World Bank Variable."Product" definitions for EVI, LST, TSI, TCW and TCB: Monthly - average value over study month; All-years synoptic - mean EVI for all years 2000-2015; Delta dynamic - difference between monthly value and synoptic product; Monthly synoptic - mean of study month across all years; Delta monthly - difference between study month and monthly synoptic product; Delta annual - difference between study month and study year (e.g. July 2008 - Mean 2008). "Lag" defines the number of months that the covariate dataset lags behind the month of each household survey dataset point (e.g. if a household survey data point is recorded in July 2008, a covariate with a lag of 2 months will be taken from May 2008).

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
primary_school	7.203	Proportion of children in primary school (WB National)	-	N/A	Yearly	N/A
pregnant	5.880	Percentage of pregnant women who receive prenatal care (WB National)	-	N/A	Yearly	N/A
DPT	4.373	DPT immunisation coverage (WB annual)	-	N/A	Yearly	N/A
public_exp	2.656	Public expenditure on health system (WB national)	-	N/A	Yearly	N/A
GDP_grow	2.604	Annual GDP growth (WB national)	-	N/A	Yearly	N/A
prec57p2	1.704	Precipitation	-	N/A	Stationary	N/A
prec57p3	1.618	Precipitation	-	N/A	Stationary	N/A
LST_night_delta_dynamic_mean_1	1.252	LST night	Delta dynamic	Mean	Fully dynamic	1
EVI_delta_annual_min_0	1.237	EVI	Delta annual	Minimum	Delta annual	0
LST_night_delta_monthly_range_4	1.102	LST night	Delta monthly	Range	Fully dynamic	4
EVI_delta_monthly_stdev_4	1.002	EVI	Delta monthly	Standard deviation	Fully dynamic	4
LST_delta_delta_annual_mean_0	1.002	LST delta	Delta annual	Mean	Fully dynamic	0
EVI_delta_dynamic_mean_1	0.977	EVI	Delta dynamic	Mean	Fully dynamic	1
LST_day_delta_annual_max_1	0.972	LST day	Delta annual	Maximum	Fully dynamic	1
TSI.monthly.mean.synoptic.stdev_2	0.970	TSI	Monthly synoptic	Mean	Month only	2
prec57a0	0.924	Precipitation	-	N/A	Stationary	N/A
LST_day.monthly.range.synoptic.stdev_2	0.893	LST day	Monthly synoptic	Standard deviation	Month only	2
LST_day_delta_dynamic_range_2	0.892	LST day	Delta dynamic	Range	Fully dynamic	2
LST_delta.monthly.mean.synoptic.stdev_0	0.875	LST delta	Monthly synoptic	Mean	Month only	0
LST_day_delta_monthly_min_1	0.870	LST day	Delta monthly	Minimum	Fully dynamic	1
TSI_delta_monthly_max_0	0.853	TSI	Delta monthly	Maximum	Fully dynamic	0
LST_night_delta_monthly_min_0	0.838	LST night	Delta monthly	Minimum	Fully dynamic	0
prec57p1	0.822	Precipitation	-	N/A	Stationary	N/A
EVI.monthly.min.synoptic.stdev_4	0.821	EVI	Monthly synoptic	Minimum	Month only	4
TSI.monthly.range.synoptic.mean_3	0.811	TSI	Monthly synoptic	Range	Month only	3

Additional Table 4 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
TSI_delta_monthly_min_4	0.774	TSI	Delta monthly	Minimum	Fully dynamic	4
EVI_delta_monthly_min_1	0.757	EVI	Delta monthly	Minimum	Fully dynamic	1
TCB_delta_annual_stdev_4	0.755	TCB	Delta annual	Standard deviation	Fully dynamic	4
TCB_delta_annual_max_3	0.749	TCB	Delta annual	Maximum	Fully dynamic	3
Africa_TMI_90m.max	0.748	TMI	-	Maximum	Stationary	N/A
accessibility_50k_5km.stdev	0.737	Accessibility	-	Standard deviation	Stationary	N/A
fraction.class.14	0.735	Land cover class fraction	-	N/A	Yearly	N/A
TSI.monthly.mean.synoptic.stdev_3	0.732	TSI	Monthly synoptic	Mean	Month only	3
TCB_delta_monthly_mean_1	0.689	TCB	Delta monthly	Mean	Fully dynamic	1
LST_night_delta_dynamic_min_0	0.678	LST night	Delta dynamic	Minimum	Fully dynamic	0
LST_delta_delta_monthly_mean_0	0.672	LST delta	Delta monthly	Mean	Fully dynamic	0
TCB.monthly.mean.synoptic.stdev_4	0.663	TCB	Monthly synoptic	Mean	Month only	4
LST_delta.monthly.mean.synoptic.stdev_1	0.643	LST delta	Monthly synoptic	Mean	Month only	1
EVI.monthly.range.synoptic.stdev_2	0.640	EVI	Monthly synoptic	Range	Month only	2
LST_night_delta_dynamic_mean_3	0.633	LST night	Delta dynamic	Mean	Fully dynamic	3
EVI_delta_monthly_min_0	0.615	EVI	Delta monthly	Minimum	Fully dynamic	0
TCW_delta_monthly_mean_1	0.606	TCW	Delta monthly	Mean	Fully dynamic	1
LST_day_delta_monthly_stdev_4	0.599	LST day	Delta monthly	Standard deviation	Fully dynamic	4
Africa_TMI_90m.min	0.592	TMI	-	Minimum	Stationary	N/A
LST_night.monthly.stdev.synoptic.stdev_3	0.576	LST night	Monthly synoptic	Standard deviation	Month only	3
EVI_delta_monthly_range_2	0.557	EVI	Delta monthly	Range	Fully dynamic	2
LST_night.monthly.min.synoptic.stdev_2	0.552	LST night	Monthly synoptic	Minimum	Month only	2
fraction.class.9	0.545	Land cover class fraction	-	N/A	Yearly	N/A
TSI_delta_annual_min_4	0.543	TSI	Delta annual	Minimum	Fully dynamic	4
LST_night.monthly.range.synoptic.stdev_1	0.542	LST night	Monthly synoptic	Range	Month only	1
TSI_delta_monthly_max_2	0.540	TSI	Delta monthly	Maximum	Fully dynamic	2
TSI.monthly.min.synoptic.stdev_4	0.539	TSI	Monthly synoptic	Minimum	Month only	4
TCB_delta_annual_stdev_2	0.538	TCB	Delta annual	Standard deviation	Fully dynamic	2
LST_night.monthly.mean.synoptic.stdev_0	0.516	LST night	Monthly synoptic	Mean	Month only	0
LST_delta.monthly.max.synoptic.mean_2	0.510	LST delta	Monthly synoptic	Maximum	Month only	2
prec57a3	0.508	Precipitation	-	N/A	Stationary	N/A

Additional Table 4 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
TSI_delta_monthly_stdev_4	0.507	TSI	Delta monthly	Standard deviation	Fully dynamic	4
TCB_monthly_min_1	0.501	TCB	Monthly	Minimum	Fully dynamic	1
LST_night_delta_dynamic_max_2	0.498	LST night	Delta dynamic	Maximum	Fully dynamic	2
LST_day.monthly.range.synoptic.stdev_1	0.497	LST day	Monthly synoptic	Standard deviation	Month only	1
TSI.monthly.range.synoptic.stdev_2	0.493	TSI	Monthly synoptic	Standard deviation	Month only	2
LST_night_delta_monthly_max_3	0.488	LST night	Delta monthly	Maximum	Fully dynamic	3
LST_night.monthly.stdev.synoptic.stdev_0	0.487	LST night	Monthly synoptic	Standard deviation	Month only	0
LST_night_delta_monthly_mean_4	0.481	LST night	Delta monthly	Mean	Fully dynamic	4
LST_night_delta_monthly_max_2	0.478	LST night	Delta monthly	Maximum	Fully dynamic	2
LST_night_delta_annual_max_2	0.477	LST night	Delta annual	Maximum	Fully dynamic	2
TSI_delta_monthly_range_3	0.474	TSI	Delta monthly	Range	Fully dynamic	3
TCB_delta_annual_range_1	0.454	TCB	Delta annual	Range	Fully dynamic	1
LST_night.monthly.stdev.synoptic.stdev_2	0.449	LST night	Monthly synoptic	Standard deviation	Month only	2
LST_day.monthly.stdev.synoptic.stdev_3	0.444	LST day	Monthly synoptic	Standard deviation	Month only	3
TSI_delta_monthly_mean_1	0.444	TSI	Delta monthly	Mean	Fully dynamic	1
LST_day_delta_monthly_max_4	0.439	LST day	Delta monthly	Maximum	Fully dynamic	4
TCW_delta_annual_stdev_0	0.436	TCW	Delta annual	Standard deviation	Fully dynamic	0
LST_day_delta_dynamic_stdev_0	0.435	LST day	Delta dynamic	Standard deviation	Fully dynamic	0
EVI.monthly.mean.synoptic.stdev_2	0.435	EVI	Monthly synoptic	Standard deviation	Month only	2
EVI_all_years_synoptic_min	0.431	EVI	All-years synoptic	Minimum	Stationary	N/A
EVI.monthly.stdev.synoptic.stdev_4	0.429	EVI	Monthly synoptic	Standard deviation	Month only	4
EVI_delta_dynamic_min_4	0.427	EVI	Delta dynamic	Minimum	Fully dynamic	4
EVI_delta_monthly_stdev_0	0.423	EVI	Delta monthly	Standard deviation	Fully dynamic	0
LST_night.monthly.mean.synoptic.stdev_1	0.415	LST night	Monthly synoptic	Mean	Month only	1
LST_night.monthly.max.synoptic.stdev_4	0.413	LST night	Monthly synoptic	Maximum	Month only	4
TCW_delta_monthly_mean_4	0.413	TCW	Delta monthly	Mean	Fully dynamic	4
population_covariates	0.412	Population density	-	N/A	Yearly	N/A
LST_night_delta_dynamic_stdev_0	0.410	LST night	Delta dynamic	Standard deviation	Fully dynamic	0
Africa_FA_90m.mean	0.409	Elevation (flow accumulation)	-	Mean	Stationary	N/A
TCW_monthly_stdev_3	0.408	TCW	Monthly	Standard deviation	Fully dynamic	3
TSI.monthly.max.synoptic.stdev_4	0.407	TSI	Monthly synoptic	Maximum	Month only	4

Additional Table 4 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
EVI_delta_monthly_min_2	0.403	EVI	Delta monthly	Minimum	Fully dynamic	2
LST_day_delta_monthly_range_1	0.403	LST day	Delta monthly	Range	Fully dynamic	1
EVI_delta_monthly_stdev_1	0.400	EVI	Delta monthly	Standard deviation	Fully dynamic	1
adjacencies.class.8	0.398	Land cover adjacencies	-	N/A	Yearly	N/A
LST_day.monthly.min.synoptic.stdev_2	0.395	LST day	Monthly synoptic	Minimum	Month only	2
TCW_delta_monthly_mean_0	0.394	TCW	Delta monthly	Mean	Fully dynamic	0
TSI_delta_monthly_max_4	0.389	TSI	Delta monthly	Maximum	Fully dynamic	4
PET_1950.2000_5km.stdev	0.388	PET	-	Standard deviation	Stationary	N/A
viirs_nighttime_5km.mean	0.385	Nighttime lights	-	Mean	Stationary	N/A
EVI.monthly.range.synoptic.stdev_0	0.380	EVI	Monthly synoptic	Range	Month only	0
LST_day_delta_annual_stdev_3	0.379	LST day	Delta annual	Standard deviation	Fully dynamic	3
Global_Urban_Footprint_5km_PropUrban	0.379	Proportion urban in cell (GUF)	-	N/A	Stationary	N/A
LST_night.monthly.range.synoptic.mean_1	0.375	LST night	Monthly synoptic	Range	Month only	1
fraction.class.2	0.369	Land cover class fraction	-	N/A	Yearly	N/A
TCW_delta_annual_stdev_3	0.358	TCW	Delta annual	Standard deviation	Fully dynamic	3
LST_night_delta_annual_range_1	0.356	LST night	Delta annual	Range	Fully dynamic	1
population_density_5km.min	0.355	Population density	-	Minimum	Stationary	N/A
LST_day_delta_monthly_min_3	0.350	LST day	Delta monthly	Minimum	Fully dynamic	3
LST_day_delta_monthly_range_0	0.348	LST day	Delta monthly	Range	Fully dynamic	0
EVI_delta_dynamic_stdev_1	0.346	EVI	Delta dynamic	Standard deviation	Fully dynamic	1
LST_day.monthly.stdev.synoptic.stdev_4	0.341	LST day	Monthly synoptic	Standard deviation	Month only	4
TCW_delta_monthly_mean_2	0.341	TCW	Delta monthly	Mean	Fully dynamic	2
TSI_delta_monthly_stdev_2	0.340	TSI	Delta monthly	Standard deviation	Fully dynamic	2
TCB_delta_monthly_mean_0	0.339	TCB	Delta monthly	Mean	Fully dynamic	0
TCB_delta_dynamic_mean_4	0.337	TCB	Delta monthly	Mean	Fully dynamic	4
prec57a1	0.335	Precipitation	-	N/A	Stationary	N/A
TCW_delta_monthly_mean_3	0.332	TCW	Delta monthly	Mean	Fully dynamic	3
TCB_delta_monthly_mean_4	0.330	TCB	Delta monthly	Mean	Fully dynamic	4
TSI.monthly.min.synoptic.stdev_0	0.329	TSI	Monthly synoptic	Minimum	Month only	0
LST_day.monthly.mean.synoptic.stdev_3	0.325	LST day	Monthly synoptic	Mean	Month only	3
EVI_delta_dynamic_range_0	0.320	EVI	Delta dynamic	Range	Fully dynamic	0

Additional Table 4 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
TCB_monthly_max_4	0.320	TCB	Monthly	Maximum	Fully dynamic	4
TSI_delta_monthly_max_3	0.320	TSI	Delta monthly	Maximum	Fully dynamic	3
LST_night_delta_monthly_max_1	0.318	LST night	Delta monthly	Maximum	Fully dynamic	1
LST_delta_delta_monthly_mean_2	0.316	LST delta	Delta monthly	Mean	Fully dynamic	2
TCB_delta_monthly_mean_2	0.312	TCB	Delta monthly	Mean	Fully dynamic	2
TSI_delta_monthly_min_2	0.312	TSI	Delta monthly	Minimum	Fully dynamic	2
LST_delta_all_years_synoptic_max	0.311	LST delta	All-years synoptic	Maximum	Stationary	N/A
LST_night.monthly.stdev.synoptic.mean_4	0.311	LST night	Monthly synoptic	Standard deviation	Month only	4
LST_night_delta_dynamic_max_4	0.310	LST night	Delta dynamic	Maximum	Fully dynamic	4
EVI_delta_monthly_mean_3	0.307	EVI	Delta monthly	Mean	Fully dynamic	3
LST_night_delta_monthly_range_0	0.295	LST night	Delta monthly	Range	Fully dynamic	0
EVI_delta_monthly_range_3	0.293	EVI	Delta monthly	Range	Fully dynamic	3
LST_night_delta_annual_stdev_3	0.281	LST night	Delta annual	Standard deviation	Fully dynamic	3
LST_night_delta_dynamic_stdev_4	0.281	LST night	Delta dynamic	Standard deviation	Fully dynamic	4
TSI_monthly_stdev_1	0.277	TSI	Monthly	Standard deviation	Fully dynamic	1
EVI_delta_dynamic_range_4	0.276	EVI	Delta dynamic	Range	Fully dynamic	4
EVI.monthly.mean.synoptic.stdev_0	0.275	EVI	Monthly synoptic	Mean	Month only	0
LST_day_delta_monthly_stdev_3	0.269	LST day	Delta monthly	Standard deviation	Fully dynamic	3
fraction.class.5	0.268	Land cover class fraction	-	N/A	Yearly	N/A
prec57a2	0.260	Precipitation	-	N/A	Stationary	N/A
LST_night_delta_monthly_stdev_2	0.256	LST night	Delta monthly	Standard deviation	Fully dynamic	2
TCW_delta_annual_stdev_1	0.253	TCW	Delta annual	Standard deviation	Fully dynamic	1
TCB_delta_annual_range_3	0.247	TCB	Delta annual	Range	Fully dynamic	3
TCW_delta_annual_stdev_4	0.247	TCW	Delta annual	Standard deviation	Fully dynamic	4
EVI_delta_monthly_max_2	0.244	EVI	Delta monthly	Maximum	Fully dynamic	2
TSI.monthly.mean.synoptic.stdev_1	0.241	TSI	Monthly synoptic	Mean	Month only	1
TSI_delta_monthly_min_3	0.239	TSI	Delta monthly	Minimum	Fully dynamic	3
LST_night_delta_annual_stdev_2	0.238	LST night	Delta annual	Standard deviation	Fully dynamic	2
LST_day.monthly.range.synoptic.mean_4	0.231	LST day	Monthly synoptic	Range	Month only	4
EVI_all_years_synoptic_range	0.229	EVI	All-years synoptic	Range	Stationary	N/A
LST_day_delta_annual_range_4	0.226	LST day	Delta annual	Range	Fully dynamic	4

Additional Table 4 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
LST_day.monthly.range.synoptic.stdev_0	0.226	LST day	Monthly synoptic	Range	Month only	0
TSI_delta_monthly_range_0	0.226	TSI	Delta monthly	Range	Fully dynamic	0
LST_delta_delta_annual_max_2	0.223	LST delta	Delta annual	Maximum	Fully dynamic	2
TCW_delta_annual_stdev_2	0.223	TCW	Delta annual	Standard deviation	Fully dynamic	2
accessibility_ESRI_5km.range	0.222	Accessibility	-	Range	Stationary	N/A
Africa_TMI_90m.stdev	0.214	TMI	-	Standard deviation	Stationary	N/A
EVI_delta_annual_stdev_2	0.206	EVI	Delta annual	Standard deviation	Delta annual	2
fraction.class.7	0.206	Land cover class fraction	-	N/A	Yearly	N/A
TCW_delta_dynamic_mean_2	0.200	TCW	Delta dynamic	Mean	Fully dynamic	2
fraction.class.12	0.199	Land cover class fraction	-	N/A	Yearly	N/A
LST_night.monthly.min.synoptic.stdev_3	0.197	LST night	Monthly synoptic	Minimum	Month only	3
TSI_monthly_stdev_2	0.188	TSI	Monthly	Standard deviation	Fully dynamic	2
EVI_delta_monthly_mean_4	0.171	EVI	Delta monthly	Mean	Fully dynamic	4
LST_night.monthly.stdev.synoptic.stdev_4	0.164	LST night	Monthly synoptic	Standard deviation	Month only	4
EVI_delta_dynamic_stdev_3	0.163	EVI	Delta dynamic	Standard deviation	Fully dynamic	3
TSI.monthly.range.synoptic.stdev_1	0.156	TSI	Monthly synoptic	Standard deviation	Month only	1
population_density_5km.stdev	0.145	Population density	-	Standard deviation	Stationary	N/A
DMSP_F18_5km.max	0.113	Nighttime lights	-	Maximum	Stationary	N/A
fraction.class.10	0.069	Land cover class fraction	-	N/A	Yearly	N/A
fraction.class.11	0.065	Land cover class fraction	-	N/A	Yearly	N/A
majclass_covariates	0.064	Land cover majority class	-	N/A	Yearly	N/A
Africa_slope_90m.min	0.026	Elevation (slope angle)	-	Minimum	Stationary	N/A
TCW_delta_annual_max_2	0.005	TCW	Delta annual	Maximum	Fully dynamic	2
Global_Urban_Footprint_5km_AnyUrban	0.000	Any urban in cell (GUF)	-	N/A	Stationary	N/A
Global_Urban_Footprint_5km_SignificantUrb	0.000	Significant urban in cell (GUF)	-	N/A	Stationary	N/A
adjacencies.class.16	0.000	Land cover adjacencies	-	N/A	Yearly	N/A

Additional Table 5. Predictor variables for BRT model for BRT[treat] listed by contribution to the final model. EVI: Enhanced Vegetation Index; GUF: Global Urban Footprint; LST: Land Surface Temperature; PET - potential evapotranspiration; TCB - Tassled Cap Brightness; TCW - Tassled Cap Wetness; TMI - Topographic Moisture Index; TSI - Temperature Suitability Index; WB - World Bank Variable."Product" definitions for EVI, LST, TSI, TCW and TCB: Monthly - average value over study month; All-years synoptic - mean EVI for all years 2000-2015; Delta dynamic - difference between monthly value and synoptic product; Monthly synoptic - mean of study month across all years; Delta monthly - difference between study month and monthly synoptic product; Delta annual - difference between study month and study year (e.g. July 2008 - Mean 2008). "Lag" defines the number of months that the covariate dataset lags behind the month of each household survey dataset point (e.g. if a household survey data point is recorded in July 2008, a covariate with a lag of 2 months will be taken from May 2008).

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
GDP_grow	14.157	Annual GDP growth (WB national)	-	N/A	Yearly	N/A
public_exp	7.680	Public expenditure on health system (WB national)	-	N/A	Yearly	N/A
primary_school	3.972	Proportion of children in primary school (WB National)	-	N/A	Yearly	N/A
prec57p3	1.820	Precipitation	-	N/A	Stationary	N/A
LST_delta_delta_annual_max_2	1.753	LST delta	Delta annual	Maximum	Fully dynamic	2
prec57a0	1.701	Precipitation	-	N/A	Stationary	N/A
prec57a1	1.582	Precipitation	-	N/A	Stationary	N/A
LST_night_delta_monthly_max_3	1.418	LST night	Delta monthly	Maximum	Fully dynamic	3
fraction.class.10	1.385	Land cover class fraction	-	N/A	Yearly	N/A
pregnant	1.360	Percentage of pregnant women who receive prenatal care (WB National)	-	N/A	Yearly	N/A
LST_night_delta_dynamic_max_4	1.252	LST night	Delta dynamic	Maximum	Fully dynamic	4
population_covariates	1.101	Population density	-	N/A	Yearly	N/A
LST_night.monthly.mean.synoptic.stdev_1	1.081	LST night	Monthly synoptic	Mean	Month only	1
TSI_delta_monthly_min_3	1.055	TSI	Delta monthly	Minimum	Fully dynamic	3
PET_1950.2000_5km.stdev	1.049	PET	-	Standard deviation	Stationary	N/A
TSI_delta_monthly_max_3	1.007	TSI	Delta monthly	Maximum	Fully dynamic	3
LST_night_delta_monthly_max_1	0.998	LST night	Delta monthly	Maximum	Fully dynamic	1
EVI_delta_dynamic_min_4	0.965	EVI	Delta dynamic	Minimum	Fully dynamic	4
LST_day_delta_monthly_max_4	0.956	LST day	Delta monthly	Maximum	Fully dynamic	4
LST_delta.monthly.mean.synoptic.stdev_1	0.949	LST delta	Monthly synoptic	Mean	Month only	1

Additional Table 5 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
LST_night.monthly.stdev.synoptic.stdev_0	0.901	LST night	Monthly synoptic	Standard deviation	Month only	0
LST_day_delta_dynamic_stdev_0	0.884	LST day	Delta dynamic	Standard deviation	Fully dynamic	0
TSI_delta_monthly_max_4	0.845	TSI	Delta monthly	Maximum	Fully dynamic	4
LST_day.monthly.range.synoptic.stdev_0	0.814	LST day	Monthly synoptic	Range	Month only	0
LST_night.monthly.stdev.synoptic.stdev_3	0.795	LST night	Monthly synoptic	Standard deviation	Month only	3
LST_delta_delta_monthly_mean_0	0.767	LST delta	Delta monthly	Mean	Fully dynamic	0
TCB_delta_dynamic_mean_4	0.758	TCB	Delta monthly	Mean	Fully dynamic	4
EVI_delta_monthly_mean_3	0.737	EVI	Delta monthly	Mean	Fully dynamic	3
population_density_5km.min	0.731	Population density	-	Minimum	Stationary	N/A
TSI_delta_monthly_stdev_4	0.703	TSI	Delta monthly	Standard deviation	Fully dynamic	4
Global_Urban_Footprint_5km_PropUrban	0.700	Proportion urban in cell (GUF)	-	N/A	Stationary	N/A
EVI.monthly.range.synoptic.stdev_2	0.699	EVI	Monthly synoptic	Range	Month only	2
LST_night_delta_annual_stdev_2	0.674	LST night	Delta annual	Standard deviation	Fully dynamic	2
TCB_monthly_max_4	0.663	TCB	Monthly	Maximum	Fully dynamic	4
LST_delta_all_years_synoptic_max	0.655	LST delta	All-years synoptic	Maximum	Stationary	N/A
prec57a3	0.634	Precipitation	-	N/A	Stationary	N/A
TCW_delta_monthly_mean_4	0.634	TCW	Delta monthly	Mean	Fully dynamic	4
EVI_delta_monthly_stdev_1	0.629	EVI	Delta monthly	Standard deviation	Fully dynamic	1
LST_night.monthly.stdev.synoptic.stdev_4	0.626	LST night	Monthly synoptic	Standard deviation	Month only	4
LST_delta.monthly.mean.synoptic.stdev_0	0.618	LST delta	Monthly synoptic	Mean	Month only	0
EVI_delta_monthly_mean_4	0.614	EVI	Delta monthly	Mean	Fully dynamic	4
LST_night_delta_monthly_max_2	0.609	LST night	Delta monthly	Maximum	Fully dynamic	2
EVI_delta_dynamic_mean_1	0.598	EVI	Delta dynamic	Mean	Fully dynamic	1
LST_day_delta_monthly_range_0	0.587	LST day	Delta monthly	Range	Fully dynamic	0
LST_night_delta_monthly_mean_4	0.574	LST night	Delta monthly	Mean	Fully dynamic	4
TCW_delta_annual_stdev_0	0.559	TCW	Delta annual	Standard deviation	Fully dynamic	0
TSI_delta_monthly_max_0	0.532	TSI	Delta monthly	Maximum	Fully dynamic	0
LST_night_delta_annual_stdev_3	0.514	LST night	Delta annual	Standard deviation	Fully dynamic	3
TSI.monthly.mean.synoptic.stdev_3	0.506	TSI	Monthly synoptic	Mean	Month only	3
LST_day.monthly.range.synoptic.stdev_1	0.500	LST day	Monthly synoptic	Standard deviation	Month only	1
TSI_delta_monthly_min_4	0.495	TSI	Delta monthly	Minimum	Fully dynamic	4

Additional Table 5 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
TCB_delta_monthly_mean_0	0.477	TCB	Delta monthly	Mean	Fully dynamic	0
viirs_nighttime_5km.mean	0.465	Nighttime lights	-	Mean	Stationary	N/A
TSI_delta_annual_min_4	0.459	TSI	Delta annual	Minimum	Fully dynamic	4
prec57p1	0.456	Precipitation	-	N/A	Stationary	N/A
LST_day_delta_monthly_range_1	0.455	LST day	Delta monthly	Range	Fully dynamic	1
TSI.monthly.mean.synoptic.stdev_2	0.441	TSI	Monthly synoptic	Mean	Month only	2
fraction.class.12	0.437	Land cover class fraction	-	N/A	Yearly	N/A
LST_day.monthly.stdev.synoptic.stdev_3	0.419	LST day	Monthly synoptic	Standard deviation	Month only	3
TCB_delta_annual_range_3	0.406	TCB	Delta annual	Range	Fully dynamic	3
LST_delta.monthly.max.synoptic.mean_2	0.404	LST delta	Monthly synoptic	Maximum	Month only	2
LST_day_delta_annual_stdev_3	0.401	LST day	Delta annual	Standard deviation	Fully dynamic	3
TCW_delta_monthly_mean_2	0.395	TCW	Delta monthly	Mean	Fully dynamic	2
TCB_delta_annual_stdev_2	0.395	TCB	Delta annual	Standard deviation	Fully dynamic	2
TCB_delta_annual_stdev_4	0.394	TCB	Delta annual	Standard deviation	Fully dynamic	4
TSI_delta_monthly_range_3	0.390	TSI	Delta monthly	Range	Fully dynamic	3
prec57p2	0.386	Precipitation	-	N/A	Stationary	N/A
EVI.monthly.mean.synoptic.stdev_2	0.385	EVI	Monthly synoptic	Standard deviation	Month only	2
LST_day_delta_monthly_stdev_4	0.381	LST day	Delta monthly	Standard deviation	Fully dynamic	4
LST_night_delta_dynamic_mean_1	0.376	LST night	Delta dynamic	Mean	Fully dynamic	1
EVI_delta_annual_min_0	0.376	EVI	Delta annual	Minimum	Delta annual	0
TCB_delta_monthly_mean_4	0.373	TCB	Delta monthly	Mean	Fully dynamic	4
LST_night_delta_monthly_stdev_2	0.372	LST night	Delta monthly	Standard deviation	Fully dynamic	2
EVI_delta_dynamic_range_4	0.371	EVI	Delta dynamic	Range	Fully dynamic	4
TCW_delta_dynamic_mean_2	0.365	TCW	Delta dynamic	Mean	Fully dynamic	2
LST_night.monthly.min.synoptic.stdev_2	0.364	LST night	Monthly synoptic	Minimum	Month only	2
TSI_delta_monthly_max_2	0.355	TSI	Delta monthly	Maximum	Fully dynamic	2
EVI_all_years_synoptic_range	0.354	EVI	All-years synoptic	Range	Stationary	N/A
LST_day.monthly.min.synoptic.stdev_2	0.353	LST day	Monthly synoptic	Minimum	Month only	2
DPT	0.344	DPT immunisation coverage (WB annual)	-	N/A	Yearly	N/A
LST_night_delta_dynamic_min_0	0.343	LST night	Delta dynamic	Minimum	Fully dynamic	0
LST_night_delta_monthly_min_0	0.340	LST night	Delta monthly	Minimum	Fully dynamic	0

Additional Table 5 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
TSI_delta_monthly_stdev_2	0.339	TSI	Delta monthly	Standard deviation	Fully dynamic	2
EVI_delta_monthly_range_3	0.337	EVI	Delta monthly	Range	Fully dynamic	3
EVI_delta_monthly_range_2	0.336	EVI	Delta monthly	Range	Fully dynamic	2
TSI.monthly.mean.synoptic.stdev_1	0.332	TSI	Monthly synoptic	Mean	Month only	1
TCW_delta_annual_stdev_4	0.332	TCW	Delta annual	Standard deviation	Fully dynamic	4
LST_day_delta_annual_max_1	0.328	LST day	Delta annual	Maximum	Fully dynamic	1
LST_day_delta_monthly_min_3	0.328	LST day	Delta monthly	Minimum	Fully dynamic	3
LST_night.monthly.range.synoptic.mean_1	0.325	LST night	Monthly synoptic	Range	Month only	1
TSI_delta_monthly_min_2	0.321	TSI	Delta monthly	Minimum	Fully dynamic	2
LST_night_delta_annual_max_2	0.320	LST night	Delta annual	Maximum	Fully dynamic	2
EVI_delta_monthly_min_1	0.319	EVI	Delta monthly	Minimum	Fully dynamic	1
TCW_delta_annual_stdev_1	0.319	TCW	Delta annual	Standard deviation	Fully dynamic	1
TSI_delta_monthly_range_0	0.317	TSI	Delta monthly	Range	Fully dynamic	0
Africa_TMI_90m.min	0.317	TMI	-	Minimum	Stationary	N/A
LST_day_delta_monthly_stdev_3	0.311	LST day	Delta monthly	Standard deviation	Fully dynamic	3
EVI_all_years_synoptic_min	0.310	EVI	All-years synoptic	Minimum	Stationary	N/A
TCB_monthly_min_1	0.308	TCB	Monthly	Minimum	Fully dynamic	1
LST_night.monthly.max.synoptic.stdev_4	0.304	LST night	Monthly synoptic	Maximum	Month only	4
LST_night.monthly.mean.synoptic.stdev_0	0.303	LST night	Monthly synoptic	Mean	Month only	0
LST_night_delta_dynamic_mean_3	0.287	LST night	Delta dynamic	Mean	Fully dynamic	3
TSI.monthly.max.synoptic.stdev_4	0.286	TSI	Monthly synoptic	Maximum	Month only	4
LST_night_delta_dynamic_stdev_0	0.285	LST night	Delta dynamic	Standard deviation	Fully dynamic	0
LST_night_delta_annual_range_1	0.282	LST night	Delta annual	Range	Fully dynamic	1
LST_night.monthly.stdev.synoptic.stdev_2	0.280	LST night	Monthly synoptic	Standard deviation	Month only	2
EVI_delta_dynamic_stdev_1	0.274	EVI	Delta dynamic	Standard deviation	Fully dynamic	1
EVI_delta_dynamic_range_0	0.263	EVI	Delta dynamic	Range	Fully dynamic	0
TCB_delta_annual_range_1	0.259	TCB	Delta annual	Range	Fully dynamic	1
TSI.monthly.min.synoptic.stdev_0	0.257	TSI	Monthly synoptic	Minimum	Month only	0
TSI.monthly.range.synoptic.mean_3	0.255	TSI	Monthly synoptic	Range	Month only	3
TSI.monthly.range.synoptic.stdev_2	0.255	TSI	Monthly synoptic	Standard deviation	Month only	2
TSI.monthly.range.synoptic.stdev_1	0.252	TSI	Monthly synoptic	Standard deviation	Month only	1

Additional Table 5 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
EVI.monthly.mean.synoptic.stdev_0	0.251	EVI	Monthly synoptic	Mean	Month only	0
TCB_delta_monthly_mean_1	0.250	TCB	Delta monthly	Mean	Fully dynamic	1
EVI_delta_monthly_min_0	0.248	EVI	Delta monthly	Minimum	Fully dynamic	0
accessibility_50k_5km.stdev	0.246	Accessibility	-	Standard deviation	Stationary	N/A
LST_day_delta_monthly_min_1	0.246	LST day	Delta monthly	Minimum	Fully dynamic	1
EVI_delta_monthly_max_2	0.246	EVI	Delta monthly	Maximum	Fully dynamic	2
TSI.monthly.min.synoptic.stdev_4	0.240	TSI	Monthly synoptic	Minimum	Month only	4
TCB.monthly.mean.synoptic.stdev_4	0.237	TCB	Monthly synoptic	Mean	Month only	4
EVI.monthly.range.synoptic.stdev_0	0.233	EVI	Monthly synoptic	Range	Month only	0
LST_night_delta_monthly_range_4	0.232	LST night	Delta monthly	Range	Fully dynamic	4
TCW_monthly_stdev_3	0.230	TCW	Monthly	Standard deviation	Fully dynamic	3
TCB_delta_monthly_mean_2	0.228	TCB	Delta monthly	Mean	Fully dynamic	2
DMSP_F18_5km.max	0.228	Nighttime lights	-	Maximum	Stationary	N/A
EVI_delta_dynamic_stdev_3	0.228	EVI	Delta dynamic	Standard deviation	Fully dynamic	3
Africa_FA_90m.mean	0.226	Elevation (flow accumulation)	-	Mean	Stationary	N/A
accessibility_ESRI_5km.range	0.223	Accessibility	-	Range	Stationary	N/A
prec57a2	0.223	Precipitation	-	N/A	Stationary	N/A
EVI_delta_monthly_stdev_0	0.222	EVI	Delta monthly	Standard deviation	Fully dynamic	0
EVI_delta_monthly_min_2	0.221	EVI	Delta monthly	Minimum	Fully dynamic	2
LST_night_delta_monthly_range_0	0.220	LST night	Delta monthly	Range	Fully dynamic	0
EVI_delta_monthly_stdev_4	0.219	EVI	Delta monthly	Standard deviation	Fully dynamic	4
LST_day.monthly.range.synoptic.stdev_2	0.216	LST day	Monthly synoptic	Standard deviation	Month only	2
TCW_delta_monthly_mean_0	0.214	TCW	Delta monthly	Mean	Fully dynamic	0
LST_night_delta_dynamic_max_2	0.214	LST night	Delta dynamic	Maximum	Fully dynamic	2
LST_delta_delta_monthly_mean_2	0.212	LST delta	Delta monthly	Mean	Fully dynamic	2
TSI_delta_monthly_mean_1	0.209	TSI	Delta monthly	Mean	Fully dynamic	1
TCB_delta_annual_max_3	0.207	TCB	Delta annual	Maximum	Fully dynamic	3
fraction.class.14	0.203	Land cover class fraction	-	N/A	Yearly	N/A
EVI_delta_annual_stdev_2	0.196	EVI	Delta annual	Standard deviation	Delta annual	2
LST_night.monthly.min.synoptic.stdev_3	0.195	LST night	Monthly synoptic	Minimum	Month only	3
LST_delta_delta_annual_mean_0	0.194	LST delta	Delta annual	Mean	Fully dynamic	0

Additional Table 5 (Continued)

Variable name	Contribution to final model	Variable Type	Product type	Spatial summary	Temporal resolution	Monthly lag
LST_day_delta_dynamic_range_2	0.193	LST day	Delta dynamic	Range	Fully dynamic	2
LST_night.monthly.range.synoptic.stdev_1	0.192	LST night	Monthly synoptic	Range	Month only	1
LST_day.monthly.stdev.synoptic.stdev_4	0.192	LST day	Monthly synoptic	Standard deviation	Month only	4
EVI.monthly.min.synoptic.stdev_4	0.188	EVI	Monthly synoptic	Minimum	Month only	4
LST_day_delta_annual_range_4	0.187	LST day	Delta annual	Range	Fully dynamic	4
TCW_delta_annual_stdev_3	0.187	TCW	Delta annual	Standard deviation	Fully dynamic	3
Africa_TMI_90m.stdev	0.184	TMI	-	Standard deviation	Stationary	N/A
LST_day.monthly.mean.synoptic.stdev_3	0.182	LST day	Monthly synoptic	Mean	Month only	3
LST_night_delta_dynamic_stdev_4	0.181	LST night	Delta dynamic	Standard deviation	Fully dynamic	4
EVI.monthly.stdev.synoptic.stdev_4	0.178	EVI	Monthly synoptic	Standard deviation	Month only	4
TSI_monthly_stdev_1	0.178	TSI	Monthly	Standard deviation	Fully dynamic	1
Africa_TMI_90m.max	0.176	TMI	-	Maximum	Stationary	N/A
TCW_delta_monthly_mean_1	0.167	TCW	Delta monthly	Mean	Fully dynamic	1
adjacencies.class.16	0.163	Land cover adjacencies	-	N/A	Yearly	N/A
TCW_delta_monthly_mean_3	0.153	TCW	Delta monthly	Mean	Fully dynamic	3
LST_night.monthly.stdev.synoptic.mean_4	0.149	LST night	Monthly synoptic	Standard deviation	Month only	4
TCW_delta_annual_stdev_2	0.148	TCW	Delta annual	Standard deviation	Fully dynamic	2
TSI_monthly_stdev_2	0.146	TSI	Monthly	Standard deviation	Fully dynamic	2
LST_day.monthly.range.synoptic.mean_4	0.110	LST day	Monthly synoptic	Range	Month only	4
adjacencies.class.8	0.087	Land cover adjacencies	-	N/A	Yearly	N/A
fraction.class.7	0.071	Land cover class fraction	-	N/A	Yearly	N/A
fraction.class.2	0.059	Land cover class fraction	-	N/A	Yearly	N/A
majclass_covariates	0.058	Land cover majority class	-	N/A	Yearly	N/A
population_density_5km.stdev	0.039	Population density	-	Standard deviation	Stationary	N/A
fraction.class.9	0.033	Land cover class fraction	-	N/A	Yearly	N/A
Africa_slope_90m.min	0.029	Elevation (slope angle)	-	Minimum	Stationary	N/A
fraction.class.11	0.025	Land cover class fraction	-	N/A	Yearly	N/A
Global_Urban_Footprint_5km_AnyUrban	0.009	Any urban in cell (GUF)	-	N/A	Stationary	N/A
TCW_delta_annual_max_2	0.008	TCW	Delta annual	Maximum	Fully dynamic	2
fraction.class.5	0.001	Land cover class fraction	-	N/A	Yearly	N/A
Global_Urban_Footprint_5km_SignificantUrb	0.000	Significant urban in cell (GUF)	-	N/A	Stationary	N/A

Additional File 1

R code for generating individual-level attributions of MAF and NMFI to febrile children in household survey dataset. Code for generating tabulations and effects plots is given after model fitting section. This code must be run with a working directory containing *i)* the household survey dataset at individual-level, with column headings as detailed below, and *ii)* the TMB script given in Additional File 2. A C++ compiler must also be installed.

```
### R script for individual level predictions of malaria fever status
and case management successes
### given treatment seeking and triage data

library(INLA)
library(raster)
library(splancs)

setwd("Z:/Malaria data/Overdiagnosis paper/outputs 200718/")
rm(list=ls())

nmfi.data <- read.csv("indi.data.for.treatmentseeking.final.csv")

valid <- which(!(is.na(as.numeric(as.character(nmfi.data$LAT))) |
is.na(as.numeric(as.character(nmfi.data$LONG))) |
is.na(nmfi.data$fever) | is.na(nmfi.data$age.months) |
is.na(nmfi.data$wealth.index) | is.na(nmfi.data$mother.education)) &
!is.na(nmfi.data$slept.under.net.official))

N <- length(valid)

Pstat <- nmfi.data$rdt.result[valid]
Fstat <- nmfi.data$fever[valid]
Tstat <- nmfi.data$sought.treat[valid]
Tstat[Fstat==0] <- 0
Tstat[is.na(Tstat)] <- 0
Hstat <- nmfi.data$finger.heel[valid]
Hstat[Tstat==0] <- 0
Astat <- nmfi.data$antimalarial.received[valid]
Astat[Tstat==0] <- 0

F_BRT <- nmfi.data$Fever.BRT[valid]
T_BRT <- nmfi.data$Treatseek.BRT[valid]

library(ageStand)
```

```
approx.agestand <-
approxfun(seq(0,1,length.out=100),ageStand::convertPrevalence(seq(0,1,
length.out=100),rep(0,100),rep(4,100),rep(2,100),rep(9,100)))
RDTPR <-
pnorm((qnorm(approx.agestand(nmfi.data$nature.pr[valid]))+0.22)/0.97)
approx.agestand <-
approxfun(seq(0,1,length.out=100),ageStand::convertPrevalence(seq(0,1,
length.out=100),rep(2,100),rep(9,100),rep(0,100),rep(4,100)))
PR <- approx.agestand(RDTPR)

pcure <- nmfi.data$drug.eff[valid]
survey <- nmfi.data$survey.x[valid]
for (s in unique(survey)) {
  pcure[survey==s & is.na(pcure)] <- mean(pcure[survey==s],na.rm=T) #
impute missing pcure values from survey means
}

long.lat <-
cbind(as.numeric(as.character(nmfi.data$LONG))[valid],as.numeric(as.ch
aracter(nmfi.data$LAT))[valid])
survey <-
match(nmfi.data$survey.x[valid],unique(nmfi.data$survey.x[valid]))-1
nsurvey <- length(unique(survey))
rdt.persist <- nmfi.data$rdt.persist[valid]

act <- nmfi.data$antimalarial.type[valid]
act[is.na(act)] <- 0

net <- nmfi.data$slept.under.net.official[valid]
treatmentlocation <- nmfi.data$sought.treat[valid]
treatmentlocation[is.na(treatmentlocation)] <- 0

age.categorical <- floor(nmfi.data$age.months[valid]/12)
age.categorical[age.categorical==5] <- 4
wealth <- match(as.character(nmfi.data$wealth.index[valid]),rev(c("-
1.15","-0.5","0","0.5","1.15")))-1

mothers.education <-
match(as.character(nmfi.data$mother.education[valid]),rev(c("No
education","Primary","Secondary","Higher")))-1

weights <- nmfi.data$weight[valid]/1000000

Africa.mesh <- inla.mesh.2d(long.lat,max.edge=5,cut=0.5,offset=c(5,5))

data <- list(
  'N'=length(valid),
  'Pstat'=Pstat,
  'Fstat'=Fstat,
  'Tstat'=Tstat,
  'Hstat'=Hstat,
  'Astat'=Astat,
  'F_BRT'=F_BRT,
  'T_BRT'=T_BRT,
  'PR'=PR,
  'pcure'=pcure,
  'nsurvey'=nsurvey,
  'survey'=survey,
  'prevert'=rdt.persist,
  'wealth'=wealth,
  'mother'=mothers.education,
```

```
  'age'=age.categorical,
  'net'=net,
  'A'=as.matrix(inla.mesh.project(Africa.mesh,long.lat)$A),

'spde'=(inla.spde2.matern(Africa.mesh,alpha=2)$param.inla)[c("M0","M1"
,"M2")]
)

parameters <- list('log_kappa_pbg'=0,
                   'log_tau_pbg'=0,
                   'logit_pbg_offset'=rep(0,Africa.mesh$n),
                   'log_kappa_pr'=0,
                   'log_tau_pr'=0,
                   'logit_pr_offset'=rep(0,Africa.mesh$n),
                   'log_kappa_ptreat'=0,
                   'log_tau_ptreat'=0,
                   'mean_logit_ptreat_offset'=0,
                   'logit_ptreat_offset'=rep(0,Africa.mesh$n),
                   'mean_logit_ptreatmaf_offset'=0,
                   'log_sd_logit_ptreatmaf_offset'=0,
                   'logit_ptreatmaf_offset'=rep(0,nsurvey),
                   'mean_logit_ptreatboth_offset'=0,
                   'log_sd_logit_ptreatboth_offset'=0,
                   'logit_ptreatboth_offset'=rep(0,nsurvey),
                   'logit_prop_maf'=0,
                   'slope_maf'=0,
                   'slope_maf_sq'=0,
                   'mean_logit_pundertreat'=0,
                   'log_sd_logit_pundertreat'=0,
                   'logit_pundertreat'=rep(0,nsurvey),
                   'offset_private_pundertreat'=0,
                   'mean_logit_povertreat'=0,
                   'log_sd_logit_povertreat'=0,
                   'logit_povertreat'=rep(0,nsurvey),
                   'offset_private_povertreat'=0,
                   'mean_logit_pprick'=0,
                   'log_sd_logit_pprick'=0,
                   'logit_pprick'=rep(0,nsurvey),
                   'offset_private_pprick'=0,
                   'mean_logit_ppresumptive'=0,
                   'log_sd_logit_ppresumptive'=0,
                   'logit_ppresumptive'=rep(0,nsurvey),
                   'offset_private_ppresumptive'=0,
                   'net_effect_pr'=0,
                   'wealth_effect_pr_raw'=rep(0,4),
                   'mother_effect_pr_raw'=rep(0,3),
                   'age_effect_pr_raw'=rep(0,4),
                   'wealth_effect_pbg_raw'=rep(0,4),
                   'mother_effect_pbg_raw'=rep(0,3),
                   'age_effect_pbg_raw'=rep(0,4),
                   'wealth_effect_ptreat_raw'=rep(0,4),
                   'mother_effect_ptreat_raw'=rep(0,3),
                   'age_effect_ptreat_raw'=rep(0,4)
)

library(TMB)
compile("NMFItmb_basic.cpp")
dyn.load(dynlib("NMFItmb_basic"))
obj <-
MakeADFun(data,parameters,random=c('logit_pr_offset','logit_pbg_offset
','logit_ptreat_offset','logit_ptreatmaf_offset','logit_ptreatboth_off
```

```
set','logit_pundertreat','logit_povertreat','logit_pprick','logit_ppre
sumptive'),DLL="NMFItmb_basic")

opt <-
nlminb(obj$par,obj$fn,obj$gr,control=list(iter.max=10,eval.max=10))
opt <-
nlminb(opt$par,obj$fn,obj$gr,control=list(iter.max=200,eval.max=200))
opt <-
nlminb(opt$par,obj$fn,obj$gr,control=list(iter.max=200,eval.max=200))
opt <-
nlminb(opt$par,obj$fn,obj$gr,control=list(iter.max=200,eval.max=200))
rep <- sdreport(obj,getJointPrecision=T)
#save(opt,rep,file="optrep.dat")



### Plot key effect estimates: Wealth

pdf("Plots/wealth_pbg.pdf",width=8,height=6)
par(mai=c(0.9,1,0.2,0.2))
plot(c(1,2,3,4,5),c(rep$par.fixed[names(rep$par.fixed)=="wealth_effect
_pbg_raw"],0),ylim=c(-
1.3,1.3),xlim=c(0.5,5.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_pbg_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg_r
aw"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"][1
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg_r
aw"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"][1
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg
_raw"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"]
[1]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_p
bg_raw"][1]),border="black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_pbg_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg_r
aw"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"][2
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg_r
aw"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"][2
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg
_raw"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"]
[2]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_p
bg_raw"][2]),border="black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_pbg_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg_r
aw"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"][3
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg_r
aw"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"][3
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg
_raw"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"]
[3]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_p
bg_raw"][3]),border="black",density=20,angle=45)
```

```
polygon(c(3.5,4.5,4.5,3.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_pbg_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg_r
aw"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"][4
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg_r
aw"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"][4
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pbg
_raw"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pbg_raw"]
[4]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_p
bg_raw"][4]),border="black",density=20,angle=45)

lines(c(4.5,5.5),c(0,0))

axis(1,at=c(1,2,3,4,5),labels=rev(c("Poorest","Poorer","Middle","Riche
r","Richest")))
mtext("Household Wealth",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Background Fever (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

pdf("Plots/wealth_pr.pdf",width=8,height=6)
par(mai=c(0.9,1,0.2,0.2))
plot(c(1,2,3,4,5),c(rep$par.fixed[names(rep$par.fixed)=="wealth_effect
_pr_raw"],0),ylim=c(-
1.3,1.3),xlim=c(0.5,5.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_pr_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][1]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][1]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][1]),border="black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_pr_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][2]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][2]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][2]),border="black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_pr_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][3]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][3]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][3]),border="black",density=20,angle=45)
```

```
polygon(c(3.5,4.5,4.5,3.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_pr_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][4]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_pr_raw"][4]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_pr_ra
w"][4]),border="black",density=20,angle=45)

lines(c(4.5,5.5),c(0,0))

axis(1,at=c(1,2,3,4,5),labels=rev(c("Poorest","Poorer","Middle","Riche
r","Richest")))
mtext("Household Wealth",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Parasite Prevalence (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

pdf("Plots/wealth_ptreat.pdf",width=8,height=6)
par(mai=c(0.9,1,0.2,0.2))
plot(c(1,2,3,4,5),c(rep$par.fixed[names(rep$par.fixed)=="wealth_effect
_ptreat_raw"],0),ylim=c(-
1.3,1.3),xlim=c(0.5,5.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_ptreat_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_ptrea
t_raw"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_ptreat_r
aw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_ptrea
t_raw"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_ptreat_r
aw"][1]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effe
ct_ptreat_raw"][1],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_
ptreat_raw"][1]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wea
lth_effect_ptreat_raw"][1]),border="black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_ptreat_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_ptrea
t_raw"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_ptreat_r
aw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_ptrea
t_raw"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_ptreat_r
aw"][2]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effe
ct_ptreat_raw"][2],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_
ptreat_raw"][2]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wea
lth_effect_ptreat_raw"][2]),border="black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_ptreat_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_ptrea
t_raw"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_ptreat_r
aw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_ptrea
t_raw"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_ptreat_r
aw"][3]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effe
ct_ptreat_raw"][3],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_
```

```
ptreat_raw"][3]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wea
lth_effect_ptreat_raw"][3]),border="black",density=20,angle=45)

polygon(c(3.5,4.5,4.5,3.5),c(rep$par.fixed[names(rep$par.fixed)=="weal
th_effect_ptreat_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_ptrea
t_raw"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_ptreat_r
aw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effect_ptrea
t_raw"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_ptreat_r
aw"][4]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wealth_effe
ct_ptreat_raw"][4],rep$par.fixed[names(rep$par.fixed)=="wealth_effect_
ptreat_raw"][4]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="wea
lth_effect_ptreat_raw"][4]),border="black",density=20,angle=45)

lines(c(4.5,5.5),c(0,0))

axis(1,at=c(1,2,3,4,5),labels=rev(c("Poorest","Poorer","Middle","Riche
r","Richest")))
mtext("Household Wealth",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Treatment Seeking (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

### Plot key effect estimates: Mother's Education

pdf("Plots/education_pbg.pdf",width=8,height=6)
par(mai=c(0.9,1,0.2,0.2))
plot(c(1,2,3,4),c(rep$par.fixed[names(rep$par.fixed)=="mother_effect_p
bg_raw"],0),ylim=c(-
1.3,1.3),xlim=c(0.5,4.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_pbg_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg_r
aw"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"][1
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg_r
aw"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"][1
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg
_raw"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"]
[1]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_p
bg_raw"][1]),border="black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_pbg_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg_r
aw"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"][2
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg_r
aw"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"][2
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg
_raw"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"]
[2]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_p
bg_raw"][2]),border="black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_pbg_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg_r
aw"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"][3
```

```
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg_r
aw"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"][3
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pbg
_raw"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pbg_raw"]
[3]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_p
bg_raw"][3]),border="black",density=20,angle=45)

lines(c(3.5,4.5),c(0,0))

axis(1,at=c(1,2,3,4),labels=rev(c("No
education","Primary","Secondary","Higher")))
mtext("Mother's Education",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Background Fever (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

pdf("Plots/education_pr.pdf",width=8,height=6)
par(mai=c(0.9,1,0.2,0.2))
plot(c(1,2,3,4),c(rep$par.fixed[names(rep$par.fixed)=="mother_effect_p
r_raw"],0),ylim=c(-
1.3,1.3),xlim=c(0.5,4.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_pr_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][1]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][1]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][1]),border="black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_pr_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][2]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][2]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][2]),border="black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_pr_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][3]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_pr_raw"][3]+
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_pr_ra
w"][3]),border="black",density=20,angle=45)

lines(c(3.5,4.5),c(0,0))

axis(1,at=c(1,2,3,4),labels=rev(c("No
education","Primary","Secondary","Higher")))
```

```
mtext("Mother's Education",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Parasite Prevalence (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

pdf("Plots/education_ptreat.pdf",width=8,height=6)
par(mai=c(0.9,1,0.2,0.2))
plot(c(1,2,3,4),c(rep$par.fixed[names(rep$par.fixed)=="mother_effect_p
treat_raw"],0),ylim=c(-
1.3,1.3),xlim=c(0.5,4.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_ptreat_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_ptrea
t_raw"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_ptreat_r
aw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_ptrea
t_raw"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_ptreat_r
aw"][1]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effe
ct_ptreat_raw"][1],rep$par.fixed[names(rep$par.fixed)=="mother_effect_
ptreat_raw"][1]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mot
her_effect_ptreat_raw"][1]),border="black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_ptreat_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_ptrea
t_raw"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_ptreat_r
aw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_ptrea
t_raw"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_ptreat_r
aw"][2]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effe
ct_ptreat_raw"][2],rep$par.fixed[names(rep$par.fixed)=="mother_effect_
ptreat_raw"][2]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mot
her_effect_ptreat_raw"][2]),border="black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="moth
er_effect_ptreat_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_ptrea
t_raw"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_ptreat_r
aw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effect_ptrea
t_raw"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_ptreat_r
aw"][3]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mother_effe
ct_ptreat_raw"][3],rep$par.fixed[names(rep$par.fixed)=="mother_effect_
ptreat_raw"][3]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="mot
her_effect_ptreat_raw"][3]),border="black",density=20,angle=45)

lines(c(3.5,4.5),c(0,0))

axis(1,at=c(1,2,3,4),labels=rev(c("No
education","Primary","Secondary","Higher")))
mtext("Mother's Education",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Treatment Seeking (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

### Plot key effect estimates: Age

pdf("Plots/age_pbg.pdf",width=8,height=6)
```

```
par(mai=c(0.9,1,0.2,0.2))
plot(c(1,2,3,4,5),c(rep$par.fixed[names(rep$par.fixed)=="age_effect_pb
g_raw"],0),ylim=c(-
1.3,1.3),xlim=c(0.5,5.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_pbg_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"
][1],rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"
][1],rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][1]+2*sq
rt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"][1]
,rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][1]+2*sqrt(d
iag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"][1]),bo
rder="black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_pbg_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"
][2],rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"
][2],rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][2]+2*sq
rt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"][2]
,rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][2]+2*sqrt(d
iag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"][2]),bo
rder="black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_pbg_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"
][3],rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"
][3],rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][3]+2*sq
rt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"][3]
,rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][3]+2*sqrt(d
iag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"][3]),bo
rder="black",density=20,angle=45)

polygon(c(3.5,4.5,4.5,3.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_pbg_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"
][4],rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"
][4],rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][4]+2*sq
rt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"][4]
,rep$par.fixed[names(rep$par.fixed)=="age_effect_pbg_raw"][4]+2*sqrt(d
iag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pbg_raw"][4]),bo
rder="black",density=20,angle=45)

lines(c(4.5,5.5),c(0,0))

axis(1,at=c(1,2,3,4,5),labels=(c("0-1","1-2","2-3","3-4","4-5")))
mtext("Age",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Background Fever (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

pdf("Plots/age_pr.pdf",width=8,height=6)
par(mai=c(0.9,1,0.2,0.2))
```

```
plot(c(1,2,3,4,5),c(rep$par.fixed[names(rep$par.fixed)=="age_effect_pr
_raw"],0),ylim=c(-
1.3,1.3),xlim=c(0.5,5.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_pr_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"]
[1],rep$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"]
[1],rep$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][1]+2*sqrt
(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"][1],re
p$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][1]+2*sqrt(diag(
rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"][1]),border=
"black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_pr_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"]
[2],rep$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"]
[2],rep$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][2]+2*sqrt
(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"][2],re
p$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][2]+2*sqrt(diag(
rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"][2]),border=
"black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_pr_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"]
[3],rep$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"]
[3],rep$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][3]+2*sqrt
(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"][3],re
p$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][3]+2*sqrt(diag(
rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"][3]),border=
"black",density=20,angle=45)

polygon(c(3.5,4.5,4.5,3.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_pr_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"]
[4],rep$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"]
[4],rep$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][4]+2*sqrt
(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"][4],re
p$par.fixed[names(rep$par.fixed)=="age_effect_pr_raw"][4]+2*sqrt(diag(
rep$cov.fixed))[names(rep$par.fixed)=="age_effect_pr_raw"][4]),border=
"black",density=20,angle=45)

lines(c(4.5,5.5),c(0,0))

axis(1,at=c(1,2,3,4,5),labels=(c("0-1","1-2","2-3","3-4","4-5")))
mtext("Age",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Parasite Prevalence (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

pdf("Plots/age_ptreat.pdf",width=8,height=6)
par(mai=c(0.9,1,0.2,0.2))
plot(c(1,2,3,4,5),c(rep$par.fixed[names(rep$par.fixed)=="age_effect_pt
reat_raw"],0),ylim=c(-
```

```
1.3,1.3),xlim=c(0.5,5.5),xaxt='n',yaxt='n',col="white",xlab="",ylab=""
)
polygon(c(0.5,1.5,1.5,0.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_ptreat_raw"][1]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat_r
aw"][1],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"][1
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat_r
aw"][1],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"][1
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat
_raw"][1],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"]
[1]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptre
at_raw"][1]),border="black",density=20,angle=45)

polygon(c(1.5,2.5,2.5,1.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_ptreat_raw"][2]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat_r
aw"][2],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"][2
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat_r
aw"][2],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"][2
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat
_raw"][2],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"]
[2]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptre
at_raw"][2]),border="black",density=20,angle=45)

polygon(c(2.5,3.5,3.5,2.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_ptreat_raw"][3]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat_r
aw"][3],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"][3
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat_r
aw"][3],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"][3
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat
_raw"][3],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"]
[3]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptre
at_raw"][3]),border="black",density=20,angle=45)

polygon(c(3.5,4.5,4.5,3.5),c(rep$par.fixed[names(rep$par.fixed)=="age_
effect_ptreat_raw"][4]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat_r
aw"][4],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"][4
]-
2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat_r
aw"][4],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"][4
]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptreat
_raw"][4],rep$par.fixed[names(rep$par.fixed)=="age_effect_ptreat_raw"]
[4]+2*sqrt(diag(rep$cov.fixed))[names(rep$par.fixed)=="age_effect_ptre
at_raw"][4]),border="black",density=20,angle=45)

lines(c(4.5,5.5),c(0,0))

axis(1,at=c(1,2,3,4,5),labels=(c("0-1","1-2","2-3","3-4","4-5")))
mtext("Age",side=1,line=2.7,cex=1.35)
axis(2,las=2)
mtext("Effect on Treatment Seeking (Logit
Scale)",side=2,line=3.1,cex=1.35)
dev.off()

### Generate comprehensive output tables; full uncertainties
```

```
library(sparseMVN)
library(MASS)
name.matching <-
match(names(c(rep$par.fixed,rep$par.random)),names(rep$jointPrecision[
1,]))
name.matching[duplicated(name.matching)] <- NA
for (i in 2:length(name.matching)) {
  if (is.na(name.matching[i])) {name.matching[i] <- name.matching[i-
1]+1}
}
r.draws <-
rmvn.sparse(300,c(rep$par.fixed,rep$par.random)[sort.list(name.matchin
g)],Cholesky(rep$jointPrecision),prec=T)
par.names <- names(rep$jointPrecision[1,])

# Random effect summaries
cat("#age group:, , 0-1, , , 1-2, , , 2-3, , , 3-4,
\n",sep="",file="age_effects.csv")
cat("#posterior quantile:, 2.5%, 50%, 97.5%, 2.5%, 50%, 97.5%, 2.5%,
50%, 97.5%, 2.5%, 50%,
97.5%\n",sep="",file="age_effects.csv",append=T)
cat("age_effect_pr,",quantile(r.draws[,which(par.names=="age_effect_pr
_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=="age_effect_p
r_raw")[1]],0.50),",",quantile(r.draws[,which(par.names=="age_effect_p
r_raw")[1]],0.975),",",quantile(r.draws[,which(par.names=="age_effect_
pr_raw")[2]],0.025),",",quantile(r.draws[,which(par.names=="age_effect
_pr_raw")[2]],0.50),",",quantile(r.draws[,which(par.names=="age_effect
_pr_raw")[2]],0.975),",",quantile(r.draws[,which(par.names=="age_effec
t_pr_raw")[3]],0.025),",",quantile(r.draws[,which(par.names=="age_effe
ct_pr_raw")[3]],0.50),",",quantile(r.draws[,which(par.names=="age_effe
ct_pr_raw")[3]],0.975),",",quantile(r.draws[,which(par.names=="age_eff
ect_pr_raw")[4]],0.025),",",quantile(r.draws[,which(par.names=="age_ef
fect_pr_raw")[4]],0.50),",",quantile(r.draws[,which(par.names=="age_ef
fect_pr_raw")[4]],0.975),"\n",sep="",file="age_effects.csv",append=T)
cat("age_effect_pbg,",quantile(r.draws[,which(par.names=="age_effect_p
bg_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=="age_effect
_pbg_raw")[1]],0.50),",",quantile(r.draws[,which(par.names=="age_effec
t_pbg_raw")[1]],0.975),",",quantile(r.draws[,which(par.names=="age_eff
ect_pbg_raw")[2]],0.025),",",quantile(r.draws[,which(par.names=="age_e
ffect_pbg_raw")[2]],0.50),",",quantile(r.draws[,which(par.names=="age_
effect_pbg_raw")[2]],0.975),",",quantile(r.draws[,which(par.names=="ag
e_effect_pbg_raw")[3]],0.025),",",quantile(r.draws[,which(par.names=="
age_effect_pbg_raw")[3]],0.50),",",quantile(r.draws[,which(par.names==
"age_effect_pbg_raw")[3]],0.975),",",quantile(r.draws[,which(par.names
=="age_effect_pbg_raw")[4]],0.025),",",quantile(r.draws[,which(par.nam
es=="age_effect_pbg_raw")[4]],0.50),",",quantile(r.draws[,which(par.na
mes=="age_effect_pbg_raw")[4]],0.975),"\n",sep="",file="age_effects.cs
v",append=T)
cat("age_effect_ptreat,",quantile(r.draws[,which(par.names=="age_effec
t_ptreat_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=="age_
effect_ptreat_raw")[1]],0.50),",",quantile(r.draws[,which(par.names=="
age_effect_ptreat_raw")[1]],0.975),",",quantile(r.draws[,which(par.nam
es=="age_effect_ptreat_raw")[2]],0.025),",",quantile(r.draws[,which(pa
r.names=="age_effect_ptreat_raw")[2]],0.50),",",quantile(r.draws[,whic
h(par.names=="age_effect_ptreat_raw")[2]],0.975),",",quantile(r.draws[
,which(par.names=="age_effect_ptreat_raw")[3]],0.025),",",quantile(r.d
raws[,which(par.names=="age_effect_ptreat_raw")[3]],0.50),",",quantile
(r.draws[,which(par.names=="age_effect_ptreat_raw")[3]],0.975),",",qua
ntile(r.draws[,which(par.names=="age_effect_ptreat_raw")[4]],0.025),",
",quantile(r.draws[,which(par.names=="age_effect_ptreat_raw")[4]],0.50
```

```
),",",quantile(r.draws[,which(par.names=="age_effect_ptreat_raw")[4]],
0.975),"\n",sep="",file="age_effects.csv",append=T)

cat("#household wealth class:, , Richest, , , Richer, , , Middle, , ,
Poorer, \n",sep="",file="wealth_effects.csv")
cat("#posterior quantile:, 2.5%, 50%, 97.5%, 2.5%, 50%, 97.5%, 2.5%,
50%, 97.5%, 2.5%, 50%,
97.5%\n",sep="",file="wealth_effects.csv",append=T)
cat("wealth_effect_pr,",quantile(r.draws[,which(par.names=="wealth_eff
ect_pr_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=="wealth
_effect_pr_raw")[1]],0.50),",",quantile(r.draws[,which(par.names=="wea
lth_effect_pr_raw")[1]],0.975),",",quantile(r.draws[,which(par.names==
"wealth_effect_pr_raw")[2]],0.025),",",quantile(r.draws[,which(par.nam
es=="wealth_effect_pr_raw")[2]],0.50),",",quantile(r.draws[,which(par.
names=="wealth_effect_pr_raw")[2]],0.975),",",quantile(r.draws[,which(
par.names=="wealth_effect_pr_raw")[3]],0.025),",",quantile(r.draws[,wh
ich(par.names=="wealth_effect_pr_raw")[3]],0.50),",",quantile(r.draws[
,which(par.names=="wealth_effect_pr_raw")[3]],0.975),",",quantile(r.dr
aws[,which(par.names=="wealth_effect_pr_raw")[4]],0.025),",",quantile(
r.draws[,which(par.names=="wealth_effect_pr_raw")[4]],0.50),",",quanti
le(r.draws[,which(par.names=="wealth_effect_pr_raw")[4]],0.975),"\n",s
ep="",file="wealth_effects.csv",append=T)
cat("wealth_effect_pbg,",quantile(r.draws[,which(par.names=="wealth_ef
fect_pbg_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=="weal
th_effect_pbg_raw")[1]],0.50),",",quantile(r.draws[,which(par.names=="
wealth_effect_pbg_raw")[1]],0.975),",",quantile(r.draws[,which(par.nam
es=="wealth_effect_pbg_raw")[2]],0.025),",",quantile(r.draws[,which(pa
r.names=="wealth_effect_pbg_raw")[2]],0.50),",",quantile(r.draws[,whic
h(par.names=="wealth_effect_pbg_raw")[2]],0.975),",",quantile(r.draws[
,which(par.names=="wealth_effect_pbg_raw")[3]],0.025),",",quantile(r.d
raws[,which(par.names=="wealth_effect_pbg_raw")[3]],0.50),",",quantile
(r.draws[,which(par.names=="wealth_effect_pbg_raw")[3]],0.975),",",qua
ntile(r.draws[,which(par.names=="wealth_effect_pbg_raw")[4]],0.025),",
",quantile(r.draws[,which(par.names=="wealth_effect_pbg_raw")[4]],0.50
),",",quantile(r.draws[,which(par.names=="wealth_effect_pbg_raw")[4]],
0.975),"\n",sep="",file="wealth_effects.csv",append=T)
cat("wealth_effect_ptreat,",quantile(r.draws[,which(par.names=="wealth
_effect_ptreat_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=
="wealth_effect_ptreat_raw")[1]],0.50),",",quantile(r.draws[,which(par
.names=="wealth_effect_ptreat_raw")[1]],0.975),",",quantile(r.draws[,w
hich(par.names=="wealth_effect_ptreat_raw")[2]],0.025),",",quantile(r.
draws[,which(par.names=="wealth_effect_ptreat_raw")[2]],0.50),",",quan
tile(r.draws[,which(par.names=="wealth_effect_ptreat_raw")[2]],0.975),
",",quantile(r.draws[,which(par.names=="wealth_effect_ptreat_raw")[3]]
,0.025),",",quantile(r.draws[,which(par.names=="wealth_effect_ptreat_r
aw")[3]],0.50),",",quantile(r.draws[,which(par.names=="wealth_effect_p
treat_raw")[3]],0.975),",",quantile(r.draws[,which(par.names=="wealth_
effect_ptreat_raw")[4]],0.025),",",quantile(r.draws[,which(par.names==
"wealth_effect_ptreat_raw")[4]],0.50),",",quantile(r.draws[,which(par.
names=="wealth_effect_ptreat_raw")[4]],0.975),"\n",sep="",file="wealth
_effects.csv",append=T)

cat("#mother's education:, , Higher, , , Secondary, , , Primary,
\n",sep="",file="mother_effects.csv")
cat("#posterior quantile:, 2.5%, 50%, 97.5%, 2.5%, 50%, 97.5%, 2.5%,
50%, 97.5% \n",sep="",file="mother_effects.csv",append=T)
cat("mother_effect_pr,",quantile(r.draws[,which(par.names=="mother_eff
ect_pr_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=="mother
_effect_pr_raw")[1]],0.50),",",quantile(r.draws[,which(par.names=="mot
her_effect_pr_raw")[1]],0.975),",",quantile(r.draws[,which(par.names==
"mother_effect_pr_raw")[2]],0.025),",",quantile(r.draws[,which(par.nam
```

```
es=="mother_effect_pr_raw")[2]],0.50),",",quantile(r.draws[,which(par.
names=="mother_effect_pr_raw")[2]],0.975),",",quantile(r.draws[,which(
par.names=="mother_effect_pr_raw")[3]],0.025),",",quantile(r.draws[,wh
ich(par.names=="mother_effect_pr_raw")[3]],0.50),",",quantile(r.draws[
,which(par.names=="mother_effect_pr_raw")[3]],0.975),"\n",sep="",file=
"mother_effects.csv",append=T)
cat("mother_effect_pbg,",quantile(r.draws[,which(par.names=="mother_ef
fect_pbg_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=="moth
er_effect_pbg_raw")[1]],0.50),",",quantile(r.draws[,which(par.names=="
mother_effect_pbg_raw")[1]],0.975),",",quantile(r.draws[,which(par.nam
es=="mother_effect_pbg_raw")[2]],0.025),",",quantile(r.draws[,which(pa
r.names=="mother_effect_pbg_raw")[2]],0.50),",",quantile(r.draws[,whic
h(par.names=="mother_effect_pbg_raw")[2]],0.975),",",quantile(r.draws[
,which(par.names=="mother_effect_pbg_raw")[3]],0.025),",",quantile(r.d
raws[,which(par.names=="mother_effect_pbg_raw")[3]],0.50),",",quantile
(r.draws[,which(par.names=="mother_effect_pbg_raw")[3]],0.975),"\n",se
p="",file="mother_effects.csv",append=T)
cat("mother_effect_ptreat,",quantile(r.draws[,which(par.names=="mother
_effect_ptreat_raw")[1]],0.025),",",quantile(r.draws[,which(par.names=
="mother_effect_ptreat_raw")[1]],0.50),",",quantile(r.draws[,which(par
.names=="mother_effect_ptreat_raw")[1]],0.975),",",quantile(r.draws[,w
hich(par.names=="mother_effect_ptreat_raw")[2]],0.025),",",quantile(r.
draws[,which(par.names=="mother_effect_ptreat_raw")[2]],0.50),",",quan
tile(r.draws[,which(par.names=="mother_effect_ptreat_raw")[2]],0.975),
",",quantile(r.draws[,which(par.names=="mother_effect_ptreat_raw")[3]]
,0.025),",",quantile(r.draws[,which(par.names=="mother_effect_ptreat_r
aw")[3]],0.50),",",quantile(r.draws[,which(par.names=="mother_effect_p
treat_raw")[3]],0.975),"\n",sep="",file="mother_effects.csv",append=T)

pr <- maf <- pbg <- ptreat <- ptreatmaf <- ptreatboth <- pprick <-
pundertreat <- prevert <- povertreat <- ppresumptive <-
matrix(0,nrow=length(Fstat),ncol=300)
for (i in 1:300) {
  outputs <- obj$report(r.draws[i,])
  pr[,i] <- outputs$pr
  maf[,i] <- outputs$maf
  pbg[,i] <- outputs$pbg
  ptreat[,i] <- outputs$ptreat
  ptreatmaf[,i] <- outputs$ptreatmaf
  ptreatboth[,i] <- outputs$ptreatboth
  pprick[,i] <- outputs$pprick
  pundertreat[,i] <- outputs$pundertreat
  prevert[,i] <- rdt.persist
  povertreat[,i] <- outputs$povertreat
  ppresumptive[,i] <- outputs$ppresumptive
  cat(i,"\n")
}
#save(pr,maf,pbg,ptreat,ptreatmaf,ptreatboth,pprick,pundertreat,prever
t,povertreat,ppresumptive,file="ps.dat")

#load("Z:\\Malaria data\\Overdiagnosis paper\\outputs 200718\\ps.dat")

# Compute posterior fever type probabilities
bfactor <- 0.472
maf <- maf*bfactor
individual.pbgonly <- individual.pmafonly <- individual.pboth <-
individual.pbgonly_pos <- matrix(0,ncol=300,nrow=length(Pstat))

PposFposTpos <- which(Pstat==1 & Fstat==1 & (Tstat==1  | Tstat==2))
individual.pbgonly[PposFposTpos,] <- ((pbg*(1-maf)*ptreat)/(maf*(1-
pbg)*ptreatmaf+maf*pbg*ptreatboth+pbg*(1-maf)*ptreat))[PposFposTpos,]
```

```
individual.pmafonly[PposFposTpos,] <- (((1-
pbg)*maf*ptreatmaf)/(maf*(1-pbg)*ptreatmaf+maf*pbg*ptreatboth+pbg*(1-
maf)*ptreat))[PposFposTpos,]
individual.pboth[PposFposTpos,] <- ((pbg*maf*ptreatboth)/(maf*(1-
pbg)*ptreatmaf+maf*pbg*ptreatboth+pbg*(1-maf)*ptreat))[PposFposTpos,]
individual.pbgonly_pos[PposFposTpos,] <- ((pbg*(1-
maf)*ptreat)/(maf*(1-pbg)*ptreatmaf+maf*pbg*ptreatboth+pbg*(1-
maf)*ptreat))[PposFposTpos,]

PnegFposTposHposApos <- which(Pstat==0 & Fstat==1 & (Tstat==1  |
Tstat==2) & Hstat==1 & Astat==1)
individual.pbgonly[PnegFposTposHposApos,] <- (((1-
pr)*pbg*ptreat*povertreat+pr*((1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert)/((1-pr)*pbg*ptreat*povertreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert))[PnegFposTposHposApos,]
individual.pmafonly[PnegFposTposHposApos,] <- ((pr*(maf*(1-
pbg)*ptreatmaf)*(1.0-pundertreat)*pcure*prevert)/((1-
pr)*pbg*ptreat*povertreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert))[PnegFposTposHposApos,]
individual.pboth[PnegFposTposHposApos,] <-
((pr*(maf*pbg*ptreatboth)*(1.0-pundertreat)*pcure*prevert)/((1-
pr)*pbg*ptreat*povertreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert))[PnegFposTposHposApos,]
individual.pbgonly_pos[PnegFposTposHposApos,] <- ((pr*((1-
maf)*pbg*ptreat)*(1.0-pundertreat)*pcure*prevert)/((1-
pr)*pbg*ptreat*povertreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert))[PnegFposTposHposApos,]

PnegFposTposHnegApos <- which(Pstat==0 & Fstat==1 & (Tstat==1  |
Tstat==2) & Hstat==0 & Astat==1)
individual.pbgonly[PnegFposTposHnegApos,] <- (((1-
pr)*pbg*ptreat+pr*((1-maf)*pbg*ptreat)*pcure*prevert)/((1-
pr)*pbg*ptreat+pr*((1-pbg)*maf*ptreatmaf+pbg*maf*ptreatboth +(1-
maf)*pbg*ptreat)*pcure*prevert))[PnegFposTposHnegApos,]
individual.pmafonly[PnegFposTposHnegApos,] <- ((pr*(maf*(1-
pbg)*ptreatmaf)*pcure*prevert)/((1-pr)*pbg*ptreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-
maf)*pbg*ptreat)*pcure*prevert))[PnegFposTposHnegApos,]
individual.pboth[PnegFposTposHnegApos,] <-
((pr*(maf*pbg*ptreatboth)*pcure*prevert)/((1-pr)*pbg*ptreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-
maf)*pbg*ptreat)*pcure*prevert))[PnegFposTposHnegApos,]
individual.pbgonly_pos[PnegFposTposHnegApos,] <- ((pr*((1-
maf)*pbg*ptreat)*pcure*prevert)/((1-pr)*pbg*ptreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth +(1-
maf)*pbg*ptreat)*pcure*prevert))[PnegFposTposHnegApos,]

PnegFposTposHunkApos <- which(Pstat==0 & Fstat==1 & (Tstat==1  |
Tstat==2) & Hstat==2 & Astat==1)
individual.pbgonly[PnegFposTposHunkApos,] <- ((1-pprick)*((1-
pr)*pbg*ptreat+pr*((1-maf)*pbg*ptreat)*pcure*prevert)/((1-
pr)*pbg*ptreat+pr*((1-pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-
maf)*pbg*ptreat)*pcure*prevert))[PnegFposTposHunkApos,]+(pprick*((1-
pr)*pbg*ptreat*povertreat+pr*((1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert)/((1-pr)*pbg*ptreat*povertreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert))[PnegFposTposHunkApos,]
```

```
individual.pmafonly[PnegFposTposHunkApos,] <- ((1-pprick)*(pr*(maf*(1-
pbg)*ptreatmaf)*pcure*prevert)/((1-pr)*pbg*ptreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-
maf)*pbg*ptreat)*pcure*prevert))[PnegFposTposHunkApos,]+(pprick*(pr*(m
af*(1-pbg)*ptreatmaf)*(1.0-pundertreat)*pcure*prevert)/((1-
pr)*pbg*ptreat*povertreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert))[PnegFposTposHunkApos,]
individual.pboth[PnegFposTposHunkApos,] <- ((1-
pprick)*(pr*(maf*pbg*ptreatboth)*pcure*prevert)/((1-
pr)*pbg*ptreat+pr*((1-pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-
maf)*pbg*ptreat)*pcure*prevert))[PnegFposTposHunkApos,]+(pprick*(pr*(m
af*pbg*ptreatboth)*(1.0-pundertreat)*pcure*prevert)/((1-
pr)*pbg*ptreat*povertreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert))[PnegFposTposHunkApos,]
individual.pbgonly_pos[PnegFposTposHunkApos,] <- ((1-pprick)*(pr*((1-
maf)*pbg*ptreat)*pcure*prevert)/((1-pr)*pbg*ptreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-
maf)*pbg*ptreat)*pcure*prevert))[PnegFposTposHunkApos,]+(pprick*(pr*((
1-maf)*pbg*ptreat)*(1.0-pundertreat)*pcure*prevert)/((1-
pr)*pbg*ptreat*povertreat+pr*((1-
pbg)*maf*ptreatmaf+pbg*maf*ptreatboth+(1-maf)*pbg*ptreat)*(1.0-
pundertreat)*pcure*prevert))[PnegFposTposHunkApos,]

PnegFposTposAneg <- which(Pstat==0 & Fstat==1 & (Tstat==1  | Tstat==2)
& Astat==0)
individual.pbgonly[PnegFposTposAneg,] <- 1

PnegFposTneg <- which(Pstat==0 & Fstat==1 & Tstat==0)
individual.pbgonly[PnegFposTneg,] <- 1

PposFposTneg <- which(Pstat==1 & Fstat==1 & Tstat==0)
individual.pbgonly[PposFposTneg,] <- ((pbg*(1-maf)*(1-
ptreat))/(maf*(1-pbg)*(1-ptreatmaf)+maf*pbg*(1-ptreatboth)+pbg*(1-
maf)*(1-ptreat)))[PposFposTneg,]
individual.pmafonly[PposFposTneg,] <- (((1-pbg)*maf*(1-
ptreatmaf))/(maf*(1-pbg)*(1-ptreatmaf)+maf*pbg*(1-ptreatboth)+pbg*(1-
maf)*(1-ptreat)))[PposFposTneg,]
individual.pboth[PposFposTneg,] <- ((pbg*maf*(1-ptreatboth))/(maf*(1-
pbg)*(1-ptreatmaf)+maf*pbg*(1-ptreatboth)+pbg*(1-maf)*(1-
ptreat)))[PposFposTneg,]
individual.pbgonly_pos[PposFposTneg,] <- ((pbg*(1-maf)*(1-
ptreat))/(maf*(1-pbg)*(1-ptreatmaf)+maf*pbg*(1-ptreatboth)+pbg*(1-
maf)*(1-ptreat)))[PposFposTneg,]

weight.matrix <- weights
for (i in 1:299) {weight.matrix <- cbind(weight.matrix,weights)}

individual.pheelprick <- matrix(0,ncol=300,nrow=length(Tstat))
Hpos <- which(Hstat==1)
individual.pheelprick[Hpos,] <- 1
Hneg <- which(Hstat==0)
individual.pheelprick[Hneg,] <- 0
Hunk <- which(Hstat==2)
individual.pheelprick[Hunk,] <- pprick[Hunk,]

individual.ppos <- matrix(0,ncol=300,nrow=length(Tstat))
Ppos <- which(Pstat==1)
individual.ppos[Ppos,] <- 1
PnegApos <- which(Astat==1 & Pstat==0)
```

```
individual.ppos[PnegApos,] <- prevert[PnegApos,]

# Proportions of individuals by fever type including no fevers
cat("Class:,,p_nofever,,,p_mafonly,,,p_bgonly,,,p_both,\n",file="propo
rtions_including_nofevers.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%,
\n",file="proportions_including_nofevers.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.nofever <- colSums(weight.matrix[Fstat==0 & survey==(i-1),])
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
survey==(i-1),])
  n.tot <- n.nofever+n.maf+n.both+n.bg

cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
nofever/n.tot,0.025),",",quantile(n.nofever/n.tot,0.5),",",quantile(n.
nofever/n.tot,0.975),",",quantile(n.maf/n.tot,0.025),",",quantile(n.ma
f/n.tot,0.5),",",quantile(n.maf/n.tot,0.975),",",quantile(n.bg/n.tot,0
.025),",",quantile(n.bg/n.tot,0.5),",",quantile(n.bg/n.tot,0.975),",",
quantile(n.both/n.tot,0.025),",",quantile(n.both/n.tot,0.5),",",quanti
le(n.both/n.tot,0.975),"\n",sep="",file="proportions_including_nofever
s.csv",append=T)
}

# Proportions of individuals by fever type excluding no fevers
cat("Class:,,p_mafonly,,,p_bgonly,,,p_both,\n",file="proportions_exclu
ding_nofevers.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%,\n",file="propo
rtions_excluding_nofevers.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
survey==(i-1),])
  n.tot <- n.maf+n.both+n.bg

cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
maf/n.tot,0.025),",",quantile(n.maf/n.tot,0.5),",",quantile(n.maf/n.to
t,0.975),",",quantile(n.bg/n.tot,0.025),",",quantile(n.bg/n.tot,0.5),"
,",quantile(n.bg/n.tot,0.975),",",quantile(n.both/n.tot,0.025),",",qua
ntile(n.both/n.tot,0.5),",",quantile(n.both/n.tot,0.975),"\n",sep="",f
ile="proportions_excluding_nofevers.csv",append=T)
}

# Proportions of individuals by fever type who sought treatment
cat("Class:,,p_mafonly,,,p_bgonly,,,p_both,\n",file="proportions_among
st_those_who_sought_treatment.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%,\n",file="propo
rtions_amongst_those_who_sought_treatment.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
```

```
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.tot <- n.maf+n.both+n.bg

cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
maf/n.tot,0.025),",",quantile(n.maf/n.tot,0.5),",",quantile(n.maf/n.to
t,0.975),",",quantile(n.bg/n.tot,0.025),",",quantile(n.bg/n.tot,0.5),"
,",quantile(n.bg/n.tot,0.975),",",quantile(n.both/n.tot,0.025),",",qua
ntile(n.both/n.tot,0.5),",",quantile(n.both/n.tot,0.975),"\n",sep="",f
ile="proportions_amongst_those_who_sought_treatment.csv",append=T)
}


# Proportions of individuals by fever type who sought treatment -
public only
cat("Class:,,p_mafonly,,,p_bgonlypneg,,,p_both,,,p_bgonlyppos,,,p_mafd
ivmf,\n",file="proportions_amongst_those_who_sought_treatment_publicon
ly.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%,
2.5%,50%,97.5%,\n",file="proportions_amongst_those_who_sought_treatmen
t_publiconly.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
(Tstat==1  ) & survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
(Tstat==1  ) & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
(Tstat==1  ) & survey==(i-1),])
  n.bg.pfpos <-
colSums((weight.matrix*individual.pbgonly_pos)[Fstat==1 & (Tstat==1  )
& survey==(i-1),])
  n.bg<-n.bg-n.bg.pfpos

  n.mafdivmf<-n.mafdivmf<-(n.maf+n.both)/(n.maf+n.both+n.bg.pfpos)

  n.tot <- n.maf+n.both+n.bg+n.bg.pfpos

cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
maf/n.tot,0.025),",",quantile(n.maf/n.tot,0.5),",",quantile(n.maf/n.to
t,0.975),",",quantile(n.bg/n.tot,0.025),",",quantile(n.bg/n.tot,0.5),"
,",quantile(n.bg/n.tot,0.975),",",quantile(n.both/n.tot,0.025),",",qua
ntile(n.both/n.tot,0.5),",",quantile(n.both/n.tot,0.975),",",quantile(
n.bg.pfpos/n.tot,0.025),",",quantile(n.bg.pfpos/n.tot,0.5),",",quantil
e(n.bg.pfpos/n.tot,0.975),",",quantile(n.mafdivmf,0.025),",",quantile(
n.mafdivmf,0.5),",",quantile(n.mafdivmf,0.975),"\n",sep="",file="propo
rtions_amongst_those_who_sought_treatment_publiconly.csv",append=T)
}


# proportion of MAF amongst malaria pos fevers who sought treatment at
public
cat("Class:,,p_mafdivmf,,,\n",file="malaria pos fever at
public.csv",sep="")
cat("Posterior quantile:,2.5%,50%,97.5%,\n",file="malaria pos fever at
public.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
(Tstat==1  ) & survey==(i-1),])
```

```
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
(Tstat==1   ) & survey==(i-1),])
  n.bg.pfpos <-
colSums((weight.matrix*individual.pbgonly_pos)[Fstat==1 & (Tstat==1   )
& survey==(i-1),])

  n.mafdivmf<-(n.maf+n.both)/(n.maf+n.both+n.bg.pfpos)


cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
mafdivmf,0.025),",",quantile(n.mafdivmf,0.5),",",quantile(n.mafdivmf,0
.975),"\n",sep="",file="malaria pos fever at public.csv",append=T)
}


# Proportions of individuals by fever type who received an
antimalarial
cat("Class:,,p_mafonly,,,p_bgonly,,,p_both,\n",file="proportions_among
st_those_who_received_antimalarials.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%,\n",file="propo
rtions_amongst_those_who_received_antimalarials.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
Astat==1 & (Tstat==1   | Tstat==2) & survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
Astat==1 & (Tstat==1   | Tstat==2) & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
Astat==1 & (Tstat==1   | Tstat==2) & survey==(i-1),])
  n.tot <- n.maf+n.both+n.bg

cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
maf/n.tot,0.025),",",quantile(n.maf/n.tot,0.5),",",quantile(n.maf/n.to
t,0.975),",",quantile(n.bg/n.tot,0.025),",",quantile(n.bg/n.tot,0.5),"
,",quantile(n.bg/n.tot,0.975),",",quantile(n.both/n.tot,0.025),",",qua
ntile(n.both/n.tot,0.5),",",quantile(n.both/n.tot,0.975),"\n",sep="",f
ile="proportions_amongst_those_who_received_antimalarials.csv",append=
T)
}

# Proportions of individuals by fever type who received a heelprick
cat("Class:,,p_mafonly,,,p_bgonly,,,p_both,\n",file="proportions_among
st_those_who_received_a_heelprick.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%,\n",file="propo
rtions_amongst_those_who_received_a_heelprick.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.maf <-
colSums((weight.matrix*individual.pmafonly*individual.pheelprick)[Fsta
t==1 & (Hstat%in%c(1,2)) & (Tstat==1   | Tstat==2) & survey==(i-1),])
  n.both <-
colSums((weight.matrix*individual.pboth*individual.pheelprick)[Fstat==
1 & (Hstat%in%c(1,2)) & (Tstat==1   | Tstat==2) & survey==(i-1),])
  n.bg <-
colSums((weight.matrix*individual.pbgonly*individual.pheelprick)[Fstat
==1 & (Hstat%in%c(1,2)) & (Tstat==1   | Tstat==2) & survey==(i-1),])
  n.tot <- n.maf+n.both+n.bg

cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
maf/n.tot,0.025),",",quantile(n.maf/n.tot,0.5),",",quantile(n.maf/n.to
t,0.975),",",quantile(n.bg/n.tot,0.025),",",quantile(n.bg/n.tot,0.5),"
```

```
,",",quantile(n.bg/n.tot,0.975),",",quantile(n.both/n.tot,0.025),",",qua
ntile(n.both/n.tot,0.5),",",quantile(n.both/n.tot,0.975),"\n",sep="",f
ile="proportions_amongst_those_who_received_a_heelprick.csv",append=T)
}

# Proportions of individuals by fever type who received a heelprick:
reduced
cat("Class:,,p_mafonly+p_both,,,p_bgonly,\n",file="proportions_amongst
_those_who_received_a_heelprick_mafplusboth_vs_bgonly.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,\n",file="proportions_amongst_
those_who_received_a_heelprick_mafplusboth_vs_bgonly.csv",sep="",appen
d=T)
for (i in 1:nsurvey) {
  n.maf <-
colSums((weight.matrix*individual.pmafonly*individual.pheelprick)[Fsta
t==1 & (Hstat%in%c(1,2)) & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.both <-
colSums((weight.matrix*individual.pboth*individual.pheelprick)[Fstat==
1 & (Hstat%in%c(1,2)) & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.bg <-
colSums((weight.matrix*individual.pbgonly*individual.pheelprick)[Fstat
==1 & (Hstat%in%c(1,2)) & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.mafplusboth <- n.maf+n.both
  n.tot <- n.maf+n.both+n.bg

cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
mafplusboth/n.tot,0.025),",",quantile(n.mafplusboth/n.tot,0.5),",",qua
ntile(n.mafplusboth/n.tot,0.975),",",quantile(n.bg/n.tot,0.025),",",qu
antile(n.bg/n.tot,0.5),",",quantile(n.bg/n.tot,0.975),"\n",sep="",file
="proportions_amongst_those_who_received_a_heelprick_mafplusboth_vs_bg
only.csv",append=T)
}

# Probability of receiving a heelprick by fever type amongst those who
sought treatment
cat("Class:,,p_heelprick_given_mafonly,,,p_heelprick_given_bgonly,,,p_
heelprick_given_both,\n",file="probabilty_of_receiving_a_heelprick_by_
fever_type_amongst_those_who_sought_treatment.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%\n",file="probab
ilty_of_receiving_a_heelprick_by_fever_type_amongst_those_who_sought_t
reatment.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.heelprickmaf <-
colSums((weight.matrix*individual.pmafonly*individual.pheelprick)[Fsta
t==1 & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.heelprickbg <-
colSums((weight.matrix*individual.pbgonly*individual.pheelprick)[Fstat
==1 & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.heelprickboth <-
colSums((weight.matrix*individual.pboth*individual.pheelprick)[Fstat==
1 & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
```

```
cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
heelprickmaf/n.maf,0.025),",",quantile(n.heelprickmaf/n.maf,0.5),",",q
uantile(n.heelprickmaf/n.maf,0.975),",",quantile(n.heelprickbg/n.bg,0.
025),",",quantile(n.heelprickbg/n.bg,0.5),",",quantile(n.heelprickbg/n
.bg,0.975),",",quantile(n.heelprickboth/n.both,0.025),",",quantile(n.h
eelprickboth/n.both,0.5),",",quantile(n.heelprickboth/n.both,0.975),"\
n",sep="",file="probabilty_of_receiving_a_heelprick_by_fever_type_amon
gst_those_who_sought_treatment.csv",append=T)
}

# Probability of receiving an antimalarial by fever type amongst those
who sought treatment
cat("Class:,,p_antimalarial_given_mafonly,,,p_antimalarial_given_bgonl
y,,,p_antimalarial_given_both,\n",file="probabilty_of_receiving_an_ant
imalarial_by_fever_type_amongst_those_who_sought_treatment.csv",sep=""
)
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%\n",file="probab
ilty_of_receiving_an_antimalarial_by_fever_type_amongst_those_who_soug
ht_treatment.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.antimalarialmaf <-
colSums((weight.matrix*individual.pmafonly)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & survey==(i-1),])
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.antimalarialbg <-
colSums((weight.matrix*individual.pbgonly)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.antimalarialboth <-
colSums((weight.matrix*individual.pboth)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])


cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
antimalarialmaf/n.maf,0.025),",",quantile(n.antimalarialmaf/n.maf,0.5)
,",",quantile(n.antimalarialmaf/n.maf,0.975),",",quantile(n.antimalari
albg/n.bg,0.025),",",quantile(n.antimalarialbg/n.bg,0.5),",",quantile(
n.antimalarialbg/n.bg,0.975),",",quantile(n.antimalarialboth/n.both,0.
025),",",quantile(n.antimalarialboth/n.both,0.5),",",quantile(n.antima
larialboth/n.both,0.975),"\n",sep="",file="probabilty_of_receiving_an_
antimalarial_by_fever_type_amongst_those_who_sought_treatment.csv",app
end=T)
}

# Probability of seeking treatment by fever type
cat("Class:,,p_treatment_given_mafonly,,,p_treatment_given_bgonly,,,p_
treatment_given_both,\n",file="probabilty_of_seeking_treatment_by_feve
r_type.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%\n",file="probab
ilty_of_seeking_treatment_by_fever_type.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.treatmentmaf <-
colSums((weight.matrix*individual.pmafonly)[Fstat==1 & (Tstat==1  |
Tstat==2) & survey==(i-1),])
```

```
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
survey==(i-1),])
  n.treatmentbg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1
& (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
survey==(i-1),])
  n.treatmentboth <- colSums((weight.matrix*individual.pboth)[Fstat==1
& (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
survey==(i-1),])


cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
treatmentmaf/n.maf,0.025),",",quantile(n.treatmentmaf/n.maf,0.5),",",q
uantile(n.treatmentmaf/n.maf,0.975),",",quantile(n.treatmentbg/n.bg,0.
025),",",quantile(n.treatmentbg/n.bg,0.5),",",quantile(n.treatmentbg/n
.bg,0.975),",",quantile(n.treatmentboth/n.both,0.025),",",quantile(n.t
reatmentboth/n.both,0.5),",",quantile(n.treatmentboth/n.both,0.975),"\
n",sep="",file="probabilty_of_seeking_treatment_by_fever_type.csv",app
end=T)
}

# Probability of receiving an ACT by fever type amongst those who
sought treatment
cat("Class:,,p_act_given_mafonly,,,p_act_given_bgonly,,,p_act_given_bo
th,\n",file="probabilty_of_receiving_an_act_by_fever_type_amongst_thos
e_who_sought_treatment.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%\n",file="probab
ilty_of_receiving_an_act_by_fever_type_amongst_those_who_sought_treatm
ent.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.antimalarialmaf <-
colSums((weight.matrix*individual.pmafonly)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & act==1 & survey==(i-1),])
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.antimalarialbg <-
colSums((weight.matrix*individual.pbgonly)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & act==1 & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.antimalarialboth <-
colSums((weight.matrix*individual.pboth)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & act==1 & survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])


cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
antimalarialmaf/n.maf,0.025),",",quantile(n.antimalarialmaf/n.maf,0.5)
,",",quantile(n.antimalarialmaf/n.maf,0.975),",",quantile(n.antimalari
albg/n.bg,0.025),",",quantile(n.antimalarialbg/n.bg,0.5),",",quantile(
n.antimalarialbg/n.bg,0.975),",",quantile(n.antimalarialboth/n.both,0.
025),",",quantile(n.antimalarialboth/n.both,0.5),",",quantile(n.antima
larialboth/n.both,0.975),"\n",sep="",file="probabilty_of_receiving_an_
act_by_fever_type_amongst_those_who_sought_treatment.csv",append=T)
}

# Probability of receiving an ACT by fever type amongst those who
sought treatment and received an antimalarial
```

```
cat("Class:,,p_act_given_mafonly,,,p_act_given_bgonly,,,p_act_given_bo
th,\n",file="probabilty_of_receiving_an_act_by_fever_type_amongst_thos
e_who_sought_treatment_and_received_an_antimalarial.csv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%\n",file="probab
ilty_of_receiving_an_act_by_fever_type_amongst_those_who_sought_treatm
ent_and_received_an_antimalarial.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.antimalarialmaf <-
colSums((weight.matrix*individual.pmafonly)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & act==1 & survey==(i-1),])
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & Astat==1 & survey==(i-1),])
  n.antimalarialbg <-
colSums((weight.matrix*individual.pbgonly)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & act==1 & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & Astat==1 & survey==(i-1),])
  n.antimalarialboth <-
colSums((weight.matrix*individual.pboth)[Fstat==1 & (Tstat==1  |
Tstat==2) & Astat==1 & act==1 & survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
(Tstat==1  | Tstat==2) & Astat==1 & survey==(i-1),])


cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
antimalarialmaf/n.maf,0.025),",",quantile(n.antimalarialmaf/n.maf,0.5)
,",",quantile(n.antimalarialmaf/n.maf,0.975),",",quantile(n.antimalari
albg/n.bg,0.025),",",quantile(n.antimalarialbg/n.bg,0.5),",",quantile(
n.antimalarialbg/n.bg,0.975),",",quantile(n.antimalarialboth/n.both,0.
025),",",quantile(n.antimalarialboth/n.both,0.5),",",quantile(n.antima
larialboth/n.both,0.975),"\n",sep="",file="probabilty_of_receiving_an_
act_by_fever_type_amongst_those_who_sought_treatment_and_received_an_a
ntimalarial.csv",append=T)
}

# Probability of seeking treatment at a public facility by fever type
amongst those who sought treatment
cat("Class:,,p_treatment_given_mafonly,,,p_treatment_given_bgonly,,,p_
treatment_given_both,\n",file="probabilty_of_seeking_treatment_at_a_pu
blic_facility_by_fever_type_amongst_those_who_sought_treatment.csv",se
p="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%\n",file="probab
ilty_of_seeking_treatment_at_a_public_facility_by_fever_type_amongst_t
hose_who_sought_treatment.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.treatmentmaf <-
colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
treatmentlocation==1 & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.maf <- colSums((weight.matrix*individual.pmafonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.treatmentbg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1
& treatmentlocation==1 & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
  n.treatmentboth <- colSums((weight.matrix*individual.pboth)[Fstat==1
& treatmentlocation==1 & (Tstat==1  | Tstat==2) & survey==(i-1),])
  n.both <- colSums((weight.matrix*individual.pboth)[Fstat==1 &
(Tstat==1  | Tstat==2) & survey==(i-1),])
```

```
cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(n.
treatmentmaf/n.maf,0.025),",",quantile(n.treatmentmaf/n.maf,0.5),",",q
uantile(n.treatmentmaf/n.maf,0.975),",",quantile(n.treatmentbg/n.bg,0.
025),",",quantile(n.treatmentbg/n.bg,0.5),",",quantile(n.treatmentbg/n
.bg,0.975),",",quantile(n.treatmentboth/n.both,0.025),",",quantile(n.t
reatmentboth/n.both,0.5),",",quantile(n.treatmentboth/n.both,0.975),"\
n",sep="",file="probabilty_of_seeking_treatment_at_a_public_facility_b
y_fever_type_amongst_those_who_sought_treatment.csv",append=T)
}

# Undertreatment, overtreatment, and presumptive treatment
probabilities by survey
cat("Class:,,p_undertreatment,,,p_overtreatment,,,p_presumptive,\n",fi
le="undertreatment_overtreatment_and_presumptive_treatment_by_survey.c
sv",sep="")
cat("Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%,2.5%,50%,97.5%\n",file="undert
reatment_overtreatment_and_presumptive_treatment_by_survey.csv",sep=""
,append=T)
for (i in 1:nsurvey) {


cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",",quantile(pu
ndertreat[survey==(i-1),],0.025),",",quantile(pundertreat[survey==(i-
1),],0.5),",",quantile(pundertreat[survey==(i-
1),],0.975),",",quantile(povertreat[survey==(i-
1),],0.025),",",quantile(povertreat[survey==(i-
1),],0.5),",",quantile(povertreat[survey==(i-
1),],0.975),",",quantile(ppresumptive[survey==(i-
1),],0.025),",",quantile(ppresumptive[survey==(i-
1),],0.5),",",quantile(ppresumptive[survey==(i-
1),],0.975),"\n",sep="",file="undertreatment_overtreatment_and_presump
tive_treatment_by_survey.csv",append=T)
}

# National level PR versus MAF/(pos+fever)

cat("Class:,,PR (in the absence of
treatment),,,maf/FposPpos,,\n",file="maf_on_FposPpos_ratio_versus_PR.c
sv",sep="")
cat("#Posterior
quantile:,2.5%,50%,97.5%,2.5%,50%,97.5%\n",file="maf_on_FposPpos_ratio
_versus_PR.csv",sep="",append=T)
for (i in 1:nsurvey) {
  n.pr <- colSums((weight.matrix*individual.ppos)[survey==(i-
1),])/colSums((weight.matrix)[survey==(i-1),])
  n.maf <-
colSums((weight.matrix*(individual.pmafonly+individual.pboth))[survey=
=(i-1),])
  n.bg <- colSums((weight.matrix*individual.pbgonly_pos)[survey==(i-
1),])
  n.fraction <- n.maf/(n.maf+n.bg)

cat(unique(as.character(nmfi.data$survey.x[valid]))[i],",,",mean(n.pr)
,",,",quantile(n.fraction,0.025),",",quantile(n.fraction,0.5),",",quan
tile(n.fraction,0.975),"\n",sep="",file="maf_on_FposPpos_ratio_versus_
PR.csv",append=T)
}
```

Additional File 2

TMB code for generating individual-level attributions of MAF and NMFI to febrile children in household survey dataset. This code is compiled using the R code given in Additional File 1.

```
#include <TMB.hpp>
template<class Type>
Type objective_function<Type>::operator() ()
{
  using namespace R_inla;
  using namespace density;
  using namespace Eigen;
  using namespace density;

  DATA_INTEGER(N);

  DATA_IVECTOR(Pstat);
  DATA_IVECTOR(Fstat);
  DATA_IVECTOR(Tstat);
  DATA_IVECTOR(Hstat);
  DATA_IVECTOR(Astat);

  DATA_VECTOR(F_BRT);
  DATA_VECTOR(T_BRT);
  DATA_VECTOR(PR);
  DATA_VECTOR(pcure);

  DATA_INTEGER(nsurvey);
  DATA_IVECTOR(survey);
  DATA_VECTOR(prevert);
  DATA_IVECTOR(wealth);
  DATA_IVECTOR(mother);
  DATA_IVECTOR(age);
  DATA_VECTOR(net);

  DATA_MATRIX(A);
  DATA_STRUCT(spde,spde_t);

  PARAMETER(log_kappa_pbg);
  PARAMETER(log_tau_pbg);
  PARAMETER_VECTOR(logit_pbg_offset);

  PARAMETER(log_kappa_pr);
  PARAMETER(log_tau_pr);
  PARAMETER_VECTOR(logit_pr_offset);

  PARAMETER(log_kappa_ptreat);
  PARAMETER(log_tau_ptreat);
  PARAMETER(mean_logit_ptreat_offset);
  PARAMETER_VECTOR(logit_ptreat_offset);
```

```
PARAMETER(mean_logit_ptreatmaf_offset);
PARAMETER(log_sd_logit_ptreatmaf_offset);
PARAMETER_VECTOR(logit_ptreatmaf_offset);

PARAMETER(mean_logit_ptreatboth_offset);
PARAMETER(log_sd_logit_ptreatboth_offset);
PARAMETER_VECTOR(logit_ptreatboth_offset);

PARAMETER(logit_prop_maf);
PARAMETER(slope_maf);
PARAMETER(slope_maf_sq);

PARAMETER(mean_logit_pundertreat);
PARAMETER(log_sd_logit_pundertreat);
PARAMETER_VECTOR(logit_pundertreat);
PARAMETER(offset_private_pundertreat);

PARAMETER(mean_logit_povertreat);
PARAMETER(log_sd_logit_povertreat);
PARAMETER_VECTOR(logit_povertreat);
PARAMETER(offset_private_povertreat);

PARAMETER(mean_logit_pprick);
PARAMETER(log_sd_logit_pprick);
PARAMETER_VECTOR(logit_pprick);
PARAMETER(offset_private_pprick);

PARAMETER(mean_logit_ppresumptive);
PARAMETER(log_sd_logit_ppresumptive);
PARAMETER_VECTOR(logit_ppresumptive);
PARAMETER(offset_private_ppresumptive);

PARAMETER(net_effect_pr);
PARAMETER_VECTOR(wealth_effect_pr_raw);
PARAMETER_VECTOR(mother_effect_pr_raw);
PARAMETER_VECTOR(age_effect_pr_raw);
PARAMETER_VECTOR(wealth_effect_pbg_raw);
PARAMETER_VECTOR(mother_effect_pbg_raw);
PARAMETER_VECTOR(age_effect_pbg_raw);
PARAMETER_VECTOR(wealth_effect_ptreat_raw);
PARAMETER_VECTOR(mother_effect_ptreat_raw);
PARAMETER_VECTOR(age_effect_ptreat_raw);

Type nll = 0.0;

nll -= dnorm(net_effect_pr,Type(0.0),Type(1.0),true);

nll -= dnorm(log_kappa_pbg,Type(0.0),Type(1.0),true);
nll -= dnorm(log_tau_pbg,Type(0.0),Type(1.0),true);

SparseMatrix<Type> Q_pbg = Q_spde(spde,exp(log_kappa_pbg));
nll += SCALE(GMRF(Q_pbg),1.0/exp(log_tau_pbg))(logit_pbg_offset);

vector<Type> pbg_offset_prediction;
pbg_offset_prediction = A*logit_pbg_offset;

nll -= dnorm(log_kappa_pr,Type(0.0),Type(1.0),true);
nll -= dnorm(log_tau_pr,Type(0.0),Type(1.0),true);

SparseMatrix<Type> Q_pr = Q_spde(spde,exp(log_kappa_pr));
```

```
  nll += GMRF(Q_pr)(logit_pr_offset);
  nll += SCALE(GMRF(Q_pr),1.0/exp(log_tau_pr))(logit_pr_offset);

  vector<Type> pr_offset_prediction;
  pr_offset_prediction = A*logit_pr_offset;

  nll -= dnorm(log_kappa_ptreat,Type(0.0),Type(1.0),true);
  nll -= dnorm(log_tau_ptreat,Type(0.0),Type(1.0),true);
  nll -= dnorm(mean_logit_ptreat_offset,Type(0.0),Type(1.0),true);

  SparseMatrix<Type> Q_ptreat = Q_spde(spde,exp(log_kappa_ptreat));
  nll +=
SCALE(GMRF(Q_ptreat),1.0/exp(log_tau_ptreat))(logit_ptreat_offset);

  vector<Type> ptreat_offset_prediction;
  ptreat_offset_prediction = A*logit_ptreat_offset;

  nll -= dnorm(mean_logit_ptreatmaf_offset,Type(0.0),Type(1.0),true);
  nll -=
dnorm(log_sd_logit_ptreatmaf_offset,Type(0.0),Type(1.0),true);
  for (int i=0; i<nsurvey; i++) {
    nll -=
dnorm(logit_ptreatmaf_offset[i],mean_logit_ptreatmaf_offset,exp(log_sd
_logit_ptreatmaf_offset),true);
  }

  nll -= dnorm(mean_logit_ptreatboth_offset,Type(0.0),Type(1.0),true);
  nll -=
dnorm(log_sd_logit_ptreatboth_offset,Type(0.0),Type(1.0),true);
  for (int i=0; i<nsurvey; i++) {
    nll -=
dnorm(logit_ptreatboth_offset[i],mean_logit_ptreatboth_offset,exp(log_
sd_logit_ptreatboth_offset),true);
  }

  nll -= dnorm(mean_logit_pundertreat,Type(0.0),Type(1.0),true);
  nll -= dnorm(log_sd_logit_pundertreat,Type(0.0),Type(1.0),true);
  for (int i=0; i<nsurvey; i++) {
    nll -=
dnorm(logit_pundertreat[i],mean_logit_pundertreat,exp(log_sd_logit_pun
dertreat),true);
  }
  nll -= dnorm(offset_private_pundertreat,Type(0.0),Type(1.0),true);

  nll -= dnorm(mean_logit_povertreat,Type(0.0),Type(1.0),true);
  nll -= dnorm(log_sd_logit_povertreat,Type(0.0),Type(1.0),true);
  for (int i=0; i<nsurvey; i++) {
    nll -=
dnorm(logit_povertreat[i],mean_logit_povertreat,exp(log_sd_logit_pover
treat),true);
  }
  nll -= dnorm(offset_private_povertreat,Type(0.0),Type(1.0),true);

  nll -= dnorm(mean_logit_pprick,Type(0.0),Type(1.0),true);
  nll -= dnorm(log_sd_logit_pprick,Type(0.0),Type(1.0),true);
  for (int i=0; i<nsurvey; i++) {
    nll -=
dnorm(logit_pprick[i],mean_logit_pprick,exp(log_sd_logit_pprick),true)
;
  }
  nll -= dnorm(offset_private_pprick,Type(0.0),Type(1.0),true);
```

```
  nll -= dnorm(mean_logit_ppresumptive,Type(0.0),Type(1.0),true);
  nll -= dnorm(log_sd_logit_ppresumptive,Type(0.0),Type(1.0),true);
  for (int i=0; i<nsurvey; i++) {
    nll -=
dnorm(logit_ppresumptive[i],mean_logit_ppresumptive,exp(log_sd_logit_p
presumptive),true);
  }
  nll -= dnorm(offset_private_ppresumptive,Type(0.0),Type(1.0),true);

  for (int i=0; i<4; i++) {nll -=
dnorm(wealth_effect_pr_raw[i],Type(0.0),Type(1.0),true);}
  for (int i=0; i<3; i++) {nll -=
dnorm(mother_effect_pr_raw[i],Type(0.0),Type(1.0),true);}
  for (int i=0; i<4; i++) {nll -=
dnorm(age_effect_pr_raw[i],Type(0.0),Type(1.0),true);}
  for (int i=0; i<4; i++) {nll -=
dnorm(wealth_effect_pbg_raw[i],Type(0.0),Type(1.0),true);}
  for (int i=0; i<3; i++) {nll -=
dnorm(mother_effect_pbg_raw[i],Type(0.0),Type(1.0),true);}
  for (int i=0; i<4; i++) {nll -=
dnorm(age_effect_pbg_raw[i],Type(0.0),Type(1.0),true);}
  for (int i=0; i<4; i++) {nll -=
dnorm(wealth_effect_ptreat_raw[i],Type(0.0),Type(1.0),true);}
  for (int i=0; i<3; i++) {nll -=
dnorm(mother_effect_ptreat_raw[i],Type(0.0),Type(1.0),true);}
  for (int i=0; i<4; i++) {nll -=
dnorm(age_effect_ptreat_raw[i],Type(0.0),Type(1.0),true);}

  vector<Type> wealth_effect_pr(5);
  vector<Type> mother_effect_pr(4);
  vector<Type> age_effect_pr(5);
  vector<Type> wealth_effect_pbg(5);
  vector<Type> mother_effect_pbg(4);
  vector<Type> age_effect_pbg(5);
  vector<Type> wealth_effect_ptreat(5);
  vector<Type> mother_effect_ptreat(4);
  vector<Type> age_effect_ptreat(5);

  for (int i=0; i<4; i++) {wealth_effect_pr[i] =
wealth_effect_pr_raw[i];}
  wealth_effect_pr[4] = 0.0;
  for (int i=0; i<3; i++) {mother_effect_pr[i] =
mother_effect_pr_raw[i];}
  mother_effect_pr[3] = 0.0;
  for (int i=0; i<4; i++) {age_effect_pr[i] = age_effect_pr_raw[i];}
  age_effect_pr[4] = 0.0;

  for (int i=0; i<4; i++) {wealth_effect_pbg[i] =
wealth_effect_pbg_raw[i];}
  wealth_effect_pbg[4] = 0.0;
  for (int i=0; i<3; i++) {mother_effect_pbg[i] =
mother_effect_pbg_raw[i];}
  mother_effect_pbg[3] = 0.0;
  for (int i=0; i<4; i++) {age_effect_pbg[i] = age_effect_pbg_raw[i];}
  age_effect_pbg[4] = 0.0;

  for (int i=0; i<4; i++) {wealth_effect_ptreat[i] =
wealth_effect_ptreat_raw[i];}
  wealth_effect_ptreat[4] = 0.0;
```

```
  for (int i=0; i<3; i++) {mother_effect_ptreat[i] =
mother_effect_ptreat_raw[i];}
  mother_effect_ptreat[3] = 0.0;
  for (int i=0; i<4; i++) {age_effect_ptreat[i] =
age_effect_ptreat_raw[i];}
  age_effect_ptreat[4] = 0.0;

  vector<Type> logit_pr(N);
  vector<Type> logit_pbg(N);
  vector<Type> logit_ptreat(N);
  vector<Type> pr(N);
  vector<Type> pbg(N);
  vector<Type> ptreat(N);
  vector<Type> ptreatmaf(N);
  vector<Type> ptreatboth(N);

  for (int i=0; i<N; i++) {
    logit_pr[i] =
net_effect_pr*net[i]+pr_offset_prediction[i]+logit(PR[i])+wealth_effec
t_pr[wealth[i]]+mother_effect_pr[mother[i]]+age_effect_pr[age[i]];
    logit_pbg[i] =
pbg_offset_prediction[i]+F_BRT[i]+wealth_effect_pbg[wealth[i]]+mother_
effect_pbg[mother[i]]+age_effect_pbg[age[i]];
    logit_ptreat[i] =
ptreat_offset_prediction[i]+T_BRT[i]+mean_logit_ptreat_offset+wealth_e
ffect_ptreat[wealth[i]]+mother_effect_ptreat[mother[i]]+age_effect_ptr
eat[age[i]];
  }

  nll -= dnorm(logit_prop_maf,Type(3.0),Type(1.0),true);
  nll -= dnorm(slope_maf,Type(0.0),Type(1.0),true);
  nll -= dnorm(slope_maf_sq,Type(0.0),Type(0.5),true);
  vector<Type> maf(N);
  vector<Type> pundertreat(N);
  vector<Type> povertreat(N);
  vector<Type> pprick(N);
  vector<Type> ppresumptive(N);
  for (int i=0; i<N; i++) {
    maf[i] = invlogit(logit_prop_maf + slope_maf*invlogit(logit_pr[i])
+ slope_maf_sq*invlogit(logit_pr[i])*invlogit(logit_pr[i]));
    pr[i] = invlogit(logit_pr[i]);
    pbg[i] = invlogit(logit_pbg[i]);
    ptreat[i] = invlogit(logit_ptreat[i]);
    ptreatmaf[i] =
invlogit(logit_ptreat[i]+logit_ptreatmaf_offset[survey[i]]);
    ptreatboth[i] =
invlogit(logit_ptreat[i]+logit_ptreatboth_offset[survey[i]]);
    if ((Tstat[i]==0) | (Tstat[i]==1)) {
      pundertreat[i] = invlogit(logit_pundertreat[survey[i]]);
    } else if (Tstat[i]==2) {
      pundertreat[i] =
invlogit(logit_pundertreat[survey[i]]+offset_private_pundertreat);
    }
    if ((Tstat[i]==0) | (Tstat[i]==1)) {
      povertreat[i] = invlogit(logit_povertreat[survey[i]]);
    } else if (Tstat[i]==2) {
      povertreat[i] =
invlogit(logit_povertreat[survey[i]]+offset_private_povertreat);
    }
    if ((Tstat[i]==0) | (Tstat[i]==1)) {
      pprick[i] = invlogit(logit_pprick[survey[i]]);
```

```
    } else if (Tstat[i]==2) {
      pprick[i] =
invlogit(logit_pprick[survey[i]]+offset_private_pprick);
    }
    if ((Tstat[i]==0) | (Tstat[i]==1)) {
      ppresumptive[i] = invlogit(logit_ppresumptive[survey[i]]);
    } else if (Tstat[i]==2) {
      ppresumptive[i] =
invlogit(logit_ppresumptive[survey[i]]+offset_private_ppresumptive);
    }
  }

  for (int i=0; i<N; i++) {

    if ((Pstat[i]==1) & (Fstat[i]==0)) {
    // P:+ F:N
      nll -= log(pr[i]*(1-maf[i])*(1-pbg[i]));

    } else if ((Pstat[i]==1) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]==1) & (Astat[i]==1)) {
    // P:+ F:Y T:Y H:Y A:Y
      nll -= log(pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*pprick[i]*(1.0-pundertreat[i])*((1.0-
prevert[i])*pcure[i] + (1.0-pcure[i])));

    } else if ((Pstat[i]==1) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]==1) & (Astat[i]==0)) {
    // P:+ F:Y T:Y H:Y A:N
      nll -= log(pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*pprick[i]*pundertreat[i]);

    } else if ((Pstat[i]==1) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]==0) & (Astat[i]==1)) {
    // P:+ F:Y T:Y H:N A:Y
      nll -= log(pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*(1.0-pprick[i])*ppresumptive[i]*((1.0-
prevert[i])*pcure[i] + (1.0-pcure[i])));

    } else if ((Pstat[i]==1) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]==0) & (Astat[i]==0)) {
    // P:+ F:Y T:Y H:N A:N
       nll -= log(pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*(1.0-pprick[i])*(1.0-ppresumptive[i]));

    } else if ((Pstat[i]==1) & (Fstat[i]==1) & (Tstat[i]==0)) {
    // P:+ F:Y T:N
      nll -= log(pr[i]*(maf[i]*(1.0-pbg[i])*(1.0-
ptreatmaf[i])+maf[i]*pbg[i]*(1.0-ptreatboth[i])+(1.0-
maf[i])*pbg[i]*(1.0-ptreat[i])));

    } else if ((Pstat[i]==0) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]==1) & (Astat[i]==1)) {
    // P:- F:Y T:Y H:Y A:Y
      nll -= log((1.0-
pr[i])*pbg[i]*ptreat[i]*pprick[i]*povertreat[i]+pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
```

```
maf[i])*pbg[i]*ptreat[i])*pprick[i]*(1.0-
pundertreat[i])*prevert[i]*pcure[i]);

    } else if ((Pstat[i]==0) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]==1) & (Astat[i]==0)) {
    // P:- F:Y T:Y H:Y A:N
      nll -= log((1.0-pr[i])*pbg[i]*ptreat[i]*(1.0-
povertreat[i])*pprick[i]);

    } else if ((Pstat[i]==0) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]==0) & (Astat[i]==1)) {
    // P:- F:Y T:Y H:N A:Y
      nll -= log((1.0-pr[i])*pbg[i]*ptreat[i]*(1.0-
pprick[i])*ppresumptive[i] + pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*(1.0-
pprick[i])*ppresumptive[i]*prevert[i]*pcure[i]);

    } else if ((Pstat[i]==0) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]==0) & (Astat[i]==0)) {
    // P:- F:Y T:Y H:N A:N
      nll -= log((1.0-pr[i])*pbg[i]*ptreat[i]*(1.0-pprick[i])*(1.0-
ppresumptive[i]));

    } else if ((Pstat[i]==0) & (Fstat[i]==1) & (Tstat[i]==0)) {
    // P:- F:Y T:N
      nll -= log((1.0-pr[i])*pbg[i]*(1.0-ptreat[i]));

    } else if ((Pstat[i]==0) & (Fstat[i]==0)) {
    // P:- F:N
      nll -= log((1.0-pr[i])*(1.0-pbg[i]));

    } else if ((Pstat[i]==1) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]=2) & (Astat[i]=1)) {
      // P:+ F:Y T:Y H:? A:Y
      nll -= log( pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*pprick[i]*(1.0-pundertreat[i])*((1.0-
prevert[i])*pcure[i] + (1.0-pcure[i]))
             + pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*(1.0-pprick[i])*ppresumptive[i]*((1.0-
prevert[i])*pcure[i] + (1.0-pcure[i])));

    } else if ((Pstat[i]==1) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]=2) & (Astat[i]=0)) {
      // P:+ F:Y T:Y H:? A:N
      nll -= log(pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*pprick[i]*pundertreat[i]
        +pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*(1.0-pprick[i])*(1.0-ppresumptive[i]));

    } else if ((Pstat[i]==0) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]=2) & (Astat[i]=1)) {
      // P:- F:Y T:Y H:? A:Y
      nll -= log((1.0-
pr[i])*pbg[i]*ptreat[i]*pprick[i]*povertreat[i]+pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
```

```
maf[i])*pbg[i]*ptreat[i])*pprick[i]*(1.0-
pundertreat[i])*prevert[i]*pcure[i]
        +(1.0-pr[i])*pbg[i]*ptreat[i]*(1.0-pprick[i])*ppresumptive[i]
+ pr[i]*(maf[i]*(1.0-
pbg[i])*ptreatmaf[i]+maf[i]*pbg[i]*ptreatboth[i]+(1.0-
maf[i])*pbg[i]*ptreat[i])*(1.0-
pprick[i])*ppresumptive[i]*prevert[i]*pcure[i]);

    } else if ((Pstat[i]==0) & (Fstat[i]==1) & ((Tstat[i]==1) |
(Tstat[i]==2)) & (Hstat[i]=2) & (Astat[i]=0)) {
      // P:- F:Y T:Y H:? A:N
      nll -= log((1.0-pr[i])*pbg[i]*ptreat[i]*(1.0-
povertreat[i])*pprick[i]
        + (1.0-pr[i])*pbg[i]*ptreat[i]*(1.0-pprick[i])*(1.0-
ppresumptive[i]));
    }

  }

  REPORT(pr);
  REPORT(pbg);
  REPORT(ptreat);
  REPORT(ptreatboth);
  REPORT(ptreatmaf);
  REPORT(povertreat);
  REPORT(ppresumptive);
  REPORT(pprick);
  REPORT(pundertreat);
  REPORT(maf);

  return nll;
}
```

Appendix to Chapter 5 - What proportion of malaria infections receive effective antimalarial treatment?

This appendix includes:

1. Additional Table 1: Household survey data for children under 5 years of age used in analysis.

Additional Table 1. Household survey data for children under 5 years of age used in analysis. P+/- refers to *Plasmodium falciparum* positive/negative diagnosis via RDT at the time of interview, F+/- refers to caregiver recall of fever in the two weeks preceding the interview.

Country	Survey start year	Survey start month	Survey end year	Survey end month	N	P+F+	P+F-	P-F+	P-F-	Sought treatment (public)	Sought treatment (private)
Angola	2006	12	2007	1	1156	73	210	170	703	93	26
Angola	2011	1	2011	6	2914	173	181	903	1657	554	56
Angola	2015	12	2016	1	3012	114	344	368	2186	146	112
Benin	2011	12	2012	1	3119	125	682	240	2072	99	59
Burkina Faso	2010	5	2010	12	5640	1020	3235	317	1068	699	45
Burkina Faso	2014	9	2014	12	5448	1768	1756	616	1308	1385	83
Burundi	2012	12	2013	1	3465	473	226	1024	1742	730	140
Cameroon	2011	1	2011	8	4511	633	747	759	2372	310	467
Cote d'Ivoire	2011	12	2012	1	2638	345	828	359	1106	178	82
Democratic Republic of the Congo	2013	12	2014	1	6996	1029	1401	1288	3278	794	400
Ghana	2014	9	2014	12	2341	210	734	178	1219	204	93
Ghana	2016	10	2016	11	1423	168	308	253	694	165	91
Guinea	2012	6	2012	10	2741	503	671	445	1122	267	116
Kenya	2015	7	2015	8	2845	153	85	982	1625	583	213
Liberia	2008	12	2009	1	3024	523	511	933	1057	548	508
Liberia	2011	9	2011	12	2333	710	468	654	501	564	366
Liberia	2016	9	2016	11	2108	501	519	431	657	480	80
Madagascar	2011	3	2011	5	5212	113	210	748	4141	235	123
Madagascar	2013	4	2013	6	4476	79	199	537	3661	219	94
Madagascar	2016	4	2016	7	3139	34	71	459	2575	224	57
Malawi	2012	3	2012	4	1890	366	352	267	905	283	93
Malawi	2014	5	2014	6	1717	262	238	271	946	279	87
Mali	2012	12	2013	1	4108	231	1547	183	2147	111	57
Mali	2015	9	2015	11	6618	788	1132	1225	3473	688	240
Mozambique	2011	5	2011	12	4323	279	1188	330	2526	355	12
Mozambique	2015	6	2015	9	3709	493	715	580	1921	690	20
Nigeria	2010	10	2010	12	4302	905	1115	724	1558	447	944
Nigeria	2015	10	2015	11	4920	1158	861	1048	1853	429	998
Rwanda	2010	12	2011	1	3619	21	58	595	2945	302	36
Rwanda	2014	12	2015	1	3110	105	125	521	2359	338	48

Additional Table 1 (continued)

Country	Survey start year	Survey start month	Survey end year	Survey end month	N	P+F+	P+F-	P-F+	P-F-	Sought treatment (public)	Sought treatment (private)
Senegal	2008	12	2009	1	3519	176	248	1007	2088	408	110
Senegal	2010	12	2011	1	3278	27	81	695	2475	249	72
Senegal	2012	12	2013	1	5274	82	135	898	4159	391	98
Senegal	2015	2	2015	11	5441	21	37	928	4455	418	90
Tanzania	2007	12	2008	1	5576	240	456	792	4088	584	180
Tanzania	2011	12	2012	1	6379	249	331	1184	4615	685	385
Tanzania	2015	12	2016	1	7366	291	564	1087	5424	209	901
Togo	2013	12	2014	1	2844	309	731	367	1437	219	93
Uganda	2009	12	2010	2	3361	1037	710	570	1044	699	620
Uganda	2014	12	2015	1	4022	642	655	682	2043	541	496
Uganda	2016	6	2016	12	2753	583	291	532	1347	444	299

All surveys can be obtained with permission from the DHS Program: https://dhsprogram.com/