Economic and impact modeling to guide introduction of new tools against malaria

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Executive summary

Background

Tremendous gains have been made over the last decades in scaling-up malaria preventive and curative interventions. Through this effort, new partnerships and funding streams were mobilized to support innovation toward global malaria targets. As a result, there are many promising new tools to detect, treat, and prevent the disease in clinical development and under evaluation for regulatory approval and eventual adoption by programs. The aim of this thesis was to generate evidence on costs and impact of a new vaccine against malaria (RTS,S AS/01) and to inform downstream policy decisions on its implementation in *Plasmodium falciparum* (*Pf*) malaria endemic African countries.

Methods

A micro-costing methodology was proposed to estimate costs of the vaccine implementation and several other interventions currently deployed by malaria programs (e.g. mass drug administration, indoor residual spraying, rapid reporting, and reactive case detection). The costing models were developed around regionally relevant implementation scenarios informed with program operational documents and inputs from local partners. The vaccine implementation costs derived were then linked to an individual-based model of malaria transmission dynamics that included a vaccine model parameterized to data from the phase 3 trials. Taking into account country epidemiological and health systems features, the model predicted the incremental impact and cost-effectiveness of the new vaccine when added on top of routine prevention and treatment for each of the 43 *Pf* endemic countries in Africa. Finally, nationally representative data from the Demographic and Health Surveys (DHS) were analyzed to evaluate the scale-up and the distribution of routine malaria interventions with respect to equity. The analysis sought to identify delivery channels for deployment of the new vaccine that might offer a comparative advantage by expanding access and or by fostering equity in malaria prevention.

Results and significance

The costing studies demonstrated how prospective micro-costing approaches drawing on secondary data could be used to estimate costs of new interventions prior to their implementation in countries. The methodology developed within the thesis yielded highly contextualized and programmatically relevant costs of existing and new interventions to

inform decisions at global, country, or other levels. It demonstrated large differences in cost of RTS,S service delivery between Sub-Saharan African (SSA) countries: ranging from 0.72 USD per dose in Burkina Faso to 2.34 USD in Kenya. The impact and cost-effectiveness evaluation of RTS,S indicated that the vaccine was likely to be cost-effective under conventional GDP-based thresholds in most moderate transmission countries; the estimated cost-effectiveness varied with country vaccination coverage, within country heterogeneity in transmission, and cost of service delivery. The analyses of the DHS data further underscored the importance of monitoring adoption and scale-up of new health technologies for equity. Failure to do so could lead to lasting gradients in access to prevention and undermine effectiveness of interventions missing populations at highest risk where the benefits are likely to be greatest. These considerations are immediately relevant for RTS,S currently being evaluated for deployment through the Expanded Program for Immunization that was shown to have higher coverage than other routine malaria interventions but was also more pro-rich than interventions deployed via campaigns (i.e. long-lasting insecticide treated nets (LLINs), IRS).

In addition to clinical and field trials, models of transmission dynamics are increasingly used to support evaluation of interventions against malaria. Parameterized with field data the models adequately capture long-term effects of interventions and interactions between properties of new interventions, immunity, and features of the setting on clinical outcomes. The methodologies and the workflows developed within this thesis to support the evaluation of RTS,S for global policy recommendation can be readily adapted to other interventions against malaria. As malaria endemic countries diversify with respect to prevalence, health systems, and economic development, modeling combined with economic analysis become increasingly useful tools to inform unique prioritization of interventions within country malaria programs, including for adoption of new tools.

Chapter 1: Introduction

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Malaria

Malaria is a global health priority with over 3.4 billion people in 92 countries at risk with an estimated 219 million cases and about 435,000 deaths reported in 2017 alone (WHO, 2018). It is a mosquito-borne infectious disease caused by the *Plasmodium* parasite. Of the six *Plasmodium* species that cause malaria in humans, *Plasmodium falciparum* (*Pf*) is the deadliest.

The *Pf* parasite life cycle alternates between a female *Anopheles* mosquito and a human host (Figure 1.1). Over 5000 genes and their specialized proteins help the parasite invade and grow in multiple cell types throughout its development (Greenwood et al., 2008). The parasite surface proteins and the metabolic pathways used by the parasite change over its life cycle helping the parasite evade immune clearance and posing a challenge for the development of drugs and vaccines (Florens et al., 2002; Greenwood et al., 2008). Due to high genetic diversity within *Pf* species, people, living in endemic areas, are frequently infected by multiple *Pf* strains which slows acquisition of natural immunity and poses further challenges for the development of effective antimalarial drugs, vaccines, and vector controls strategies (Volkman et al., 2007).

The clinical symptoms of malaria start with the release of merozoites and waste substances from the infected red blood cells (see Figure 1.1, (4)). These by-products of the parasite reproduction cycle activate a myriad of inflammatory immune responses that present as a non-specific febrile illness, with increasing headache, followed by sudden shaking chills, rigors and high fever. As the malarial paroxysm is established, the symptoms recur. In most instances, the infection will eventually resolve to a low-level controlled parasitaemia. In some, the infection can worsen into life-threatening complications of malaria. The pathogenesis of severe malaria most commonly presents as severe anemia, cerebral malaria, and respiratory distress (Cowman et al., 2016).

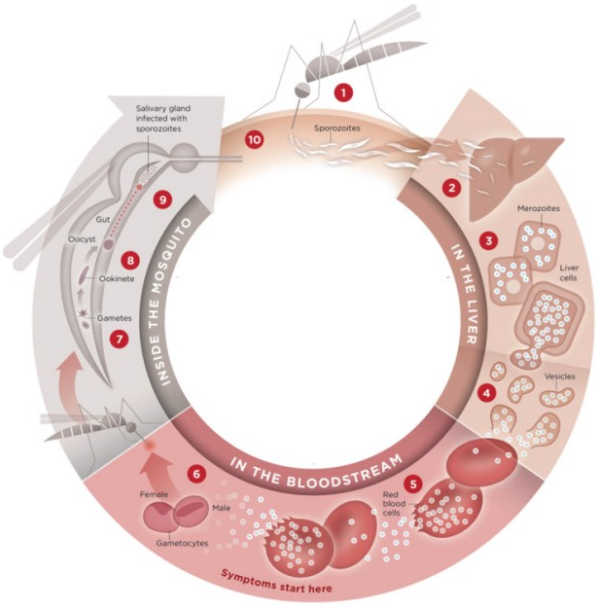

Figure 1.1 The life cycle of *Pf* parasite

Figure 1.1 illustrates the life cycle of the *Pf* parasite. (1-2) The sporozoite stage parasites enter the human blood stream through a bite of an infected female *Anopheles* mosquito and pass quickly into the liver. (3) The parasite multiplies asexually in the liver cells for 7 to 10 days developing into merozoites. (4) Once matured, the merozoites are released into the bloodstream where they invade the red blood cells and replicate for 48-72 hours. When the infected erythrocyte ruptures, released merozoite progeny move on to invade new erythrocytes to continue the cycle. (5) Some of the merozoites will develop into sexual forms of the parasite - gametocyte - that circulate in the blood stream. (6) When a mosquito bites an infected human it ingests the gametocytes. (7) In mosquito mid-gut the gametocytes develop into mature sexually differentiated cells called gametes. (8) The fertilized female gametes develop into ookinetes that burrow through the mosquito's mid-gut wall and form oocysts on the exterior surface. Inside the oocyst, thousands of active sporozoites develop. (9) The oocyst eventually bursts, releasing sporozoites into the body cavity from where the sporozoites move up to mosquito's salivary glands. (10) The cycle of human infection begins again when the mosquito bites another human. Figure adapted from PATH Malaria Vaccine Initiative (MVI, 2019).

Distribution of malaria

The mosquito vector transmitting the *Pf* parasite is predominantly found in warm and humid climates of tropical and subtropical regions. The spatial and temporal distribution of malaria is influenced by environmental factors; temperature, in particular, is critical for the vector's ability to sustain the parasite development. Temperature, rainfall, and humidity are also important for mosquito survival. Within the temperature limits, transmission is determined by frequency of contact between infected mosquitoes and humans, which, in turn, is affected by the vector density, their location, and feeding habits. Prevailing malaria control interventions, health systems, and social and economic factors further modify the distribution and intensity of malaria transmission in endemic countries (Zhao et al., 2016).

The malaria parasite likely ranks above all other in how often it causes infections (White & Watson, 2018); where conditions for transmission are most favorable, a single person can be infected more than 1000 times per year (Smith et al., 2005). In areas where transmission is unstable, all infectious bites will result in clinical disease (Cowman et al., 2016). In stable endemic areas with higher transmission intensity, acquired immunity moderates immune responses to malarial infections such that by early adulthood febrile episodes are few and mild. Clinical malaria incidence is fairly evenly distributed in the first 10 years of life at all transmission levels (Carneiro et al., 2010). Severe outcomes are primarily concentrated in younger children under the age of five; immunosuppressed adults and pregnant women are also at higher risk of severe disease (Carneiro et al., 2010). In low-to-moderate transmission, severe outcomes present as cerebral malaria. At higher transmission severe disease is primarily characterized by severe anemia. The disease burden shifts toward younger ages with increasing transmission intensity.

Globally over 90% of *Pf* malaria morbidity is born by countries in the WHO African region (WHO, 2018). Almost 80% of all malaria deaths in 2017 occurred in 17 countries in the WHO African Region and India, and about 53% of all malaria deaths globally were accounted for by Nigeria, Democratic Republic of the Congo, Burkina Faso, United Republic of Tanzania, Sierra Leone, Niger and India (WHO, 2018).

Malaria control interventions

Malaria control programs deploy multiple interventions targeting different stages of the parasite life cycle. Vector control interventions including in-door residual spraying (IRS), insecticide treated bed nets (ITNs), and larval source management (LSM) reduce mosquito

populations; ITNs additionally prevent onward transmission by providing a physical barrier between the mosquito and the human.

Preventive and curative treatment strategies target the parasite in the human; by clearing parasitemia, these drug-based interventions reduce the infectious reservoir and limit onward transmission. Preventive treatment with antimalarial chemotherapy drugs suppresses parasitemia and provides prophylaxis by halting parasite development in the blood stages. The intermittent preventive treatment in pregnancy (IPTp) and seasonal malaria chemoprevention (SMC) are two of the most common preventive drug interventions recommended in high risk populations (i.e. pregnant women, children and other high-risk groups) and or specific contexts (i.e. seasonal transmission) (WHO, 2018). Additional reactive and mass drug-based strategies (i.e. reactive case detection (RACD), mass drug administration (MDA)) have been recommended for very low transmission settings targeting elimination (WHO, 2017a).

Management of clinical disease in symptomatic cases entails treatment with the first-line antimalarial drug (commonly Artemisinin Combination Therapy (ACT)) administered following a diagnostic confirmation (WHO, 2010). Children and adults diagnosed with severe malaria are treated with intravenous or intramuscular artesunate to manage acute symptoms followed by a complete 3-day regimen of an ACT (WHO, 2012a). Treatment provides an immediate relief and prevents progression of clinical disease to severe states.

Current status of malaria control efforts

Over the last decade malaria programs have been transformed with increased investment, new technologies, economic development, and shifting paradigms in global health. The launch of the universal health coverage campaign in 2008 broadened the scope of malaria control efforts to include all ages and led to programs to shift from targeted distributions to mass campaigns and community delivery supported by routine services (*Secretary-General announces 'Roll Back Malaria Partnership' on World Malaria Day*, 2008). Through the concerted efforts by programs and partners, the *Pf* infection prevalence in endemic Africa halved and the incidence of clinical disease fell by 40% between 2000 and 2015 (Bhatt et al., 2015). Model-based analysis attributed 68% (95% CrI: 62-72) of the decline in the *Pf* prevalence to ITNs, 19% (95% CrI: 15-24) to ACTs, and 13% (95% CrI: 11-16) to IRS (Bhatt et al., 2015). These efforts and its impact on transmission and disease burden, however, have not been distributed equally across the endemic regions nor within countries (Gething

et al., 2016). Increasingly, malaria is confined to the most vulnerable and marginalized populations systematically overlooked by the prevailing health systems.

Throughout the African region, coverage and use of malaria preventive and curative interventions remain below the universal health coverage targets of 80% with large disparities within and between countries (Galactionova, Smith, et al., 2017; WHO, 2018). In 2017 about half of the population at risk of malaria slept under an ITN, use was higher – around 61% – in priority groups, including children under the age of five and pregnant women (WHO, 2018). IRS is implemented in focal areas in select countries reaching globally about 3% of population at risk. Over half of pregnant women received at least one dose of antimalarial chemoprevention drug through an IPTp program. Introduced in 2012, SMC is now implemented in 12 countries in the African region. In these countries, on average 53% of children under the age of five were treated with four monthly rounds of chemotherapy during transmission season. Compliance rates for SMC ranged from 45% in Nigeria to 88% in Burkina Faso, the wide range in coverages highlights difficulties in reaching children with multiple subsequent rounds of treatment. Finally, less than half of fevers in under-fives were treated in 2017. Among those that sought care from a public health provider over 80% were tested for malaria, and, of those treated with any antimalarial, 85% received an ACT (WHO, 2018); high rates in the two service outcomes attest to successes in scale-up diagnostics and ACTs in the region.

While globally there were 20 million fewer cases in 2017 than in 2010, the progress appears to have largely stalled since 2015 with some high-burden countries reporting resurgence in malaria cases in 2017 (WHO, 2018). The effectiveness of the core interventions against malaria is threatened by the insecticide and drug resistance, changing mosquito behavior, and increasing heterogeneity in the distribution of malaria risk. These epidemiological changes require tailored and targeted policy response by programs for which capacity in countries is largely lacking (Cotter et al., 2013; Newby et al., 2016). New tools and new delivery platforms are thus needed to sustain gains against the parasite achieved to date and to accelerate efforts toward elimination (WHO, 2015a, 2018).

Development pipeline for malaria interventions

Over the last decade malaria research and development funding averaged around 600 million USD per year. In 2017 funding reached 689 million USD, reflecting increased investment into operational research to facilitate access following introduction of new health technologies (PATH, 2018). While sustained funding was critical to stimulate innovation, the

product development pipeline for malaria was further energized by the emergence of product development partnerships (PDP). PATH, Medicines for Malaria Venture (MMV), Innovative Vector Control Consortium (IVCC), Innovation to Impact (I2I), Foundation for Innovative New Diagnostics (FIND) and other PDPs work with donors, research institutions, and industry partners to mobilize expertise and direct investment to support development of new technologies against neglected diseases (Alan Brooks, Thomas A. Smith, et al., 2012; Moran, 2005). These efforts are guided by the malaria community that set research priorities (Rabinovich et al., 2017; Roll Back Malaria Partnership, 2015) to support strategic targets outlined by the 2016- 2030 Global Technical Strategy (GTS) for malaria (WHO, 2015a).

In vector control, new classes of long-lasting nets (*i.e.* PBO nets) and longer lasting non-pyrethroid formulations for IRS (*i.e.* Actellic® 300CS) were developed to combat insecticide resistance (IVCC, 2019). New insecticide-based strategies targeting reduction of mosquito population and bite repellency including attractive toxic sugar bates and spatial repellents are tested in the field (Fiorenzano et al., 2017; Maia et al., 2018). Ivermectin – an endectocide drug that was used successfully in elimination of Onchocerciasis - is now considered for malaria prevention (Chaccour et al., 2013; Chaccour et al., 2010). Genetic techniques including gene-drive technology are being explored as a means to reduce vector populations or directly alter vector competency (Hammond & Galizi, 2017).

Over 13 new antimalarial agents currently in clinical development are being evaluated singly or as part of a multi-drug combination therapy (*i.e.* lumefantrine-KAF156) (Ashley & Phyo, 2018). The development pipeline for chemoprevention drugs shows promise but most drugs are still in early clinical stages (MMV, 2019). Single-dose primaquine is now recommended alongside antimalarial treatment in low-transmission countries targeting elimination (WHO, 2015c) and, recently, tafenoquine was approved as a radical cure drug against *Plasmodium vivax* (Tan & Hwang, 2018).

The development pipeline for malaria diagnostics focused on improvements to existing technologies (e.g. RDTs; nucleic acid tests) and innovation toward novel biomarkers (e.g. hemozoin). Multiple highly sensitive RDTs to identify low-density malaria infections and point of care G6DP tests have been recently developed and are currently awaiting regulatory approval. These new tools will help identify and target asymptomatic cases in places where malaria transmission was reduced to very low levels.

Malaria vaccine development has a long history of innovation (Kwiatkowski & Marsh, 1997; Matuschewski, 2006; Walther, 2006). In 2015 the first vaccine against malaria – RTS,S/AS01 – demonstrated protection against *Pf* in an extensive phase 3 evaluation conducted in 11 trial sites in Burkina Faso, Ghana, Kenya, Tanzania, Malawi, Mozambique (Schellenberg, 2018). Other anti-infective vaccine candidates under evaluation, including *Pf*SPZ vaccine and fractional dose RTS,S regimens, may offer improvements over RTS,S/AS01 (Birkett, 2016; Draper et al., 2018; Laurens, 2018). Blood-stage vaccines have demonstrated limited efficacy against clinical disease, and transmission-blocking vaccines are being tested in endemic areas (Birkett, 2016; Draper et al., 2018; Laurens, 2018). The first vaccine targeting pregnancy-associated malaria was developed and is under study in SSA (Birkett, 2016; Draper et al., 2018; Laurens, 2018). There are currently over 20 vaccine constructs being evaluated in clinical trials or in advanced preclinical development (WHO/IVB, 2019).

RTS,S/AS01 the world's first malaria vaccine

RTS,S/AS01 is a recombinant protein-based malaria vaccine targeted at the pre-erythrocytic stages of the *Pf* lifecycle (see Figure 1.1). It acts by inducing humoral and cellular immunity, with high antibody titers, that block the parasite from infecting the liver (White et al., 2013). RTS,S thus prevents infections and not clinical disease directly. Tested in children (5-17 months) and young infants (6-12 weeks), the vaccine showed high initial efficacy but its protection waned quickly. In phase 3 trials the vaccine efficacy against clinical disease in a 4-dose schedule at 32 months of follow-up was estimated at 36.3% (95% CI: 31.8-40.5) and 25.9% (95% CI: 19.9-31.5) in children and infants respectively (The RTSS Clinical Trials Partnership, 2015). Given its efficacy profile, RTS,S is currently evaluated for introduction by programs in endemic countries as an additional tool for preventing clinical disease in children, not a replacement for existing malaria preventive, diagnostic, and treatment measures (IVB, 2014a).

Adoption of new health technologies in LMIC

A growing number of LMIC countries are developing explicit and transparent processes to systematically evaluate new health technologies to be supported by programs; while the policy process differs between countries key considerations weighed in the adoption decision are broadly similar (Alan Brooks, Thomas A. Smith, et al., 2012; IVB, 2005). Multiple stakeholders, including Ministries of Health, disease control programs, Ministries of Finance, other relevant country agencies, the private sector as well as partners and global advisory agencies are engaged in the process. Adoption decisions consider a range of policy

and programmatic issues. The public health importance of the new intervention is established by weighing the disease burden targeted by the new tool against other health priorities. Other immediate considerations include safety and efficacy profile of the new intervention and its likely population impact. Economic considerations such as price, affordability, 'value for money' and cost-effectiveness compared to current and future policy alternatives further contribute to the decision. The new intervention is evaluated in the context of the broader health policy of the country; here the important questions pertain to the distribution of benefits achieved with the intervention, equity, and financial risk protection. Finally, the technical feasibility of deploying the new intervention is assessed against country programmatic capacity and supply constraints. A critical component in the adoption of new technologies is political will. Recognizing the role of politicians underscores the need for engagement and effective communication of evidence to policy audiences to support health innovation from policy decision to implementation and ultimately toward impact.

Modeling and simulation to inform introduction of new technologies

Mathematical models are increasingly applied to study epidemics of infectious diseases and to guide appropriate policy response (Beraud, 2018; Heesterbeek et al., 2015; Luz et al., 2010; Metcalf et al., 2015). Predictions of the likely population impact are an important consideration for selecting candidate technologies for further development and for mobilizing advocacy and resources to support the innovation. Mathematical transmission models describe the dynamics of infection in a population or an individual. The models capture two fundamental properties of the underlying process - stochasticity and non-linearity. The prior characterizes a biological phenomenon. The latter arises from the interaction between factors that drive transmission and the impact it has on the distribution of characteristics of hosts and vectors at various temporal and spatial scales. Parameterized to trial data models allow investigation of the potential impact of uncertainties about the mechanism of protection enabled by the new intervention, heterogeneity of its effect in the population, its future uptake, and or economic outcomes. Models make it possible to disentangle the individual contribution and synergistic effects of interventions that are deployed together. Capturing these effects is particularly important for evaluation of new interventions against malaria that are added on top of multiple preventive and curative interventions targeting different stages of the parasite life cycle already deployed by programs.

Economic evaluation to inform introduction of new technologies

Facing resource constraints, policy makers rely on economic evaluation to assess 'value for money' of new health technologies and to compare allocations to these new interventions

against alternative uses of scarce resources (Drummond et al., 2005). The most common type of economic evaluation is cost-effectiveness analysis (CEA). It is summarized in a ratio of the change in the costs of the program when the new intervention is added over the change in its effectiveness expressed in natural units (i.e. clinical episodes averted, deaths averted, or disability adjusted life years (DALYs) averted) compared to the current standard of care (SOC) (Drummond et al., 2005). The estimated cost-effectiveness of a new intervention is compared against either the cost-effectiveness of a set of existing interventions or a fixed price threshold representing the social willingness-to-pay (WTP) for an additional unit of health. Where WTP for health is not established the recommended threshold for evaluation of new technologies is defined with respect to multiples of country gross domestic product (GDP) (Evans et al., 2005; WHO, 2003). An incremental cost-effectiveness ratio (ICER) of up to three times the GDP per capita is considered a worthwhile investment (Evans et al., 2005; WHO, 2003).

WHO's role in supporting adoption of new technologies in LMIC

The WHO plays an important role in supporting adoption of new health technologies in low- and middle-income countries (LMIC). Under its primary mandate, the organization provides guidance to its Member States on health policy, it sets quality standards that qualify products for purchases by partner organizations including the UNICEF, UN agencies, Gavi, etc., and develops normative guidelines on the evaluation and implementation of new technologies (IVB, 2005; WHO, 2017b). The WHO's vision extends along the product development pathway; the organization seeks to identify and steer development toward products that target key global health priorities (WHO, 2015f, 2017b).

The WHO's recommendation on new health technologies is summarized in a position paper, issued following licensure by a functional regulatory agency (IVB, 2017). For malaria vaccines, a positive regulatory assessment by the European Medicines Agency (EMA) Article 58 procedure may be accepted by the WHO in-lieu of licensure to begin the review process. The recommendation is formed through a formal evidence review process conducted under the oversight of independent advisory groups (the Immunization Vaccines and Biologicals Strategic Advisory Group of Experts (SAGE) and the Malaria Global Program Strategic Advisory Technical Group (STAG)) with support from technical and narrowly-focused global advisory committees (WHO, 2017b). In addition to the benefit-risk evaluation performed by regulators, the position paper also addresses the feasibility of implementation, epidemiological factors that influence performance of the candidate technology, its value in the context of other control measures, and the likely cost-

effectiveness of the intervention in different settings. The WHO continues to monitor new vaccines post-licensure and update the recommendation with data on safety, effectiveness, and impact from phase 4 studies.
Following the global recommendation, regional technical advisory groups help identify specific regional challenges and define priorities. Taking into consideration the local context, national immunization technical advisory groups provide guidance to national policy makers. The recommendations aim to assist Member States with the development of optimal immunization schedules for diseases that have a global public health impact.

Modeling vaccine preventable diseases to inform WHO recommendation
Modeling vaccine preventable diseases has a long history of engaging with policy-makers (Beatty et al., 2012; Heesterbeek et al., 2015; Luz et al., 2010; Metcalf et al., 2015). The vaccine community developed a number of guidelines on good modeling practice to ensure quality evidence and to strengthen the role of these methodologies for policy decisions (Ultsch et al., 2016; Walker et al., 2010). SAGE framework for the evaluation of malaria vaccines outlined key features of mathematical models necessary to support WHO policy recommendation. The framework prioritized models that captured transmission dynamics on a large range of interacting scales and predicted effects of feedback within the system, including changes caused by the intervention (Heesterbeek et al., 2015). In support of the policy recommendation on the RTS,S malaria vaccine the WHO outlined questions and outcomes to be informed by models and put forward guidelines for the methodology to generate these (Moorthy et al., 2012).

Objectives and outline
The goal of this thesis is to develop methods and produce evidence to inform policy decisions on the introduction of the RTS,S malaria vaccine in *Pf* endemic African countries. This goal is supported through the following objectives:

- Develop a methodology to prospectively cost new interventions under programmatic delivery using secondary data sources
- Produce estimates of incremental cost of RTS,S introduction in *Pf* endemic African countries
- Estimate the incremental cost-effectiveness of RTS,S introduction in *Pf* endemic African countries
- Evaluate the economic gradients in the scale-up and in the distribution of malaria control interventions in *Pf* endemic African countries

Chapter 2 of the thesis presents a methodology to generate highly contextualized and program relevant costs of new interventions by triangulating multiple data sources around an explicit operational model. The methodology is applied in Chapter 3 to estimate the cost of RTS,S implementation in several *Pf* endemic countries with varying the Expanded Program for Immunization (EPI) structure, health systems capacity, and levels of economic development.

In Chapter 4 a validated malaria transmission model and new methodologies are applied to generate country-specific estimates of the vaccine impact taking into account the local Entomological Inoculation Rate (EIR) and its distribution, case management, and vaccination coverage. These impact estimates are combined with the economic outputs from Chapter 3 to predict the incremental cost-effectiveness of RTS,S introduction in 43 *Pf* endemic countries in SSA.

Chapter 5 presents descriptive analyses qualifying the scale-up and the distribution of interventions against malaria with respect to equity in SSA using the Demographic and Health Surveys (DHS) (ICF). The study supports decision-making on the introduction of new health technologies by benchmarking the relative performance of malaria interventions and the respective delivery channels in the region. It suggests pathways through which distributional failures limit effectiveness of new interventions and exacerbate health disparities.

In the final chapter, the studies that formed this thesis are discussed in the broader context of the malaria modeling literature. The chapter synthesizes findings from the thesis and the literature for the evaluation of the on-going pilot implementation of the vaccine and subsequent decisions by countries and partners should the vaccine be recommended for wide use in 2020. The discussion emphasizes the relevance of frameworks developed within this thesis for future recommendations on other new interventions against malaria. It concludes with suggestions on how the role of modeling could be strengthened toward better decision-making in global health.

Chapter 2: Costing malaria interventions from pilots to elimination programs

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Abstract

Background
Malaria programs in countries with low transmission levels require evidence to optimize deployment of current and new tools to reach elimination with limited resources. Recent pilots of elimination strategies in Ethiopia, Senegal, and Zambia produced evidence of their epidemiological impacts and costs. There is a need to generalize these findings to different epidemiological and health systems contexts.

Methods
Drawing on experience of implementing partners, operational documents and costing studies from these pilots, reference scenarios were defined for rapid reporting (RR), reactive case detection (RACD), mass drug administration (MDA), and in-door residual spraying (IRS). These generalized interventions from their trial implementation to one typical of programmatic delivery. In doing so, resource use due to interventions was isolated from research activities and was related to the pilot setting. Costing models developed around this reference implementation, standardized the scope of resources costed, the valuation of resource use, and the setting in which interventions were evaluated. Sensitivity analyses were used to inform generalizability of the estimates and model assumptions.

Results
Populated with local prices and resource use from the pilots, the models yielded an average annual economic cost per capita of 0.18 USD for RR, 0.75 USD for RACD, 4.28 USD for MDA (two rounds), and 1.79 USD for IRS (one round, 50% households). Intervention design and resource use at service delivery were key drivers of variation in costs of RR, MDA, and RACD. Scale was the most important parameter for IRS. Overall price level was a minor contributor, except for MDA where drugs accounted for 70% of the cost. The analyses showed that at implementation scales comparable to health facility catchment area, systematic correlations between model inputs characterizing implementation and setting produce large gradients in costs.

Conclusions
Prospective costing models are powerful tools to explore resource and cost implications of policy alternatives. By formalizing translation of operational data into an estimate of intervention cost, these models provide the methodological infrastructure to strengthen capacity gap for economic evaluation in endemic countries. The value of this approach for decision-making is enhanced when primary cost data collection is designed to enable analysis of the efficiency of operational inputs in relation to features of the trial or the setting, thus facilitating transferability.

Keywords
Malaria, elimination, costs, rapid reporting, IRS, RACD, MDA, comparative cost-effectiveness

Background

The 2018-2030 Global Technical Strategy for malaria declared elimination the ultimate goal for all malaria-endemic countries and outlined a tiered strategy for programs to transition from control to elimination (WHO, 2018). An increasing number of countries are moving toward this goal each year (WHO, 2018). Botswana, Eswatini, Mozambique, Namibia, South Africa, Zambia, and Zimbabwe are leading the way for the African continent (Chizema-Kawesha et al., 2010; Cotter et al., 2013; Kunene et al., 2011; Moonasar et al., 2012; Raman et al., 2016). For countries where transmission has been reduced to very low levels, progress toward elimination relies on strong surveillance systems to identify and appropriately target areas where transmission is sustained (WHO, 2017a). In addition to universal coverage with vector control and access to preventive and curative interventions, active and reactive responses to clear infection and focal vector control are recommended to find asymptomatic cases and to eliminate the infectious reservoir (WHO, 2017a).

Between 2013 and 2015 the Malaria Control and Elimination Partnership in Africa at PATH (MACEPA), together with country programs, conducted field trials in Zambia (Bridges et al., 2017; Eisele et al., 2016; Eisele et al., 2015; Larsen, Bennett, et al., 2015), Senegal (Littrell et al., 2013), and Ethiopia to evaluate the individual and synergistic effects of malaria interventions on transmission interruption. Within these trials, scale-up and optimization of routine malaria preventive interventions were evaluated alongside strategies for malaria surveillance, and both population-wide and focal approaches to clearing parasites from people. MACEPA conducted supervision, monitoring, training, and evaluation activities while the programs carried out implementation of interventions in communities (i.e. via Community Health Workers (CHWs) or other program staff). The epidemiological, operational, and economic studies carried out along the MACEPA elimination pilots produced important evidence on the effectiveness of the recommended strategies in these settings (Larsen, Chisha, et al., 2015; Larson et al., 2016; Searle et al., 2016; Silumbe et al., 2015). Programs now require tools to transfer and relate findings from these pilots to the specific contexts and the capacity constraints in which they operate in order to formulate adequate strategies toward elimination targets.

Evidence on resource needs and costs informs feasibility of implementation, affordability of the intervention by programs, appropriate delivery modality, and, when combined with data

on effectiveness, allows for comparisons between policy alternatives. However, the relevance of cost estimates obtained from research trials to policy decision-making, is limited by the scalability of piloted interventions, the extent to which economies of scale and scope impact these costs, resource and technical support provided by partners, incentives for trial participation to operational staff and population, and representativeness of the populations targeted (O'Sullivan et al., 2005). This paper shows how these limitations of field data can be overcome with prospective micro-costing models parameterized with disaggregated data on resource use and prices from trials and secondary sources. Increasing availability of economic data from Low and Middle-Income Countries (LMICs) collated in global costing databases (Vassall et al., 2016) and reporting supporting financial requests to partners (GF, 2019) make this approach attractive for evaluation of new health interventions and deployment strategies.

To provide further evidence to inform strategic decisions on optimal intervention mixes for malaria elimination, costing models were developed for four key interventions recommended for malaria eliminating countries: malaria rapid reporting (RR), reactive case detection (RACD), mass administration (MDA), and indoor residual spraying (IRS). The paper details application of these models to derive locally and programmatically relevant intervention costs for a reference setting and illustrates how these models could be further extended to cost alternative implementations of interventions in any health system or epidemiological setting, at any desired scale or price level. Sensitivity analyses further inform transferability of the cost estimates derived and guide future cost data collection efforts toward strengthening policy relevance of economic evidence on malaria elimination.

Methods

The immediate use case for the models presented here is cost-effectiveness or other optimization framework supporting prioritization of interventions within malaria elimination packages. Thus, in developing the methodology, the focus has been on ensuring that consistent comparisons could be made between interventions, that the models could be adequately tailored to different settings, and that the costs derived reflected programmatic delivery of interventions in the African region. Experience of in-country partners in delivering the interventions within the elimination pilots and their subsequent scale-up in the region were first detailed in a reference implementation scenario and then formalized in a costing model defined around that reference scenario.

Interventions

Four of the MACEPA piloted interventions were evaluated in this study. Malaria RR is defined here as a surveillance intervention that entails weekly reporting of malaria indicators by health facility staff using the District Health Information System 2 (DHIS 2) (Health Information Systems Programme, 2019) and a mobile client. RACD refers to reactive focal testing and treatment by CHWs of malaria RDT-positives in the home of an index case (a clinical malaria case identified in either community or health facility) and those in the neighboring households. MDA describes a strategy for administering anti-malarial drugs by CHWs without prior testing. IRS entails insecticidal spraying of surfaces in inhabited houses; deployment of IRS for elimination is conducted by district teams in a subset of houses targeted by malaria incidence.

Reference implementation scenarios

The starting point in developing intervention implementation scenarios was global normative guidance. The World Health Organization (WHO) and other partner guidelines (Appendix A, Table A1) were consulted to define intervention implementation stages and to develop a list of operational activities that take place at each stage (Appendix A, Table A2). The following activities were costed: (1) “planning” – micro-planning and meetings at central and district levels; (2) “community sensitization” – meetings with community leaders and local authorities and district and community levels, dissemination of information materials, radio and public announcements; (3) “training” – training of supervisors, trainers, and CHWs or facility staff at central and district levels; (4) “procurement, storage, and distribution” – procurement of drugs and supplies including where applicable mobile phones and bikes and expenses related to their storage and distribution to facilities; (5) “program management and supervision” – program support at central, regional, district and facility levels, and supervision by appropriate levels of service provision; (6) “implementation” – activities conducted at point of service delivery including reporting; (7) “other” – all other intervention specific activities (i.e. environmental compliance and waste management for IRS). Detailed resource lists were developed for each operational activity specifying resource requirements by programmatic level (i.e. central, regional). These were derived through a process similar to micro-planning, conducted by programs or trial teams in the planning stages of the project. Unlike programs, this study drew on guidelines, literature, operational documents from the pilots and inputs from MACEPA staff to acquire an understanding of the context, capacity, service delivery and other programmatic aspects that impact resource requirements for the four interventions.

By comparing operational details across the pilot sites, it was possible to isolate aspects of intervention design that reflected the trial research objectives or were specific to the setting, and features that were common and generalizable to broader geographies outside the pilots. To allow consistent comparisons of costs between interventions, the scope of resources evaluated was standardized across the four interventions and the resource use assumptions were explicitly related to the reference setting. Additionally, assumptions on intensity of activities implemented were aligned both across interventions and over time (i.e. greater planning and coordination needs for IRS compared to RR).

Reference setting

The reference setting was described by a geography summarized with the distance between programmatic levels, scale of implementation that translates to a population target (1 region, 3 districts, 6000 people per health facility catchment area (HFCA)), and program infrastructure captured with number of health facilities (33 per 10000 population or an average of 20 HFCAs per district), number of community health workers (1 CHW per 750 people or 8 CHW per HFCA), and access to care (80% (refers to access to any formal health care provider including CHW)). The Plasmodium falciparum parasite all-age prevalence (*Pf*PR) was fixed at 4% and RDT- positivity rate around an index case at 18%. These reference values approximate annual averages taken from MACEPA trials conducted in Zambia (Larson et al., 2016).

Framing of the evaluation

The framing of the costing study formalized in the costing models presented here, reflects the health system's perspective. The models capture resource use incremental to existing program infrastructure. Assumptions on capacity to absorb the new intervention were informed by the implementation partner and are reflected in the operational inputs made explicit in the reference scenario. The existing workforce was assumed to be sufficient to deploy the additional interventions at reference levels, capacity constraints then were reflected by how that capacity translated to programmatic outputs (i.e. number of supervision days per campaign round, number of people treated per day by CHW). The models produce both financial and economic costs. The financial costs illustrate the incremental investment needed to deliver the intervention. The economic costs also capture the opportunity cost of using resources, including the health system infrastructure, that were paid through other sources (including wages of program staff, program vehicles) or donated (i.e. time of CHWs) (Drummond et al., 2005). Resource use and costs were traced across the programmatic levels and, comprehensively, throughout the intervention implementation stages. Costs were

evaluated over five years matching the strategic planning horizon of malaria programs. All nominal values were expressed in 2014 USD to allow comparisons with the MACEPA trials.

Costing models

The micro-costing methodology (Gold et al., 1996) is illustrated in Figure 2.1. Capitalizing on the high resolution of data in the costing studies and operational documents from the trial, cost functions were defined at a low level of aggregation. Within each activity, costs were evaluated by resource category with economic valuation formalized in an equation. These represent largely linear combinations of prices and quantities summed over the corresponding staff or resource units, programmatic levels, and implementation stages. Capital items were annualized, and, also discounted, when reporting economic costs. The start-up costs related to planning, sensitization, and training activities supporting introduction of new interventions were treated as capital items, with utility life-years (ULY) top-coded to the number of years the intervention is implemented. Shared resources and overheads were valued based on use (i.e. number of days). Models were implemented and evaluated in Stata 14 SE (StataCorp, 2015).

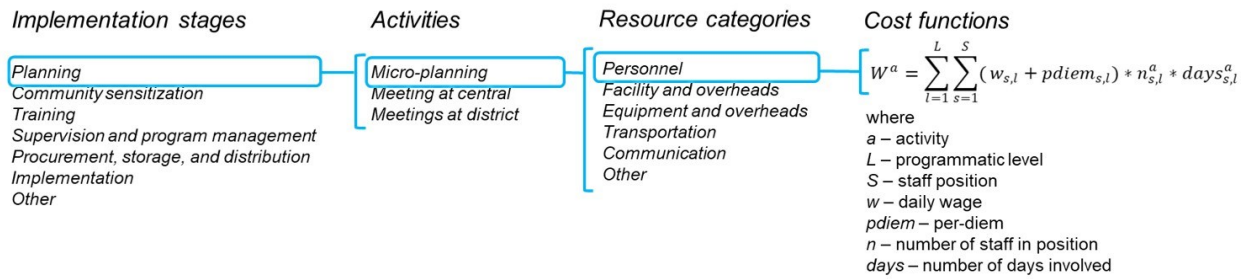


Figure 2.1 Schematic illustration of components of the micro-costing methodology

The figure illustrates the micro-costing approach by zooming in on the planning stage of implementation. For all interventions modelled here operational activities supporting planning covered micro-planning, meetings at central level, and meetings at district level. The chart details resource categories into which resource line items were grouped for purposes of evaluation and reporting; consistent resource groupings were adopted for all operational activities. The last column of the chart shows how micro-inputs (i.e. daily wages of program staff, number staff days, number of staff, etc.) are combined within a cost-function to estimate cost of personnel supporting micro-planning. Similar cost-functions were defined for all other relevant resource categories within each operational activity along the intervention implementation cycle.

For each intervention, the costing model formalized how resource use and service outputs (i.e. number of households sprayed per spray team per day) related to the setting. These relationships were quantified from data from the pilots and drew on expert opinion of the implementation partner to fill in the gaps. Capacity constraints at higher programmatic levels were reflected in the number of days dedicated to sensitization, training, and supervision activities. In RR model, setting and health infrastructure were incorporated with parameters describing the number of health facilities per population target. For RACD the number of index cases followed-up was modelled as a function of *Pf*PR, health seeking for malaria, number of health facilities, number of CHWs and the capacity of CHWs to follow-up cases. For MDA these features determined duration of the campaign; it was assumed that CHWs could be recruited from nearby villages to support drug distribution as needed. For IRS the number of spray operators was modelled as a function of population size of the targeted area, target coverage (requiring information on the number of people per structure), and the number of structures that could be sprayed per operator per day.

The costing models were populated with quantities of resources that varied by intervention, and prices that were fixed within the setting. The prior were sourced directly from the reference implementation scenario, while the latter were obtained from the trials, published studies, President's Malaria Initiative (PMI) country reports, and global cost depositories including the WHO-CHOICE and the country Multi-Year Plans for Immunization (cMYP). Data sources by intervention are reported in Appendix A, Table A1.

Sensitivity analysis

Several strategies were pursued to assess generalizability of the cost estimates and the underlying cost model assumptions. First, a value range was defined for each model input and 500 sets of vectors of model parameters were simultaneously drawn from within that range, assuming uniform distribution, using Latin Hypercube sampling. These sets were re-sampled 10,000 times. Parameter ranges were sourced from the trial and the literature for all inputs characterizing the intervention, while a generic range between 50% and 200% of reference parameter value was used to introduce variability in inputs describing program overheads. Inputs of the costing model that were plausibly correlated were grouped together. One variable – "a multiplier" - was sampled for the group; all inputs were then adjusted by the same sampled value within the draw. Intervention costs were re-estimated with these sampled values.

Using the simulated data, the relative contribution of model inputs was evaluated by regressing the unit cost on inputs of the costing model and calculating the ratio of the variation explained (sum of squares) by the respective parameter as a fraction of total variation explained by the model. Since different parameterizations of costing models are possible, inputs of the costing model were grouped into five categories and the joint contribution of all inputs within the category was reported. Specifically, inputs that describe operational details of the implementation process were grouped under “intervention” category (1); inputs that characterize the health systems, parasite prevalence, and geography ¬under “setting” (2); number of regions, districts, and HFCA population size under “scale” (3); prices of commodities, wages of program staff under “price” (4), and inputs related to the economic valuation of resource use (i.e. discount rate and ULY assumptions) under “methods” (5). The list of model inputs by category is reported in Appendix A, Table A2.

To highlight the contribution of individual parameters one-way sensitivity analyses were also implemented. Here, unit cost estimates were derived by setting one parameter at a time to the lowest and highest values of the corresponding range while keeping other inputs at reference values.

Finally, the cost implications of systematic correlations between the context and implementation of interventions at varying scales were explored using scenario analyses. The context was categorized by geographic accessibility and health system’s capacity. Scenarios modelled then hypothesized how implementation of interventions and the operational constraints due to features of the setting might change from the reference. Cost trajectories were obtained by smoothing point estimates generated by recalculating costs over different scales of implementation (i.e. allowing the number of regions, districts, and the size of HFCAs to vary) with lowess regression (Cleveland, 1981).

Results

Reference implementation scenarios

Table 2.1 presents key operational assumptions highlighting resource use at service delivery where implementation varies most between settings. Full implementation scenarios are shared in Appendix A, File A1.

Table 2.1 Reference implementation scenarios by intervention

	Rapid Reporting	Reactive Case Detection	Mass Drug Administration	Indoor Residual Spraying
Definition	Localized rapid reporting system of malaria diagnosed and treated cases and related commodities	Reactive focal testing and treatment of individuals living near clinical cases diagnosed and treated passively at health facilities or in community	Mass drug administration in a defined area without previous testing	Spraying interior surfaces of dwellings in a defined area with a residual insecticide
Scale	1 region, 3 districts, 20 HFCA each, 6000 population per HFCA	1 region, 3 districts, 20 HFCA each, 6000 population per HFCA	1 region, 3 districts, 20 HFCA each, 6000 population per HFCA	1 region, 3 districts, 50% of district HFCA targeted, 6000 population per HFCA
Level	HFCA	HFCA	HFCA	District
Staff	1 nurse/ HF	8 CHW/ HFCA	8 CHW/ HFCA	42 operators/ district
Operational details	- 2 days of training - 1 nurse 0.5 days/ month collating entries and reporting - Mobile phone and data - Supervised by district and regional staff - DHIS2 malaria module, 20% of server, server maintenance fees, and IT support allocated to malaria reporting[1]	- 4 days of training - 1 CHW 1 day to follow-up an index case - 5 person radius around an index case - Bicycle -1 CHW per HFCA receives a mobile phone and data - Supervised by HF nurses, district and regional staff - Existing DHIS2, 6% of DHIS2 running costs allocated to reporting for RACD[2]	- 4 days of training - 1 adherence officer per 2 CHWs - 75 persons reached per pair per day - Supervised by HF nurses, district, regional and central staff - NMCP vehicles and drivers used for distribution and supervision - Length of campaign is 10 days[3] - 2 rounds per year	- 7 days of training - 6 spray operators, 1 team leader per pair, 8 pairs per district - 60 structures sprayed per day by team - 5 people per structure - Supervised by HF nurses, district, regional and central staff - NMCP vehicles and drivers used for distribution and supervision - Length of campaign is 29 days[4] - 1 round per year
Commodities		RDT, ALU	DHAP	*Actellic* 300 SC
Coverage	100%	100% of index cases; up to 5 index cases per CHW per week	85%	90% of targeted areas
Time valuation	- Wages allocated based on time supporting rapid reporting - Reporting nurse receives a monthly incentive for complete reporting	- Economic value of time 0.36 USD/ day - 1 CHW per HFCA collates and reports cases in the community and receive a monthly incentive for complete reporting	- Economic value of time 0.36 USD/ day - CHWs receive daily food allowances and an incentive award at the end of each MDA round	- Spray operators receive wages, per-diems, and daily food allowances - 20% receive a travel and lodging allowance to cover hard to reach areas

[1] DHIS2 infrastructure was allocated to RR assuming 20% of health facility visits are malaria-related; [2] DHIS2 running costs were allocated to RACD as a fraction of RR costs calculated as a ratio of the number of people tested in the community during RACD activities to the total number of people tested at health facilities in Zambia trial (MACEPA reporting); [3] Length of MDA campaign was fixed at 10 days aligned with WHO recommendation (WHO, 2017c); [4] Length of IRS campaign was calculated based on the recommended number of spray operators, size of the district, and number of strictures sprayed per operator per day (WHO, 2015b). HF= Health Facility; HFCA= Health Facility Catchment Area; CHW= Community Health Worker; RDT= Rapid Diagnostic Test; ALU= Artemether- Lumefantrine.

Malaria RR, as modelled here, relies on nurses to collate and report monthly information on diagnosis and treatment of malaria cases at health facilities and community. It was assumed that introduction of RR will not change reporting by CHWs that already routinely document on paper information on treatment and diagnosis in the community. To the extent that the introduction of RR in a given setting alters the workload of the community cadre (i.e. with training) or requires other additional resources (i.e. mobile phones), the corresponding inputs of the costing model would need to be updated to adequately capture these additional costs. Another important assumption is a pre-existing DHIS2 system to which a malaria module is added to support RR. Costs related to server purchase and maintenance overheads account for a significant fraction of the intervention costs, thus assumptions on how these are shared between the program and reporting for other diseases will have important implications for costs. Here, server costs and other shared resources were allocated to RR assuming that about 20% of health facility visits in low-endemicity settings are malaria related.

Reference RACD implementation relies on an existing network of CHWs to follow up malaria cases. RACD-related reporting is assumed to be integrated within the existing surveillance infrastructure. The costing model accommodates the effectiveness cascade of RACD by allowing parameters related to access to treatment following an infection, fraction of index cases followed up, proportion of residents in eligible households present for testing and treatment during an RACD visit, as well as *Pf*PR to be varied (Searle et al., 2016). At reference *Pf*PR and health-seeking rates, an average of four cases per week per HFCA would be counted in the model. This aligns well with the capacity for follow-up by CHWs suggested by the malaria elimination guidelines and the experience of the Zambia program (5-10 cases per month can be followed up per CHW) (PMI, 2018; WHO, 2017a).

For MDA trade-offs between the number of CHWs mobilized for the campaign, the number of people that can be reached by a CHW per day, and the length of the campaign will determine the cost of the program. Following normative guidance, it was assumed that drugs were distributed within 10 days in a given target area and that CHWs from neighboring villages were recruited where capacity was insufficient to cover the area in 10 days. CHWs were assumed to receive a daily food allowance and an incentive at the end of each campaign round. This is similar to how MDA was programmatically implemented for control of soil-transmitted helminths infections and lymphatic filariasis (Fitzpatrick et al., 2016; Goldman et al., 2007).

Unlike MDA that relies on community resources, IRS is a district level intervention. Spray teams move within the district from one targeted area to the next with the number of teams and the number of spray operators assigned based on the scale of implementation. Length of an IRS campaign is then determined by the number of spray operators recruited, the number of houses sprayed per day, and the population size. To reflect targeting of IRS at areas prone to outbreaks or identified as transmission sources the reference scenario assumed deployment in 50% of HFCAs. As transmission is further reduced across eliminating countries implementation of IRS might be shifted further down to HFCA level (Johns et al., 2016). This would change the level and the distribution of costs and could be further explored with the costing model.

Costing models

A summary of programmatic activities and key resource line items costed are reported in Appendix A, Table A3, and fully in Appendix A, File A1. Operational details of the reference scenario, described above, along with other setting and economic inputs were collated into an Excel dataset (Appendix A, File A2). The costing models coded in Stata (Appendix A, File A3) source this dataset to produce estimates of intervention costs under the reference implementation. To facilitate adoption of these cost models in optimization studies, these were further summarized in R functions that can be linked directly with epidemiological models (Appendix A, Tables A4-A7). The functions yield an estimate of total intervention cost corresponding to the reference implementation. The analysts can either work with the full costing model or update cost components within the R function (a narrow menu of inputs) to propagate uncertainty in costs.

Intervention costs

Under the reference implementation average annual cost across the four interventions ranged from about 0.12 USD for RR to 4.63 USD for two annual rounds of MDA per capita (Table 2.2, cost summaries per service output are reported in Appendix A, Table A8). The difference between financial and economic cost highlights the contribution of health infrastructure including community resources. For RACD and MDA, where the operational model, consistent with programmatic experience from the region, assumed CHWs were incentivized for delivering these interventions, but were not directly compensated with either a per-diem or a wage, financial payments fail to adequately reflect the economic value of CHW time. Costs are higher in the first year reflecting expenditures related to initial start-up activities (i.e. micro-planning, sensitization, and training (Appendix A, Tables A9-A10)). The

Table 2.2 Average annual financial and economic cost per capita by intervention: reference implementation (USD, 2014)

Number of years	Financial cost				Economic cost			
Intervention	RR	RACD	MDA	IRS*	RR	RACD	MDA	IRS*
1	0.19	1.07	4.00	1.71	0.27	1.27	4.63	2.06
5	0.15	0.65	3.72	1.57	0.22	0.75	4.28	1.86

Intervention costs per capita (total population) reflect reference implementation presented in Table 1 above and Appendix A, File A1. Estimates in the first-row show costs incurred in the first year (*i.e.* the year the intervention is first introduced), assuming the intervention is only to be deployed for one year. The second row gives the average annual economic cost assuming each intervention is implemented annually for five years. * In the reference implementation 50% of structures/ population targeted by IRS (denominator for the unit cost is total population). Equivalent cost summaries per output are reported in Appendix A, Table A7. Costs by implementation stage and cost structure are reported in Appendix A, Tables A9-A10.

difference between the average annual cost and the first-year cost gives some indication of the penalty for switching between strategies.

Intervention costs per capita (total population) reflect reference implementation presented in Table 2.1 and Appendix A, File A1. Estimates in the first-row show costs incurred in the first year (i.e. the year the intervention is first introduced), assuming the intervention is only to be deployed for one year. The second row gives the average annual economic cost assuming each intervention is implemented annually for five years. Note that in the reference implementation only 50% of structures/ population targeted by IRS (denominator for the unit cost is total population). Equivalent cost summaries per output are reported in Appendix A, Table A7. Costs by implementation stage and cost structure are reported in Appendix A, Tables A9-A10.

The models can also be applied to explore costs of intervention packages. Introducing the four interventions at reference implementation will add up to 8.1 USD per capita in the first year, nearly four times the current spending on malaria in high burden countries, and two to four times above the current malaria spending in E8 countries (WHO, 2018). IRS and MDA - the two “accelerator” interventions – make the largest contribution to total cost of the strategy accounting for 25% and 57% of total expenditure in the first year. Scaling down MDA in subsequent years to half of HFCAs will lower cost of the package to 5.9 USD per capita, further reducing IRS to 25% of HFCA areas will decrease cost of the strategy to 5 USD. This translates to savings of over a million USD compared to the reference package.

Models can help quantify possible cost savings from co-introduction or co-deployment of interventions. For instance, simultaneous introduction of RACD and MDA might be possible, since both rely on the CHW delivery platform. Suppose that when RACD and MDA are co-deployed planning, sensitization, and training activities could be shared thus lowering cost of the reference strategy to 7.5 USD per capita in the first year.

Sensitivity analysis

Moving away from the reference implementation, variation in costs of the four interventions was assessed by sampling model inputs; thus, relaxing all parameter assumptions, and evaluating the resulting cost distributions (Appendix A, Figures A1-A2). Reference costs were found to be on the lower side for all four interventions: the distribution mode of average

annual economic cost per capita over five years was estimated at 0.21, 1.17, 6.42, and 2.79 USD for RR, RACD, MDA, and IRS, respectively (compare these to Table 2.2 estimates). Comparing reference input values against the parameter range characterizes the reference implementation modelled as a well-resourced setting with high operational efficiency (Figure 3). Across the four interventions, assumptions on key operational inputs and health systems capacity are at the higher end of the range, corresponding to a lower unit cost.

In Figure 2.2 and Appendix A, Figure A3, these sampled cost distributions were decomposed into relative contributions of model inputs aggregated into five core categories. One-way sensitivity analyses highlight inputs within each parameter category that have the highest impact on cost per capita (Figure 2.3; Appendix A, Figure A4). The relative importance of individual parameters depends on the selected range over which these were varied and the model structure. Parameter ranges chosen were loosely informed by the literature. These tabulations are presented here as a further validation of the model: given a plausible range of input values, model outputs are consistent with current understandings of cost drivers of these programs.

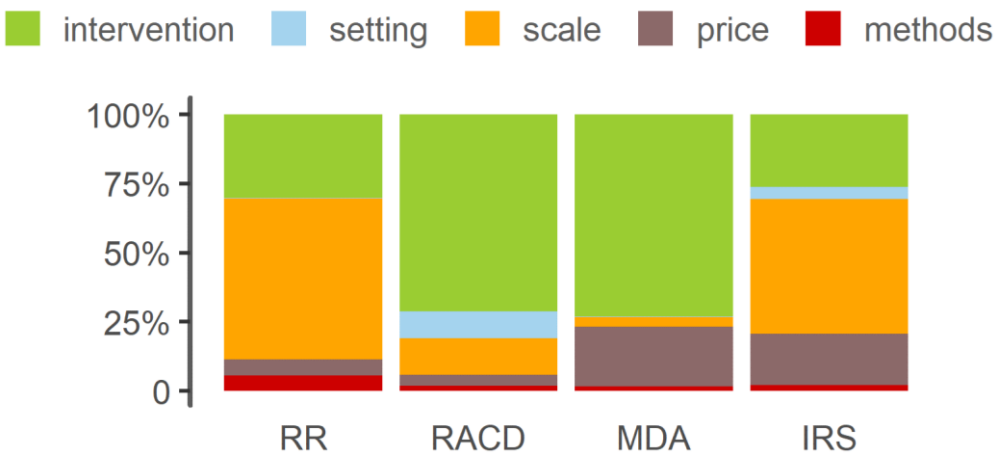


Figure 2.2 Bootstrap analysis of average annual economic cost per capita: unit cost (USD, 2014) and relative contribution of inputs by category

Colour segments of the stacked bars above correspond to the relative joint contribution of model inputs grouped into either of the five categories, describing intervention (green), setting (blue), scale (orange), price level (brown), and methods (red) to intervention unit cost. Proportions represent the joint contribution of model inputs within each category as a fraction of total variation in average annual economic cost per capita explained by the model. These were obtained by regressing cost per capita on model inputs sampled from 500 model parameter sets simultaneously drawn 10,000 times from a uniform distribution within the corresponding parameter range (Appendix A, File A3). Model inputs by category are listed in Appendix A, Table A2. Equivalent distributions for cost per outputs are shown in Appendix A, Figure A1. RR= Rapid Reporting; RACD= Reactive Case Detection; MDA= Mass Drug Administration; IRS= Indoor Residual Spraying.

Overall, parameters related to intervention design, service output and use of resources at delivery explain most of the variation in cost per capita for all interventions except RR and IRS. For RR and IRS, scale is the dominant driver due to the large initial investment needed to introduce these interventions. It covers spray pumps and spray operator kits for IRS and server and module development for RR as well as planning, training, and sensitization in the first year. Intervention-related inputs describing the volume of insecticide per structure and the number of structures sprayed per operator per day produce large gradients in unit cost of IRS; increasing the volume per m2 from 200 to 600 cm3 increases unit cost from 1.9 USD to nearly 3 USD per capita in the reference implementation. For RR - increasing the time for malaria reporting to 4 days per month (as seen in Ethiopia MACEPA pilot) instead of a quarter of a day in the reference implementation nearly doubles the intervention cost. For RACD costs, the target search radius and per-diems paid to CHWs dominate intervention parameters. Increasing the search radius to 30 people, as seen in the Senegal pilot, and some of the HFCAs in Zambia, will increase cost of RACD to nearly 2 USD per capita. For MDA the number of rounds per year and the number of people treated per CHW per day have the largest impact on cost when varied singly. Parameters characterizing the setting including the number of health facilities and number of CHWs per population target, access to treatment, and distances between programmatic levels are important for RACD and IRS. The number of people per structure – another setting parameter – modulates translation of population to structures targeted for IRS which in turn determines requirements for spray operators and insecticide in the cost model. Price is a key driver for interventions with a high fraction of costs attributable to commodities such as MDA.

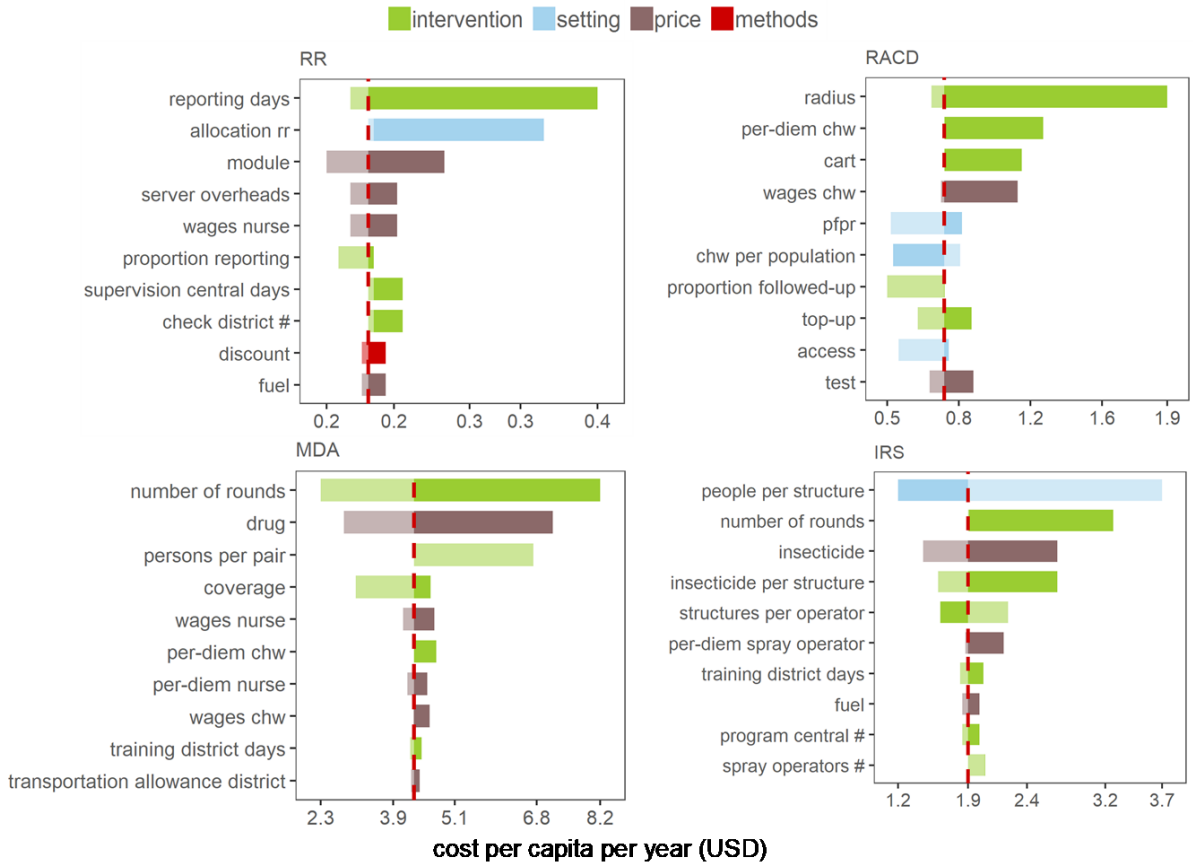
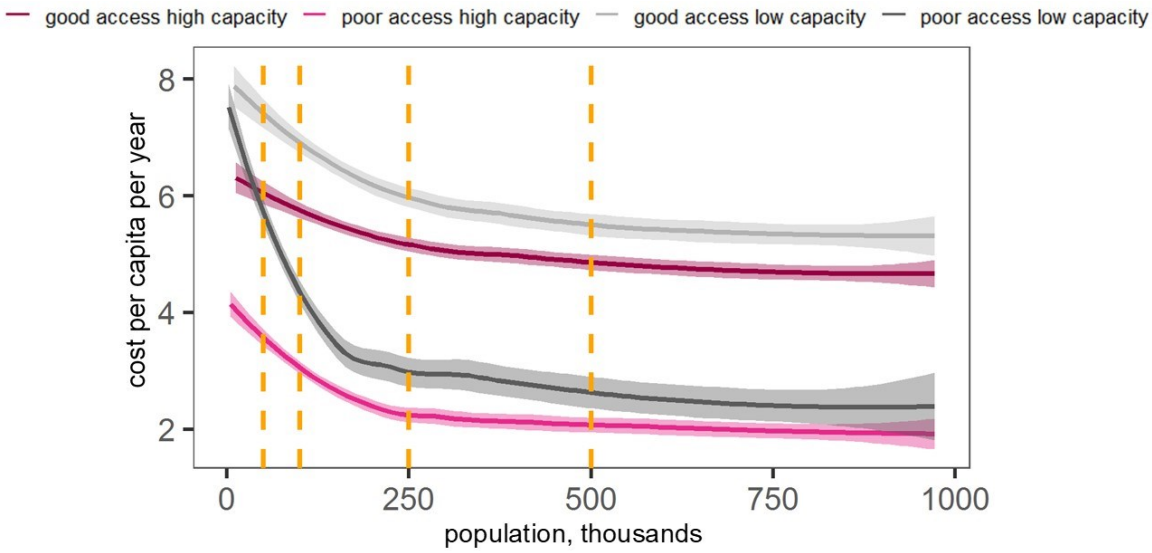


Figure 2.3 One-way sensitivity analysis of average annual economic cost per capita (USD, 2014) at reference implementation*

Tornado plots show top 10 model inputs with the highest impact on intervention unit cost when varied over its' minimum and maximum while keeping all other inputs at reference values (Appendix A, Table A11). Bar lengths indicate the value of unit cost at highest – darker shade, and lowest – lighter shade, value of the respective parameter. Bar colour highlights input category. Red dashed lines give the reference estimate. Inputs describing scale of implementation (number of people reached) dominate the unit cost defined in terms of cost per capita; tabulations are thus shown only for parameters related to intervention (green), setting (blue), price (brown), and methods (red). Equivalent tabulations for cost per output are presented in Appendix A, Table A2. Impact of scale parameters on estimated unit costs is explored in Figure 4, and Appendix A, Figure A3. * Reference implementation detailed in Table 1, further details in Appendix A, Table A3 and File A2**.** RR= Rapid Reporting; RACD= Reactive Case Detection; MDA= Mass Drug Administration; IRS= Indoor Residual Spraying.

Cost implications arising from systematic correlations between model inputs within a setting were explored using scenario analyses. Specifically, of interest here is the magnitude of cost gradients resulting from interactions between contextual features and implementation of interventions. For the four setting types, characterized by geographic accessibility and resource capacity, explicit assumptions were made on how implementation of interventions and key operational inputs might vary in response to these features (Appendix A, Table A12). MDA coverage was assumed to decrease from 90% to 50% and the annual number of rounds to decrease from two to one in low compared to high capacity setting; the number of people treated per day to decrease from 75 to 50 in low compared to high geographic accessibility setting. Figure 2.4 illustrates how these, and other correlations detailed in Appendix B, File B1, modify the relationship between MDA cost and scale.

Scenarios with lower efficiency are more sensitive to scale - notice steeper slopes at lower scales for the two poor accessibility settings. Capacity is dominated by scale and other parameters at higher population targets showing convergence of costs for the two low capacity scenarios. When varied singly at a reference scale, these parameters result in a range between 2.3 and 4.7 USD per capita per year compared to the reference estimate of 4.2 USD. Allowing implementation to vary by setting yields a range between 3.6 and 7.4 USD per capita if deployed in a population of 50,000, 3.2 and 7 USD per capita in a population of 100,000, and 2.1 and 5.6 USD per capita in a population of 500,000. Population size targets between 50,000 and 100,000 are in between district and region levels. Variation in costs is even greater at lower population scales between 2,000 and 10,000 people representative of HFCA.



Implementation scale	good geographic accessibility setting, high capacity	poor geographic accessibility setting, high capacity	good geographic accessibility setting, low capacity	poor geographic accessibility setting, low capacity
50,000	6.04	7.41	3.57	5.80
100,000	5.78	6.97	3.15	4.81
250,000	5.30	6.17	2.50	3.42
500,000	4.92	5.61	2.12	2.72

Figure 2.4 Mass Drug Administration cost per capita per year by setting and scale (USD, 2014)

Each curve represents the intervention cost trajectory for the four setting types obtained by fitting a Loess curve to cost estimates modelled at various implementation scales. Shaded areas around the curves illustrate variation in the cost estimate due to different ways in which a given implementation scale can be achieved: by increasing the population size of the HFCA, increasing the number of HFCAs, or increasing the number of districts or regions where the intervention is deployed. Setting types are described in Appendix A, Table A12. Equivalent figures for other interventions are shown in Appendix A, Figure A5.

Economies of scale are evident in cost trajectories of all interventions up to population size of 200,000 (See Appendix A, Figure A5). The relative importance of scale for different interventions is consistent with cost summaries in Appendix A, Tables A9 and A10 (note the share fixed costs (i.e. related to start-up activities and capital items). The figure demonstrates that differences in cost of interventions between settings are greatest at lower implementation scales, which further implies that the relative ranking of interventions may differ depending on the operational level at which strategies are defined.

Discussion

This paper proposes models that rely on data from pilot studies and secondary sources to derive an estimate of intervention costs to inform introduction of new tools and optimization of malaria intervention strategies. Grounded in operational insight, the models produce locally relevant estimates of costs and should enable programs to explore potential efficiency gains and cost savings from alternate delivery strategies. By formalizing the translation of operational data into an estimate of intervention costs, these models overcome one of the important challenges in standardizing economic evaluation of malaria programs.

From pilot implementation to programmatic delivery

Cost data are increasingly collected along field trials to inform economic evaluation of new health interventions. While efficient, the short-comings of this strategy often restrict extrapolation beyond pilots and thus limit relevance of the evidence for policy guidance (Ramsey et al., 2015). In the costing studies conducted along MACEPA pilots that were guided by a well-defined methodology (Larson et al., 2016), variation in choices analysts made with respect to the scope of resources to be costed, assumptions on utility life-years of sensitization and training, and time at delivery were the primary sources of differences in cost of interventions between sites. Analysts relied on own judgement to adjust for co-deployment of interventions within the pilots and to disentangle resources used for research from implementation activities. For instance, in MACEPA pilots diagnostic testing to inform epidemiological outcomes was conducted alongside drug distribution, requiring additional community workers and increasing the length of household visits and length of the campaign, compared to what would have been required to support drug distribution within an MDA campaign. When the models were applied to derive intervention costs from the trial data, thus adjusting for these inconsistencies, estimates differed by an order of magnitude from those reported in the pilot studies (Appendix A, Table A14). Finally, isolating resource

use attributable to partner contribution for trial management and oversight, supervision, technical support, etc. was both challenging and raised further questions about local capacity to support these functions and about implications for effectiveness of interventions outside of the trial. Updating resource use assumptions on these inputs with values representative of experience of programs in endemic African countries resulted in about 20% lower cost across the four interventions (Appendix A, Table A14).

Intervention cost drivers

The operational inputs were shown to be important drivers of costs and key to understanding trade-offs between interventions. While limitations of the trial data precluded empirical evaluation of the relationship between service output and context, these dimensions were incorporated into our costing models by explicitly defining a level of health infrastructure for the setting and drawing on expert opinion of in-country partners and secondary data sources to inform the translation. The strategy broadly aligns with earlier work within the WHO-CHOICE project that sought to incorporate health systems into optimization frameworks (Baltussen et al., 2002; Johns & Baltussen, 2004). The scenario analyses highlighted how the cost implications of intervention design might be magnified by setting specific features.

The value of trial data for programmatic decisions could be further strengthened by designing data collection to understand variability in resource use with respect to the setting and aspects of intervention design. For IRS, important quantities relate to the number of people protected/ structures sprayed per day and the volume of insecticide. PMI already routinely collects information on these parameters (Cico & Johns, 2018); what is missing, however, is the link between these quantities and the broader context of the program. For interventions relying on community volunteers, understanding the importance of incentives paid in the trials and contribution of supportive supervision for service outputs are key when evaluating delivery at scale. Compensation of community cadre varies greatly across the region from a volunteer basis with some incentives and per-diems for training (i.e. Zambia) to a paid Ministry of Health staff position integrated within the formal health sector (i.e. Senegal, Ethiopia) (Taylor, Griffiths, et al., 2017). During the early stages of RACD introduction in Southern Province in Zambia, less than a quarter of eligible index cases were followed by CHWs with human resource constraints cited as the primary reason for low follow-up (Larsen, Chisha, et al., 2015). Thus, when evaluating malaria elimination strategies demands on CHW time need to be considered (Kasteng et al., 2016).

Commodities are key cost drivers for RACD (at assumed prevalence and positivity rate), MDA, and IRS (Appendix A, Tables A9-A10). Second to commodities, costs incurred at point of delivery (i.e. at drug distribution or house spraying) are the next most important driver. These costs primarily cover compensation of field workers which are in turn a function of length of the campaign and other features related to intervention design and the setting (including age target, population density, number of houses that can be sprayed per operator per day). For RR, that requires an initial investment to acquire the server, the bulk of costs is driven by program support and supervision. A key challenge for RR, but equally for other interventions is poor evidence base on how these and other supportive activities modify resource requirements impact on intervention effective coverage and cost.

Using the models to derive an estimate of intervention costs

In this paper, the models were applied to extrapolate from MACEPA trials to a generic setting, yielding cost estimates that broadly align with the literature (Appendix A, Table A15). In the same manner as the authors proceeded here, by critically evaluating normative guidance on implementation of interventions against the operational data from the trials, analysts and program managers could update the respective inputs of the models to contextualize further interventions modelled to derive setting specific costs.

The detailed enumeration of resources and operational activities supported by the models ensures that every aspect of intervention, as it is implemented in a specific setting, can be adequately represented and costed. This flexibility is the key strength of the approach detailed here, it comes, however, at a price - the extensive data requirements to populate the model. The paper showed how trial and secondary data could be triangulated to source these data. The low level of aggregation within the models supports transferability of data across studies within a setting (i.e. wages of nurses are the same within a setting regardless of the intervention they deliver). Curated databases of prices for an extensive menu of micro-inputs (Egger et al., 2017; WHO, 2011a), developed recently to strengthen the evidence base for economic evaluation in LMICs, make the strategy presented viable for future prospective evaluation of new interventions.

Using the models to inform resource allocation

Modelling and simulation of infectious disease dynamics are increasingly applied to guide thinking on optimal intervention strategies (including use of new tools) to achieve burden reduction or elimination (Gerardin et al., 2017). By linking-in costs, such modelling allows decision makers to evaluate trade-offs between different strategies on the basis of costs and

benefits and informs optimal allocation across interventions within the available budget envelop. The costing models presented here facilitate alignment of assumptions between epidemiological and economic inputs. Importantly, by fixing the scope of the evaluation, harmonizing assumptions on resource use, setting-specific inputs, and through a consistent application of economic valuation methods the models enable unbiased comparison between interventions.

Operational details of interventions, scale of implementation and capacity were all shown to have important implications for costs and effectiveness of elimination strategies. Operational scenarios presented and, more formally the cost models, relate these features to service outputs thus informing modelling toward optimal intervention design. Work by Gao and colleagues is an example of a modelling study that explicitly incorporated setting, operational and logistic constraints on implementation of MDA for elimination to inform program design. The authors demonstrated that shorter campaigns enabled by larger drug distribution teams would increase the likelihood of elimination in areas with true *Pf*PR under 3% and where population is highly mobile; in more static populations, deploying smaller teams would be cost optimal and as impactful. Systems capacity can be further incorporated in impact models by limiting the level to which interventions can be scaled-up, varying time over which target coverages are reached, and through scenario analyses where coverages and effectiveness of interventions are varied depending on the context (Stresman et al., 2010).

In low-endemicity settings, in particular, due to reactive nature of programmatic response, the spatial and temporal pattern of outbreaks, the health infrastructure, and the capacity of the surveillance systems to adequately identify outbreaks need to be explicitly considered by economic and impact models aiming to inform policy decisions (Reiker, Chitnis, et al., 2019). This further suggests the need to accommodate dependencies between the surveillance interventions such as RR and RACD and the effectiveness of targeted strategies and reactive responses and the underlying case management. A recent modelling study that explicitly considered these dependencies showed that although RACD may bring qualitative benefits in low-endemicity settings, improving case management may be more impactful (WHO, 2017c).

Conclusion

This paper illustrated the utility of costing models to synthesize data from pilot studies and secondary sources to inform evaluation of tools and optimization of intervention strategies by programs. Grounded in operational insight, the models produce locally relevant estimates of intervention costs and allow programs to explore potential efficiency gains and cost savings from alternate delivery strategies and intervention mixes. An important innovation of the models presented here is the explicit link between service outputs (i.e. effective coverage) and the health infrastructure. The value of this approach for decision-making is enhanced when primary cost data collection is designed to enable analysis of the efficiency of operational inputs in relation to features of the trial or the setting, thus facilitating transferability.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files

Competing interests

The authors declare that they have no competing interest.

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Authors' contributions

KG collected the data, performed the analysis and drafted the manuscript. VM and AMcD collected the data. JM and KS contributed the data, supported interpretation of the data, and informed the reference implementation scenarios. KG, TAS, MAP and RA contributed to conceiving and designing the analysis and writing the final draft. TAS, MAP and RA contributed to analysis and interpretation of the data.

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Chapter 3: Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data

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Abstract

Recent results from the phase 3 trial of RTS,S/AS01 malaria vaccine show that the vaccine induced partial protection against clinical malaria in infants and children; given the high burden of the disease it is currently considered for use in malaria endemic countries. To inform adoption decisions the paper proposes a generalizable methodology to estimate the cost of vaccine introduction using routinely collected and publicly available data from the cMYP, UNICEF, and WHO-CHOICE. Costing is carried out around a set of generic activities, assumptions, and inputs for delivery of immunization services adapted to a given country and deployment modality to capture among other factors the structure of the EPI program, distribution model, geography, and demographics particular to the setting. The methodology is applied to estimate the cost of RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda. At an assumed vaccine price of 5 USD per dose and given our assumptions on coverage and deployment strategy, we estimate total economic program costs for a 6-9 months cohort within 23.11 to 28.28 USD per fully vaccinated child across the 6 countries. Net of procurement, costs at country level are substantial; for instance, in Tanzania these could add as much as 4.2 million USD per year or an additional 2.4 USD per infant depending on the level of spare capacity in the system. Differences in cost of vaccine introduction across countries are primarily driven by differences in cost of labor. Overall estimates generated with the methodology result in costs within the ranges reported for other new vaccines introduced in SSA and capture multiple sources of heterogeneity in costs across countries. Further validation with data from field trials will support use of the methodology while also serving as a validation for cMYP and WHO-CHOICE as resources for costing health interventions in the region.

Keywords

malaria, costing, vaccine introduction, vaccine, RTS,S

Introduction

RTS,S vaccine against *P. falciparum* malaria has demonstrated moderate levels of efficacy in phase 3 trials in Africa and is currently considered for use within the Expanded Program on Immunization (EPI) in endemic countries (Ballou, 2009). Tested in children (5-17 months) and young infants (6-12 weeks) the vaccine has shown high initial efficacy, but its protection waned quickly with efficacy against clinical disease at 36.3% and 25.9% depending on age at immunization (The RTSS Clinical Trials Partnership, 2014, 2015). The vaccine is thus evaluated as an additional tool for preventing clinical disease in children, not a replacement for existing malaria preventive, diagnostic, and treatment measures (IVB, 2014a). Despite being partially effective, modelling studies predict RTS,S to have a substantial public health impact on disease burden (M. Penny, K. Galactionova, et al., 2015).

With a positive scientific opinion on vaccine efficacy and safety issued by the European Medicines Agency earlier this year, the WHO is expected to follow-up with a policy recommendation on the use of RTS,S (IVB, 2014a). As countries, donors, and international organizations consider RTS,S introduction, data on program costs are needed. Combined with effectiveness, cost data allow policy makers to assess the value of this new intervention in the context of a malaria control strategy (Moorthy et al., 2012; Walker et al., 2010). Decision-making at the country level is further concerned with financing and feasibility of mobilizing and maintaining the level of resources to support the new vaccine (Alan Brooks, Julia Nunes, et al., 2012; Makinen et al., 2012).

To inform these decisions the study proposes a generalized methodology to estimate costs of RTS,S introduction in the EPI program. We apply it to assess these costs in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda. Costing is implemented around a set of generic and easily modifiable assumptions describing vaccine introduction; these capture among other factors the structure of the EPI program, distribution model, geography, and demographics particular to the setting. Our findings illustrate the broad ranges for costs of introduction dependent on the level of spare capacity to accommodate the vaccine. We show that differences in EPI structure, cost of labor, and intensity of use of resources within the system translate into significant differentials in cost of vaccine delivery between settings.

We base our assumptions about vaccine presentation on (MVI, 2008; The RTSS Clinical Trials Partnership, 2012). RTS,S is a monovalent lyophilized vaccine reconstituted with an adjuvant; both require cold chain storage at 2 to 8^0 C. The vaccine and the diluent are clipped together with a packed volume of 9.68cm^3 per two-vial package. Two doses per vial are yielded after reconstitution.

Clinical trial data suggest that at least three doses are required for protection against malaria. Following the trial design (The RTSS Clinical Trials Partnership, 2012), we evaluate four immunization schedules: a program targeting infants at 6, 10 and 14 weeks of age (EPI); children at 6, 7 and 9 months (6-9 months); and a four dose schedule in the two age groups including a booster at 18 months after the 3rd dose. We assume national roll-out to scale through routine outlets with immunization schedule tied to DTP. For 6-9 months implementation we assume first and third doses to be administered along with vitamin A and measles vaccine and treat these as routine immunization visits for purposes of costing. New, out-of-routine schedule, visits are assumed for the second dose in 6-9 months and booster doses.

Methods

Perspective

A broad provider perspective is adopted in this evaluation; all resources required to introduce the RTS,S into the national program are included in the analysis.

Scope

We estimate both the economic and the financial costs of introducing the malaria vaccine into the EPI. Financial costs represent actual expenditures on goods and services. Economic costs “define costs in terms of the alternative uses that have been forgone by using a resource in a particular way”; these include, in addition to the financial costs, a valuation of resources that do not have financial transactions (i.e. donated goods and services or capital goods, health care resources diverted from other uses or shared with other health programs, and inputs whose prices are distorted (Drummond et al., 2005)). Given paucity of data on the level of existing capacity in the system, the financial costs are estimated under an assumption of 100% spare capacity to accommodate the vaccine. In reality, however, some countries might need to invest in scaling-up across a range of service inputs be it cold chain, vehicle fleet, or labor to deliver the new intervention. Assumptions for capacity scale-up,

while not used to produce estimates here, are shared in Appendix B, File B1. The economic costs are implicitly evaluated under the assumption of no spare capacity. Taken together, the two sets of estimates give a wide but informative range for potential vaccine introduction costs.

Assumptions for delivery of immunization services

We defined a set of essential activities for RTS,S introduction based on WHO (IVB, 2004; Walker et al., 2010; WHO, 2002), USAID (USAID, 2003, 2005), and other guidelines on immunization (PATH, 2001, 2003). Assumptions about operational aspects of the program were further informed by published micro-costing studies that evaluated the introduction of new vaccines in low-income countries (Edmunds et al., 2000; Griffiths et al., 2009; Hutton & Tediosi, 2006; Hutubessy et al., 2012; Levin et al., 2013). No campaigns or additional outreach activities outside of the routine EPI delivery were considered. For deployment modalities requiring out-of-routine schedule visits we assumed lower coverage rates and adjusted service delivery assumptions to reflect the longer time needed to administer the vaccine, increased IEC, and supervision to maintain coverage. Assumptions on activities costed and key inputs are presented in detail in Table 1.

Resource lists

Resource lists were populated following the activities defined for vaccine introduction. These were adapted to countries using comprehensive Multi-Year Plans (cMYP) for immunization (Burkina Faso Ministry of Health, 2006; Department of Medical Prevention, 2012; DVI, 2011; Mainland, 2011; Ministry of Health Ghana, 2010; Uganda Ministry of Health, 2012). The latter were particularly useful in identifying staff categories, equipment, and quantities of resources used by the EPI program at each level. Resource lists and prices for each country are documented in Appendix B, File B2.

Input prices and unit costs

Data on input prices and unit costs came from several sources. Information on wages by level of EPI staff, per-diems, and some other line items were taken from cMYP (Burkina Faso Ministry of Health, 2006; Department of Medical Prevention, 2012; DVI, 2011; Mainland, 2011; Ministry of Health Ghana, 2010; Uganda Ministry of Health, 2012). We also used data from the UNICEF (UNICEF, 2012) for prices of immunization supplies, and related equipment. Additionally data from the WHO-CHOICE databases were used to cost facility rental, hotel rates, fuel, and other commodities (WHO-Choice, 2011). Prices of commodities

obtained from the international price lists were adjusted for freight, insurance and wastage (WHO, 2002).

Shared inputs were attributed to RTS,S based on the direct allocation (Drummond & Sculpher, 2005); except for vaccinators whose contribution to the new intervention was costed based on time required to administer the vaccine. Similarly, cost of cold chain and vehicles were allocated to RTS,S based on use; for these inputs use refers to the volume of the vaccine and immunization supplies and time for storage or distance over which these were transported or stored.

Cost of capital items including vehicles, facilities, and equipment was annualized over the respective estimated useful life. Expenditures associated with activities held in the introductory stage were considered capital goods and were annualized and discounted over 5 years at 3%.

Algorithm for calculating cost of immunization

For each activity outlined in Table 3.1 we defined formulas to combine price and unit cost data with assumptions on resource use. These start with the general representation of an activity in terms of cost components, break it down to micro inputs and detail how unit costs are combined with quantities to obtain total cost per activity. Formulas are presented in Appendix B, File B3; these are generalized and could be adapted to alternate assumptions on service delivery. Costs are estimated for a single cohort of surviving infants and are reported in terms average annual, per FVC, and per dose administered metrics.

Table 3.1 Activities, assumptions, and inputs for delivery of immunization services

Stage	Program component	Activity	Activity Assumptions	Resource Assumptions	Economic costs	Financial costs
Introduction	Planning	- Micro-planning - Development of training materials - Development of EIC materials	- Micro-planning at central level assuming a total of 1 month of preparatory work	- 3 1-day workshops for planning and development of training and IEC materials at central level including national and regional EPI managers (2 from each region)	- Wages - Per-diems - Hotel - Vehicle - Vehicle maintenance and overheads - Consumables - Stationaries - Printed materials - Facility rental	- Per-diems - Hotel - Vehicle - Vehicle maintenance and overheads - Consumables - Stationaries - Printed materials
	Cold store assessment	- Inventory of cold chain, assessment of spare capacity for introduction of new vaccine	- Assessment conducted by EPI cold store staff	- Costed based on estimates from cMYP	- Cold store assessment	
	Revision of immunization cards and tally sheets	- Revision of immunization cards and tally sheets to include new vaccine	- Revised cards and tally sheets printed for the target cohort	- 25% reserve stock - Full cost of revised cards and tally sheets printed for the target cohort allocated to RTS,S in the first year, thereafter a proportion allocated to RTS,S	- Printing tally sheets - Printing immunization cards	- Printing tally sheets - Printing immunization cards
	Training	- Training of trainers - Training of regional supervisors - Training of immunization staff	- 5 day training of trainers (2 nurses per district) at central level - 2 day training workshop for regional supervisors at central level - 1 day training of vaccinators at district level (5 nurses from regional and district	- Start training the year of vaccine introduction - After first year RTS,S specific training integrated into routine EPI training for new staff and refresher courses	- Wages - Per-diems - Hotel - Vehicle - Vehicle maintenance and overheads - Consumables - Stationaries - Printed materials - Facility rental	- Per-diems - Hotel - Vehicle maintenance and overheads - Consumables - Stationaries - Printed materials

Stage	Program component	Activity	Activity Assumptions	Resource Assumptions	Economic costs	Financial costs
			facilities; 1 from all other levels)			
	Social Mobilization and IEC	- Launching ceremony at central level - Sensitization meetings at district level - TV advertisement - Radio advertisement - Flyers and posters	- Launching ceremony including 5 speakers, band, volunteers (1/50 attendees), technical staff - IEC meetings at district level involving regional EPI officers(1/district); band, volunteers	- First year of program roll-out, thereafter integrated with routine EPI IEC activities	- Wages - Per-diems - Speaker fees - Band fees - Volunteers - Hotel - Vehicle - Vehicle maintenance and overheads - Consumables - Stationaries - Printed materials - Facility rental - TV, radio advertisement - Flyers, posters	- EPI per-diems - Speaker fees - Band fees - Hotel - Vehicle maintenance and overheads - Consumables - Stationaries - Printed materials - TV, radio advertisement - Flyers, posters
Recurrent	Supervision	- Supervision over program implementation	- EPI staff at central and subnational levels	- Number of supervisory visits and staff involved in supervision of EPI including drivers based on cMYP records - Proportion of wages, per-diems, transport costs allocated to RTS,S	- Wages - Per-diems - Vehicle - Vehicle maintenance and overheads	- For deployments including doses outside of routine schedule include EPI wages, per-diems, transportation for the increase in intensity of supervision activities
	Monitoring and program management	- Collecting data on vaccine stock and coverage - Strategic planning - Administrative support - Printing of immunization cards and tally sheets - Post introduction evaluation	- NIP staff at central and subnational EPI levels - Post introduction evaluation conducted externally	- Proportion of EPI wages allocated to RTS,S - Proportion of annual printing costs allocated to RTS,S - Post introduction evaluation costed based on estimates from cMYP	- Wages - Tally sheets - Immunization cards - Post introduction evaluation	- Tally sheets - Immunization cards - Post introduction evaluation

Stage	Program component	Activity	Activity Assumptions	Resource Assumptions	Economic costs	Financial costs
				- Post introduction evaluation annualized over 5 years		
	Training	- Refresher training and training of new staff	- Integrated into routine EPI training	- Proportion of annual EPI budget for training allocated to RTS,S	- Proportion of annual EPI budget for training allocated to RTS,S	
	Social Mobilization and IEC	- Social mobilization and IEC on RTS,S	- Integrated into routine EPI Social Mobilization and IEC activities	- Proportion of annual EPI budget for Social Mobilization and IEC	- Proportion of annual EPI budget for Social Mobilization and IEC	
	Procurement	- Procurement of vaccines and supplies	- Procurement of vaccines and supplies through the UNICEF Supply Division	- Including freight and insurance, wastage - UNICEF procurement and handling fee	- Vaccines - Syringes - Alcohol - Cotton wool - Safety boxes - UNICEF handling fee	- Vaccines - Syringes - Alcohol - Cotton wool - Safety boxes - UNICEF handling fee
	Storage	- Storage of vaccines and immunization supplies	- Type of cold store equipment assigned by administrative level based on cold and dry storage volume required	- Storage costs calculated based on volume of vaccines and supplies - Months of storage based on number of deliveries at each level	- Wages - Cold store equipment - Equipment maintenance, overheads - Facility - Facility overheads	- Equipment maintenance, overheads - Facility overheads
	Transportation	- Transport of vaccines and immunization supplies to sub-national stores and health facilities	- Type of vehicle by administrative level - Grossing factors by level and type of equipment used to transport the vaccines	- Fuel, and maintenance based on average distance between administrative units - Transit costs scaled by volume of the vaccine and supplies to be transported by delivery route over vehicle storage	- Wages - Vehicle - Vehicle maintenance and overheads - Cold boxes	- Vehicle maintenance and overheads - Cold boxes annual replacement (20%)

Stage	Program component	Activity	Activity Assumptions	Resource Assumptions	Economic costs	Financial costs
				capacity of the vehicle		
	Vaccination	- Fixed site vaccination - Outreach vaccination	- Vaccines administered by nurses - Outreach from facilities to remote areas by nurses on bikes	- 7 minutes per dose when administered alone; 5 minutes when administered with another vaccine - Outreach costed based on number of days conducting outreach activities as per cMYP - Immunization office of 20 m2	- Wages - Per-diems - Facility - Facility overheads - Furniture - Stationaries - Vaccine carrier - Bicycle	- Facility overheads - Stationaries
	Waste Management	- Incineration of syringes and vials	- Incinerator at national, regional, and district facilities - Fire pit at lower level health centers		- Wages - Incinerator, bottle, protective gear crusher - Equipment maintenance and overheads - Bottle crusher - Fuel	- Fuel - Equipment maintenance and overheads

Sensitivity analysis

The most critical assumptions made when estimating cost of vaccine delivery relate to coverage, wastage rates, and use of labor at service point. These parameters were varied over an inclusive range while keeping all other inputs at base values. Assumptions on wastage, discount rate, and time to administer the vaccine were generic; country data were used in the baseline for all other inputs varied. Resulting estimates of cost of vaccine delivery are summarized by country in tornado plots.

Results

Overview of key demographic, coverage, and EPI inputs by country

Differences in country cohorts and the EPI system detailed in Table 3.2 help interpret the level and variation in costs across countries. The cohort size of Tanzania of 1.7 million infants is about 4 times as large as that of Senegal. There is variation not only in the level of coverage achieved but also in the level of coverage sustained between the doses. In Uganda coverage at third dose is 8 percentage points lower than the first dose; the drop-off is about 3 percentage points in Ghana and Senegal. There is variation in wages at facility level: nearly 800 USD per month are reported for Kenya, 421 USD and 115 USD per month for Tanzania and Burkina Faso respectively. Interestingly the ordering of countries changes when we look at wages at higher levels of EPI; both at central and district levels highest wages are reported for officers in Ghana. Finally, there are differences in the number of days and number of EPI staff conducting supervision visits across countries; these vary from 0.5 to about 10 days per month with as few as 4 to as many as 9 officers per district involved in supervisory capacity.

Table 3.2 Overview of key demographic, coverage, and EPI inputs by country

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Number of surviving infants[1]	719'218	767'114	1'220'634	453'259	1'716'679	1'450'141
6-9 months coverage dose 1[2*]	71%	71%	62%	72%	74%	67%
6-9 months coverage dose 3[2*]	66%	68%	57%	69%	68%	59%
Wages nurse (USD)	115	263	791	565	421	216
Per-diems outreach nurse (USD)	10	4	27	12	11	5
Days outreach nurse	2.5	5	3	3	4	5
Wages EPI manager central level (USD)	563	2'482	2'373	1'131	1'506	705
Wages EPI manager district level (USD)	428	1'880	791	1'019	948	867
Per-diems EPI managers at district level (USD)	10	26	16	17	37	11
Days supervision EPI managers at district level	2	5	2	2-10	4-14	5-10
EPI managers at district level conducting supervision	9	3	7	6	5	4

Unless otherwise stated, estimates are extracted from country cMYP costing tool (Burkina Faso Ministry of Health, 2006; Department of Medical Prevention, 2012; DVI, 2011; Mainland, 2011; Ministry of Health Ghana, 2010; Uganda Ministry of Health, 2012); nominal values inflated to 2013 via US GDP deflator. [1] CIA, The World Factbook (2013). *Surviving infants.* Retrieved from https://www.cia.gov/library/publications/the-world-factbook/ ; [2] UNICEF, Child Health, Immunization (2013). *Immunization Coverage by Antigen*. Retrieved from: http://data.unicef.org/child-health/immunization (WUENIC, 2013 revision)**.** *An assumption; coverage in 6-9 months schedule is taken to be 75% of DTP.

Table 3.3 Summary of average annual costs of RTS,S immunization deployed via 6-9 months schedule in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction costs per surviving infant *financial*[1]	1.04	1.72	1.58	1.59	0.97	0.76
Recurrent costs per dose administered *financial*[2]	6.99	7.01	7.17	7.01	6.92	7.08
Total *financial* costs per FVC	21.82	21.74	22.63	21.71	21.81	22.86
Total *economic* costs per FVC	23.11	24.08	28.28	25.49	24.62	24.80
Total procurement costs[3]	9'903'660	10'679'279	14'591'719	6'447'159	24'677'812	18'322'750
Total *financial* costs	10'361'365	11'259'059	15'741'310	6'789'375	25'551'472	19'388'822
Total *economic* costs	10'970'655	12'469'923	19'674'652	7'972'356	28'846'864	21'037'518

[1] Total financial cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.) without annualization or discounting. See Table 3.1 for details; [2] Average annual financial costs of running the program, net of introduction costs. [3] Cost of vaccines, immunization equipment, and supplies.

Cost of RTS,S immunization

Unless noted, costs are presented for the 6-9 months schedule assuming a vaccine price per dose of 5 USD; estimates for other implementation strategies are reported in Appendix B, Tables B2-9. Vaccine introduction costs expressed in terms of financial cost per infant range between 0.76 and 1.72 USD (Table 3.3); these costs assume an existing capacity and represent a minimum initial investment needed at country level to introduce the new antigen. Program costs including annualized introduction and annual recurrent costs range from about 21.71 to 22.86 USD per FVC in financial terms; the range for the economic costs is wider – from 23.11 to 28.28 USD per FVC across the 6 countries. Annual program costs increase with size of the cohort; cost of procurement accounts for most of these expenditures: vaccines and immunization supplies make up about 95% of financial and 84% of economic costs.

Differences in cost of RTS,S immunization by country

Country differences in cost of vaccine delivery are a function of program design, coverage, EPI structure, number of antigens in the EPI schedule, and prices, the most critical of which is cost of labor. The lowest economic cost of delivery is estimated for Burkina Faso at 0.72 USD and highest for Kenya - at about 2.34 USD per dose administered (Figure 3.1 A). Over a three-fold difference between the countries is largely driven by wage differentials: compared to Burkina Faso, wages of EPI officers in Kenya are nearly five times higher; the differentials persist across all distribution levels although at lower levels wage differences are smaller (Table 3.2). In addition, compared to other countries, Kenya has one of the lowest projected coverage rates resulting in a lower denominator and, consequently, a lower base over which the fixed costs, including introduction investment, are allocated. When summarized in terms of economic cost per FVC, variation between countries is much smaller: the lowest estimate is for Burkina Faso at 23.11 USD and the highest - for Kenya at 28.28 USD (Figure 3.1 B). Convergence in costs at this level is due to differences in coverage between countries; cost per FVC increases steeply with drop-off between doses.

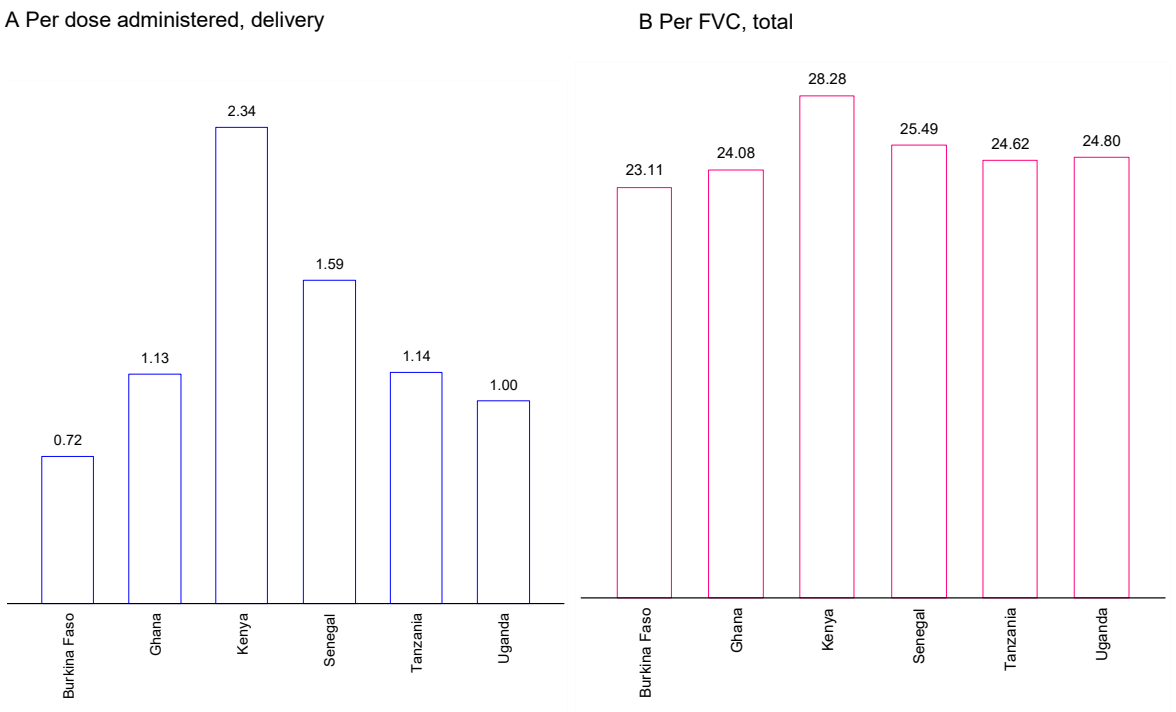

Figure 3.1 Average annual economic cost of RTS,S immunization deployed via 6-9 months schedule in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda (USD, 2013)

Figure A. bars represent cost of vaccine delivery (program costs net of vaccine and immunization supplies) per dose administered; Figure B. bars represent total program cost per FVC (child, receiving 3 doses of the vaccine) including vaccines, immunization supplies, and cost of delivery.

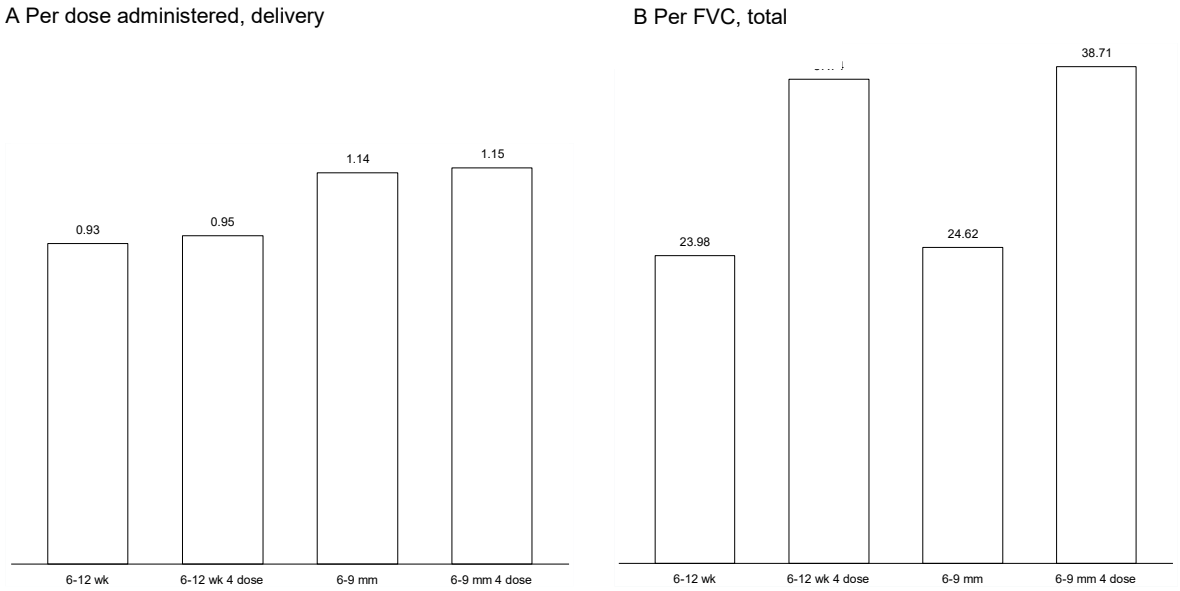

Figure 3.2 Average annual economic cost of RTS,S immunization in Tanzania by deployment modality (USD, 2013)

Figure A. bars represent cost of vaccine delivery (program costs net of vaccine and immunization supplies) per dose administered; Figure B. bars represent total program cost per FVC (child, receiving 3 doses of the vaccine) including vaccines, immunization supplies, and cost of delivery.

Differences in cost of RTS,S immunization by schedule

Differences in cost by schedule are similar across the 6 countries; these are illustrated in Figure 2 for Tanzania. For EPI and EPI booster implementations, the cost of delivery is lowest; higher costs are estimated for 6-9 months modalities, although at this level differences between strategies are modest. When summarized as cost per FVC, program costs for modalities including doses outside of the routine schedule are significantly higher. The much higher cost per FVC for boosting schedules is again due to coverage assumptions, namely we assumed 80% of 3rd dose coverage for booster, resulting in a lower denominator for these strategies.

Cost Drivers of RTS,S immunization

Resource requirements for each program component as a proportion of average annual delivery costs are illustrated in Figure 3.3. Costs at the facility level associated with the immunization visit account for the largest proportion of total delivery costs. The relative weight of other inputs varies across settings with differences across input categories mainly driven by differences in the structure of EPI program (levels of cold storage, number of staff at each unit, etc.), resource use, and wages. For instance, in Kenya labor heavy vaccination activities account for almost 60% of total delivery costs compared to only about 35% in Burkina Faso where, as discussed, reported wages are significantly lower. Activities such as supervision, monitoring and introduction incorporate heterogeneities in wage structure across countries as well as levels of resource use. The latter is illustrated with supervision activities; in Tanzania supervision accounts for nearly 16% of total program costs based on reported 4-14 days per month devoted to the activity across EPI levels; in contrast, in Kenya and Burkina Faso an average of only 3 days per months are allocated to supervision.

Sensitivity analysis

Results of the sensitivity analysis show that cost of service delivery changes almost proportionally with immunization coverage (Figure 3.4). These are sensitive to assumptions on time to administer the vaccine both within and outside of the EPI schedule; if instead of 5 minutes to administer an additional vaccine dose (Hutton & Tediosi, 2006; Pelliser et al., 2000) 15 minutes are required, to allow, for instance, for information and incentivization, service costs would increase by as much as 25%. Use of EPI shared resources including cold chain, vehicles, and program management are among other influential parameters.

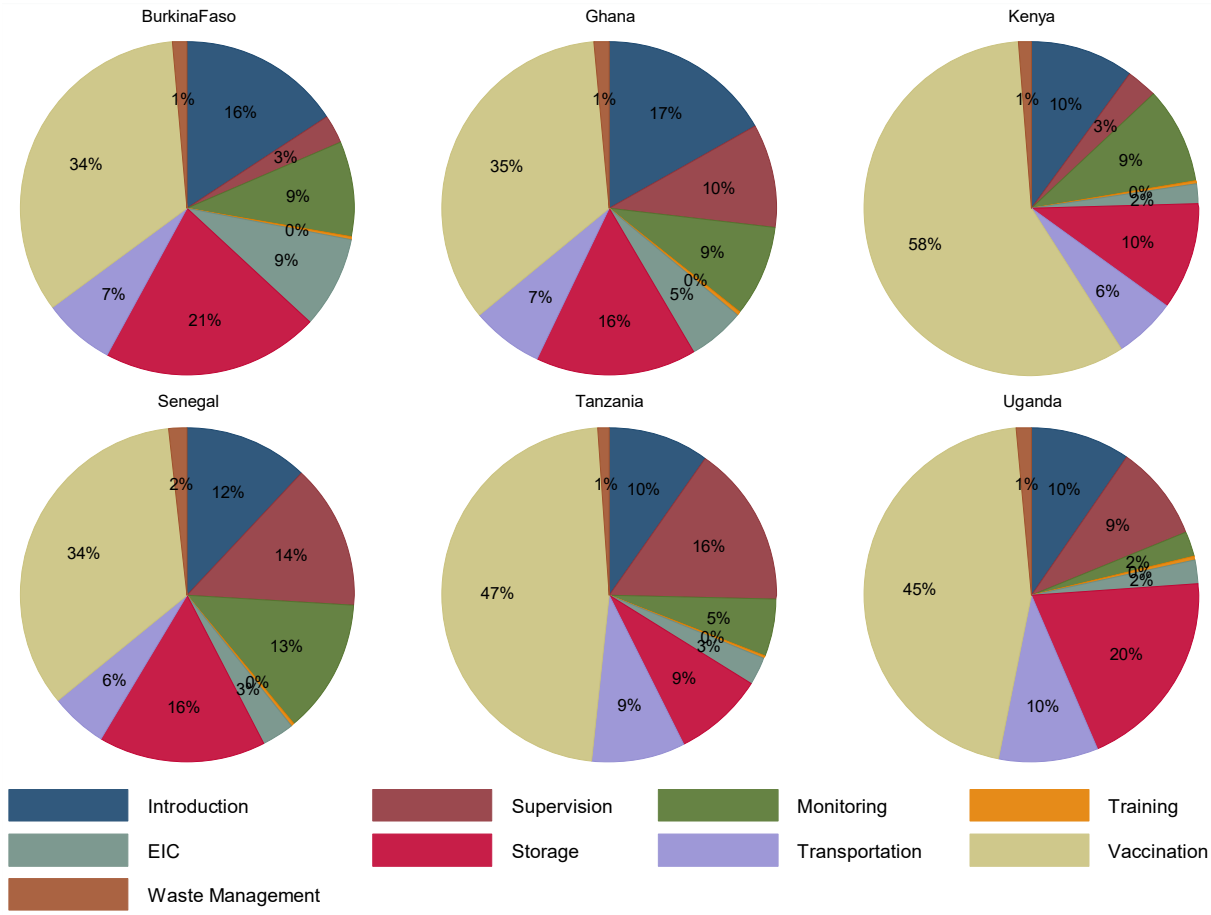

Figure 3.3 Distribution of average annual economic costs of RTS,S immunization deployed via 6-9 months schedule in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: Service delivery

Pie charts represent the distribution of cost of vaccine delivery (program costs net of vaccine and immunization supplies) by activity; "Vaccination" category covers all costs incurred at point of delivery excluding vaccines and immunization supplies

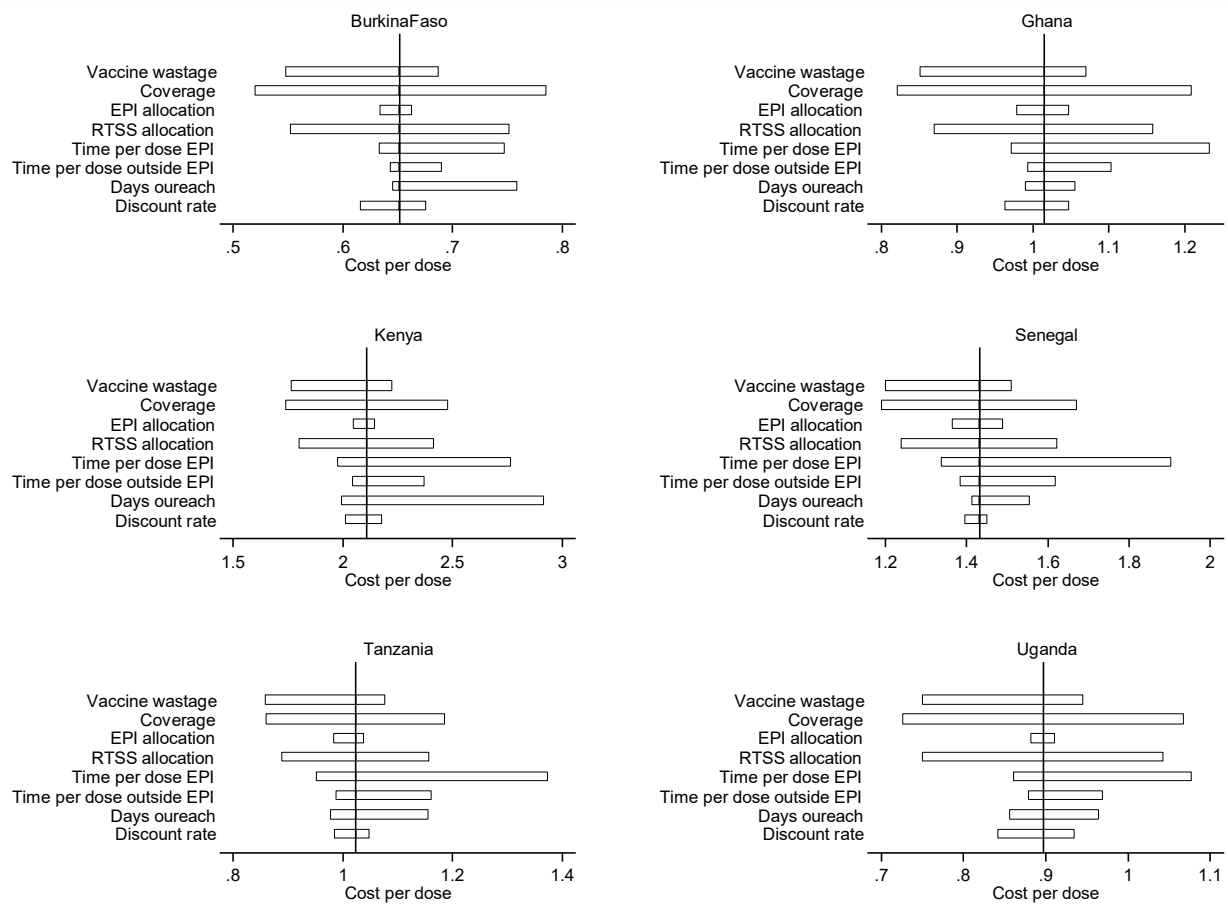

Figure 3.4 One-way sensitivity analysis on average annual economic cost of RTS,S immunization deployed via 6-9 months schedule in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: Service delivery (USD, 2013)

"Vaccine wastage" low value of 5% and a high of 25% are tested. "Coverage" under low scenario is assumed to be 75% of baseline value, at high scenario it is taken to be 125% of baseline. "EPI allocation" and "RTS,S allocation" of shared inputs are scaled down to 75% of baseline value and up to 125% under high scenario. "Time per dose EPI" is varied from 5 minutes at baseline to 3 and 15 minutes under low and high scenarios respectively. "Time per dose outside EPI" is varied from 7 minutes at baseline to 5 and 15 minutes under low and high scenarios respectively. "Days outreach" under low scenario are set to 2 and to 15 under high scenario. "Discount rate" values of 0% and 10% are evaluated.

Discussion

Costing an intervention that has not been implemented is a difficult undertaking further complicated by the absence of country policy with respect to its use. This study presented an approach to estimate the prospective costs of RTS,S introduction that can be easily adapted to the specifics of the vaccine presentation, country EPI program, and implementation strategy. One of the main advantages of the methodology is that it can be implemented using routinely collected and publicly available.

Estimates presented should be interpreted in the context of assumptions made on vaccine price, coverage, delivery modality, and data constraints. While we made every attempt to adapt these to country settings, lack of detail on operational aspects of the program might have resulted in a more normative distribution model. Aside from concerns about relevance of activities costed for a given setting, more general concerns about the quality of cMYP reports, borrowing of data and extrapolation across countries to fill in the data gaps introduced additional uncertainty.

One previous study assessed prospective costs of RTS,S introduction via routine EPI in Tanzania (Hutton & Tediosi, 2006); these were estimated using a similar methodology and relying on local data including system capacity use. The incremental cost of vaccine introduction was estimated at 0.66 USD per dose, which is lower than 0.93 USD per dose estimated in our study for Tanzania, but comparable given differences in scope. The contribution of the main cost drivers to the vaccine delivery costs were of the same order of magnitude in the two studies. Consistent with these earlier analyses, delivery costs account only for a small proportion of total program costs. At a vaccine price of 5 USD per dose about 95% of financial and 84% of economic costs are accounted for by vaccines and immunization supplies.

Although comparability with other antigens is limited given differences in vaccine properties, deployment strategies, immunization rate, etc., costs estimated here for RTS,S delivery are similar to other vaccines recently introduced in the region. De la Hoz-Restrepo (De la Hoz-Restrepo et al., 2013) cited non-vaccine costs associated with the introduction of rotavirus and pneumococcal conjugate vaccines in developing countries at 0.74 USD (IQR: 0.58-1.32) and 1.27 USD (IQR: 0.99-1.37) per dose, respectively. Griffith (Griffiths et al., 2009) estimated the incremental cost of introducing DTwP-hepatitis B-Hib vaccine in Ethiopia at 1.15 USD per FVC. The estimate is closest in scope to financial vaccine delivery costs

presented in this study - 0.90 to 1.91 USD per FVC across the 6 countries. Klinger (Klinger et al., 2012) reported cost per an additional birth dose of Hepatitis B in Mozambique at 1.46 USD (1.27-2.27 USD) . Hutubessy (Hutubessy et al., 2012) presented costs for HPV introduction in Tanzania using a similar methodology; the deployment strategy for the vaccine required reaching older children outside of the routine EPI delivery schedule with estimated costs of delivery ranging from 1.36 USD per dose for financial to 3.56 USD for economic costs. While these findings are yet to be replicated, we note that costs reported here are tied to explicit assumptions on vaccine deployment including labor; as countries decide on the operational strategy for RTS,S introduction estimates could be revised accordingly.

Costs estimated by the study are of interest to a diverse set of stakeholders. At country level these provide baseline values of resources required to introduce and maintain the intervention. Information particularly vital for Gavi graduating countries that will assess not only the additional resource needs for the new antigen but also the increased cost-sharing for provision of immunization for the current schedule and sustainability of the new schedule in the longer term. We show that delivery costs at country level are substantial; for instance, in Tanzania these could range between 0.8 to 4.1 million USD per year depending on scope of costing and level of spare capacity in the system.

For donors and global institutions supporting immunization programs the analysis presents some initial estimates of resource needs for vaccine introduction; moreover, it highlights the extent of resource use beyond procurement supplied by countries when introducing the intervention. Donors, in particular Gavi, might be interested in the cost of particular program components like vaccine introduction investment to gauge the size of introduction grants to support RTS,S in endemic countries. We show that the costs are higher in particular if vaccine is delivered outside of routine schedule and if new visits would be required. For the 6 countries, we estimate introduction costs between 0.76 and 1.72 USD per infant in the surviving cohort; the amount is much higher than what was awarded by Gavi for routine EPI vaccines of 0.30 USD per infant, and closer to 0.80 USD per infant awarded for HPV vaccine (Gavi, 2015).

Declarations

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Conflict of interest

This work was supported with a research grant from PATH - Malaria Vaccine Initiative - a partner contributing funding, through the Bill and Melinda Gates Foundation, to RTS,S development; KG was supported with this grant. No funding bodies had any role in the study design, data analysis, decision to publish, or preparation of the manuscript. Other contributors have no conflicts of interest to report.

Chapter 4: Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa

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Abstract

Background
RTS,S/AS01 is a safe and moderately efficacious vaccine considered for implementation in endemic Africa. Model predictions of impact and cost-effectiveness of this new intervention could aid in country adoption decisions.

Methods
The impact of RTS,S was assessed in 43 countries using an ensemble of models of Plasmodium falciparum epidemiology. Informed by the 32 months follow-up data from the phase 3 trial, vaccine effectiveness was evaluated at country levels of malaria parasite prevalence, coverage of control interventions and immunization. Benefits and costs of the program incremental to routine malaria control were evaluated for a four-dose schedule: first dose administered at six months, second and third - before 9 months, and fourth dose at 27 months of age. Sensitivity analyses around vaccine properties, transmission, and economic inputs were conducted.

Results
If implemented in all 43 countries the vaccine has the potential to avert 123 (117;129) million malaria episodes over the first 10 years. Burden averted averages 18'413 (range of country median estimates 156 to 40'054) DALYs per 100'000 fully vaccinated children with much variation across settings primarily driven by differences in transmission intensity. At a price of 5 USD per dose program costs average 39.8 USD per fully vaccinated child with a median cost-effectiveness ratio of 188 USD (range 78 to 22'448) per DALY averted; the ratio is lower by one third – 136 USD (range 116 to 220) - in settings where parasite prevalence in children aged 2-10 years is at or above 10%.

Conclusion
RTS,S/AS01 has the potential to substantially reduce malaria burden in children across Africa. Conditional on assumptions on price, coverage, and vaccine properties, adding RTS,S to routine malaria control interventions would be highly cost-effective. Implementation decisions will need to further consider feasibility of scaling up existing control programs, and operational constraints in reaching children at risk with the schedule.

Key Terms
RTS,S, malaria vaccine, cost-effectiveness, modeling and simulation

Introduction

With its safety and efficacy upheld in the phase 3 trial (The RTSS Clinical Trials Partnership, 2012, 2015) and a positive scientific opinion issued by the European Medicines Agency (EMA, 2015), the RTS,S/AS01 malaria vaccine is closer to domestic licensure and implementation in endemic Africa. A global recommendation with respect to vaccine use has been issued by the WHO (WHO, 2016a). It argues for pilot implementation in distinct epidemiological settings to demonstrate feasibility of delivering the schedule to the target age group and to assess vaccine`s impact on mortality and potential adverse effects. The recommendation has been informed with modelled estimates of vaccine`s impact and cost-effectiveness in generic prevalence settings (M. Penny et al., 2016). Relevance of these predictions to endemic countries requires further evaluation of the vaccine given geographic specific distribution of malaria exposure, coverage of preventive and control interventions and their dynamics, as well as cost of care in these specific settings. Countries might be interested in these data and explorations of predictions of vaccine impact taking into account local contexts before engaging in a considered effort identifying and testing strategies to deploy this new intervention.

Stochastic models of malaria epidemiology have previously been used to predict the likely epidemiological impact (Griffin et al., 2010; Maire, Tediosi, et al., 2006; M. Penny, K. Galactionova, et al., 2015) and cost-effectiveness (M. A. Penny et al., 2016; Fabrizio Tediosi et al., 2009) of pre-erythrocytic vaccines against *Plasmodium falciparum* (*Pf*). These studies indicate that both the disease burden averted and the cost-effectiveness will be highly dependent on transmission intensity and on vaccine properties including the decay rate of the vaccine effect, and the degree of homogeneity in host response. Recent data make it necessary to revise these predictions. *Pf* transmission has decreased dramatically over the last decade owing to scale-up of control interventions and roll-out of artemisinin combination therapy; infection prevalence in endemic Africa halved and incidence of clinical disease fell by 40% between 2000 and 2015 (Bhatt et al., 2015). Updated distributions of malaria exposure that capture these trends along with the methodology to translate them for inputs into models for geographic locations have only recently become available (Bhatt et al., 2015; M. Penny, N. Maire, et al., 2015). With the release of the final phase 3 data in 2015 the vaccine properties can now be determined with greater confidence. These data suggest that the initial efficacy against infection of RTS,S is higher but that the effect decays more

rapidly, than was previously estimated from phase 2 and from the shorter follow-up from phase 3 (M. Penny, P. Pemberton-Ross, et al., 2015; White et al., 2015).

Using the most recent phase 3 data, a series of new methodologies (Galactionova, Bertram, et al., 2015; Galactionova, Tediosi, et al., 2015; M. Penny, K. Galactionova, et al., 2015; M. Penny, N. Maire, et al., 2015) are applied to obtain predictions of the likely public health impact and cost-effectiveness of RTS,S administered in a four dose schedule starting at six month. We predict at national level for each of the 43 endemic Sub-Saharan African (SSA) countries and avoid speculative choice on geographic areas for pilot studies or sub-national implementation. In contrast to a recent study (M. Penny et al., 2016), our geographic specific predictions allow for differences in epidemiological context and health systems across settings, thus the generated predictions are apt to inform policy decision-making for malaria control in those settings.

Methods

Intervention

The RTS,S vaccine prevents infection by inducing humoral and cellular immunity, with high antibody titers, that block the parasite from infecting the liver (Regules et al., 2011). It is a monovalent lyophilized vaccine reconstituted with an adjuvant (AS01); both require cold chain storage (MVI, 2008). Trial data showed the vaccine to be more efficacious and enabling protection against severe disease only when administered in a four dose schedule in children (The RTSS Clinical Trials Partnership, 2012). Mapping trial design into the routine immunization schedule representative of SSA suggests a program targeting children between six and nine months with three doses and an additional fourth dose administered 18 months after the third. This schedule aligns with routinely administered vitamin A supplementation at six months and measles containing vaccine at nine months, reducing the number of new visits to only two in countries where these interventions already exist.

Our assumptions on coverage adjust for the challenges of scaling-up new interventions and those of reaching children outside of routine schedule: 75% of the country Diphtheria-Tetanus-Pertussis (DTP) rate was taken for the primary schedule, a 20 percentage point drop-off was assumed between third and fourth doses consistent with observed drop-off for measles vaccination (UNICEF & WHO, 2013). The vaccine is assumed to be rolled-out

through routine outlets and to achieve projected coverage within the first year of implementation.

Vaccine protection against infection

Vaccine profiles were parameterized with data from the 32 month or longer follow-up of the phase 3 clinical trial of RTS,S/AS01 (The RTSS Clinical Trials Partnership, 2015). Vaccine efficacy profiles were estimated by Bayesian MCMC fitting of model predictions to the site- and time-specific incidence of clinical malaria in both trial arms over the follow-up (M. Penny, P. Pemberton-Ross, et al., 2015). For the primary schedule, the initial efficacy against infection at third dose was estimated at 91.1% with a half-life of 7.32 months (with non-exponential decay); the initial efficacy at fourth dose reached only 49% (M. Penny, P. Pemberton-Ross, et al., 2015).

Estimating the public health impact of RTS,S immunization

Using a micro-simulation model of malaria epidemiology and control (*OpenMalaria*, 2016; T. Smith et al., 2006), disease burden was predicted for a range of immunization schedules, vaccine properties, entomological inoculation rates (EIR), and levels of treatment both in the absence and with the addition of the vaccine. Impact estimates were then computed as weighted averages over all simulations with weights dependent on country levels of treatment, coverage, and exposure (M. Penny, K. Galactionova, et al., 2015). *Pf*PR2-10 distributions in 2014 for each country were taken from (Bhatt et al., 2015) and treatment rates - from a previous analysis (Galactionova, Tediosi, et al., 2015). Assumptions on coverage of control interventions including LLINs reflect those underlying MAP 2014 prevalence surface estimates. Produced by the Oxford group (Bhatt et al., 2015) coverage of control interventions (ITNs, ACTs, IRS) for the region is estimated with a spatiotemporal Bayesian geostatistical model that draws on national malaria control program and household survey data. The level of malaria prevalence (measured by patent parasitemia in children between ages 2 and 10 (*Pf*PR_{2-10})), control interventions, immunization rate, population growth, and demography were held constant throughout the evaluation period. Further details on methodology and data are given in Appendix C, File C1.

By relating clinical disease to severe outcomes and death using historical data, the model enables predictions of vaccine`s impact for clinical outputs not explicitly measured in the trial, such as mortality, and under levels of coverage of preventive and control interventions representative of the endemic Africa (Ross et al., 2006). In this analysis public health impact of the vaccine was expressed in terms of uncomplicated and severe malaria episodes, deaths, and disability-adjusted life years (DALYs) (C. Murray et al., 2012), enabling

comparison to other malaria interventions and vaccines. DALYs were estimated based on a comprehensive measure of deaths that included both direct malaria deaths and deaths due to malaria co-morbidities (Ross et al., 2006). For comparison, estimates based on direct malaria deaths only were also reported.

Estimating program costs

Vaccine price was assumed to be 5 USD per dose; price points of 2 and 10 USD per dose were evaluated in the sensitivity analysis consistent with assumptions in (M. Penny, K. Galactionova, et al., 2015). Program costs included service delivery and direct household expenditures related to vaccination visit. These were extrapolated from a recent micro-costing study that estimated prospectively cost of RTS,S introduction in 6 SSA countries (Galactionova, Bertram, et al., 2015). Costs capture the economic value of the program and cover activities carried out both in the introductory stage and routine delivery. Given the broad scope of the analysis country specific values were not estimated for this study, instead a median of service delivery costs from (Galactionova, Bertram, et al., 2015) was applied to all countries. Heterogeneity in operational aspects of the program, unit costs, and use of resources within the EPI across the region, however, were addressed in the sensitivity analysis by re-estimating cost-effectiveness ratios over a broad and representative range of service delivery costs informed by (Galactionova, Bertram, et al., 2015).

Total program costs were based on the number of doses in the schedule, assumed coverage, and the cohort of surviving infants in each country. Further details in Appendix C, File C2.

Estimating treatment cost savings

Treatment costs savings were estimated by multiplying the number of cases averted by the vaccine over routine malaria control with respective cost per case. It included cost of diagnostics, antimalarial drugs, consumables (syringes, etc.), as well as facility charges such as labor and overheads, and direct household expenditures related to treatment-seeking. Costs reflect country levels and patterns in health seeking for malaria, compliance with the recommended first-line treatment, adherence with the drug regimens (Galactionova, Tediosi, et al., 2015), and cost of care (WHO, 2011b). Costing methodology is detailed in Appendix C, File C3.

Estimating cost-effectiveness

The impact of the program was evaluated from the societal perspective; only direct benefits and costs were considered in this analysis. Cost of the RTS,S immunization program net of

treatment cost savings was related to burden averted by the vaccine; the two outputs were summarized in terms of an incremental cost-effectiveness ratio (ICER). Unless otherwise noted, cost-effectiveness ratios are presented without discounting of health effects and with discounting of costs (3%) (C. J. L. Murray et al., 2012); ratios based on discounted DALYs averted are reported for comparison with previous analyses.

Program impact and cost-effectiveness were evaluated over a 10 year horizon with an assumed introduction date in 2017.

Sensitivity analysis

We assessed robustness of the impact predictions by varying key model inputs along their plausible ranges singly and in combination (Appendix C, Table C3). Choice of parameters was informed by an earlier extensive analysis of uncertainties around RTS,S predictions (Maire et al., 2011) that identified malaria transmission, price, and vaccine properties as key drivers. Further, multivariate scenarios were defined to capture the higher ranges of ICERs under conservative assumptions about vaccine properties, coverage, and transmission. Broad ranges over which parameters were varied were chosen to inform our understanding of the direction and magnitude of the potential bias in impact estimates induced by uncertainty around these key inputs at the country level.

Results

Overview of transmission, health system, economic, and demographic inputs

PfPR_{2-10} averages about 15% across the continent with an equal number of countries with parasite prevalence below and above 10%; weighted average *Pf*PR_{2-10} is above 40% only in Guinea and Mali (Table 1; Appendix C, Table C4). Coverage and effectiveness of malaria case management is highest in settings with higher transmission intensity; however, the immunization rate appears to be substantially lower in medium compared to low *Pf*PR_{2-10} countries. Treatment health savings only marginally offset the cost of the RTS,S program; with about half of fevers treated and cost of care significantly below cost per FVC even at conservative price assumptions. There is much variation across these key inputs within the narrow transmission ranges; differences that help explain variation in predicted effectiveness and cost-effectiveness of the vaccine across countries.

Table 4.1 Summary of key inputs used for country specific predictions of RTS,S impact and cost-effectiveness grouped by levels of PfPR2-10 and Gavi eligibility status

Input	*Pf*PR$_{2-10}$				GAVI eligible (GNI< 1'580 USD)	All countries
	<5%	5-10%	10-40%	>40%		
*Pf*PR$_{2-10}$ (%)[a]	2.6	7	23.3	43.8	15.7	14.8
	[2.0-4.8]	[5.1-9.2]	[10.7-39.9]	[42.2-45.5]	[2.0-45.5]	[2.0-45.5]
EIR[b]	0.29	1.64	5.27	6.68	3.27	3.12
	[0.00-1.04]	[0.43-3.53]	[0.18-17.38]	[6.56-6.81]	[0.01-17.38]	[0.00-17.38]
Health seeking (%)[c]	48.3	53.5	61.9	44.1	51.8	55.3
	[13.0-75.6]	[16.0-77.3]	[32.0-84.0]	[40.2-48.1]	[13.0-84.0]	[13.0-84.0]
Effective coverage (%)[d]	31.7	34.4	36.4	20.6	30.6	33.8
	[7.8-71.3]	[8.3-54.3]	[16.7-65.9]	[19.9-21.3]	[7.8-65.9]	[7.8-71.3]
Coverage 3rd dose (%)[e]	63.1	58.6	55.9	49.1	58.4	58.4
	[31.5-74.0]	[34.7-72.0]	[11.8-70.0]	[44.3-54.0]	[29.2-74.0]	[11.8-74.0]
Coverage 4th dose (%)[f]	50.5	46.9	44.7	39.3	46.8	46.7
	[25.2-59.2]	[27.8-57.6]	[9.4-56.0]	[35.4-43.2]	[23.4-59.2]	[9.4-59.2]
Cost per uncomplicated case (USD)	3.82	3.49	4.04	1.45	2.18	3.76
	[1.62-13.19]	[0.56-10.01]	[1.08-22.70]	[1.31-1.59]	[0.56-4.02]	[0.56-22.70]
Cost per severe case (USD)	102.93	86.98	179.84	45.95	54.24	133.46
	[40.91-422.59]	[36.20-238.78]	[37.07-1884.67]	[45.36-46.54]	[36.20-86.90]	[36.20-1'884.67]
GDP per capita (USD)[g]	1'648	1'697	2'528	629	744	2'018
	[133-7'411]	[267-5'783]	[237-20'581]	[531-726]	[133-1'610]	[133-20'581]
Government health care expenditures per capita (USD)[h]	113	78	113	39	44	103
	[17-423]	[18-267]	[13-714]	[25-53]	[13-110]	[13-714]
Total infants (millions)[i]	7.5	5.3	18.9	1.1	22.1	32.8
Total population (millions)[j]	230.3	145.6	500.3	27.8	610.8	904.0
Number of countries	14	7	20	2	32	43

Estimates represent medians across countries within the group, range (min-max) reported in parenthesis below; Nominal values are expressed in 2013 USD; [a] Population weighted median *Pf*PR$_{2-10}$ based on 2014 *estimates* from MAP(12); [b] Population weighted median EIR based on 2014 estimates from MAP(12); [c] Author tabulations based on country DHS data, 14 day recall; [d] Defined as an expected probability of clinical and parasitological cure for an episode of malaria fever. Updated country estimates based on (15); [e] Projected from country DTP coverage(19) assumed 75% of country DTP3 coverage; [f] Projected from country DTP coverage(19) assumed 60% of country DTP3 coverage; [g, h, i, j] (38); Country estimates are reported in Appendix C, Table C4.

Public health impact and cost-effectiveness of RTS,S immunization

Across the 43 countries the program is estimated to avert over 123 million malaria episodes and over half a million malaria related deaths within the first ten years (Tables 2; Appendix C, Tables C5-C6). Countries with higher levels of *Pf*PR_{2-10}will benefit most from the vaccine introduction. At these higher *Pf*PR_{2-10} ranges, vaccine`s impact averages over 26'000 DALYs and about 500 deaths averted per 100'000 FVC; the impact is half as large when estimated across countries with *Pf*PR_{2-10} between 5 and 10%, and about a quarter - in countries with prevalence below 5%. Half of the total predicted impact of RTS,S vaccination will be incurred in four countries: Nigeria, Democratic Republic of the Congo, Uganda, and Tanzania; Nigeria alone accounts for over 20% of total DALYs averted (Appendix C, Figure C1).

Predicted cost-effectiveness ratios vary similarly with *Pf*PR_{2-10}: at a vaccine price per dose of 5 USD the ICER averages 188 USD (range of country median estimates 78 to 22'448) per DALY averted across the 43 countries. The range is widened substantially by a handful of countries with low *Pf*PR_{2-10} including Botswana, Djibouti, Eritrea, and Ethiopia where predicted impact is highly imprecise. When averaged across countries with *Pf*PR_{2-10} above 10% the estimated ICER is about 136 USD per DALY averted with a much more narrow range between 115 and 220 USD.

The impact of the vaccine increases with *Pf*PR_{2-10} and generally plateaus between *Pf*PR_{2-10} 10 and 40% (Figure 4.1). While impact estimates are always positive, the uncertainty around them is large. It reflects both structural and stochastic uncertainty in the modelled estimates. Variation in the vaccine`s impact and cost-effectiveness between countries within the narrow transmission ranges is due to epidemiological and health systems factors; their role can be illustrated by examining predictions for Gabon and Niger- countries with the same estimated weighted *Pf*PR_{2-10} of 15%. Compared to Gabon, the immunization rate in Niger is lower, and so is the risk and distribution of *P. falciparum*, all resulting in a projected impact of the vaccine of about 20% lower and an ICER twice as high (Appendix C, Tables C4 and C6). On average, however, the ratio is fairly similar with predicted median ICERs below 200 USD per DALY averted across countries with *Pf*PR_{2-10} above 10%.

Predicted impact is highest in Central African Republic and a group of coastal West African countries, where over 500 deaths averted per 100'000 FVC are estimated compared to an average of about 350 for the region (Figure 4.2). Lowest impact is predicted for countries at the Horn of Africa. It is in these low prevalence settings, including Ethiopia, Eritrea, and Djibouti that the ICERs are also highest (Appendix C, Table C6).

Table 4.2 Cumulative predictive impact and cost-effectiveness of RTS,S immunization: disease averted, costs of the program, and cost-effectiveness grouped by country levels of PfPR2-10 and GAVI eligibility status

	*Pf*PR$_{2-10}$				GAVI eligible	All countries
	<5%	5-10%	10-40%	>40%		
Total episodes averted (millions)	7	21.8	89.3	5.1	81.3	123.2
	(6.5; 7.5)	(20.3; 23.3)	(85.3; 93.3)	(5.0; 5.3)	(77.4; 85.3)	(117.3; 129.1)
Total deaths [a] averted (thousands)	36	106.2	443.9	28.1	404.2	614.2
	(32.3; 39.7)	(96.3; 116.1)	(415.1; 472.8)	(26.5; 29.6)	(375.7; 432.6)	(571.7; 656.8)
Total direct deaths [b] averted (thousands)	20.5	56.3	221	13.5	206.1	311.2
	(18.4; 22.6)	(50.9; 61.7)	(205.7; 236.3)	(12.6; 14.3)	(190.7; 221.4)	(288.4; 334.0)
Total DALYs averted (millions)	1.9	5.6	23.4	1.5	21.2	32.3
	(1.7; 2.1)	(5.1; 6.1)	(21.8; 24.9)	(1.4; 1.6)	(19.7; 22.7)	(30.0; 34.5)
DALYs averted /100,000 FVC	6'006	15'289	25'949	28'402	18'050	18'413
	[156-26'135]	[4'822-36'946]	[8'937-40'054]	[17'730-36'008]	[156-40'054]	[156-40'054]
Deaths averted /100,000 FVC	115	291	495	540	345	350
	[3-500]	[92-703]	[170-761]	[337-682]	[3-761]	[3-761]
Total net program costs (millions)[c]	1'396	1'198	3'329	189	4'309	6'111
	(1'395; 1'396)	(1'197; 1'199)	(3'327; 3'331)	(189; 189)	(4'307; 4'310)	(6'108; 6'114)
USD/ DALY averted	581	226	132	122	192	188
	[133-22'448]	[93-723]	[78-387]	[96-196]	[87-22'448]	[78-22'448]
USD/ Direct DALY averted	994	407	267	261	369	360
	[271-67'529]	[174-1'678]	[147-763]	[182-358]	[161-67'529]	[147-67'529]
USD/ Discounted DALY averted	1'140	444	260	241	378	370
	[262-43'601]	[182-1'419]	[154-759]	[190-385]	[171-43'601]	[154-43'601]
USD/ Discounted direct DALY averted	1'937	797	525	514	725	707
	[532-133'830]	[342-3'292]	[288-1'492]	[358-704]	[316-133'830]	[288-133'830]

Group totals for events averted and program costs are reported as averages and 95th percentile prediction intervals cumulated over 10 years and over all countries in the respective group. Narrow prediction intervals on totals do not imply high precision of these estimates but rather are an artifact of variation being "cancelled out" when summing country predictions by model and stochastic seed. See Appendix C, File C1 for further details. Cumulative program output metrics per 100'000 FVC and cost-effectiveness ratios are reported as medians and min and max range of country median estimates averaged over uncertainty predictions from the model. Unless otherwise noted DALYs are estimated without age-weighting and discounting. [a] "Total deaths" inlcude malaria deaths attributable to malaria and deaths that occur with a co-mornbidity and malaria. [b] "Total direct deaths" inlcude only deaths directly attributable to malaria. [c] "Total net program costs" represent cumulative program costs minus any health savings resulting from averted malaria mortality and morbidity incurred by the health systems and patients; costs are discounted at 3%. Total net program costs and ICER`s estimated from health systems perspective are reported in Appendix C, File C7. Nominal values expressed in 2013 USD.

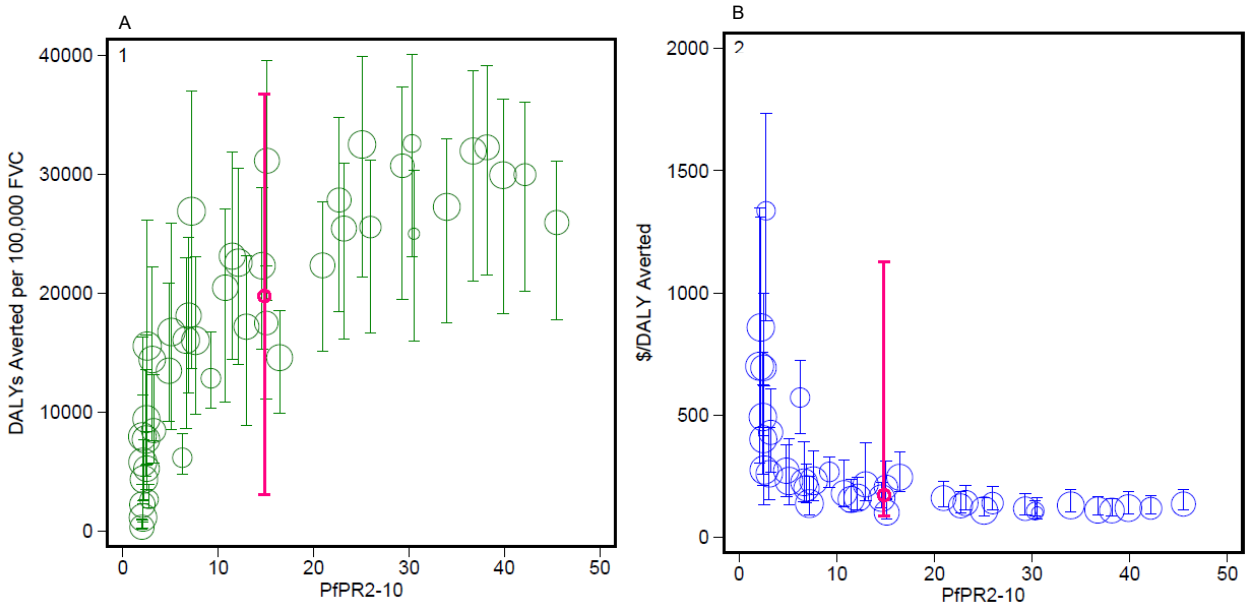

Figure 4.1 Figure 1. Cumulative predicted impact and cost-effectiveness of RTS,S immunization by PfPR2-10

Predicted impact of the vaccine summarized in terms of DALYs averted per 100'000 FVC (A) and cost per DALY averted (B) are plotted against *Pf*PR_{2-10} with data points proportional to immunization coverage. Estimates represent country cumulative statistics averaged across the uncertainty predictions from the model and are overlaid with 95th percentile prediction intervals. Four countries with extremely high cost per DALY averted were omitted from the plot for ease of viewing. These inlcude countries with very low weighted *Pf*PR_{2-10} for which model estimates are highly uncertain, namely Botswana (1'389 USD (208; 12'519), Djibouti (1'858 (877; 3'696)), Eritrea (3'252 USD (1'522; 4'532)), and Ethiopia (12'764 USD (3'427; 22'448)). Median and 95th percentile prediction intervals across the 39 countries are plotted in pink.

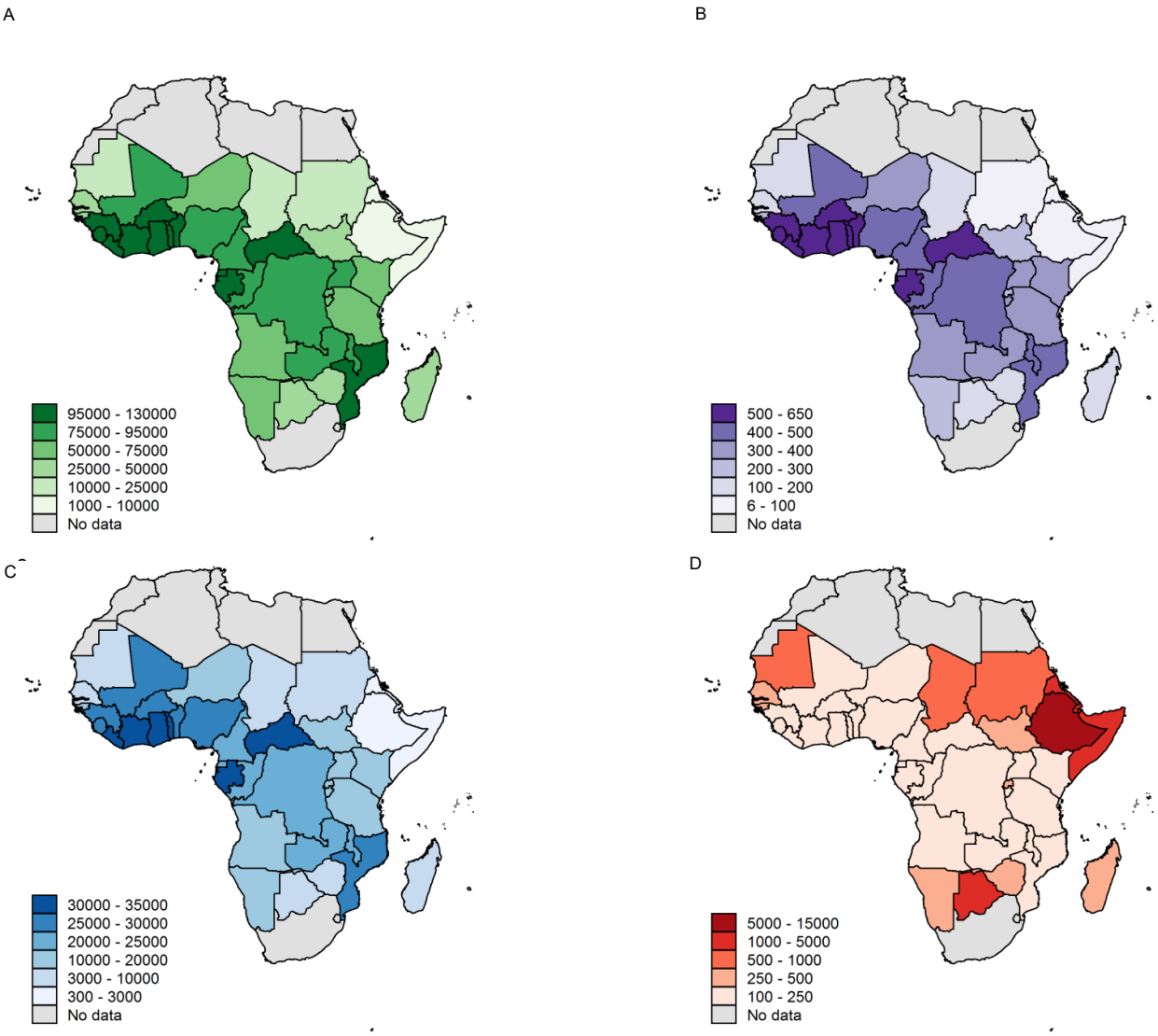

Figure 4.2 Cumulative impact and cost-effectiveness of RTS,S immunization by country

Cumulative number of clinical cases (A), deaths (B), DALYs (C) averted per 100'000 FVC, and cost per DALY averted (2013 USD) (D) at year 10 following vaccine introduction. Country estimates represent mean values averaged over uncertainty predictions from the model.

Sensitivity analysis

Over the ranges tested and when varied singly parameter uncertainty translates in predicted ICER and DALY ranges that are on average, at most, double or half the baseline values (Figure 4.3). There is more heterogeneity across countries in response to varying parameters related to transmission (scenarios 1,2) and immunization coverage (scenarios 3, 19). Small changes in these inputs result in disproportionally large changes in predictions in lower *Pf*PR_{2-10} settings. The largest increase in the ICER is estimated for scenarios 5 and 20. In the prior the vaccine price per dose is set to 10 USD -twice the baseline assumption- resulting in predicted ICERs that are also doubled. In the latter, the vaccine is evaluated under low assumptions on efficacy, half-life, and coverage; here again the predicted ICERs double.

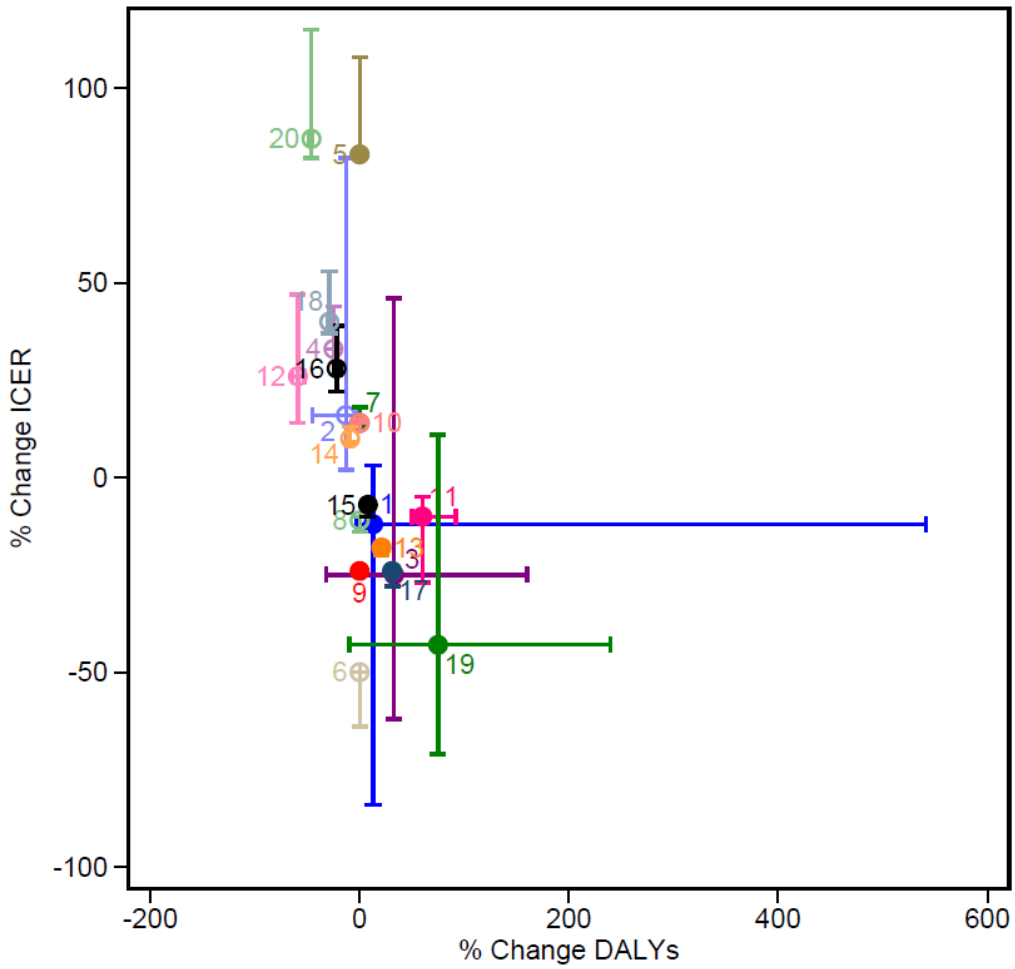

Figure 4.3 Sensitivity analysis over range of vaccine properties and country specific inputs: percent change in predicted ICER and DALYs averted from baseline scenario

Estimates represent change in predicted DALYs averted and ICER in response to varying single or multiple parameters from baseline to its low and high values (See Appendix C, Table C3 for ranges simulated). The change in predicted DALYs averted is summarized as a median and a range (min-max) across 43 countries. Values of predicted ICERs and DALYs averted for each scenario are reported in Appendix C, Table C7. The following scenarios were simulated: 1 Transmission high; 2 Transmission low; 3 Immunization rate high; 4 Immunization rate low; 5 Price high; 6 Price low; 7 Delivery cost high; 8 Delivery cost low; 9 Discount rate high; 10 Discount rate low; 11 Time horizon high; 12 Time horizon low; 13 Half-life high; 14 Half-life low; 15 Efficacy high; 16 Efficacy low; 17 Initial efficacy and half-life high; 18 Initial efficacy and half-life low; 19 Initial efficacy, half-life, and immunization rate high; 20 Initial efficacy, half-life, and immunization rate low.

Discussion

Following 10 years of implementation, RTS,S/AS01 is predicted to substantially reduce malaria burden in children across endemic countries in SSA. Consistent with the predictions of a recent multi-model study (M. Penny et al., 2016), higher impact is expected in counties with higher *Pf*PR_{2-10}, and thus higher burden for RTS,S to avert. Country level estimates, however, differ in magnitude from the corresponding generic prevalence predictions in (M. Penny et al., 2016). Local estimates reflect differences in assumptions on vaccination coverage (country range between 9 and 59% at fourth dose assumed in this study compared to 72% in (M. Penny et al., 2016)), exposure heterogeneity (not explored in (M. Penny et al., 2016), case management (country range between 8 and 71% compared to 45% in (M. Penny et al., 2016)(5)), and country costs, including service delivery (only cost of commodities were included in (M. Penny et al., 2016)). We show that country specific epidemiological and health systems factors result in substantial variation around generic prevalence averages in both public health impact and cost-effectiveness estimates.

RTS,S is predicted to be highly cost-effective in most countries; the estimated ICERs are significantly below the regional GDP per capita (median 842 USD, IQR: 531-1'668) (Evans et al., 2005; WHO, 2003). Affordability of this new intervention, however, is to be further assessed against program financing and budgets for other vaccines as well as broader resources for health. Direct comparisons of the vaccine with other malaria control interventions were not undertaken in this evaluation. Drawing on literature to provide indicative ranges for comparison is subject to a number of limitations including differences in methodological approaches, scope of costs and effects considered, scale of the program, relevance of operational aspects of the program to a particular setting, as well as transmission effects (Johns et al., 2005; White et al., 2011). The importance of the latter is particularly well illustrated by the large differentials in the vaccine`s predicted impact and cost-effectiveness across the transmission ranges, variation that has been documented for other malaria control interventions as well (Hanson et al., 2004; White et al., 2011). Ranges of cost-effectiveness from the literature suggest the vaccine might be more expensive than current means of malaria control (White et al., 2011) and some of the new vaccines being added to EPI schedules in the region (Ayieko et al., 2009; Bar-Zeev et al., 2016; Johansson et al., 2015; Rheingans et al., 2012). However, incremental analyses that consider a control intervention package, including this new intervention, might be more favorable for the vaccine if effectiveness is evaluated in the same transmission intensity and scale-up beyond current levels of control programs is properly accounted for (Johns et al., 2005).

As with all modelling and simulation studies there are a number of limitations to our analysis. Firstly, predicted vaccine impact is dependent on the extent of follow-up of immunized children in the trial and if further follow-up data becomes available it will be important to reassess the underlying protection of the vaccine. Secondly, as indicated in a previous analysis (M. A. Penny, K. Galactionova, et al., 2015), predictions of deaths and thus DALYs averted are dependent on the simulation model fits to historical data of clinical incidence and mortality. Results are also dependent on quality of data informing country levels of current burden, prevalence, immunization coverage, and demographics. We have attempted to partially address these uncertainties with sensitivity analysis.

Consistent with previous studies, the level of *Pf*PR_{2-10} and heterogeneity in transmission are key drivers of the vaccine`s impact and cost-effectiveness. Impact estimates presented here, however, are generated under an assumption of stable transmission, which implies that there is no additional benefit in terms of reduction in transmission that could be achieved with current levels of malaria control. Further, by assuming constant levels of control interventions the vaccine`s impact may be overstated if one believes that the recent scale-up of control programs and economic development will be sustained into the future (Griffin et al., 2016). If these trends are to continue and as malaria intensity subsides, re-evaluation of vaccine`s viability and cost-effectiveness might be needed. At low *Pf*PR_{2-10} (<10%) the vaccine`s impact is predicted to be modest; here the risk of the disease is shifting to older ages (Pemberton-Ross et al., 2015) and the new intervention competes with routine malaria control for cases to avert. Deployments considering sub-national implementation targeting pockets of malaria transmission rather than national campaigns might be more appropriate in these settings.

Coverage is another key parameter subject to uncertainty; tying it to routine immunization might have been optimistic given the vaccine's properties and short-lived protection it enables. Estimated ICERs increase to 256 USD [134-12'528] per DALY averted when coverage is reduced by 25% (Appendix C, Table C8). Alternatively, if the program achieves coverage rates similar to country DTP levels, the ratio decreases to 139 USD [70-7'047] per DALY averted and in settings with *Pf*PR_{2-10} above 10% it is reduced to 95 USD [70-173]. Several studies have been conducted to assess the vaccine`s acceptability in endemic countries (Bingham et al., 2012; Febir et al., 2013; Ojakaa et al., 2011; Romore et al., 2015); while community response has been positive, it is difficult to judge whether it will translate to as high uptake, particularly as protection begins to wane and vaccinated children continue to fall ill. Careful and sustained communication will be key to the program`s success.

For an RTS,S program to reach its full potential, it is not only important to ensure vaccination at rates similar to those achieved with routine vaccines in the general population but reaching groups with the highest risk of malaria becomes pivotally important. Achieving high coverage for these vulnerable children will require addressing social and cultural perceptions about the vaccines, improving systems for providing health care, and devising innovative delivery strategies to reach these generally underserved populations.

Furthermore, the predictions were made at national levels of coverage of control interventions and immunization rates; these do not incorporate inequities in access to health services, particularly with respect to heterogeneity in malaria transmission. Not only is malaria risk higher among these marginalized groups, but given lower coverage of control interventions, the outcomes of malaria episodes are also more severe (Barat et al., 2004; Houngbedji et al., 2015). Policies should thus consider the operational advantages of targeting these populations with the vaccine, and the extent to which RTS,S immunization could be combined with strengthening delivery of other preventive and control measures, including interventions aimed at health risks other than malaria.

At country level, introducing the vaccine into the National Immunization Program (NIP) will have broad implications for the health systems (Wang et al., 2013). It might undermine routine care provision if resources, including medical staff and cold chain, are diverted away to accommodate the new intervention. One the other hand, new vaccination visits provide another opportunity for health providers to reach children that may lead to improvements in health beyond malaria related outcomes. Most directly, malaria burden averted will reduce use of outpatient and, to a lesser extent, inpatient services by children. At assumed coverage rates for the new program and at current levels of malaria case management a reduction of 9.14% [1.29-18.86] in visits for uncomplicated malaria is predicted and 7.06% [0.79-14.84] for severe episodes across the 43 countries (Appendix C Table C5) - a substantial decrease in service volume.

At the same time introduction of RTS,S will also require significant resources. Estimates of cost-effectiveness presented in this analysis rely on generic assumptions about cost of vaccine delivery and as such do not capture the heterogeneity cost of service delivery across countries. Yet, at vaccine price of 5 USD per dose these costs account for 10- 26% of total program costs; the fraction is higher in settings where cost of labor is high (Galactionova, Bertram, et al., 2015). This suggests that variation in cost of service delivery, assuming routine deployment, contributes only marginally to uncertainty in predicted ratios (Appendix C, Table C8 scenarios 7-8). As ICERs vary almost linearly with price, estimates

can be updated with setting specific information on cost of service delivery or costs of alternate vaccine deployment modality if available.

WHO`s recommendation for a large scale trial implementation of RTS,S targets primarily uncertainties around the operational aspects of the program, namely the feasibility of delivering a four dose schedule that includes new immunization visits in a weak health systems environment (WHO, 2016a). While the details of the program are best tested in a trial setting, our analysis provides further support to the recommendation`s focus on “how best to” introduce the vaccine. We show that at higher transmission intensities RTS,S remains highly cost-effective even under most conservative assumptions on vaccine properties, coverage, and price. Pilot studies should prioritize deployment modalities that include delivery of the vaccine along other health services and seek broader synergies within the National Immunization Program. Our analysis suggests scope for sub-national implementation in settings with heterogeneous transmission and highlights the advantages of targeted and outreach strategies to populations at highest risk where most impact is likely to be achieved. Furthermore, the analysis offers some initial *setting-specific* predictions of potential vaccine impact against which trial results could be scaled to inform country adoption decisions.

Declarations

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Contributors

KG and MAP conceived the study and designed the analysis. PG provided prevalence data and advice. KG, MAP, FC did the analyses. TAS and FT supported the analyses. KG, MAP, TAS, and FT supported interpretation and policy contextualization. KG wrote the first draft of the manuscript. KG, MAP, TAS, and FT wrote the manuscript. All authors discussed the results and contributed to revision of the final manuscript.

Conflict of interest

All authors declare no competing interests.

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Chapter 5: State of inequality in malaria intervention coverage in Sub-Saharan African countries

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Abstract

Background
Scale-up of malaria interventions over the last decade yielded a significant reduction in malaria transmission and disease burden in Sub-Saharan Africa. We estimated economic gradients in distribution of these efforts and of their impacts within and across endemic countries.

Methods
Using Demographic and Health Surveys we computed equity metrics to characterize distribution of malaria interventions in 30 endemic countries proxying economic position with an asset-wealth index. Gradients were summarized in a concentration index, tabulated against level of coverage, and compared among interventions, across countries, and against respective trends over 2005-2015 year period.

Results
There remain broad differences in coverage of malaria interventions and their distribution by wealth within and across countries. In most - economic gradients are lacking or favor the poorest for vector control; malaria services delivered through the formal health-care sector are much less equitable. Scale-up of interventions in many countries improved access across the wealth continuum, in some - these efforts consistently prioritized the poorest. Expansions in control programs generally narrowed coverage gaps between economic strata; gradients persist in countries where growth was slower in the poorest quintile or where baseline inequality was large. Despite progress, malaria is consistently concentrated in the poorest; the degree of inequality in burden far surpassing that expected given gradients in the distribution of interventions.

Conclusions
Economic gradients in the distributions of interventions persist over time limiting progress toward equity in malaria control. We found that in countries with large baseline inequality in distribution of interventions even a small bias in expansion favoring the least poor yielded large gradients in intervention coverage while pro-poor growth failed to close the gap between the poorest and least poor. We demonstrated that dimensions of disadvantage compound for the poor; lack of economic gradients in distribution of malaria services does not translate to equity in coverage nor can it be interpreted to imply equity in distribution of risk or disease burden. Our analysis testifies to the progress made by countries in narrowing economic gradients in malaria interventions and highlights the scope for continued monitoring of programs with respect to equity.

Keywords
malaria, malaria intervention coverage, equity, concentration index, asset-wealth quintiles, DHS

Background

Over the last decade malaria programs have been transformed with increased investment, new technologies, economic development, and shifting paradigms in global health (WHO, 2016b). Prior to 2008 control efforts in the region focused on groups at highest risk of adverse outcomes, especially pregnant women and children under the age of five (WHO, 2008). Control programs prioritized distribution channels most likely to reach these populations such as routine vaccination campaigns, antenatal clinics, and social marketing where malaria commodities were subsidized or rendered for free (O'Connell et al., 2011; Willey et al., 2012). These channels benefitted most those with access to health facilities, which tended to be the less poor urban households (Steketee & Eisele, 2009; Webster et al., 2005). In 2008 a global call from the UN Secretary General placed the universal coverage of malaria interventions at the center of control efforts (*Secretary-General announces 'Roll Back Malaria Partnership' on World Malaria Day*, 2008). The aim was reflected in the Global Action Plan for Malaria launched the same year by the Roll Back Malaria laying out a blueprint for control, elimination, and eventual eradication of malaria (Roll Back Malaria, 2008). It states that a vision of a “malaria free world” is brought about by “achieving and sustaining universal access to and utilization of preventive measures; achieving universal access to case management in the public and private sectors and in the community; and accelerating the development of surveillance systems (Roll Back Malaria, 2011).” The aim broadened the scope of control efforts in endemic countries to include all ages and led to programs shifting from targeted distribution of insecticide treated nets (ITNs) to mass distribution campaigns and community delivery supported by routine services. In malaria case management, fast-acting artemisinin-based combination therapies (ACTs) replaced monotherapy (“non artemisinin” drug formulations) as the recommended first-line treatment for uncomplicated malaria in 2004 in response to emerging parasite resistance (WHO, 2006). Initially costly and scarce, these drugs became increasingly available through the Global Fund and the novel financing mechanisms it enabled such as the Affordable Medicines Facility - malaria (AMFm) (Gelband & Seiter, 2007; *Overview*). Innovative delivery channels were introduced in many endemic countries to directly tackle distributional failures; these engaged the informal health sector and emphasized community health workers in servicing vulnerable and hard-to-reach populations (Young et al., 2012). As endemic countries adopted and adapted to these new policies the malaria service gap between the poorest and the least poor began to narrow (Gwatkin, 2017).

Economic gradients and progress toward equity in malaria control and curative interventions have been documented in several broad strands of literature. A large number of studies evaluated ITN coverage following a mass-distribution campaign in narrow geographic areas or within a single country showing improvement in equity after the campaign (Bonner et al., 2011; Mbachu et al., 2012; Ntuku et al., 2017; Zollner et al., 2015). Socio-economic status has also been included as one of covariates explaining coverage and use of malaria interventions; while its relative importance varied by setting and model specification, it has generally been found to be an important predictor with both use and coverage increasing with economic status (Barat et al., 2004; Hill et al., 2013; Ruyange et al., 2016). Several multi-country analyses included ITN use among children under the age of five into a composite index for maternal and child health to track country and regional progress toward the Millennium Development Goals (Victora et al., 2012); these studies found that although relative inequalities have generally been narrowing, appreciable differences between the poorest and the least poor persist. There have been a number of evaluations that focused on a single malaria intervention (most commonly ITNs) (Taylor et al., 2015; Taylor, Florey, et al., 2017). To the best of our knowledge only one earlier study (Steketee & Eisele, 2009) assessed equity across a range of malaria interventions in a large number of endemic African countries; the analysis drew on survey reports from 2006 to 2008 and as such was constrained to comparisons between asset-wealth quintiles. It showed that in 13 out of 25 countries ITN ownership was equitable while malaria treatment for febrile children and intermittent preventive treatment in pregnant women were predominantly inequitable. There has been no comprehensive assessment of malaria interventions with respect to equity since.

Monitoring equity in intervention coverage takes a new meaning today as malaria control programs mobilize efforts toward elimination (Cotter et al., 2013). Scale-up of interventions and introduction of new technologies can enhance inequities if implemented without an explicit focus on equity (Gwatkin, 2005). While wealth-related gradients have been narrowing, these gains were achieved at very low baseline coverages and with extensive donor support (Snow et al., 2010); sustaining these gains and scaling-up toward populations at highest risk of malaria might be a challenge for many countries (Rodriguez et al., 2017). This study presents an update on the state of inequality in malaria intervention coverage in endemic Sub-Saharan African countries through to 2015. We follow a standard framework for assessment of equity in health (WHO, 2013) and interpret the estimates it yields with respect to their relevance to control programs.

Methods

Data sources

The Demographic and Health and Malaria Indicator Surveys (DHS/MIS) are the primary sources of data for this study. Comparable in scope (Burgert et al., 2012), these nationally representative household surveys collect data on a range of health behaviors and household characteristics by interviewing women of reproductive age (MEASURE DHS, 2013). In endemic countries the questionnaire also covers access to, and use of, malaria interventions; in a subset of these measurements of malaria parasite levels and anemia in a sample of children and pregnant women are included (Florey, 2014). In the primary analysis, we included countries that conducted at least one survey between 2011 and 2016; of these, countries with repeated surveys between 2003 and 2016 were included in trend analysis. Surveys by country are listed in Appendix D, Table D1.

In auxiliary analysis we additionally used 2015 modeled surfaces of malaria endemicity (mean *P falciparum* prevalence in children aged between two and ten (*Pf*PR_{2-10})) from the Malaria Atlas Project (MAP) (*Malaria Atlas Project*) to characterize malaria transmission at sub-national level. This was accomplished by mapping GPS locations of survey clusters into malaria endemicity surfaces (Bennett et al., 2017; Burgert et al., 2012); *Pf*PR_{2-10} value at the centroid coordinates of the cluster was assigned to all households.

To enhance graphical representation of estimates we also merged in 2015 country mean *Pf*PR_{2-10} from MAP and population estimates from the World Bank (WB, 2015).

Outcomes

We assessed intervention coverage with a subset of standard monitoring and evaluation indicators adopted in global malaria strategic documents and endorsed by endemic countries to track progress toward control and elimination targets (Barat et al., 2004; Hill et al., 2013; Ruyange et al., 2016). The indicators selected for the analysis relate most directly to malaria outcomes (protection or cure). For instance, we focus on adequate access to ITNs within households covering all members and compliant malaria prophylaxis for pregnant women during an ANC visit rather than the broader indicators of household access to any ITN or receipt of at least one dose of SP during pregnancy. These more stringent definitions will yield lower coverages and potentially higher inequality than estimates based on indicators defined more broadly.

We assessed six malaria intervention coverage indicators (*coverage* is used here loosely to cover both access and use of interventions). To capture the reach of national malaria control programs we evaluated ITN coverage as a proportion of households with at least one ITN for every two persons. ITN use was estimated as the proportion of population that slept under an ITN in the previous night. Coverage of IRS was expressed as a proportion of households residing in dwellings sprayed with an insecticide within the last 12 months. This definition is broader than the population targeted by the intervention. Unlike other malaria interventions that are deployed nationally, IRS is implemented only in foci of high malaria transmission in a subset of countries in the region. Constrained by the data, malaria prophylaxis was evaluated only among women; we calculated the proportion of recent mothers (live birth within last two years) that received at least three doses of sulphadoxine-pyrimethamine (SP) during antenatal care (ANC) visits. Distribution of curative interventions was estimated among children under the age of five and conditional on fever. Despite progress, access to ACTs (current WHO recommended first-line treatment for uncomplicated malaria (WHO, 2010)) remains low with many antimalarial drugs other than the country recommended first-line medication in wide circulation (Bennett et al., 2017; Galactionova, Tediosi, et al., 2015). To allow for a broader snapshot of malaria case management we included two indicators: proportion of children with fever that sought care at a formal provider (i.e. OPD, IPD, government and private health centers), and proportion of children with fever that were treated with any antimalarial medication including both ACT and non-ACT antimalarials. More narrow definitions of malaria case management were also assessed including the proportion of children with fever that received the first-line antimalarial according to country policy and are reported in Appendix D Table D9; we refer to these estimates when discussing malaria treatment.

Of health indicators, we evaluated malaria parasitemia in children aged 6 to 59 months according to microscopy. Given the lack of a gold standard diagnostic test for malaria that is practical for use in national survey settings (Florey, 2014), we also report prevalence according to RDT (Appendix D, Table D10). RDT parasite prevalence estimates are generally higher and show somewhat stronger economic gradients than those based on microscopy.

Socio-economic status stratifier

Distribution of malaria intervention coverage and health indicators was evaluated against an asset-wealth index; this stratifier reflects the relative economic standing of households in a given country at the time of the survey (Rutstein & Johnson, 2004). Derived from a national distribution of assets weighted with principal component analysis and adjusted for place of

residence the index has been shown to perform well in identifying the most disadvantaged groups akin to other measures of relative poverty. It has been used extensively in health equity research in low-income settings including for malaria (Mwageni et al., 2005; Steketee & Eisele, 2009; Taylor et al., 2015; Tusting et al., 2016; Victora et al., 2012).

Statistical analysis

We calculated absolute and relative differences in indicators between households in lowest and highest wealth quintiles. We also assessed the degree of inequality in indicators across the whole distribution of asset-wealth scores with a concentration index (CIX). CIX is a relative measure of inequality that indicates the extent to which an indicator is concentrated among the disadvantaged or the advantaged within a particular setting. It is defined as twice the area between the concentration curve and the line of equality (O`Donnell et al., 2007). Negative values of CIX denote a disproportionate concentration of service or health variable among the poorest, positive – among the least poor. The index and the corresponding 95% confidence intervals were computed with *conindex* command in Stata 14 SE (O'Donnell et al., 2016). Changes in coverage over time were expressed in terms of excess change (WHO, 2013). This metric represents the difference in average annual change in a given indicator between the lowest and highest asset-wealth quintiles. Considered along the absolute change in population average the metric allows categorization of the trend in outcome with respect to equity. A negative excess change at increasing population average suggests the expansion is pro-poor (higher average annual increase in the poorest quintile compared to the least poor) and so forth (WHO, 2015e). We refer to distributions or changes in distribution that favor the least poor as “inequitable”, while inequalities and changes that favor the poor are termed "pro-poor" (WHO, 2013).

The indicators were coded following (Roll Back Malaria, 2013) and replicate DHS estimates in final country reports (MEASURE DHS). All reported statistics are population weighted and account for the complex survey design. The analysis was implemented in Stata 14 SE (StataCorp, 2015).

Results

Overall, across countries and coverage indicators malaria programs in the region are inequitable (Table 5.1). Yet, in 16 out of 30 countries ITN ownership is distributed equally or favors the poorest; in over half of the countries ITN use and IRS are distributed equally or

favor the poorest; for interventions relying on the formal health sector such as IPTp and access to formal care provider inequities are not evident in nearly half of the countries. These categorizations refer to relative differences in coverage of malaria interventions across the asset-wealth continuum within countries and do not take into account the level of intervention. For instance, in Benin where household access to at least one ITN for every two persons is disproportionately higher among the least poor (CIX=0.07) the poorest strata have better access to ITNs in absolute terms than the poorest strata in Cote d'Ivoire where the indicator is equitably distributed (42% and 34% respectively) (Appendix D, Table D3).

Table 5.1 Summary of distribution of malaria interventions across asset-wealth index in Sub-Saharan African countries in 2015*

Intervention	Pro-Poor	Inequitable	No difference across the asset-wealth index distribution
Household with at least one ITN for every 2 persons	CIV, COG, GAB, GHA, LBR, NAM, ZWE	AGO, BDI, BEN, BFA, CMR, COM, KEN, MLI, MOZ, MWI, NER, RWA, TZA, ZMB	COD, GIN, MDG, NGA, SEN, SLE, TCD, TGO, UGA
Population who slept under an ITN last night	CIV, COG, GAB, GHA, GIN, LBR, MDG, NAM, SLE, TGO, UGA, ZWE	AGO, BDI, CMR, COM, KEN, MOZ, MWI, NER, RWA, TCD, TZA	BEN, BFA, COD, MLI, NGA, SEN, ZMB
Household with IRS in the past 12 months	BDI, BEN, COM, GHA, LBR, NAM, SEN, UGA, ZWE	BFA, CIV, CMR, GAB, GIN, MOZ, NER, SLE, TCD, ZMB	MDG, MLI, MWI, NGA, TZA
Mother received 3+ doses of SP during ANC visit		AGO, BEN, CIV, CMR, GHA, GIN, MLI, MOZ, NER, NGA, TCD, TGO, TZA, ZMB	BDI, COD, COG, COM, GAB, KEN, LBR, MDG, MWI, NAM, SEN, SLE, UGA
Child (<5) with fever sought care at a formal provider		AGO, BEN, BFA, CIV, CMR, COG, GIN, KEN, LBR, MLI, MOZ, NER, NGA, RWA, TCD, TGO, TZA, UGA, ZWE	BDI, COD, COM, GAB, GHA, MDG, MWI, NAM, SEN, SLE, ZMB
Child (<5) with fever treated with an antimalarial	MOZ, MWI, TZA, ZMB	AGO, BEN, BFA, CIV, CMR, COD, GAB, GIN, NER, NGA, TCD	BDI, COG, COM, GHA, KEN, LBR, MDG, MLI, NAM, RWA, SEN, SLE, TGO, UGA, ZWE

For each country (indicated by ISO3 codes), distribution of malaria intervention coverage indicators were assessed over population ranked by asset-wealth; the degree of inequality in distribution of interventions was summarized in concentration index (CIX). Interventions were classified as "Pro-poor" if the estimated CIX was negative, "Inequitable" if was CIX is positive, and as "No difference across the asset-wealth index distribution" if CIX was equal to zero or lacked statistical significance. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (ISO3 codes and years of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey

In Figure 5.1 we illustrate the strength of economic gradients in distribution of malaria interventions qualified above; thereby addressing the question of how much inequality there is and compare it across interventions. The concentration index (CIX) for access to formal care – the most consistently inequitable coverage indicator – is plotted against country mean in Figure 5.1 A. Inequity is highest in settings with lowest access. Most high *Pf*PR_{2-10} countries (in shades of red) are at this end of the distribution. Ghana is one notable exception. For all other intervention coverage indicators we find little correlation between level and degree of inequality (Appendix D, Tables D3-D11); that is higher coverage is not necessarily described by a more equitable distribution nor is low coverage consistently inequitable.

Compared to access to formal care, ITN use is distributed more equitably (most country estimates above the equality diagonal) (Figure 5.1 B). High *Pf*PR_{2-10} countries with large inequities in access to formal care (positive values of concentration index on y-axis) appear to be equitable or pro-poor in distribution of ITN use (clustering of points around zero and -10 values of rescaled CIX on x-axis). In Congo, Democratic Republic of the Congo, Togo, and Uganda access to formal care strongly favors the least poor while ITN use - the poorest. On the opposite end of the plane are a handful of lower *Pf*PR_{2-10} countries including Burundi, and Malawi where inequality in ITN use exceeds that in access to formal care.

Anti-malarial treatment is equitable or slightly pro-poor in low *Pf*PR_{2-10} countries (shown in shades of blue) (Figure 5.1 C). In high *Pf*PR_{2-10} countries, antimalarial treatment favors the least poor; though the degree of inequality is lower than that estimated for formal care. There are a few exceptions to this general trend. In Democratic Republic of the Congo and Nigeria – medium *Pf*PR_{2-10} countries - the distribution of antimalarial treatment is more inequitable than that of formal care. In Togo - high *Pf*PR_{2-10} country - antimalarial treatment is distributed equitably despite large gradients in formal care favoring the less poor. Distribution of first-line medication is consistent with that of receipt of any antimalarial described above (Appendix D, Figure D2). The two indicators are correlated most closely in settings with lower *Pf*PR_{2-10} where first-line drugs account for a large fraction of antimalarials dispensed. In higher *Pf*PR_{2-10} countries inequities in first-line treatment are lower than those estimated for any antimalarial medication; however, access to these medications is also significantly lower. For instance, in Nigeria about 33% of children with fever are treated with an antimalarial, while only about 6% receive the first-line drug; the least poor are more than twice as likely as the poorest to receive either of the medications (Appendix D, Tables D8-D9).

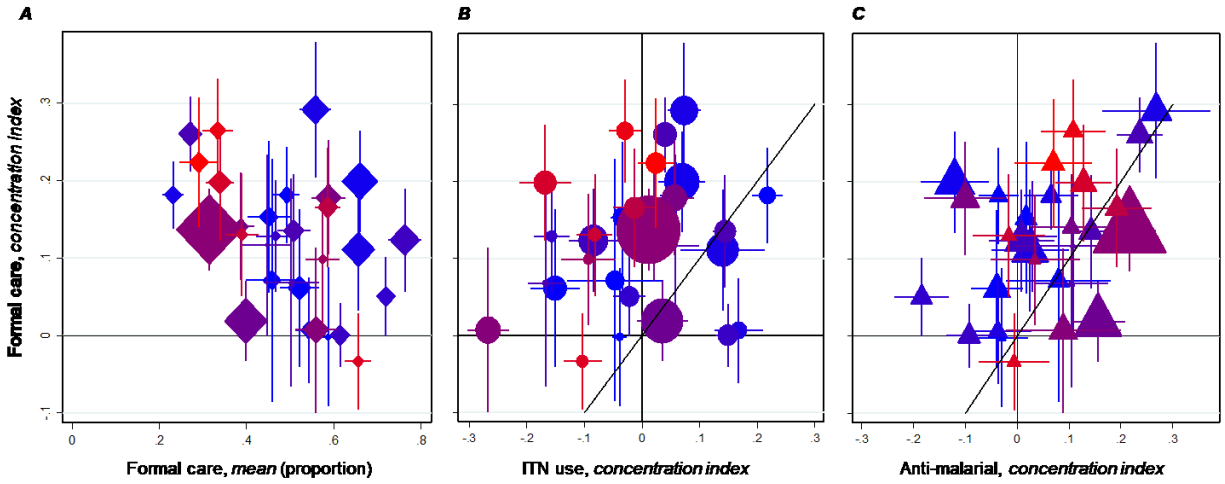

Figure 5.1 Degree of asset-wealth inequality in distribution of malaria interventions in Sub-Saharan African countries in 2015*

For each country concentration index (CIX) for access to formal care for fever among children under the age of five is plotted against its population mean (proportion) in *A*, CIX for ITN use in *B* and CIX for receipt of antimalarial medication for children under the age of five with fever in *C*. Whiskers denote the 95% confidence interval of the estimate. Country marker size is weighted with population size. Marker color code changing from bright blue to bright red refers to country mean malaria prevalence based on 2015 MAP estimates (corresponding values are given in Appendix D, Tables D1-D2). *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *MAP* Malaria Atlas Project, *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey

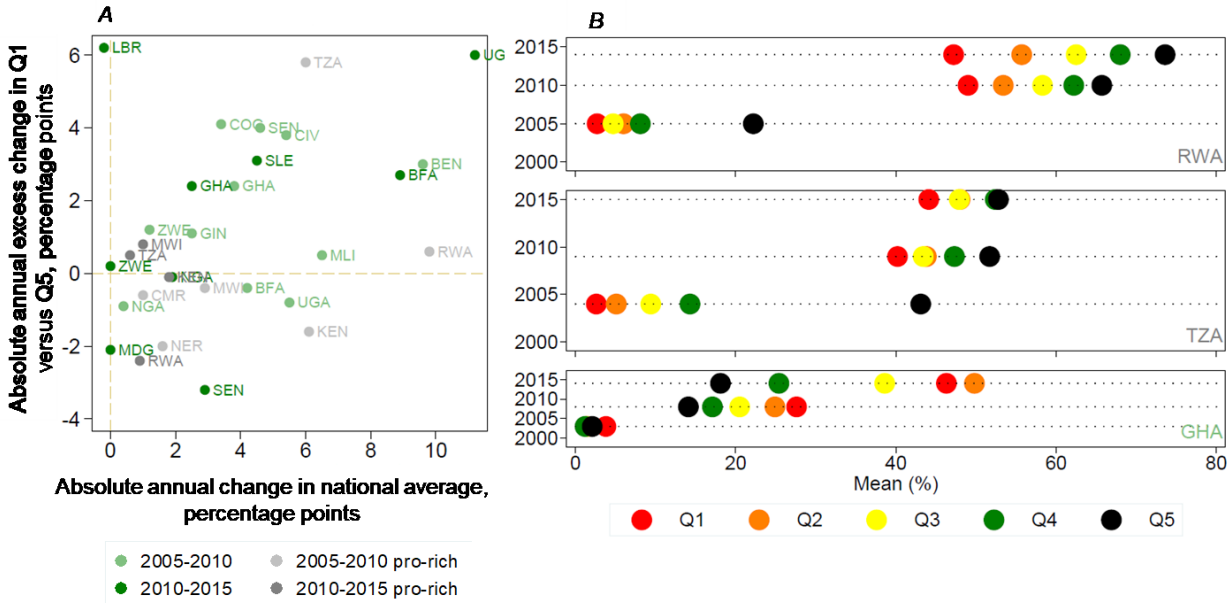

Figure 5.2 Changes in distribution of ITN use by asset-wealth in Sub-Saharan African countries from 2005 to 2015*

A illustrates for each country the difference in average annual change in the proportion of population that slept under an ITN the night prior to the survey in the lowest asset-wealth quintile and that of the highest (annual absolute excess change) against average annual change in the population (percentage points). *B* illustrates for each of the DHS surveys the proportion of population that slept under an ITN the night prior to the survey in each of the five wealth quintiles (Q1-Q5) for Rwanda (RWA), Tanzania (TZA), and Ghana (GHA). Data drawn from a subset of countries with repeated DHS/MIS conducted between 2005 and 2015 (country list, ISO3 code, and years of data collection detailed in Appendix D, Table D2). *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey

ITN use is the most equitably distributed malaria intervention coverage indicator. Figure 5.2 illustrates changes in its distribution over the last decade. ITN use expanded in all countries (positive values of annual absolute change on the x-axis) between 2005 and 2015 (Figure 5.2 A); it increased somewhat faster between 2005 and 2010 compared to the later period. In most countries these expansions were pro-poor (positive values of excess change on the y-axis). Where expansions favored the least poor (negative values of excess change on the y-axis), the relative gains in coverage were smaller in absolute terms than the excess change in settings where growth was pro-poor (positive values of excess change on the y-axis). It is primarily in these countries where interventions expanded faster in the least poor strata where we see inequities in distribution of ITN use today (in shades of grey). Figure 5.2 B presents a more nuanced picture of intervention expansion path in three countries. It shows that failure to sustain pro-poor focus in expansion yields greater inequality in later periods (Rwanda); that high baseline inequality in service coverage defies pro-poor growth (Tanzania), and that in some countries expansion in ITN use consistently prioritized the poorest strata (Ghana).

While relatively smaller, improvements in coverage occurred across all interventions delivered by malaria control programs (Appendix D, Figure D3). In about half of the countries these expansions were pro-poor or distributed equally across asset-wealth strata for ITN ownership and access to formal care. Changes in IPTp were mainly driven by improvements in the least poor strata from 2005 to 2010, with somewhat more equitable growth in the later period. Interpretation of changes in use of antimalarial medication with respect to program performance is confounded by changes in malaria epidemiology and the shift toward diagnostically confirmed treatment. Overall use of antimalarials decreased in most countries with relatively lower reduction in the least poor compared to the poorest strata. There is limited evidence that the direction of change reversed toward expansion in the poorest strata in the most recent period.

By pursuing malaria intervention coverage targets, countries aim at a broader health and health equity agenda. Tabulating malaria prevalence for a subset of DHS/MIS countries that included malaria diagnosis we find that parasitemia remains disproportionally concentrated in the poorest; prevalence gradients are substantially higher than what might have been expected given distribution of coverage indicators (Table 5.2). Even in countries where malaria interventions are equitable or favor the poor (i.e. Ghana) differences in burden between the poorest and least poor are large.

Table 5.2 Distribution of malaria prevalence across asset-wealth quintiles in Sub-Saharan African countries in 2015*

Country	Total	Poorest quintile Q1	Richest quintile Q5	Difference Q5-Q1	Ratio Q5:Q1	Concentration index (x100)
Benin	28.5 (26.6 to 30.4)	39.6 (35.2 to 44.0)	15.4 (12.0 to 18.9)	-24.1 (-29.8 to -18.5)	39.0 (29.2 to 48.8)	-21.0 (-25.3 to -16.8)
Burkina Faso	45.9 (43.1 to 48.7)	57.9 (53.1 to 62.7)	13.9 (8.8 to 19.1)	-44.0 (-51.0 to -36.9)	24.1 (14.9 to 33.2)	-32.8 (-37.6 to -28.0)
Burundi	17.3 (13.6 to 21.0)	25.9 (19.6 to 32.2)	8.4 (4.7 to 12.1)	-17.5 (-24.4 to -10.6)	32.4 (16.8 to 48.0)	-14.3 (-19.7 to -9.0)
Congo, Democratic Republic	22.6 (20.4 to 24.8)	23.0 (19.6 to 26.5)	12.4 (9.2 to 15.6)	-10.6 (-15.4 to -5.9)	54.0 (37.8 to 70.1)	-7.7 (-11.8 to -3.6)
Cote d'Ivoire	18.0 (15.3 to 20.8)	28.2 (22.8 to 33.6)	4.3 (1.8 to 6.7)	-24.0 (-29.9 to -18.0)	15.1 (6.0 to 24.1)	-20.6 (-25.8 to -15.5)
Ghana	26.7 (23.9 to 29.6)	42.1 (36.0 to 48.3)	7.5 (3.9 to 11.2)	-34.6 (-41.8 to -27.5)	17.9 (8.9 to 26.8)	-30.8 (-36.3 to -25.2)
Guinea	43.9 (40.5 to 47.2)	56.9 (51.7 to 62.2)	8.3 (4.0 to 12.6)	-48.6 (-55.5 to -41.8)	14.6 (6.9 to 22.3)	-32.1 (-38.2 to -26.1)
Kenya	5.0 (3.7 to 6.2)	5.8 (3.2 to 8.4)	0.9 (-0.2 to 1.9)	-4.9 (-7.7 to -2.1)	15.3 (-4.2 to 34.8)	-4.1 (-6.5 to -1.7)
Madagascar	6.9 (4.8 to 9.0)	14.1 (9.8 to 18.4)	0.4 (-0.1 to 0.9)	-13.7 (-18.1 to -9.4)	2.6 (-1.1 to 6.3)	-11.6 (-15.2 to -7.9)
Mali	51.6 (48.7 to 54.5)	69.4 (65.4 to 73.4)	15.1 (11.8 to 18.3)	-54.3 (-59.5 to -49.1)	21.7 (16.8 to 26.6)	-41.6 (-46.2 to -37.1)
Mozambique	35.1 (32.0 to 38.2)	53.3 (47.8 to 58.7)	6.5 (4.2 to 8.8)	-46.8 (-52.5 to -41.0)	12.2 (7.8 to 16.6)	-37.7 (-42.7 to -32.7)
Rwanda	2.2 (1.6 to 2.9)	4.7 (3.1 to 6.3)	0.2 (-0.2 to 0.5)	-4.5 (-6.2 to -2.8)	3.9 (-3.9 to 11.7)	-3.7 (-5.1 to -2.3)
Senegal	1.2 (0.6 to 1.8)	3.5 (1.6 to 5.4)	0.4 (-0.4 to 1.3)	-3.1 (-5.2 to -0.9)	12.4 (-13.8 to 38.6)	-2.7 (-4.4 to -1.1)
Tanzania	5.6 (4.6 to 6.5)	8.0 (6.0 to 10.0)	1.0 (0.4 to 1.6)	-7.0 (-9.1 to -4.9)	12.2 (3.9 to 20.5)	-6.8 (-8.6 to -4.9)
Togo	36.4 (33.3 to 39.5)	49.1 (44.1 to 54.0)	9.2 (6.0 to 12.4)	-39.8 (-45.7 to -33.9)	18.8 (12.1 to 25.6)	-35.2 (-40.2 to -30.2)
Uganda	20.1 (17.2 to 22.9)	29.8 (24.5 to 35.1)	4.0 (2.1 to 5.9)	-25.8 (-31.6 to -20.1)	13.3 (6.4 to 20.3)	-19.4 (-24.0 to -14.9)

Microscopy confirmed malaria prevalence (percent) in children aged 6 to 59 months assessed in a representative sub-sample of the DHS/MIS surveyed population. 95% confidence intervals adjusted for survey design are reported in parenthesis. Prevalence estimates according to RDT are reported in Appendix D. Data drawn from a subset of countries with DHS/MIS conducted after 2010 (year of data collection detailed in Appendix D, Table D1). *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey

Discussion

Decisive strides against malaria over the last decade enabled significant expansion of control programs across endemic countries (Bhatt et al., 2015); in some - these efforts also achieved equity in intervention coverage (Steketee & Eisele, 2009; Suzuki et al., 2012; Taylor et al., 2015; Victora et al., 2012; Wagstaff et al., 2014). More recent data analyzed here show that not only has the number of countries with equitable or pro-poor ITN ownership and use increased by 2015, the degree of inequality in countries where inequities persisted is modest with the exception of a handful of low *Pf*PR_{2-10} settings. Large wealth-related gaps previously shown in access to antimalarial medication (Steketee & Eisele, 2009) narrowed with 19 out of 30 countries reporting equitable or pro-poor coverage. These include most AMFm pilot phase countries except Niger and Nigeria where access to antimalarial medication remains substantially inequitable. Important gains have also been made in delivering IPTp to poor women: in 13 out of 27 countries this preventive intervention is equitable. In Namibia and Senegal all malaria control interventions are distributed equitably; in Ghana and Liberia all - except IPTp, in Sierra Leone all - except IRS.

Where asset-wealth differences in coverage persist, the relative performance of malaria interventions with respect to equity both within and between countries provides useful benchmarks. The large economic gradients in the distribution of curative interventions across countries highlight the difficulty of delivering routine care to the poor, but differences in relative degree of inequality (i.e. highly inequitable CIX of 0.27 in distribution of access to formal care in Guinea compared to CIX of 0.02 in Democratic Republic of the Congo) suggest that it is feasible to substantially reduce these inequities. Benin and Mali achieve coverage and use of ITNs at rates that are about 20 and 40 percentage points above those estimated for formal care; in these countries ITN use is also distributed equitably across asset-wealth strata in contrast to large economic gradients in curative care. The differential performance of interventions within control programs indicates that there is technical capacity to identify and deliver services to poor; what is needed is implementation insight to transfer efficiency of high-performing interventions to those lagging behind (Rasanathan & Diaz, 2016). Review of malaria programs covering health systems, financing, and operational contexts is needed to gather and synthesize institutional expertise from within the region.

Differences in the level and distribution of malaria interventions within endemic countries also impact adoption, prioritization, and deployment of new malaria tools. Our analyses suggest that in high endemic settings interventions deployed via campaign are likely to be more equitably distributed than those requiring routine delivery through the formal sector. These considerations are immediately relevant for countries currently considering introduction of new malaria interventions such as malaria vaccines (WHO, 2016a). Economic gradients estimated here for access to the formal sector are representative of the EPI coverage in endemic settings (Hosseinpoor et al., 2016) suggesting that much of the vaccine's impact is likely to be missed due to distributional failures unless routine immunization is supplemented with periodic intensification and outreach campaigns.

In many high PfPR2-10 countries, coverage of malaria interventions remains low; how programs scale-up has important implications for equity (Taylor et al., 2015). In agreement with a previous analysis (Barat et al., 2004) showing that, where ITN use increased gains were made across the asset-wealth continuum, often with accelerated growth in the poorest stratum. We find this conclusion also holds for other malaria coverage indicators, indicating that expansions in malaria programs in the region have largely circumvented the inverse care law (Hosseinpoor et al., 2016). Yet, despite pro-poor growth, progress toward equitable distribution of malaria interventions in many settings is limited by past high levels of inequality; turning these programs around is a challenge. For these countries failure to sustain a focus on equity in service delivery leads to greater inequality in subsequent periods while narrowing the gap between poorest and least poor requires disproportionately faster and sustained growth in the poorest strata.

These dynamics can partially explain systematic differences in the level and distribution of malaria coverage indicators by *Pf*PR_{2-10}. Most high *Pf*PR_{2-10} countries were late to scale-up ITNs; these efforts relied heavily on donor assistance that financed mass distribution campaigns outside the formal health sector, enabling equitable coverage in these settings. In lower *Pf*PR_{2-10} countries ITN delivery relied more on routine channels propagating disparities in access to formal care to ITN coverage. Distributional failures in the formal health sector limit progress toward equity across malaria interventions as programs rely on routine channels to maintain coverage between campaign rounds (i.e. ITN, IPTp), to strengthen access for priority groups, and to inform planning, and resource allocation decisions with data sourced from governmental health facilities. Tackling malaria requires a holistic view of the program; to succeed there should be a focus on strengthening the health systems at large.

Evidence of economic gradients in intervention coverage lends itself to a clear programmatic interpretation – the poor are left behind, but analogous interpretation of equitable or pro-poor gradients may be misleading. First, as dimensions of social and economic disadvantage overlap, analyses limited to broad comparisons between the poorest and the least poor might average over important gradients understating the true degree of disparity (Tugwell et al., 2006). Second, it is not obvious whether gradients defined over an asset-wealth index capture policy-relevant dimensions of economic or social disadvantage in malaria endemic countries (Houweling et al., 2003; Mwageni et al., 2005; Tusting et al., 2016). Lastly, geographic and demographic clustering of malaria in low transmission settings might undermine the capacity of conventional tools to identify and monitor high-risk populations (Cotter et al., 2013). To illustrate, we analyzed ITN use by a number of common equity stratifiers and an interaction of these dimensions with the asset-wealth index for Liberia - a country with a pro-poor or egalitarian distribution of most malaria interventions (Figure 5.3). Here, ITN use is equally distributed across the economic strata at national level (solid and dashed pink lines); it is effectively equal to national average when stratified by place of residence, education, or *Pf*PR_{2-10} (colored bars) (Figure 5.3 A). However, large gradients for Liberia emerge when either of the dimensions is overlapped with the asset-wealth index (Figure 5.3 A). There are large regional differences around the national average and, even stronger economic gradients within these regions. While pro-poor at national level, ITN use is concentrated among the least poor in rural settings, areas of high *Pf*PR_{2-10}, and in all regions except for the South Central region of Liberia that includes country capital.

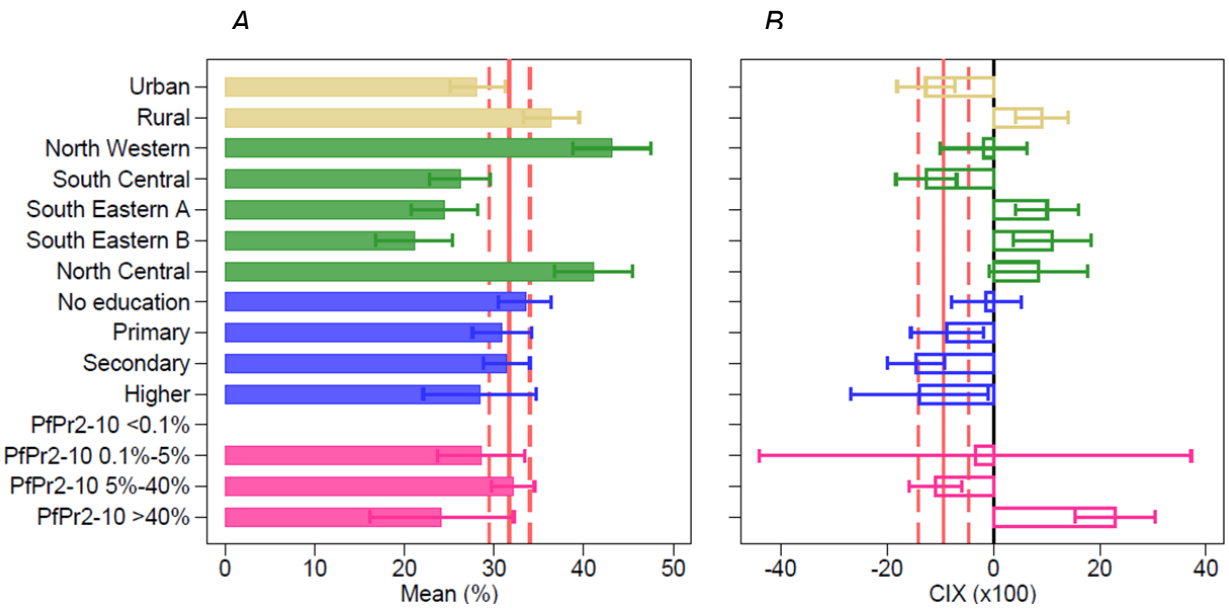

Figure 5.3 Heterogeneity in distribution of malaria interventions over transmission and alternate socio-economic stratifiers in Liberia in 2015*: proportion of population who slept under an ITN last night

A presents mean and 95% confidence interval for the proportion of population who slept under an ITN last night within each dimension: place of residence (urban or rural), region ((North Western, South Central, South Eastern A, South Eastern B, North Central), mother's highest education level (no education, primary, secondary, higher), *Pf*PR_{2-10} level (<0.1%, 0.1-5%, 5-40%, >40%). The national average and the corresponding confidence interval are shown in solid and dash pink lines respectively. *B* shows the degree of inequality, summarized here in a concentration index and 95% confidence interval, in distribution of ITN use with respect to asset-wealth index within each dimension. National average of the concentration index and the corresponding confidence interval are shown in solid and dash pink lines respectively. *Data drawn from Liberia DHS 2013. *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey

Equality across wealth quintiles in coverage, or concentration of interventions in the poorest is likely to be more effective in reducing burden than concentration of interventions in the richer quintiles because of the association of malaria infection with low socio-economic status (Table 2) (Tusting et al., 2013). The areas and individuals at highest risk contribute disproportionately to onward infection (Woolhouse et al., 1997) so targeting them is highly effective if they can be identified (Bousema et al., 2012). However, identifying them is challenging (Bejon et al., 2014). Economic and social dimensions have a role in this, and thus need to be considered as important components (alongside epidemiological and geographic data) in new approaches in malaria mapping, in development of more comprehensive measures of malaria vulnerability (Keinberger & Hagenlocher, 2014; Tatem et al., 2014), and in analytical tools to help malaria control programs direct efforts towards vulnerable sub-populations (Bosco et al., 2017; Steele et al., 2017).

By eliminating disparities in proximal determinants (access to preventive and curative interventions) of malaria morbidity and mortality, control programs in endemic countries address only a part of the causal pathway from exposure to disease; the underlying socio-ecological conditions could manifest through other mechanisms further perpetuating health inequities (Bejon et al., 2014).

The consideration is relevant to evaluation and performance targets for control programs. Differential tracking of coverage indicators by malaria endemicity and or other context-specific dimensions of social or economic disadvantage, as shown here, can enhance equity analyses (Florey, 2014; Rodriguez et al., 2017) by focusing most directly on populations at risk. Expanding the scope of monitoring indicators to also include quality dimensions could help direct efforts toward increasing efficiency of current control tools. To this end the equity effectiveness framework can be applied to disentangle the impact of various factors on the gap in the effectiveness of interventions across socio-economic gradients (Hosseinpoor et al., 2016). For instance, compounding of disadvantage along the service delivery path has been shown for malaria case management where the poor are not only less likely to seek care but also less likely to do so in the formal sector, or to receive appropriate diagnosis, and treatment (Florey, 2014).

There are a number of limitations to consider when interpreting our findings. Due to varying survey cycles between countries there is some inconsistency in reference years for reported statistics. To the extent that expansion in malaria services accelerated closer to 2015 or accelerated differently with respect to equity, estimates based on less recent surveys understate the level of service provision, overstate the degree of inequality in their

distribution across the wealth strata, and overstate differences in the two statistics between countries. Timing of campaigns (i.e. IRS or ITN distribution) with respect to survey implementation is another variable affecting estimated level of malaria services and comparisons thereof between countries. Finally, by design DHS surveys are to be conducted during low transmission season, while MIS – at peak. Survey implementation in the field, however, spans months averaging over the seasonality pattern in the data collected (Burgert et al., 2012). To the extent that in some countries the pattern is maintained comparisons will be biased.

Conclusions

The global health and development agenda place a special emphasis on universal health coverage (Roll Back Malaria Partnership, 2015; UN, 2015; WHO, 2015a). The Global Technical Strategy for Malaria 2016–2030, in particular, argues for universal access to interventions for malaria prevention, diagnosis and treatment as a path toward elimination (WHO, 2015a). For endemic countries, given historically low access among the poorest, adopting this vision would require overall gains in coverage to be accompanied with accelerated improvements in disadvantaged populations. Our analysis testifies to the progress made by countries in the region in narrowing economic gradients in malaria intervention coverage and highlights the scope for continued monitoring of these programs with respect to equity.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The analysis drew on publicly available data, as referenced in Methods section of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KG, TAS, and MAP conceived the study. KG designed and implemented the analysis. KG drafted the manuscript. DDS supported interpretation. All authors discussed the results, contributed to revisions of the manuscript, and approved the final version.

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Chapter 6: Conclusions and discussion

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Summary of research findings

The aim of this thesis was to apply economic and epidemiological models to weigh the resources required to introduce and maintain the RTS,S malaria vaccine within the routine EPI in *Pf* endemic African countries against the potential public health benefit of this new intervention in these settings. This section summarizes the methodology and presents the key findings toward the aim of this thesis.

Prospective evaluation of costs of new interventions

Chapters 2 and 3 of the thesis illustrated how prospective micro-costing approaches could be used to provide highly contextualized and programmatically relevant costs of new interventions. The micro-costing strategy is particularly useful for early evaluation of candidate interventions for which at-scale programmatic implementation is yet to be determined.

In Chapter 2 this methodology was applied to derive costs of surveillance, mass and reactive drug-based and vector control interventions for malaria elimination. The strength of this approach is in highly detailed enumeration of resources that makes it possible for each and every cost component to be updated to reflect delivery in any given setting yielding locally relevant estimates of the cost. The costing models allow one to transfer and to generalize the economic evidence across settings by isolating inputs that characterize capacity of programs and by explicitly relating costs to the setting.

In the process of evaluation, several insights emerged that are broadly applicable across diseases and interventions against them. Inputs characterizing operational details of implementation were identified as key cost drivers for all interventions. Of these, details on resource use at service delivery including the category, number, time, compensation, and service output of program cadre deploying the intervention were of primary importance. The analysis demonstrated that health infrastructure (*i.e.* number of community health workers (CHW)) and productive capacity of these resources (*i.e.* number of people that can be treated by CHW per day) interact in non-linear ways with both service output and costs. The analysis highlighted the challenges of translating economic evidence from research trials to programmatic decisions. It stressed the need for data collection along research pilots and trials to prioritize transferability of the economic evidence. Specifically, to strengthen

policy relevance of costing studies conducted in research pilots, the evaluation should aim to also demonstrate or provide guidance on how resource use and service outputs achieved relate, or can be related, to features of the pilot and or the setting.

Cost of RTS,S implementation in Pf endemic African countries

In contrast to Chapter 2, where the primary motivation was to develop a tool to explore *broadly* trade-offs between interventions and intervention strategies for global guidance (with an emphasis on the generalizability of implementation model across the region, consistency of assumptions within a settings and between interventions within a setting, etc.), in Chapter 3 the evaluation explored secondary data sources to capture the *unique* features of immunization programs in different countries and to estimate cost gradients associated with these features. Here, the prospective costing methodology from Chapter 2 was extended to evaluate the cost of RTS,S introduction in Ghana, Kenya, Senegal, Tanzania, and Uganda. The strategy drew on global databases of costs and operational data on immunization programs to develop an understanding of the implementation process and populate cost model inputs (*The cMYP Immunization Financing Database*, 2015; IVB, 2014b). While the EPI – the currently recommended delivery platform for the vaccine ("Malaria vaccine: WHO position paper-January 2016," 2016) – has been evaluated previously (De la Hoz-Restrepo et al., 2013; Garcia et al., 2013; Hutton & Tediosi, 2006; Le Gargasson et al., 2015; Levin et al., 2014; Ozawa et al., 2012), we undertook an extensive costing analysis in order to address uncertainty about the cost of delivering the vaccine outside of the routine vaccination schedule. The comprehensive representation of resource use detailed by the costing model allowed evaluation of a range of alternative assumptions on the vaccine delivery outside of routine schedule and the respective cost implications. Transparency in reporting further increased confidence in the cost estimates derived by the study.

Consistent with findings in Chapter 2, operational details of service delivery and compensation of nurses administering the vaccine were highlighted as important cost drivers. Additionally, the EPI structure, the number of antigens in the EPI schedule, coverage, cohort size, and allocation of shared resources within the EPI to the new vaccine were among the other inputs that explained differences in cost of delivery between countries. These features resulted in a broad range in the estimated average annual economic cost of vaccine delivery across the six countries: in the 6-9 months schedule without the booster 0.72 USD per dose estimated for Burkina Faso and a high of 2.34 USD for Kenya. Delivery costs for doses administered outside of the routine schedule were shown to differ only marginally from those administered along with other vaccine antigens; cost differences

reflected additional sensitization and supervision activities and greater time for vaccination when the vaccine was administered on its own.

The analysis highlighted the large contribution, beyond the cost of the vaccine, which would be required by programs and health systems in endemic countries to deliver this new intervention; the incremental resource requirements would be higher in places where spare capacity was low. At a vaccine price of 5 USD per dose about 95% of the financial and 84% of the economic costs were accounted for by vaccines and immunization supplies. Thus, despite the potentially large differences in cost of vaccine service delivery between countries in the region, these costs accounted for a relatively small fraction of the total cost of the program; vaccine price, coverage, drop-off between doses, and vaccine wastage had the greatest impact on program costs.

Incremental cost-effectiveness of RTS,S in Pf endemic African countries

The analyses presented in Chapter 4 applied an individual-based malaria transmission model (Smith et al., 2012) to synthesize the evidence on the efficacy profile from the trial, the current understandings of malaria transmission dynamics, country data on key inputs driving impact (*i.e.*, the level and distribution of malaria risk, coverage of preventive and curative interventions, and assumptions on the likely coverage the country implementation of the Diphtheria-tetanus-pertussis vaccine (DPT3)) and by linking costs of the RTS,S vaccination program from Chapter 3 produced country-specific estimates of the vaccine cost-effectiveness. The outputs of Chapter 4 are immediately relevant to country programs and partners; the estimates allow broad comparisons of this new intervention against country/partner acceptability thresholds used to evaluate new health technologies.

If introduced through the routine EPI in the recommended 4-dose schedule in 6 to 9 months the vaccine has the potential to avert over a million of malaria episodes in the first 10 years in 43 *Pf* endemic African countries. Nearly all of it in countries currently eligible for GAVI support. The estimated burden averted averages 18'413 (range of country median estimates 156–40'054) DALYs per 100'000 fully vaccinated children with much variation across settings primarily driven by differences in transmission intensity. At a price of 5 USD per dose the median cost-effectiveness ratio of 188 USD (range 78–22'448) per DALY averted; the ratio is lower by one third in settings where parasite prevalence in children aged 2–10 years is at or above 10%. The estimated ICERs are below country GDP per capita in most countries.

These findings are consistent with conclusions from earlier modeling studies that suggested that despite partial efficacy and fairly short duration of protection RTS,S is likely to substantially reduce malaria morbidity, decrease mortality and be cost-effective across a wide range of transmission intensities, health systems contexts, and vaccine price assumptions (Maire et al., 2011; Tediosi et al., 2006; Fabrizio Tediosi et al., 2009). RTS,S thus merits further consideration within the respective country programs, country-available budgets and financing options, and partner investment portfolios.

Equity in the distribution of routine malaria control and implications for introduction of new tools

In addition to the economic considerations discussed in Chapters 2-4 policy decisions on new health technologies further evaluate candidate interventions with respect to the broader health policy objectives such as equity and distributional impacts. To this end Chapter 5 presents evidence on the scale-up pathway, current levels of coverage, and economic gradients in the distribution of malaria interventions currently deployed across the endemic African countries.

Economic gradients were detected in all malaria interventions in most countries; strongest for interventions delivered through the formal sector and fairly modest for interventions deployed through campaigns (i.e. LLINs, IRS). Differences in relative inequality between malaria interventions within and between countries highlighted the technical expertise in the region to effectively identify and deliver services to the poor. The analysis further emphasized the importance of monitoring scale-up of new interventions with respect to equity. It showed that in countries where in the early stages of the introduction the uptake of new health technologies was highest in the least poor population strata (consistent with the inverse care law (Hart, 1971)) disparities in coverage persisted for many years; overcoming these disparities required service delivery to consistently prioritize the poorest.

The findings from Chapter 5 provided further support to the urge for innovation in delivery platforms and tools against malaria. The analysis suggested that deploying RTS,S through the well-established EPI program (Arevshatian et al., 2007; Clements et al., 2008) might have advantages also in expanding access to malaria prevention as coverage for antigens targeting age-groups recommended for the vaccine (*i.e.* DTP3) were above those for current malaria interventions. However, inequalities in access to vaccination have been shown to be as high as those reported for access to formal care demonstrated in Chapter 5, thus, to be impactful the implementation strategy for the new vaccine should explicitly consider

appropriate outreach to minimize distributional failures and ensure that the intervention reaches children that most require prevention.

Economic evaluation as a framework for making choices in health

As a foreword to the discussion of the work that formed this thesis and the policy dialogue to which it contributed, this section highlights key theoretical constructs behind the cost-effectiveness method and clarifies implications of the theory for framing and interpretation of results of cost-effectiveness studies. It reflects on the use of these methodologies in LMICs to inform decisions on new health interventions.

Economic evaluation

Economic evaluation comprises many tools and methodologies that facilitate societal choices on the allocation of available resources to the production of health services and on the distribution of those health services between those that want them (McPake et al., 2002). Normative in scope, the evaluation concerns with judging which choices *should* be made. This judgment requires an explicit objective(s). Economic evaluation thus considers whether appropriate services have been adopted in the health sector or whether there is an alternative mix of technologies and interventions which would achieve better outcomes toward societal objectives.

Theoretical basis for economic evaluation

The welfare theory provides theoretical foundation for economic evaluation. Within this framework choices with respect to health interventions are judged by whether or not they represent a potential Pareto improvement in social welfare (McPake et al., 2002). The idea of Pareto efficiency being that those that gain from a policy can compensate those that lose and remain in a better position than before the policy change. This emphasis on the societal welfare has been challenged (Sen, 1979) which led to a more narrow interpretation of the economic evaluation that endorsed health and equity rather than utility as objectives to be maximized by the health sector. Cost-effectiveness analysis (CEA) is a form of evaluation that applies these principles to resource allocation.

Implications of the theoretical basis for framing and interpretation of the evaluation

There are several implications for the interpretation of the economic evaluation that stem from the theoretical foundations of this methodology. First, the theory justifies making trade-

offs between health and costs which, in turn, suggests interpretation of inefficiency as health foregone or excess morbidity. Second, within this framework, decisions are made by comparing among alternatives. This implies that the decision depends on the choice set and that there is no absolute threshold of health that would justify the decision (there might be an alternative that enables a higher health gain for the same pay-off). Finally, by moving away from the welfare the decision is to be further considered against other relevant objectives (*i.e.* priority groups).

Framing the evaluation

In planned health sectors, where this methodology originates, the government makes decisions on health on behalf of the society. It is the societal perspective thus that is often adopted for the evaluation. The perspective then determines which costs and which impacts the evaluation should consider. For pragmatic reasons, the focus is often on costs and impacts that are most likely to alter the choice between policy alternatives. This saves time and effort for the evaluation but limits its generalizability outside of the study.

Measuring costs

An important theoretical construct when measuring costs is the time value of money that reflects our collective preference for consumption today over consumption tomorrow and the existence of a positive interest rate. These phenomena give rise to the so called opportunity cost which is the cost of using a resource in a particular way (as opposed to other income or interest earning allocation). In practice, these considerations are accommodated with a discount rate.

Measuring health impact

Measuring health impact of policy alternatives against infectious diseases poses unique challenges related to disease transmission, herd immunity and sources of heterogeneity in rates of infection and disease that lead to population-level effects that are complex and non-linear (den Boon et al., 2019; Smith et al., 2008). To capture these effects, transmission dynamic models are needed. Smith noted that for adequate predictions of vaccine impact and cost-effectiveness on malaria outcomes of public health significance the models ought to capture both pre-existing and acquired immunity and heterogeneity in the vaccine immune responses at individual level and how the vaccine effects impact efficacy against infection and modify how this efficacy then translates to efficacy against clinical outcomes (T. A. Smith et al., 2006).

Applications to LMIC

Despite the recent explosion of literature on cost-effectiveness of interventions against infectious diseases, including malaria, the primary audience for these evaluations appears to be multilateral and bilateral agencies that draw on cost-effectiveness evidence to plan and justify their investments in LMIC (Mills, 2014). Recent studies of decision-making processes on new vaccines (Brooks & Ba-Nguz, 2012) and other interventions suggested that governments in LMIC pay little attention to cost-effectiveness evidence, it is rather funding availability and political factors that appear to dominate decision-making in these countries (Behague et al., 2009).

Modeling of RTS,S vaccine in the broader context of malaria modeling literature

This section gives a brief overview of the methodological development, that supported, in particular, analyses in Chapter 4 of the thesis, and presents key findings that emerged from the malaria modeling literature. It highlights the application of the modeling methodologies to guide R&D and policy response for malaria. Here the chapters of the thesis are placed within this broader body of literature.

Early applications of mathematical modeling to malaria

The first application of mathematical modeling to malaria dates back to Sir Ronald Ross who in 1910 described malaria transmission dynamics with a deterministic population model of parasite densities in susceptible and infected mosquitoes and human hosts to derive entomological thresholds for malaria elimination (Ross, 1911). Late in the 1950's Professor George Macdonald applied the concept of the basic reproduction number (R_0) to malaria and used modeling to demonstrate that the most effective way to reduce the number of secondary infectious cases was by increasing the adult mosquito mortality rate (MacDonald, 1957). Many variations of these early models, known as Ross-Mcdonald models, have been applied since the 1950's. Further methodological development focused on incorporating immunity and parameterizing malaria models with field data (Dietz et al., 1974). These early population-based deterministic models produced important insights to guide malaria control efforts and continue to be used today. However as the policy target shifted from elimination to control of malaria, modeling studies began to focus on optimizing strategies to not only reduce transmission but also to reduce malaria morbidity. Because malaria interventions induce complex responses in human hosts and mosquitos, models that accommodate malaria pathogenesis and heterogeneity of infection and immunity between individuals were

needed to make predictions of the likely impact of different interventions on malaria health outcomes.

Vaccine R&D stimulate development of first individual-based model of malaria

One of the first comprehensive individual-based stochastic models of malaria epidemiology and control – OpenMalaria – was developed in 2006 at the Swiss Tropical and Public Health Institute by Smith and colleagues (T. Smith et al., 2006; Smith et al., 2008). OpenMalaria model components describe the progression of *Pf* infection in humans, predicted from a seasonal pattern of transmission (Entomological Inoculation Rate (EIR)) and adjusted for naturally acquired and or vaccine-induced immunity, blood-stage parasite densities, infectiousness to mosquitos, incidence of morbidity including hospitalization and mortality, and pre-erythrocytic and blood stage immunity. Stochastic approaches make it possible to model rare events (such as deaths) and heterogeneity in exposure and immune response as functions of probabilistic distributions. A key feature of the suite of models that make up the OpenMalaria simulation platform is that the models were extensively parameterized to field data from endemic settings. A deterministic model of malaria in mosquitoes was later added to improve predictions of impact of vector control interventions (Chitnis et al., 2008).

Innovation in malaria modeling methodology to inform policy

Subsequent model development sought to propagate structural uncertainty by moving away from a single model to predictions with an ensemble of models that allow for different assumptions about decay in immunity, heterogeneities in exposure and access to treatment (Smith et al., 2012). New methods were developed to *efficiently* update parameterizations of vaccine properties and to predict vaccine impact (M. Penny, K. Galactionova, et al., 2015). The methodology further incorporated recent advances in geospatial modeling (*Malaria Atlas Project*) and understandings on the care cascade of the malaria case management (Galactionova, Tediosi, et al., 2015) to derive the distribution of malaria exposure conditional on treatment that resulted in more accurate predictions of the underlying burden and the likely public health impact of interventions (M. Penny, N. Maire, et al., 2015).

Other individual-based models of malaria epidemiology have been subsequently developed (Eckhoff, 2013; Griffin et al., 2010). As OpenMalaria these models as well have been applied to evaluate the potential impact of interventions and strategies against malaria including malaria vaccines (Brady et al., 2017; Gerardin et al., 2017; Hogan et al., 2018; Okell et al., 2011; Walker et al., 2016). Parameterized to different field data the models further differ in clinical outcomes monitored and respective case definitions, extent of spatial heterogeneity and interactions captured, treatment of multiplicity of infection, assumptions on immunity,

and structural elements underlying the biological phenomena (M. A. Penny, K. Galactionova, et al., 2015).

Economic and impact modeling of malaria vaccines prior to release of phase 3 data on RTS,S

Prior to release of the RTS,S final phase 3 trial data, malaria vaccine modeling studies focused on developing and applying methodologies to determine the vaccine efficacy profile from the trial data (Maire, Aponte, et al., 2006; M. Penny, K. Galactionova, et al., 2015; M. Penny, P. Pemberton-Ross, et al., 2015; Smith et al., 2012), predicted public health impact of the vaccine for an estimated and a range of hypothetical profiles deployed through the EPI (A. Brooks et al., 2012; Eckhoff, 2013; Griffin et al., 2010; Maire, Tediosi, et al., 2006; Pemberton-Ross et al., 2015; M. Penny, K. Galactionova, et al., 2015; Penny et al., 2008; Sauboin et al., 2015; Smith et al., 2012) and other delivery channels (A. Brooks et al., 2012; Eckhoff, 2013; Griffin et al., 2010; Smith et al., 2012; Wenger & Eckhoff, 2013), on its own or in combination with other interventions (Bhatt et al., 2015; Eckhoff, 2013; Griffin et al., 2010; White et al., 2009), and explored the minimum efficacy profiles needed to reach an explicit prevalence reduction or elimination target (Eckhoff, 2013; Griffin et al., 2010; Penny et al., 2008). Along with these investigations prospective costing studies of vaccine implementation within the EPI (Hutton & Tediosi, 2006) and other delivery channels (Fabrizio Tediosi et al., 2009) in Tanzania were conducted to inform cost-effectiveness of malaria vaccines (Maire et al., 2011; M. A. Penny et al., 2016; Tediosi et al., 2006; Fabrizio Tediosi et al., 2009; Winskill et al., 2017).

Economic and impact modeling of RTS,S

With the release of the final phase 3 data modeling efforts shifted away from exploring vaccines with hypothetical efficacy profiles to explicitly evaluating the likely public health impact of the RTS,S/AS01 vaccination program in generic transmission settings and explicitly in *Pf* endemic African countries (Galactionova, Tediosi, et al., 2017; Pemberton-Ross et al., 2015; M. Penny, K. Galactionova, et al., 2015; M. Penny, P. Pemberton-Ross, et al., 2015; Sauboin et al., 2019; Sauboin et al., 2015; White et al., 2015; Winskill et al., 2019; Winskill et al., 2017; Winskill et al., 2018). Estimates presented in Chapter 3 (now published under (Galactionova, Bertram, et al., 2015)) expanded the evidence base on the cost of RTS,S introduction with explicit costing of the vaccine implementation in six high malaria burden countries (before only Tanzania was costed) and addressed uncertainty about the cost of vaccine delivery outside of the routine schedule. This work was further extended to derive the cost of vaccine delivery for 43 *Pf* endemic countries additionally allowing for decreasing marginal returns to scale at high levels of coverage (Winskill et al., 2019).

Analyses documented in Chapter 4 and later published under (Galactionova, Tediosi, et al., 2017) presented the first country estimates of average cost-effectiveness of RTS,S allowing for within country heterogeneity in transmission and seasonality, representative efficiency of programs (*i.e.* country DTP3 and MMR2 coverage proxies allowing for drop-off between doses in the primary series), case management, and incorporating cost of vaccine service delivery and treatment. Several recent studies explored the relative cost-effectiveness of the vaccine compared to the scale-up of routine prevention and treatment (Sauboin et al., 2019; Winskill et al., 2019; Winskill et al., 2017; Winskill et al., 2018).

Key insights from modeling on role of malaria vaccines for control and elimination

Modeling of the hypothetical vaccine profiles led to an appreciation of the relative importance of vaccine properties for different operational targets be it interruption of transmission or burden reduction. The models suggest that duration of protection is relatively more important than initial efficacy for burden reduction, whereas initial efficacy is more critical for interruption of transmission (Maire, Tediosi, et al., 2006; Smith et al., 2012; Tediosi et al., 2006). Studies have shown that the distribution of vaccine impact in the population depends on the vaccine half-life: for shorter half-lives impact will be concentrated in the youngest children while for longer - the benefits will shift toward older age groups (Hogan et al., 2018). Heterogeneity in immune response to vaccination is another important property that has been studied. A vaccine providing partial protection to more people is preferable to a vaccine that provides complete protection to some and no protection to others (Maire, Tediosi, et al., 2006; Penny et al., 2008; Tediosi et al., 2006); the former, fitting the profile of the RTS,S, will have a larger population impact and less age-shifting of clinical disease.

Modeling studies demonstrated how vaccine impact is modified by features of the setting (Maire, Aponte, et al., 2006; Pemberton-Ross et al., 2015; M. Penny, K. Galactionova, et al., 2015; Smith et al., 2012). Specifically, vaccine efficacy is decreasing and impact increasing with increasing transmission (Maire, Aponte, et al., 2006; M. Penny, K. Galactionova, et al., 2015); efficacy is lower where transmission is more heterogeneous (Smith et al., 2012). There is more vaccine-induced age-shifting and it will set in sooner in higher transmission settings (Maire, Aponte, et al., 2006; Pemberton-Ross et al., 2015; M. Penny, K. Galactionova, et al., 2015; Smith et al., 2012). Malaria vaccines thus would be most effective in moderate to high transmission settings where coverage of existing tools is saturated (Eckhoff, 2013; Griffin et al., 2010; Wenger & Eckhoff, 2013; Winskill et al., 2017) and where vectors are primarily out-door biting (Eckhoff, 2013; Wenger & Eckhoff, 2013). Despite differences in the absolute magnitude, there is an overall consensus within the modeling literature on the important contribution the pediatric malaria vaccines could make to reducing

Pf morbidity and mortality in young children; the conclusion held across a range of vaccine efficacy profiles and transmission intensities (A. Brooks et al., 2012; Eckhoff, 2013; Maire, Tediosi, et al., 2006; Smith et al., 2012). Modeling studies further agree that, due to the narrow age-target, partially efficacious malaria vaccines deployed through the EPI would not impact transmission and have only marginal, if any, impact on prevalence (A. Brooks et al., 2012; Eckhoff, 2013; Maire, Tediosi, et al., 2006; Smith et al., 2012).

On the economics side, the most important contribution of the modeling literature has been in establishing value for money of AIV pediatric malaria vaccines. For EPI deployment ICER's were shown to plateau between EIR 2 and 20 and with a median range across the studies between 48 to 244 USD per DALY, higher ICERs in lower transmission (Galactionova, Tediosi, et al., 2017; Maire et al., 2011; M. Penny et al., 2016; Tediosi et al., 2006; F. Tediosi et al., 2009). Overall modeling evidence suggests that RTS,S would be highly cost effective based on the conventional GDP per capita threshold; it will be most attractive in moderate to high transmission settings where coverage of existing tools is saturated (Eckhoff, 2013; Griffin et al., 2010; Maire et al., 2011; Wenger & Eckhoff, 2013) and where vectors are primarily out-door biting (Eckhoff, 2013; Wenger & Eckhoff, 2013). There is less agreement in this literature on the prioritization of RTS,S relative to scale-up of current means of prevention and treatment. The one consistent observation acknowledged by modeling studies is that the decision is context dependent with the relative ranking of interventions modified by the level and constraints to scale-up of preventive interventions and the corresponding cost functions in specific settings (Sauboin et al., 2019; Winskill et al., 2019; Winskill et al., 2017; Winskill et al., 2018).

Sensitivity analyses of the incremental cost-effectiveness of the vaccine further highlighted that aside from vaccine price, parameters informing effectiveness including transmission intensity and efficacy profile (i.e. homogeneity in immune response, efficacy, and efficacy decay) would have the largest impact on the ratio (Maire et al., 2011) ; these conclusions were corroborated by (M. Penny, K. Galactionova, et al., 2015; Penny et al., 2008; Sauboin et al., 2015). Malaria co-morbidity and case fatality rate are two other parameters with a great degree of uncertainty which dominate vaccine impact on mortality (Maire et al., 2011).

The contribution of economic and impact modeling to the WHO 2016 recommendation on RTS,S vaccine

The section discusses the contribution of the malaria vaccine modeling, including the thesis, to policy development leading to the WHO 2016 recommendation on RTS,S. Modeling

studies of the public health impact and cost-effectiveness of the vaccine in settings representative of the current levels of on-going transmission were requested by the WHO following the regulatory approval of the vaccine (Moorthy et al., 2012). In compliance with the WHO guidelines, outputs from four malaria transmission models that encompass a range of structures and levels of complexity were formally compared to inform the recommendation (M. A. Penny, R. Verity, et al., 2015). Additional modeling analyses were conducted by select modeling groups on narrow technical questions (WHO, 2015d; Winskill et al., 2015).

Modeling evidence on mechanism of action

While the precise protective mechanism of RTS,S/AS01 is not known, its demonstrated impact on reducing the rate of acquisition of new blood stage infections, the initial inoculum of blood stage infection, and the multiplicity of infections was hypothesized to have resulted from the induction of CS-specific antibodies and/or CD4+ T cells (Olotu et al., 2011; White et al., 2013). An antibody dynamics model fitted to longitudinal data on anti-circumsporozoite antibody titres from the trial provided further support to the link between the high CS antibodies and the vaccine induced protection against clinical malaria (White et al., 2015). It showed that the pattern of waning efficacy mirrors dynamics of the anti-circumsporozoite antibodies waning rapidly in the first six months followed by slower waning over the next four years. Additionally, the analysis highlighted the low anti-circumsporozoite antibody responses after the booster, compared to the primary series, and argued for further investigation of the immunogenicity and efficacy of the fourth dose.

Modeling evidence on efficacy profile

Other models inferred efficacy of the vaccine against the infection by fitting malaria models to aggregated 3-monthly incidence or efficacy data in each trial site. In the 5-17 month cohort the four modeling groups estimated a high initial post third dose efficacy against infection (>75%) with fast waning during the first 12 months post third dose (M. Penny et al., 2016). Predictions of the waning profile past one year after the third dose diverged between the groups: two groups reported some protection for up 7.5 years and the other two - a slower decay with protection for over 10 years. For the fourth dose the initial efficacy was estimated at about half of the primary series with slower waning compared to the third dose. The discrepancies in the estimated vaccine profiles between the groups reflected differences in model structure and the underlying relationship between the parasite prevalence and clinical incidence, case definitions, assumptions on immunity and differences in datasets used to parameterize the models (M. Penny et al., 2016). Predictions of the efficacy decay shape following the fourth dose were more uncertain due to short follow-up (the fourth dose

administered 18 months after the third (14 months follow-up)) and loss of statistical power in the trial (half of the vaccinated cohort received the fourth dose).

Modeling evidence on population impact

The estimated vaccine properties were then used to make predictions of the likely impact of this new intervention in settings representative of transmission and levels of case management and vector control of *Pf* endemic African countries. Despite the moderate and quickly waning efficacy profile, the models predicted a substantial public health impact: in *Pf*PR_{2-10} between 10 and 65% with high coverage of LLINs (68%) and moderate treatment (45%) the vaccine deployed in the four dose schedule in children aged 5 to 17 months was estimated to avert a median of 116,480 (range across model predictions, 31,450-160,410) clinical cases and 484 (189-859) deaths per 100,000 fully-vaccinated children (FVC) over 15 years. These consensus findings helped establish the public health importance of this new intervention.

Modeling evidence on cost-effectiveness

The key question for the decision analysis was articulated from the perspective of a country policy maker in a setting where other vector control and curative interventions were deployed at scale thus deciding only on whether or not to introduce RTS,S as an additional malaria control measure (Moorthy et al., 2012). This narrow perspective is appropriate for the setting defined by the decision problem. The evaluation conducted within this framing informs the vaccine's value for money but not its *prioritization* within a control strategy (*i.e.*, relative to other interventions that are currently deployed or might be available in the near future). That is concluding that the vaccine is good value leaves the question of whether more of it would also be good value open.

The findings from the costing analyses of RTS,S in Chapter 3 of the thesis informed economic inputs. The relevant insights related to the variation in cost of service delivery between countries (varies greatly), cost of service delivery relative to price of the vaccine (relatively small) and wastage and drop-off assumptions (big implications), and the differences in the cost of the vaccine delivery between the three- and the four-dose schedules (small). Given the broad scope of the evaluation supporting the recommendation and the focus on the average cost-effectiveness it was decided to treat vaccine price as a composite cost that includes the vaccine and service delivery without making an explicit assumption on delivery costs.

The model consensus findings indicated the vaccine was likely to be highly cost-effective – good value for money – in moderate to high transmission settings at high coverages of preventive and curative interventions. The median cost-effectiveness ratio across the four malaria modeling groups for the generic prevalence profiles at an assumed price of 5 USD per dose was estimated at 87 USD (range 48-244) per DALY averted in *Pf*PR_{2-10} between 10 and 65%, higher at *Pf*PR_{2-10} at or below 10%. Recognizing limited transferability of economic evidence between settings (McPake et al., 2002), these average cost-effectiveness ratios appear to be somewhat higher than the literature averages for LLIN (median 27 USD per DALY averted (8.15-110)), and broadly comparable to IRS (143 USD (135-150)) and SMC (68 USD (62-75)) (White et al., 2011). While it is tempting to interpret differences in ICERs as an indication that current preventive interventions might be preferred over RTS,S, the broad similarity in estimates and the wide and overlapping ranges between the interventions suggest the prioritization would require a further evaluation of RTS,S in the same context and *relative* to further scale-up of preventive interventions.

Outside of the model comparison exercise, one of the modeling groups evaluated cost-effectiveness of the scale-up of the vaccine relative to the scale-up of other malaria preventive interventions ((Winskill et al., 2015) later published under (Winskill et al., 2017) and revised (Winskill et al., 2019)). Cost of vaccine implementation from Chapter 3 was used by this study to account for service delivery and inform uncertainty ranges. Winskill and colleagues concluded that the vaccine was likely to be most cost-effective when coverage of other preventive interventions was saturated. The authors further noted that under these conditions, effectiveness and cost of interventions become increasingly non-linear, dependent on the underlying health systems infrastructure and the incremental resource needs to increase coverage beyond current capacity. It is these setting-specific features that determine the relative trade-off between interventions and strategies.

No formal critique of the initial Winskill paper or subsequent revisions is offered here, rather, the discussion highlights the key methodological flaw in the optimization algorithm from the perspective of the economic evaluation that limits relevance of these analyses for policy recommendation. The evidence generated does not inform trade-offs between different strategies in countries that might want to consider introducing the RTS,S/AS01 vaccine, rather the order in which individual interventions could be scaled up. Reliance on the local optima at which the next most-cost effective intervention-coverage option is selected informs a hypothetical trajectory which suggests that LLINs, IRS, and SMC might be prioritized over RTS,S. In reality, however, malaria interventions are not mutually exclusive and most interventions have already been scaled up to moderate and, in some settings, fairly high

levels (WHO, 2018). The programs thus are not choosing whether to deploy IRS at 10% population coverage or to deploy LLINs at 10% population coverage as suggested by this hypothetical trajectory, rather at what coverages to deploy IRS, LLINs, SMC, and potentially also RTS,S. Not only do programs deploy multiple interventions at the same time, their individual effectiveness is modified through synergism with other interventions deployed within the strategy (i.e. LLINs and case management, RTS,S and case management, RTS,S and MDA) further emphasizing the need to frame the decision problem in terms of intervention bundles and not individual interventions. This issue is discussed further in subsequent sections.

The implications of economic and impact modeling for evaluation of the RTS,S pilots

In 2016, following the formal review process of the RTS,S/AS01 trial data and the modeling evidence discussed above, the WHO recommended further evaluation of the vaccine in large-scale pilot implementation to resolve safety signals identified in phase 3, to generate evidence of the vaccine's impact on mortality, and to demonstrate feasibility of deploying the four-dose vaccine series through the routine EPI in *Pf* endemic African countries ("Malaria vaccine: WHO position paper-January 2016," 2016). The pilots are currently on-going in Ghana, Kenya, and Malawi to collect data to inform the WHO 2020 policy recommendation on the wide-scale implementation of RTS,S. In this section learnings from the consensus modeling exercise and malaria vaccine modeling literature are highlighted to illustrate utility of the modeling framework that supported the RTS,S evaluation to facilitate evaluation of new interventions and to direct data collection toward outcomes most critical to policy decisions.

Modeling of trial can motivate further investigation when data are weak

The model comparison exercise highlighted two areas where conclusions from modeling studies diverged from the trial. The first - relates to impact of the vaccine on severe outcomes with the primary series. While the trials, by design, were not powered to detect impact on mortality, it was further not possible to detect impact on severe disease as cases were promptly and effectively managed within the trial (M. Penny et al., 2016). In contrast, all models predicted a net positive impact on severe disease and mortality with the primary series (M. Penny et al., 2016; M. A. Penny, R. Verity, et al., 2015). Significance of these outcomes and congruity between the models supports for further investigation of the vaccine.

The second apparent discrepancy relates to the relative importance of the fourth dose. The trial data were interpreted as suggesting that the fourth dose was necessary for protection against severe outcomes (WHO, 2015d). In contrast to the trial, all models predicted impact on severe outcomes in both three and four dose schedules. All models predicted an incremental benefit of the fourth dose, however, diverged in its magnitude and duration of protection, with two out of four groups reporting only minor additional benefit (M. Penny et al., 2016; M. A. Penny, R. Verity, et al., 2015). A three dose schedule improves the operational feasibility of the vaccine implementation; in most settings all three doses will be delivered along with other routine visits or at most requiring one additional visit outside of the routine schedule. Within the study documented in Chapter 4 the two schedules were directly compared; the incremental cost-effectiveness of the fourth dose was estimated to be twice the primary series suggesting that coverage of the primary series is to be scaled-up before the fourth dose is considered. These findings imply that should the effectiveness of the vaccine against severe outcomes with the primary series be established in pilot evaluation, a revision to the currently recommended vaccination schedule may be something worth considering.

Uncertainty analyses can be used direct data collection

Probabilistic sensitivity analysis, such as work by Maire *et al* (Maire et al., 2011) discussed earlier, are an effective tool to identify and quantify uncertainties in the policy outcome of interest and direct data collection toward inputs that would be most likely to alter the recommendation. For instance, another costing study on vaccine service delivery is not likely to improve the quality of modeling evidence if this evidence is to inform the next recommendation. On the other hand addressing some of the fundamental questions about within host dynamics, or malaria mortality and comorbidities would make a strong contribution to decisions supporting RTS,S and other malaria interventions. This is discussed further in the concluding section of the thesis. Most immediately the analysis suggests that understanding the distribution of risk, use and access to preventative and curative interventions against malaria that will modify effectiveness of the vaccine at both individual and population levels could be informative.

Malaria modeling insights can be useful to inform indicators for pilot evaluation

Modeling studies of malaria vaccines illustrated how effectiveness and impact of vaccination on different health outcomes vary across transmission intensities, age groups, and over time (Maire, Aponte, et al., 2006; M. Penny, K. Galactionova, et al., 2015). These understandings could guide data collection along the pilots toward populations, outcomes, and designs that would yield data relevant to the recommendation. At population level, children age into

eligibility thus in any given year vaccine effectiveness represents cumulative impact at different levels of waning; this means that only by the fifth year of the pilot implementation the full extent of the vaccine effectiveness in the under-five age group will be captured, age-shifting is not likely to be captured except in very high transmission settings closer to the end of the 2 or 3rd year provided transmission/ coverage of other control tools remains the same (Pemberton-Ross et al., 2015).

Economic evaluation can inform data collection

As argued earlier, the economic evaluation framework makes a strong case for making decisions on new interventions based on their relative performance compared to available policy alternatives. For RTS,S this implies that programs would not only require information on the costs of the vaccine delivery but also on effectiveness and cost of other preventive and curative interventions. Methodologies in Chapter 2 and 3 of the thesis provide the framework needed to collect consistent cost estimates and account appropriately for settings specific features, program design, and capacity constraints specific to each delivery channel.

Assessing the distribution of malaria interventions including the new vaccine within the population (i.e. by age) and in priority groups (i.e. by income or rural residence) as argued in Chapter 5 of the thesis could inform the broader societal benefits of RTS,S both in terms of expanding access to prevention to groups that are currently not protected or protected sub-optimally (i.e. RTS,S protecting children that are already covered with LLINs and or have access to effective treatment) and the potential for RTS,S to foster equity or conversely exacerbate inequities in health.

Unlike many traditional vaccines that provide long lasting protection, children vaccinated with RTS,S will eventually get malaria if transmission is sustained. These malaria episodes will occur and re-occur as vaccine protection wanes in the pilots, thus developing strategies to monitor changes in the perceived value of the vaccine and changes in its uptake and ways to address these effectively will be important for sustainability of the program. These behavioral aspects will also change the cost-effectiveness of the vaccine and its relative value over time.

Future modeling to inform 2020 recommendation, funding, and adoption decisions on RTS,S following MVIP

Using RTS,S as an example, this section discusses how new interventions are evaluated by different stakeholder and illustrates how the modeling frameworks developed to support

RTS,S can be applied to produce outputs to inform concrete strategic and operational decisions by global partners and countries on new interventions that are recommended for wide use or targeted areas.

Modeling outputs can inform decisions by manufacturers

Supply side decisions to support production of RTS,S following the pilots are multi-faceted and would be influenced by both internal and external politics around the vaccine, financial standing of the company, agreements on the cost-sharing of development and production costs with partners and countries, as well as commercial potential of the technologies behind the innovation that led to RTS,S. These considerations reflect strategic positions of the company. The public health significance of the vaccine and the potential to save lives with RTS,S offer a strong selling point to enhance the public value of the company and allow it to capitalize on social corporate responsibility. Outputs already generated by the modeling groups to date support advocacy for continued engagement.

Modeling outputs can inform decisions by partners

For PDPs negotiating with industries, advance market commitment agreements is one strategy to ensure stable supply and production capacity for neglected tropical diseases. Modeling can and has contributed in the past to informing demand and impact projections for RTS,S under varying scenarios adjusting for feasibility of implementation, changes in *Pf*PR, population dynamics, coverages, and scale-up rate, etc.

Global development partners and philanthropies currently contribute the large bulk of resources for malaria control in *Pf* endemic Africa (WHO, 2018). Decisions made by these supranational entities on where and how to invest expand the resource pool for country programs and re-direct policy action and local resources toward priorities and interventions advocated by partners. How these decisions are made is not well documented; however, it is clear that these are a result of a whole series of decision problems that span from selecting a health priority to target, to decisions on which tools to support, to which countries to engage with. Cost-effectiveness threshold-based decision rules applied by countries represent the resource constraints of the country reflecting *local affordability* and are not immediately relevant to a global decision maker. For the latter, prioritization with respect to health gain per investment where each unit of health has the same weight directs funding toward areas or interventions where impact is greatest. The distinction is illustrated in Chapter 4 where the relative ranking of countries for RTS,S introduction changes radically when switching from impact per FVC (local efficiency) to burden (greatest impact) (Appendix C, Figure C1). In practice, partner decision rules might be more nuanced with differential

weights assigned to specific target populations, feasibility of implementation, social or political climate, or other partner defined priorities.

Modeling outputs can inform decisions by countries

Outputs from Chapter 5 present most interest to country programs. While overall consistent with predictions for the generic prevalence profiles (M. Penny et al., 2016), country estimates of average cost-effectiveness of RTS,S are overall higher with the median and range across the 43 SSA estimated at 136 USD (116–220) in countries with median population weighted *Pf*PR_{2-10} at or above 10%. The difference reflects within country heterogeneity in transmission and seasonality, representative efficiency of programs (i.e. country DTP3 and MMR2 coverage proxies allowing for drop-off between doses in the primary series), case management, and cost of vaccine service delivery and treatment. And as highlighted in Chapter 5 while transmission is the main driver of the vaccine's impact and cost-effectiveness there is substantial variation in estimated CER within the narrow transmission brackets due to within country heterogeneity and health systems.

Where the potential benefits of the RTS,S vaccination meet the country affordability threshold and where there is a strong political will to support introduction of this new vaccine, questions on existing capacity, funding and its long-term sustainability, prioritization relative to current and future policy alternatives, optimal allocation with respect to impact and within the available funding envelope will come to the forefront of policy discussions (Moree & Ewart, 2004; Romore et al., 2016). Modeling approaches discussed in this thesis can be applied to evaluate the relative performance of alternative implementation modalities of RTS,S formulated by country stakeholders and aligned with the programmatic targets (*i.e.* sub-national strategies, co-deployment with other interventions). Mapping available sources of funding for malaria control and the new vaccine will further inform the appropriate short-term comparator with which the new vaccine will compete for funding.

Program budgets and earmarked disease funding by partners would require comparisons with interventions against malaria currently deployed by programs. And not between individual interventions but rather prioritizing between intervention bundles where the current strategy is augmented with the new tool and trade-offs consider scaling-up existing interventions within the strategy over varied levels of coverage with the new vaccine. Economic and impact models discussed in this thesis are apt at making these comparisons across epidemiological and health systems contexts. Broader cross-disease and cross-sectorial comparisons might need to be considered to the extent that the introduction of the new malaria vaccine will shift funding away from other health priorities. Tools including LIST

could inform these broader considerations (Walker et al., 2013). Finally, targeted funding from GAVI that is directed at immunization programs would require comparisons against other vaccines supported by the PPP; the decision, however, likely rests with the PPP (i.e. prioritizing which new vaccines to support) rather than the country given that programs have little discretion over these targeted grants and might need to only decide on whether or not to apply for funding for RTS,S in addition to other new vaccines.

Thus if global modeling studies are to produce outputs to inform the prioritization of RTS,S by country programs the decision problem needs to be framed within local contexts and with input and in partnership with country stakeholders. Ahead of the pilot evaluation, the WHO could support a longer-term normative priority setting exercise by convening a panel including regional EPI and NMCP programs to define a set of programmatically and regionally relevant intervention bundles and constraints that could then be explicitly modeled to evaluate the relative contribution of RTS,S to the regional malaria strategy.

Probabilistic sensitivity analyses capturing uncertainty in prioritization of different strategies would further strengthen the recommendation. For instance representing policy alternatives on the cost-effectiveness plane and using acceptability curves to summarize the probability a strategy meets a given thresholds are some of the ways to present results of decision analysis in an accessible way and without overstating the confidence in the recommendation (Drummond et al., 2005).

To improve generalizability of these findings for country decision makers, the analyses could be stratified by transmission, seasonality profile, vector bionomics as has been illustrated in (Winskill et al., 2017), and, additionally, by varying constraints on coverage of other malaria interventions. Potentially the most useful output of such a global evaluation would be a set of general rules articulated in terms of explicit contexts where the prioritization is clearly established as well as conditions where local heterogeneity will be critical and thus require further investigation. Directives on which contextual parameters would be most likely to influence prioritization locally and how to evaluate and adjust the outputs from global analyses to account for these might be further helpful for local policy makers.

Other methodologies including constrained optimization supported by transmission models could further inform optimal intervention mixes toward a specific public health target or allocation within a defined budget. These types of evaluations are most useful to inform immediate funding questions and would require in addition to epidemiological and entomological inputs, an understanding of the operational contexts of programs including the

locally relevant mix of interventions, funding sources, past and current levels of coverage and its distribution within the population, capacity, and other relevant constraints. Supporting these questions with existing malaria transmission models would require a platform in which modelers directly engage with programs or tools developed with a transmission model running in the background that would allow local policy makers to conduct these types of evaluations locally. Another approach toward reducing complexity is currently implemented in Spectrum (Hamilton et al., 2017).

From modeling malaria vaccines to informing decisions on new tools against malaria

This chapter discusses learnings from evaluation of RTS,S and generalizability of modeling frameworks that supported the evaluation for decisions on new interventions. It outlines the limitations of these methodologies and directions for future development to support evaluation of new malaria tools in light of malaria epidemiology and policy targets.

Learnings from RTS,S policy development process

Development and evaluation of RTS,S highlighted the complex politics around the vaccine and the need for processes to steer and engage with a diverse group of stakeholders. The MVI and, later on, also the WHO Malaria Vaccine Implementation Project (MVIP) developed decision making frameworks to facilitate these exchanges and ensure continuity in decision-making throughout pilot evaluation and transparency over the policy development process (Brooks & Ba-Nguz, 2012; Alan Brooks, Julia Nunes, et al., 2012). These frameworks guided the evaluation and modeling efforts towards outcomes that were prioritized by key stakeholders. Engaging with modeling community earlier in the planning stages could ensure that models are used to inform optimal trial/ pilot design and to identify additional metrics that might help better differentiate the new technology from tools currently deployed by programs (i.e. extending access, synergies with existing tools or toward specific target, distribution of benefit with respect to age or other priority characteristic).

For traditional vaccines and drugs establishing impact on mortality has been a key evaluation criterion. It is less obvious how much weight should mortality outcomes play in the evaluation of malaria vaccines or other new interventions that target infection. This issue generated substantial discussion within the evaluation of RTS,S/AS01 for the global recommendation. Impacts on mortality are difficult to measure in the context of a vaccine clinical trial where enrollment into the trial itself improves survival through access to care in

the population enrolled. These discussions are on-going as data are being collected within the pilot evaluation and should inform evaluations of new preventive interventions.

Next generation malaria vaccines and, equally, other new malaria interventions will be considered within a complex programmatic landscape with multiple layered interventions where their *incremental* benefit will need to be established. The previous section of this Chapter discussed how these considerations can be adequately addressed to inform the 2020 recommendation on RTS,S. The malaria vector control community currently faces a similar challenge in developing a policy recommendation on PBO treated nets (Ten Brink et al., 2018). The WHO Vector Advisory Group is yet to endorse cost-effectiveness as a criterion for prioritization of new vector control technologies and in doing so can draw on the process and frameworks developed to support the RTS,S evaluation. As advisory boards move toward incorporating economic evidence into policy development process the membership on these boards and among research partners providing evidence should also include economists and health systems specialists to appropriately frame and guide analyses supporting the broader health policy considerations.

Finally, evaluation and modeling support of RTS,S placed modelers in direct dialogue with global stakeholders. The modelers were represented in the Working Group steering the MVIP and presenting and discussing results with the policy audience. The continued collaboration between the modeling groups and the WHO and its technical advisory groups fostered understanding within the academic and policy communities of the utility of modeling approaches and best ways these methodologies can support a global recommendation on new health technologies.

RTS,S modeling as a platform for evaluation of new tools

Previous sections discussed the many insights modeling contributed throughout product development and evaluation cycle of RTS,S. Important to highlight here is that model and methodological development prior to and following completion of the clinical trials and evaluation of RTS,S by now amounted to a sound platform that could fairly quickly generate predictions on outcomes of interest and as such speed up evaluation and inform R&D targets for next generation malaria vaccines and other malaria interventions. Most recently, these workflows have been applied to evaluate fractional dosing of RTS,S (Hogan et al., 2018).

Another important contribution motivated by the WHO evaluation of RTS,S is the systematic comparison of the key individual-based malaria transmission models (M. A. Penny, K.

Galactionova, et al., 2015). Through the comparison exercise model assumptions on malaria pathogenesis and immunity and the methodologies used by different groups were documented and related to differences in model predictions. This is a valuable reference document that highlights strengths of different methodologies and points to gaps in the data and out understanding of processes driving immunity and pathogenesis; most immediately the document allows adequate interpretation of model outputs in the context of model differences.

Limitations of RTS,S frameworks and way forward

The modeling frameworks that supported evaluation of RTS,S were developed to promptly incorporate new data from clinical trials as it were released and provide updated predictions of the public health impact and other outcomes of interest (M. Penny, K. Galactionova, et al., 2015). This methodology enabled a substantial computational advantage by generating impact predictions by re-weighting an existing database of simulations from a full-factorial design experiment covering a comprehensive range of vaccine properties, schedules, coverages, case management, and transmission parameters compared to generating predictions by explicitly re-simulating impact estimates for each desired efficacy profile or setting. The framework served this purpose very well. However it is not adequate for evaluation of intervention bundles and as such is not suitable for the immediate questions on the relative cost-effectiveness of the vaccine. These combination scenarios would need to be modeled explicitly (as done by other groups). New methodologies, however, are being developed to address this.

Modeling combinations of interventions is highlighted as priority by the malERA research agenda (Interventions & Modelling, 2017). OpenMalaria has been applied previously to evaluate combinations of interventions for different programmatic targets (Reiker, Chitnis, et al., 2019; Stuckey et al., 2014), linking in costing models developed within this thesis allow further efficiency in evaluation and application of these methodologies to broader contexts. On-going work within the group has been exploring new methods for modeling malaria elimination and effectiveness of combinations of interventions and their optimal pathways toward elimination targets that also incorporate the costing models presented here. These new methods optimize use of OpenMalaria with Machine Learning algorithms to explore faster and better the multi-dimensional parameter space for optimization to find optimal combinations of interventions without explicitly simulating thousands of possibilities (Golumbeanu et al., 2019).

Otherwise, most limitations of individual based malaria models are shared by all modeling groups that work in this space. The overall complexity of the models given the breadth of the processes captured limit the scope for probabilistic sensitivity analyses and use of these models outside of the groups that develop them; difficulties in estimating impacts on mortality, co-morbidities, and predicting impacts and capturing transmission dynamics in low endemicity settings given that the data to parameterize a the relationships between transmission and clinical outcomes came from before the scale-up of malaria interventions when transmission was high everywhere. To this end, work is on-going to re-parameterize OpenMalaria with recent epidemiological studies using new algorithms and incorporating methodological advances in model fitting (Reiker, Cameron, et al., 2019). These developments continue to improve the quality of model predictions.

A unique challenge for OpenMalaria at the moment is that the model is not geographically explicit; however, a clever strategy has been devised and applied successfully to evaluate reactive case detection - a strategy that entails following up cases and testing and treating family members and residents within a radius around an index case – currently trialed in low endemicity settings (Reiker, Chitnis, et al., 2019).

Strengthening the role of modeling for guiding policy decisions in global health

The thesis concludes with practical suggestions on how the contribution of modeling to policy development and other decisions at global and local levels can be strengthened. The opportunities for mutual learning between the modeling and policy communities are emphasized.

Integration of modeling into WHO guideline development guidelines
Modeling offers unique insights on the long term impact of interventions and allows evaluation of new interventions relative to the tools currently deployed by programs. While these considerations are equally relevant to decisions on new vector control tools and other preventive and curative products, so far it is only JTEG/QUIVER – the WHO's vaccine advisory groups - that set explicit standards for modeling studies (den Boon et al., 2019; Hutubessy et al., 2001; Moorthy et al., 2012). Guidance on use of modeling is generally lacking in assessment of other health technologies against malaria and infectious diseases more broadly. Moreover, while modeling studies have been solicited by different advisory groups, modeling evidence is not formally integrated into the WHO guidelines for guideline development which form the basis of the policy recommendation (WHO, 2012b). It is thus

not clear how the strength of modeling evidence compares to evidence from clinical trials and other primary data, nor how the quality of modeling evidence and its contribution to the recommendation are determined. Egger *et al* propose a strategy for defining and integrating modeling into policy development by extending the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, used by the WHO to evaluate evidence toward a policy recommendation, to cover modeling evidence (Egger et al., 2017). This necessary step would go a long way toward strengthening the role of modeling studies in policy decisions on malaria vaccines as well as other interventions against malaria and in other WHO priority areas.

If modeling evidence is to gain equal footing with experimental evidence from clinical trials there needs to be a concerted effort to address uncertainties underlying model predictions. Recent reviews highlighted data gaps and uncertainty about spatial and temporal variations in disease prevalence and transmission intensity, host–pathogen interactions and infection outcomes, and human behavior that pose fundamental challenges for modeling infectious diseases including malaria (Childs et al., 2015). An appreciation of the implications of model uncertainties for policy recommendation should foster support from the policy community and stakeholders that use modeling toward resolving these uncertainties with experimental evidence that would ultimately strengthen the evidence base for global health.

For key individual-based malaria models predictions of transmission dynamics and clinical outcomes are challenging at low endemicities as these models were parameterized with data from predominantly high transmission settings (Ross et al., 2006; Smith et al., 2005). This translates to larger confidence intervals in model predictions at low transmission, and, for comparative evaluations, inability of the models to distinguish statistically between different scenarios of interest. The relationship between parasitemia and morbidity outcomes are a further challenge as these were estimated with data collected prior to the scale-up of the EPI program and health services in endemic settings with high child mortality and co-morbidities rates (Ross et al., 2006; Smith et al., 2005). This in itself does not bias comparisons of different scenarios evaluated within the model, but might suggest a greater burden, better value for money, and a greater significance of interventions against malaria when compared to other health priorities. These biases result in inefficient health programs and excess morbidity.

From global policy to informing decisions at country level

Explicit in the WHO guideline development guideline is the need to contextualize and offer guidance to countries on how to interpret the recommendation with the country context

(WHO, 2012b). Malaria interventions in the development pipeline are likely to offer only partial protection and like RTS,S will need to be considered by programs along with a range of other interventions that are currently deployed by programs at fairly high levels. The thesis touched on the difficulties in drawing broad guidance in this context that requires a fairly thorough understanding of the health systems capacity and constraints to issue a recommendation for a specific setting.

At the same time increasing availability of high resolution epidemiological (*Malaria Atlas Project*), health services (MEASURE DHS; Roll Back Malaria, 2013), and economic data (*The cMYP Immunization Financing Database*, 2015; IVB, 2006) from LMIC and *Pf* endemic countries, along with advances in geospatial modeling and computational power stimulated interest in the scientific community in application of mathematical modeling to infectious diseases. Predictions are often made at global and local levels with explicit recommendations for policy makers in the South by researchers in the North. At best these evaluations are offer limited insight. At worst these evaluations are ignored or seed confusion if recommendations do not align across the modeling studies and undermine the role modeling could play in supporting decisions at local and global levels.

Two recently published studies by Sauboin *et al* (Sauboin et al., 2019) and Winskill *et al* (Winskill et al., 2019) on prioritization of RTS,S that arrived at opposite conclusions on the relative importance of the vaccine within a control strategy are one example of conflicting evidence that might be challenging for a non-specialist to interpret. Sauboin and colleagues use a static cohort model to compare adding RTS,S to current levels of LLINs, IRS, and SMC toward reducing under-five malaria mortality at lowest cost in Ghana. The authors concluded that in Ghana, RTS,S would be the optimal first step for reducing under-five malaria mortality at the lowest cost, followed by SMC in relevant areas, and then by further scaling-up of IRS and LLINs. The conclusion, as acknowledged by the authors, primarily driven by the *specific* set of constraints imposed on the level of coverage that could be achieved with each intervention and costs. LLIN coverage at baseline was estimated at 54% and could only be scaled-up to a maximum coverage of 60%. This means that the incremental impact of RTS,S was compared to the incremental impact of LLIN at half the coverage of RTS,S (optimization step of 10%). Assumptions on costs further inflated cost of LLINs by loading cost of nets that were not used (40% of nets distributed) and understated cost of RTS,S by using a unit costs that assumed 100% coverage in the full four-dose schedule (not stated, but illustrated with a difference of over 50% compared to Winskill *et al* that allowed for drop-off between doses). There are other potential incongruities that are difficult to assess based on the information in the paper that could have further biased the

evaluation undermining the effectiveness of vector control (*i.e.* it is not clear how the translation from EIR reduction (enabled by IRS and LLINs) to clinical disease was implemented and whether individual protection from LLINs were captured (much smaller than transmission effects, but further biases down the effectiveness of LLINs compared to RTS,S)) (Killeen et al., 2007). The evaluation further ignores treatment which is the only intervention that directly impacts mortality in children under five which implies the prioritization suggested by this optimization framework might not be optimal with respect to the outcome of interest. To conclude while the work by Sauboin *et al* is some improvement over Winskill paper discussed earlier, in that it explicitly seeks to evaluate the scale-up of combinations of interventions, the assumptions and the model stricture adopted might be not be appropriate for the policy question.

The WHO developed guidance on the criteria to assess the model structure, assumptions, robustness and limitations of economic decision-making tools (den Boon et al., 2019; Ultsch et al., 2016; Walker et al., 2010). Recent guidelines by technical groups such as ISPOR offer further guidance on economic modeling (Mauskopf et al., 2018). A clarification of interpretation of results produced by different economic evaluation methodologies and explicit statement on appropriate evaluation methods to support recommendation of new interventions would be of use for broader audience at this stage.

Despite the seeming abundance of evidence and technical guidance recent evaluations of introduction of new health interventions in LMIC suggest that neither the cost-effectiveness metrics nor other modeling evidence are currently utilized to inform adoption decisions in these countries (Mills, 2014). Policy makers in LMICs find the questions addressed removed from the realities of the programs (Behague et al., 2009). Moreover stakeholders reportedly find the methods and the interpretation of results from cost-effectiveness studies complex and therefore challenging to use in the decision-making process (Behague et al., 2009). Other studies highlighted the difficult political environment in which these decisions are made largely driven by partners and motivated by funding availability (Mills, 2014).

A model for future engagement and a strategy to capitalize and transfer the expertise of malaria modeling community to country programs might be through modeling support and training within the high burden to high impact (HBHI) collaboration between modelers and malaria control programs in the region facilitated by the WHO (WHO, 2019). In this, for now short-term consultancy, partnership modelers and programs apply malaria transmission models fitted to local data to optimize strategies toward programmatic targets using impact and costing models to optimize intervention packages. The aspiration is for the evidence

generated in this collaboration and structured and transparent process that these methodologies for decision-making require to earn a wider appreciation of these tools with local stakeholders.

The ultimate goal of country modeling and the HBHI initiative is local capacity building and transfer of decision-making tools to local stakeholders. In support of the longer view where the expertise and the models are with local teams key malaria transmission models are already open source. The costing methodologies and their application illustrated in Chapters 3 and 4 of the thesis emphasized transferability of research findings and produced methodologies that support local capacity for decision-making on malaria control and elimination policies.

Mutual learning

Interventions modeled represent an abstraction of the program; most are summarized within a transmission model with a coverage level and a hypothesized or known mode of action on infection. To a program officer the intervention might by best represented by a budget line, a list of operational activities and a series of service outputs. Both have important insights to offer toward an actionable strategy, the quality of modeling evidence is best when there is scope and room for these two perspectives to inform thinking. To be impactful modeling approach requires a close interaction between the policy stakeholders and the modeling community to formulate the question and interpret modeling evidence. Models allow a great degree of flexibility in representing a given problem, in contrast, the interest of stakeholders is often narrow. By engaging with the question the two communities can ensure that the appropriate methodology is adopted for the question and, in turn, the policy community can benefit from the broader insight and exploration the models allow to sharpen policy focus.

Much has been said about clear communication on the assumptions and uncertainties of the models by modelers. The modeling community has gone a long way to adequately capture and represent both structural and parameter uncertainty underlying model estimates (Maire et al., 2011; Smith et al., 2012). And while these uncertainties are often communicated by modelers interpreting these for policy guidance and building these into recommendation is currently lacking within the policy community. As modelers learn the language of public health so is there a need for policy stakeholders that commission the evidence to get comfortable with uncertainty and focus policy action and effort toward resolving it.

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Appendix A. Supplementary files to Chapter 2: Costing malaria interventions from pilots to elimination programmes

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Table A1. References supporting implementation scenarios by intervention

Intervention	Published studies	Normative guidelines
Rapid Reporting	Githinji et al (2017), Kariuki et al (2016), Kiberu et al (2014), Quan et al (2014), WHO (2018)	WHO (2018)
Reactive Case Detection	Larsen et al (2016), Larson et al (2016), Littrell et al (2013), Sturrock et al (2013), Searle et al (2016)	WHO (2017a)
Mass Drug Administration	Hodges et al (2012), Bridges et al (2017), Castellani et al (2016), Medzihradsky et al (2018), von Seidlein et al (2019), Cook et al (2015), Scott et al (2016), Silumbe et al (2015), Newby et al (2015)	WHO (2017b)
Indoor Residual Spraying	Cico et al (2018), Johns et al (2016)	WHO (2015)

Table A2. Parameters of the costing model by input category

Input category	Rapid Reporting	Reactive Case Detection	Mass Drug Administration	Indoor Residual Spraying
Intervention	data use by dCHF nurses, days checking data by district staff, days planning meetings, days planning, days program management, days reporting by HF nurses, days supervision, days training, number district staff supporting audits at HF, number district staff checking data, number staff planning, number staff program management, number staff sensitization, number staff supervision, number staff training, proportion HF reporting, top-up paid to nurses for reporting, number of trainees per training session	data use by CHW, data use by HF nurses, days checking data by district and HF staff, days to follow-up an index case, days planning meetings, days planning, days program management, days reporting by HF nurses, days supervision, days training, food allowance, CHW kit, number district staff conducting data audit, number of district staff checking data, number of mobile phones per HFCA, number staff planning, number staff program management, number staff sensitization, number staff supervision, number staff training, number of vehicles for drug distribution, number of sensitization activities per district, number of CHWs per pair following-up index cases, per-diem to CHW, proportion of index cases followed-up, proportion of HF reporting, radius around index case, top-up paid to dCHW for reporting, number of trainees per training session	coverage, data use by HF nurses, days planning meetings, days planning, days program management, days reporting by HF nurses during MDA campaign, days supervision, days training, CHW kit, days sensitization, number of persons treated per CHW pair per day, number of MDA CHW teams supervised by HF nurse, number staff planning, number staff program management, number staff sensitization, number staff training, number of sensitization activities per district, number of CHWs per pair conducting MDA, per-diem to CHW, number of MDA rounds per year, incentive paid to CHW at the end of MDA round, number of trainees per training session	coverage, days planning meetings, days planning, days program management, days supervision, days training, structures sprayed per day per operator, spray operator kit, number of spray operators per team, number staff planning, number staff program management, number staff sensitization, number staff supervision, number spray operators per team, number staff training, number vehicles per district, number of sensitization activities per district, volume of insecticide per structure, number of IRS rounds per year, number of trainees per training session
Setting	health seeking for malaria, distances between program levels, number of CHW per population target, number of HF per population target, *Pf*PR, proportion allocation of shared resources to RR	health seeking for malaria, distances between program levels, number of CHW per population target, number of HF per population target, *Pf*PR, positivity rate around an index case, proportion allocation of shared resources to RR, proportion allocation of shared resources to RACD, proportion of population within the target radius available for fTAT	health seeking for malaria, distances between program levels, number of CHW per population target, number of HF per population target, *Pf*PR	health seeking for malaria, distances between program levels, number of CHW per population target, number of HF per population target, persons per structure, percent vehicles rented
Scale	number of districts, number regions, HFCA population size	number of districts, number regions, HFCA population size	number of districts, number regions, HFCA population size	number of districts, number regions, HFCA population size, proportion of HFCA's targeted
Price	prices of equipment, vehicles, fuel, facility and vehicle	prices of equipment, vehicles, fuel, facility and vehicle rental, overheads, wages and	prices of equipment, vehicles, fuel, facility and vehicle rental, overheads, wages	prices of equipment, vehicles, fuel, facility and vehicle rental, overheads, wages

	rental, overheads, wages and per-diems of program staff, allowances, stationaries, consumables	per-diems of program staff, gifts, drugs, diagnostics, allowances, stationaries, sensitization activities and materials, other print, consumables	and per-diems of program staff, gifts, drugs, diagnostics, allowances, stationaries, sensitization activities and materials, other print, consumables	and per-diems of program staff, gifts, insecticide, environmental compliance and waste management, allowances, stationaries, sensitization activities and materials, other print, consumables
Methods	ULY of all capital items (i.e. buildings, equipment, furniture, etc.), ULY of training and sensitization activities, discount rate	ULY of all capital items (i.e. buildings, equipment, furniture, etc.), ULY of training and sensitization activities, discount rate	ULY of all capital items (i.e. buildings, equipment, furniture, etc.), ULY of training and sensitization activities, discount rate	ULY of all capital items (i.e. buildings, equipment, furniture, etc.), ULY of training and sensitization activities, discount rate

Table A3. List of operational activities and key resource line items by intervention implementation stage

Implementation stage	Operational activities	Resource line items	Rule for allocation of shared resources to intervention
Planning	Micro-planning at central, regional, and district levels, planning meetings at central level and district levels	Wages and per-diems of program staff, transportation, equipment, facility and related overheads, supplies	Number of meetings, number of days
Procurement	Procurement	Commodities (i.e. drugs, RDTs, etc.) and related equipment, wastage, CHW/ spray operator kits	100%
Storage	Storage of commodities and related equipment at central and district and/or HFCA levels	Facility and overheads, store-keeper	Volume, days of storage
Distribution	Distribution of commodities and related equipment from central to district/HFCA levels	Vehicles and overheads, fuel, driver wages and per-diems, program staff wages and per-diems, loaders/ off-loaders per-diems	Volume, distance
Training	Training of supervisors, trainers, implementation staff at central, regional/district and HFCA levels	Wages and per-diems of program staff, transportation, equipment, bus rental for piloting and field practice, facility and related overheads, commodities, supplies and consumables	Number of days
Community sensitization	Advocacy meetings with community members, community forum, community entry meetings at central and district levels, social mobilization at community level	Wages and per-diems of program staff, gifts and incentives to community members, print materials, transportation, equipment, facility rental (hall or tent), chair rental, sound equipment rental, drama group fees, supplies and consumables, public announcement system, radio broadcasts	Number of meetings, number of days
Program management and supervision	Program management at central, regional, district levels and supervision by central, regional, district, and HF staff, IT infrastructure (RR, RACD)	Wages and per-diems of program staff, transportation, equipment, facility and related overheads, supplies	Number of days, distance
Implementation	Service delivery in community, reporting at HF level (RACD, MDA), stock management (MDA, IRS),	Wages and per-diems of program staff, food allowance, lodging allowance, data, transportation, equipment, facility and related overheads, supplies	Number of HF (RR), number of index cases (up to capacity) (RACD), number of campaign days (MDA, IRS), % of households targeted (IRS), scale
Other intervention specific	Data audit (RR), routine data quality checks (RR, RACD), pharmacovigilance (MDA), inspection (IRS), environmental compliance (IRS), waste management (MDA, IRS), review meeting at central level (IRS)	Wages and per-diems of program staff, transportation, equipment, facility and related overheads, environmental compliance, waste management, supplies	Number of days, distance, volume

Table A4. Economic cost ingredients summaries of costing models for the reference implementation and R functions for linking with impact models: malaria rapid reporting

Activity	Parameter	Unit cost (first year/ thereafter)	Units	Impact model inputs for linking
Planning	*p*	0.0339	per person per year	pop, yrs
Procurement and distribution of mobile phones and supplies	*k*	0.0042	per person per year	pop, yrs
Training	t_1/ t_2	0.0293/ 0.0079	per person per year	pop, yrs
Program management, IT support, and supervision			per person per year	pop, yrs
- Server	*y*	15000	per year proportional to use for malaria RR	yrs, prop_rr
- Server overheads	*q*	50000	per year proportional to use for malaria RR	yrs, prop_rr
- Module	*l*	114000	per program	
- Other program	*m*	0.0122	per person per year	pop, yrs
Implementation	*f*	0.0538	per person reporting per year	pop, prop_report, yrs
Other: data quality	*o*	0.0256	per person per year	pop, yrs

$$TC = \frac{p + t_1}{a_p} * uly_p + \frac{t_2}{a_t} * \left((yrs - 1) \div 3\right) + \left(k + m + f * prop_{report} + o\right) * yrs) * pop + \frac{l}{a_l} * uly_l + (y + q) * prop\_rr * yrs$$

where

TC is total cost of malaria RR under reference implementation
a_p, a_t and a_l are annualization factors for start-up activities and routine training (t, conducted every 3 years following introduction), and RR module
pop is total population in the area where RR program is implemented
prop_report is proportion on CHWs reporting
prop_rr is proportion of DHIS2 server and server overheads to be allocated to malaria RR
pos_rate is positivity rate around index case
yrs is number of years RACD program is implemented
uly_p is ULY for activities conducted in preparatory, start-up stage of implementation
uly_l is ULY for malaria RR module

ProR function:

```
calc_RR_Costs<- function(yrs,pop,prop_rr,prop_report,r) {
  ingr<- list ("p"= 0.0339, "k"=0.0042, "t1"=0.0293, "t2"=0.0079, "y"=15000, "q"=50000,
               "l"=114000, "m"=0.0122, "f"= 0.0538, "o"=0.0256)
  uly_p<- if(yrs<5) yrs else 5
  uly_t<- if (yrs<3) yrs else 3
  uly_l<- if(yrs<10) yrs else 10
  a_p<- ((1-(1+r)^(-uly_p))/r)
  a_t<- ((1-(1+r)^(-uly_t))/r)
  a_l<- ((1-(1+r)^(-uly_l))/r)
  totalCost<- with(ingr, (((p+t1)/a_p)*uly_p+(t2/a_t)*((yrs-1)%/%3)+
                          (k+m+o+f*prop_report)*yrs)*pop +l/a_l*uly_l+(y+ q)*prop_rr*yrs)
  return(totalCost)
}
calc_RR_Costs(5,360000,0.2000,1,0.03)
```

Table A5. Economic cost ingredients summaries of costing models for reference implementation and R functions for linking with impact models: malaria reactive case detection

Activity	Parameter	Unit cost (first year/ thereafter)	Units	Impact model inputs for linking
Planning	*p*	0.0573	per person per year	pop, yrs
Procurement, storage, and distribution of commodities				
- CHW kits and supplies (including mobile phones for dCHW)	*k*	0.1001	per person per year	pop, yrs
- RDTs	*w*	1.5507	per person tested around an index case per year	pop, n_index, prop_follow, radius, prop_tat, yrs
- Antimalarial drugs	*d*	1.9851	per positive case around an index case per year	pop, n_index, prop_follow, radius, prop_tat, pos_rate, yrs
Training	t_1/ t_2	0.5375/ 0.1605	per person per year	pop, yrs
Sensitization	*s*	0.0788	per person per year	pop, yrs
Program management and supervision	*m*	0.0624	per person per year	pop, yrs
Implementation*	*f*	5.4329	per index case followed up per year	pop, n_index, prop_follow, yrs
Other: data quality	*o*	0.0077	per person per year	pop, yrs

$$TC = \left(\frac{p+s+t_1}{a_p} * uly_p + \frac{t_2}{a_t} * \left((yrs-1) \div 3\right) + (k+m+o) * yrs\right) * pop + \left(\left((d * pos_{rate} + w) * prop_{tat} * radius + f\right) * n_{index} * prop_{followed}\right) * yrs$$

where

TC is total cost of RACD program under reference implementation
a_p and a_t are annualization factors for start-up activities and routine training (t, conducted every 3 years following introduction)
pop is total population in the area where RACD program is implemented
n_index is number of index cases per year
prop_follow is proportion on index cases followed-up by CHWs
radius is number of people around and index case tested during RACD
prop_tat is proportion of residents around index case available for testing and treatment
pos_rate is positivity rate around index case
yrs is number of years RACD program is implemented
uly_p is ULY for activities conducted in preparatory, start-up stage of implementation

R function:

```
calc_RACD_Costs<- function(yrs,pop,n_index,prop_follow,radius,prop_tat,pos_rate,r) {
  ingr<- list ("p"= 0.0573, "k"=0.1001, "w"=1.5507, "d"= 1.9851,  "t1"=0.5375, "t2"=0.1605,
               "s"=0.0788, "m"=0.0624, "f"= 5.4329, "o"=0.0077)
  uly_p<- if(yrs<5) yrs else 5
  uly_t<- if(yrs<3) yrs else 3
  a_p<- ((1-(1+r)^(-uly_p))/r)
  a_t<- ((1-(1+r)^(-uly_t))/r)
  totalCost<- with(ingr, ((p+s+t1)/a_p*uly_p+t2/a_t*((yrs-1)%/%3)+ (k+m+o)*yrs)*pop+
                         (((d*pos_rate+w)*radius*prop_tat+f)*n_index*prop_follow)*yrs)
  return(totalCost)
}
calc_RACD_Costs(5,360000,11520,1,5,0.8,0.183333,0.03)
```

Table A6. Economic cost ingredients summaries of costing models for reference implementation and R functions for linking with impact models: mass drug administration

Activity	Parameter (first year/ thereafter)	Unit cost (first year/ thereafter)	Units	Impact model inputs for linking
Planning	p_1/ p_2	0.0573/ 0.0093	per person per year	pop, yrs
Procurement, storage and distribution of CHW kits and supplies				
- CHW kits and supplies	k	0.0694	per person per year	pop, yrs
- Antimalarial drugs	d	1.7549	per person treated per round per year	pop, yrs, rnds, cov
Training	t_1/ t_2	0.4991/ 0.1605	per person per year	pop, yrs
Community sensitization	s_1/ s_2	0.0983/ 0.0321	per person per year	pop, yrs
Program management	m	0.0061	per person per year	pop, yrs
Supervision	s	0.0891	per person per round per year	pop, yrs, rnds
Implementation	f	0.4343	per person treated per round per year	pop, yrs, rnds, cov

$$TC = \left(\frac{p_1 + t_1 + s_1}{a_p} * uly_p + (p_2 + s_2 + t_2) * (yrs - 1) + (k + m + (s + (d + f) * cov) * rnds) * yrs\right) * pop$$

where

TC is total cost of MDA program under reference implementation
a_p and a_t are annualization factors for start-up activities
pop is total population in the area where MDA program is implemented
rnds is number of MDA rounds per year
cov is MDA coverage per round
yrs is number of years MDA program is run
uly_p is ULY for activities conducted in preparatory, start-up stage of implementation

R function

```
calc_MDA_Costs<- function(yrs,pop,rnds,cov,r) {
  ingr<- list ("p1"= 0.0573, "p2"= 0.0093, "k"=0.0694, "d"= 1.7549, "t1"=0.4991,
"t2"=0.1605,
               "s1"=0.0983, "s2"=0.0321,"m"=0.0061, "s"=0.0891, "f"= 0.4343)
  uly_p<- if(yrs<5) yrs else 5
  a_p<- ((1-(1+r)^(-uly_p))/r)
  totalCost<- with(ingr,((p1+t1+s1)/a_p*uly_p+(p2+s2+t2)*(yrs-
1)+(k+m+(s+(d+f)*cov)*rnds)*yrs)
                        *pop)
  return(totalCost)
}
calc_MDA_Costs(5,360000,2,0.85,0.03)
```

Table A7. Economic cost ingredients summaries of costing models for reference implementation and R functions for linking with impact models: in-door residual spraying

Activity	Parameter	Unit cost (first year/ thereafter)	Units	Impact model inputs for linking
Planning	p_1/p_2	0.1309/ 0.0071	*per person per year*	*pop, yrs*
Procurement including storage and distribution				
- Spray operator kit	*k*	0.0929	*per person targeted per year*	*pop, target, yrs*
- Spray pumps and supplies	*p*	0.1637	*per person targeted per year*	*pop, target, yrs*
- Insecticide (Actellic)	*c*	1.8744	*per person protected per round per year*	*pop, target, cov, rnds, yrs*
Training	t_1/t_2	0.4722/ 0.3249	*per person targeted per year*	*pop, target, yrs*
Community sensitization	s_1/s_2	0.1033/ 0.0371	*per person per year*	*pop, yrs*
Program management	*m*	0.1072	*per person per year*	*pop, yrs*
Supervision	*s*	0.1934	*per person targeted per round per year*	*pop, target, rnds, yrs*
Implementation	*f*	0.8042	*per person protected per round per year*	*pop, target, cov, rnds, yrs*
Other				
- Environmental compliance	*e*	0.0174	*per person targeted per round per year*	*pop, target, rnds, yrs*
- Waste management	*w*	0.0113	*per person protected per round per year*	*pop, target, cov, rnds, yrs*
- Inspection	*i*	0.0332	*per person targeted per round per year*	*pop, target, rnds, yrs*
- Annual review	*v*	0.038	*per person targeted per year*	*pop, target, yrs*

$$TC = \left(\frac{p_1+s_1}{a_p} * uly_p + (p_2+s_2) * (yrs-1) + m * yrs + \left(\frac{t_1}{a_p} * uly_p + t_2 * (yrs-1) + (k+p+v+(e+i+s+(c+f+w)*cov)*rnds)*yrs\right)*target\right) * pop$$

where

TC is total cost of MDA program under reference implementation
a_p and a_t are annualization factors for start-up activities
pop is total population in the area where IRS program is implemented
rnds is number of IRS rounds per year
cov is MDA coverage per round
yrs is number of years IRS program is implemented
uly_p is ULY for activities conducted in preparatory, start-up stage of implementation

R function

```
calc_IRS_Costs<- function(yrs,pop,target,rnds,cov,r) {
  ingr<- list ("p1"= 0.1309, "p2"= 0.0071, "k"=0.0929, "p"= 0.1637, "c"=1.8744,
"t1"=0.4722,
               "t2"=0.3249, "s1"=0.1033, "s2"=0.0371,"m"=0.1072, "s"=0.1934, "f"= 0.8042,
               "e"= 0.0174, "w"=0.0113, "i"=0.0332, "v"=0.038)
  uly_p<- if(yrs<5) yrs else 5
  a_p<- ((1-(1+r)^(-uly_p))/r)
  totalCost<- with(ingr, ((p1+s1)/a_p*uly_p+(p2+s2)*(yrs-1)+m*yrs+(t1/a_p*uly_p+
                          t2*(yrs-1)+(k+p+v+(e+i+s+(c+f+w)*cov)*rnds)*yrs)*target)*pop)
  return(totalCost)
}
calc_IRS_Costs(5,360000,0.5,1,0.90,0.03)
```

Table A8. Average annual financial and economic cost per output by intervention: reference implementation (USD, 2014)

Number of years	Financial cost				Economic cost			
	RR	RACD	MDA	IRS	RR	RACD	MDA	IRS
1	6.05	33.31	2.35	3.81	8.40	39.60	2.72	4.57
5	4.82	20.20	2.19	3.49	6.73	23.36	2.52	4.12

Intervention costs per output reflect reference implementation presented in Table 1 above and Additional file 2. The denominator (unit of output) varies by intervention: for RR the estimate represents cost per case reported; for RACD – cost per index case followed-up; for MDA – cost per person treated per round; for IRS – cost per person protected per round. Estimates in the first row show costs incurred in the first year (*i.e.* the year the intervention is first introduced), assuming the intervention is only to be deployed for one year. The second row gives the average annual economic cost assuming each intervention is implemented annually for five years. * Under the reference implementation assumed 50% of the population were targeted by IRS (the denominator refers to the total population). Equivalent cost summaries per capita are reported in Table 2. Costs by implementation stage and cost structure are reported in Appendix A, Tables A9-A10.

Table A9. Average annual financial cost and cost structure by intervention: reference implementation (USD, 2014)

	Total costs, USD				Cost profile, %			
Activity/ Intervention	Rapid Reporting	Reactive Case Detection	Mass Drug Administration	Insecticide Residual Spraying	Rapid Reporting	Reactive Case Detection	Mass Drug Administration	Insecticide Residual Spraying
Planning	1’309	1’930	1’935	5’603	2.36	0.83	0.14	0.99
Procurement	194	120’308	1’082’706	335’998	0.35	51.70	80.82	59.48
Distribution	352	3’105	12’887	602	0.63	1.33	0.96	0.11
Storage	0	0	0	513	0.00	0.00	0.00	0.09
Training	826	34’557	69’135	53’912	1.49	14.85	5.16	9.54
Sensitization	0	5’089	14’853	15’399	0.00	2.19	1.11	2.73
Program management and supervision	39’133	13’208	30’689	25’167	70.44	5.68	2.29	4.46
Implementation	9’407	53’217	127’440	113’952	16.93	22.87	9.51	20.17
Other	4’334	1’300	0	13’736	7.80	0.56	0.00	2.43
Total	55’556	232’713	1’339’645	564’883	100	100	100	100

Table A10. Average annual economic cost and cost structure by intervention: reference implementation (USD, 2014)

	Total costs, USD				Cost profile, %			
Activity/ Intervention	Rapid Reporting	Reactive Case Detection	Mass Drug Administration	Insecticide Residual Spraying	Rapid Reporting	Reactive Case Detection	Mass Drug Administration	Insecticide Residual Spraying
Planning	2'667	4'505	7'196	12'326	3.44	1.67	0.47	1.85
Procurement	1'061	120'510	1'082'706	337'514	1.37	44.78	70.27	50.54
Distribution	450	3'697	15'230	716	0.58	1.37	0.99	0.11
Storage	0	65	1'066	11'596	0.00	0.02	0.07	1.74
Training	2'501	46'334	85'452	65'353	3.22	17.22	5.55	9.79
Sensitization	0	6'193	16'968	18'821	0.00	2.30	1.10	2.82
Program management and supervision	42'283	22'454	66'334	73'417	54.52	8.34	4.31	10.99
Implementation	19'369	62'586	265'808	130'275	24.97	23.26	17.25	19.51
Other	9'226	2'768	0	17'786	11.90	1.03	0.00	2.66
Total	77'557	269'113	1'540'762	667'804	100	100	100	100

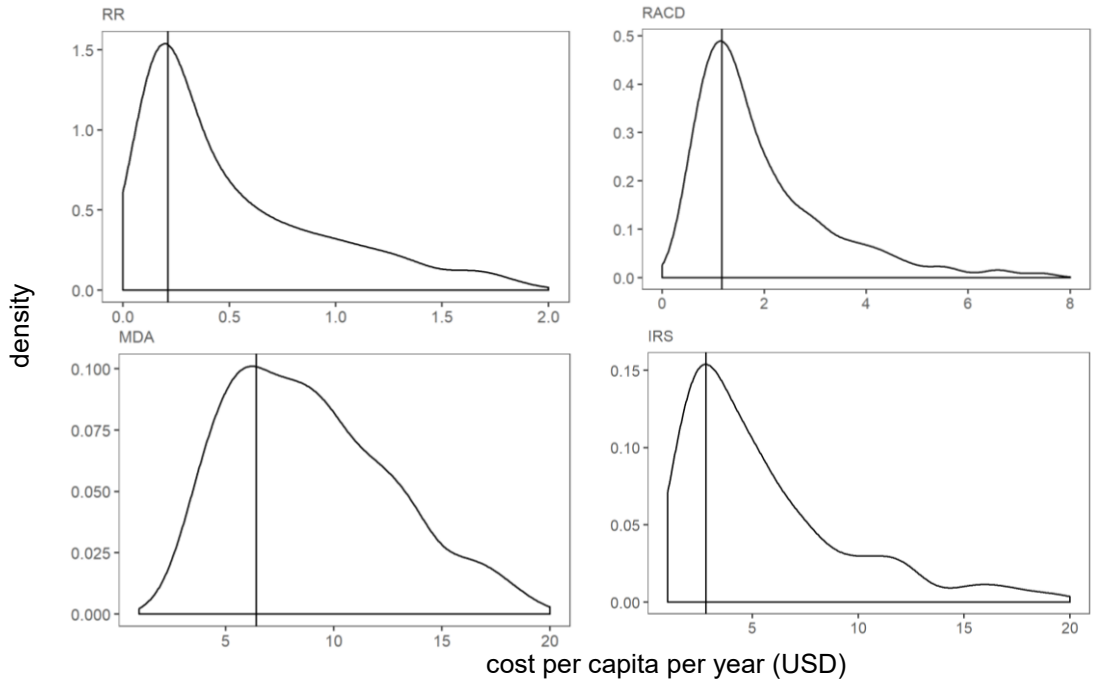

Figure A1. Bootstrap analysis: density plots of average annual economic cost per capita (five years) estimated from sampled parameters

The plots show Kernel distribution of estimated costs per capita obtained from 500 model parameter sets simultaneously sampled 10,000 times from a uniform distribution within the corresponding parameter range (Additional file 3). Lines indicate mode value of the density distribution. RR= Rapid Reporting; RACD= Reactive Case Detection; MDA= Mass Drug Administration; IRS= Indoor Residual Spraying.

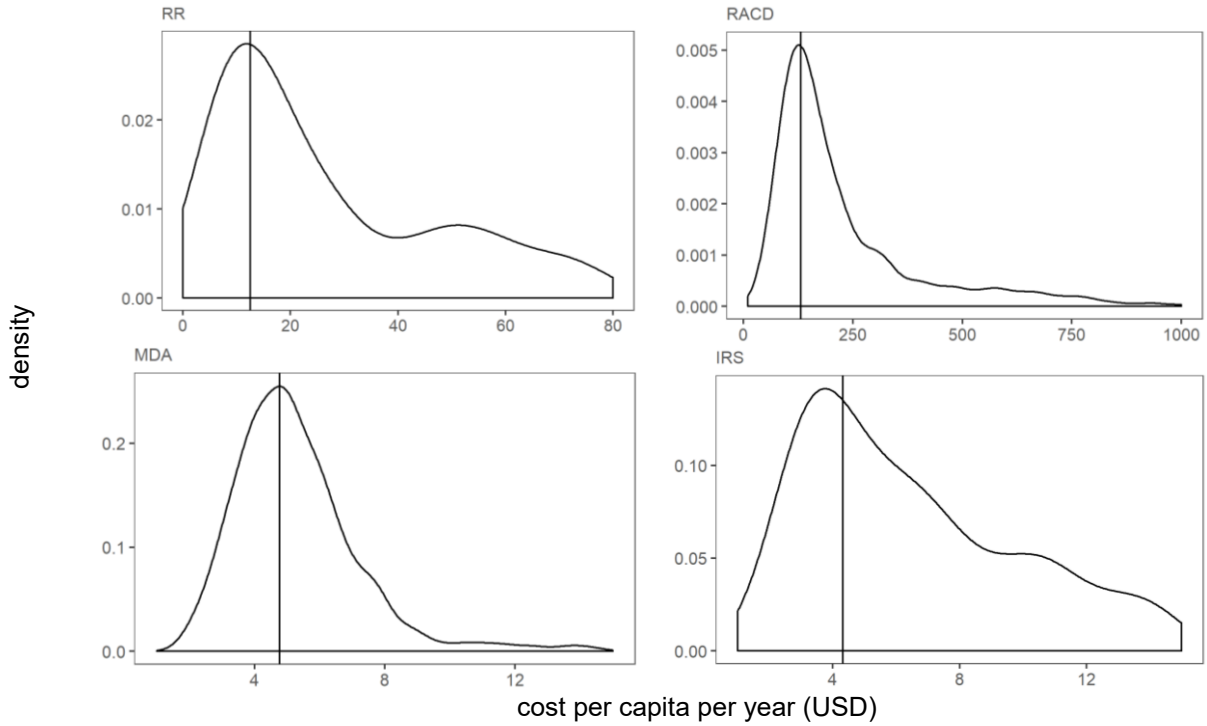

Figure A2. Bootstrap analysis: density plots of average annual economic cost per output (five years) estimated from sampled parameters

The plots show Kernel distribution of estimated costs per capita obtained from 500 model parameter sets simultaneously sampled 10,000 times from a uniform distribution within the corresponding parameter range (Additional file 3). The denominator (unit of output) varies by intervention: for RR the estimate represents cost per case reported; for RACD – cost per index case followed-up; for MDA – cost per person treated per round; for IRS – cost per person protected per round. Lines indicate mode value of the density distribution. RR= Rapid Reporting; RACD= Reactive Case Detection; MDA= Mass Drug Administration; IRS= Indoor Residual Spraying.

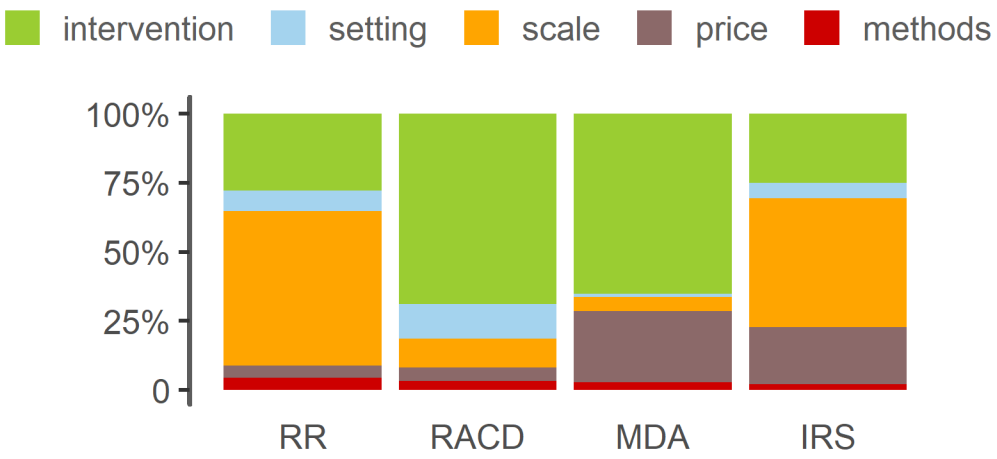

Figure A3. Bootstrap analysis cost per output: relative contribution by input category

Color segments of the stacked bars above correspond to the relative joint contribution of model inputs grouped into either of the five categories, describing intervention (green), setting (blue), scale (orange), price level (brown), and methods (red), to intervention unit cost. Model inputs grouped into each category are listed in Appendix A, Table A2. The proportions represent the joint contribution of model inputs within each category as a fraction of total variation in average annual economic cost per capita explained by the model. These were obtained by regressing cost per output on model inputs sampled from 500 model parameter sets simultaneously drawn 10,000 times from a uniform distribution within the corresponding parameter range (Appendix A File A2). Model inputs by category are listed in Appendix A, Table A2. Equivalent distributions for cost per outputs are shown in Figure 2. RR= Rapid Reporting; RACD= Reactive Case Detection; MDA= Mass Drug Administration; IRS= Indoor Residual Spraying.

Table A11. Values corresponding to reference, minimum and maximum values of parameters highlighted in tornado plots in Figure 3 (highest impact on economic cost per capita when varied singly) by intervention

Rapid reporting				Reactive Case Detection				Mass Drug Administration				Insecticide Residual Spraying			
Parameter	Ref	Low	High	Parameter	Ref	Low	High	Parameter	Ref	Low	High	Parameter	Ref	Low	High
Reporting days per month	0.5	0.25	4.00	Radius	5	3.6	30	Number of rounds per year	2	1	4	People per structure	5	2	11
Allocation RR	20%	20%	100%	Per-diem CHW	$0	$0	$15	Antimalarial drug	$1.64	$0.82	$3.27	Number of rounds	1	1	2
Module	$114000	$57000	$228000	Cart, daily rental	$0	$0	$12.6	Persons reached per CHW pair per day	75	20	75	Insecticide, per l	$29.7	$14.9	$59.4
Module ULY	10	5	20	Wages CHW, daily	$0.36	$0	$11	MDA coverage	85%	50%	95%	Insecticide per structure	300	200	600
Server overheads, yearly	$50000	$25000	$100000	*Pf*PR, all ages	4%	1%	5%	Wages nurse, monthly	$500	$250	$1000	Structures per operator per day	10	5	32
Supervision central days	$0	$0	$15	CHW per population	750	500	3000	Per-diem CHW	$0	$0	$15	Per-diem spray operator	$10	$7.84	$39
Fuel per l	$1.29	$0.65	$2.58	Proportion followed-up	100%	20%	100%	Per-diem nurse	$20	$10	$40	Training district days	7	3.5	14
Wages nurse, monthly	$500	$250	$1000	Top-up	$5	$0	$10	Wages CHW, daily	$0.36	$0	$11	Fuel per l	$1.29	$0.65	$2.58
Proportion reporting	100%	50%	100%	Access to care provider	80%	30%	85%	Training district days	4	2	8	Central staff	3	1.5	6
Discount rate	3%	1%	10%	Diagnostic test	$1.12	$0.56	$2.24	Transportation allowance district	20	10	40	Number of spray operators per team	7	2	7

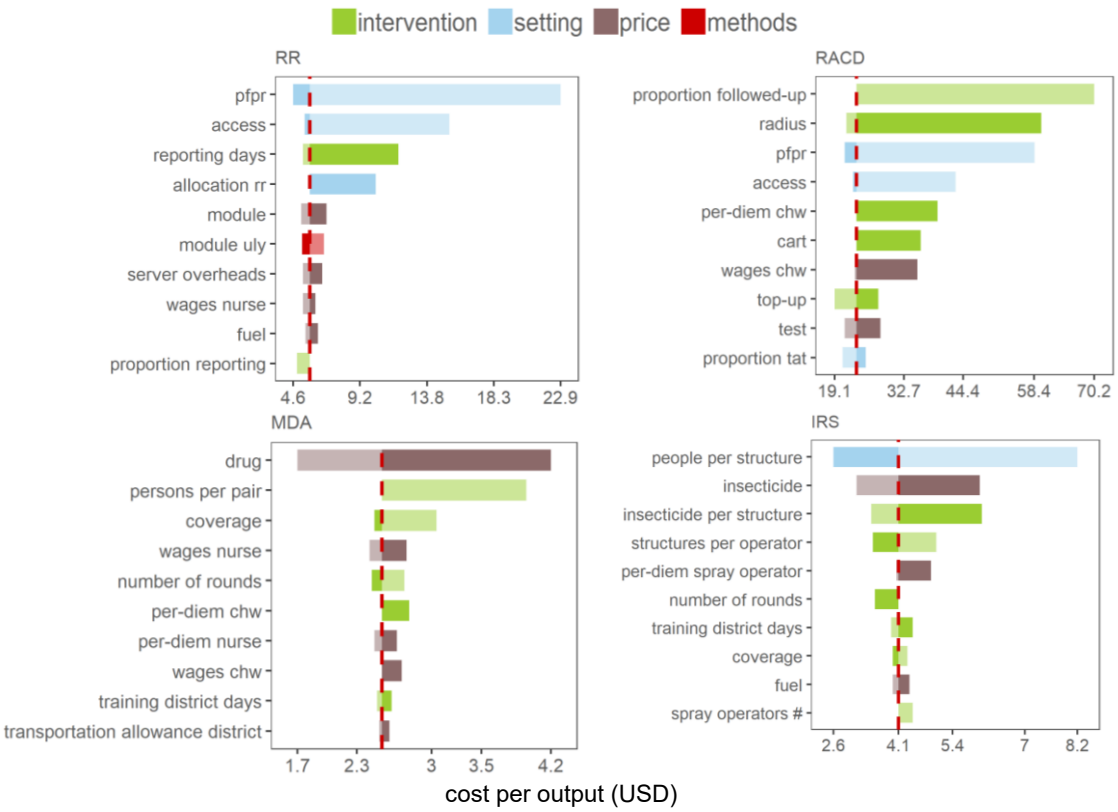

Figure A4. One-way sensitivity analysis of average annual economic cost per output (USD, 2014) at reference implementation*

Tornado plots show top 10 model inputs with the highest impact on intervention unit cost when varied over its' minimum and maximum while keeping all other inputs at reference values (Appendix A, Table A11). Bar lengths indicate the value of unit cost at highest – darker shade, and lowest – lighter shade, value of the respective parameter. Bar colour highlights input category. Red dashed lines give the reference estimate. Inputs describing scale of implementation (number of people reached) dominate the unit cost defined in terms of cost per capita; tabulations are thus shown only for parameters related to intervention (green), setting (blue), price (brown), and methods (red). The denominator (unit of output) varies by intervention: for RR the estimate represents cost per case reported; for RACD – cost per index case followed-up; for MDA – cost per person treated per round; for IRS – cost per person protected per round. Impact of scale parameters on estimated unit costs is explored in Figure 4, and Appendix A, Figure A5. * Reference implementation detailed in Table 1, further details in Appendix A, Table A3 and Appendix A File A1. RR= Rapid Reporting; RACD= Reactive Case Detection; MDA= Mass Drug Administration; IRS= Indoor Residual Spraying.

Table A12. Model inputs and ranges varied by setting in scenario analyses

	parameter varied by setting	good geographic accessibility setting, high capacity	poor geographic accessibility setting, high capacity	good geographic accessibility setting, low capacity	poor geographic accessibility setting, low capacity
	Geographic and epidemiological setting				
	Distance between administrative areas	reference	referencex2	reference	referencex2
	Population density*	high	low	high	low
	*Pf*PR	0.01	0.02	0.02	0.05
	Health systems capacity				
	Number of HF per 10,000 population	reference	referencex0.8	referencex0.5	referencex0.2
	Number of people per CHW	750	500	1500	3000
	Health seeking for malaria	80%	80%	60%	40%
	Days of sensitization	reference	referencex0.8	referencex0.5	referencex0.2
	Days of training	reference	reference	referencex0.5	referencex0.5
	Days of supervision	reference	referencex0.8	referencex0.5	referencex0.2
	Number of trainees per training	40	40	80	80
	Intervention				
RR	DHIS2	yes	yes	no	no
RR	% allocation to RR	20%	20%	100%	100%
RR	% reporting	100%	80%	60%	40%
RACD	% of index cases followed-up	100%	80%	40%	20%
RACD	Search radius	10	5	10	5
RACD	% of population present for TaT	80%	50%	80%	50%
RACD	Positivity rate around index case	0.1	0.2	0.2	0.5
MDA	Number of persons treated per day per pair	75	50	75	50
MDA	Number of rounds per year	2	2	1	1
MDA	% targeted population treated	90%	90%	50%	50%
IRS	Number of spray operators deployed per district	36	36	15	15
IRS	Number of structures sprayed per operator per day	20	10	20	10
IRS	Insecticide volume used per m2	300	300	600	600
IRS	% rental vehicles	0%	0%	40%	40%
IRS	% of targeted structures sprayed	90%	70%	70%	50%

Parameter values for each setting are *assumed* to illustrate the potential magnitude of these correlations and their impact on intervention costs. We did not explicitly model the relationship between population density and service outputs of interventions, rather assumed that lower output will be observed in more remote settings (i.e. lower bound number of persons treated per day, lower bound number of structures sprayed per day were assumed for poor accessibility settings). IRS= Indoor Residual Spraying; MDA= Mass Drug Administration; RACD= Reactive Case Detection; RR= Rapid Reporting.

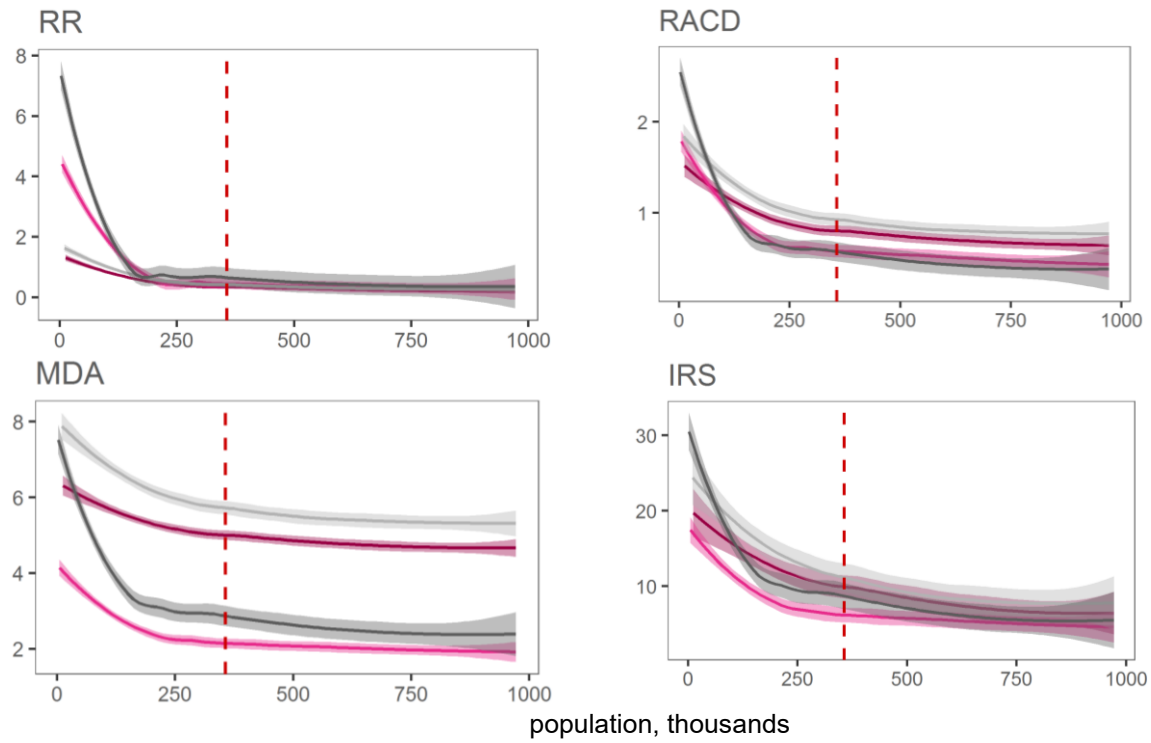

Figure A5. Scenario analysis cost per capita per year by setting and scale

Each curve represents the intervention cost trajectory for the four settings, described in Appendix A, Table A12, obtained by fitting a Loess curve to cost estimates modelled at various implementation scales. Shaded areas around the curves illustrate variation in the cost estimate due to different ways in which an implementation scale can be represented: by increasing the population size of the HFCA, increasing the number of HFCAs, or increasing the number of districts or regions where the intervention is deployed. RR= Rapid Reporting; RACD= Reactive Case Detection; MDA= Mass Drug Administration; IRS= Indoor Residual Spraying.

Table A13. MACEPA reported unit costs from implementation pilots, per capita per year (USD, 2014)

	Rapid Reporting	Case Investigation	Mass Drug Administration*	In-door Residual Spraying
Zambia	0.137	1.177	11.150	1.662
Senegal	0.217	0.801		
Ethiopia	0.388	1.632		

*The duration of MDA campaign in the pilot averaged 32 days compared to 10 days in the reference implementation; moreover, the scale of the pilots covered 10 districts compared to 3 in the reference implementation, and included a 10 USD per-diem for CHWs distributing drugs that was not costed in the reference implementation. Estimates from MACEPA/PATH "Evaluating the costs of implementing interventions and surveillance systems designed to achieve and maintain malaria elimination. Final report." (2015)

Table A14. Average annual economic cost of running MDA per capita in Zambia pilots: MACEPA reported vs. standardized (USD, 2014)

	MACEPA report		Model mapped to MACEPA scope		Model full scope	
	Total	%	Total	%	Total	%
Planning	-	-	-	-	0.984	7%
Procurement	2.097	19%	2.414	27%	2.760	19%
Storage and distribution	0.021	0%	0.028	0%	0.048	0%
Training	3.339	30%	3.195	36%	3.973	27%
Community sensitization	0.315	3%	0.312	4%	0.553	4%
Program management and supervision	4.180	37%	1.539	17%	4.456	30%
Implementation (cMDA)	1.287	12%	1.385	16%	2.135	14%
Total	11.150		8.873		14.908	

Estimates from MACEPA/PATH "Evaluating the costs of implementing interventions and surveillance systems designed to achieve and maintain malaria elimination. Final report." (2015).

While standardized unit costs are relatively similar in absolute terms to unit costs in MACEPA report, these represent a very different scope of resources captured with the models presented here. To appreciate this, first compare cost estimates under "MACEPA report" to "Swiss TPH models MACEPA mapped scope". The first column presents cost estimates as these appear in MACEPA report, the second set of estimates were produced with Swiss TPH costing models mapped into the scope of resources covered in the original analysis of the trial. When moving from first to second set of estimates we fixed any inconsistencies in valuation of resources (i.e. in application of per-diems, transportation, units of measurement (for further details refer to assumptions database)), replaced MACEPA wages and per-diem with the corresponding program wages, and updated vehicle rental costs with NMCP vehicles operational costs. Our costing model does very well replicating unit costs in the report. As expected, the biggest difference is in the two cost categories that are dominated by MACEPA wages and rental vehicles ("Training" and "Program management and supervision"); MACEPA costs accounted for over 20% of the total intervention costs. By design, costing analyses within the MACEPA trials excluded any costs occurring above district level and ignored economic value of health systems infrastructure other than labour. Cost estimates produced with the Swiss TPH methodology address these limitations by explicitly defining and evaluating resource use at higher programmatic levels and valuing the full scope of resources (for economic costs) used to deliver the interventions. Comparing the second set of estimates to the third (i.e. "Swiss TPH models full scope") shows that the original scope of the costing analysis only captured about 60% of the overall cost of the intervention.

Differences in costs by category are due to the following:

(1) "Planning" was not previously evaluated, important for MDA (relatively high contribution to overall costs) as it is an activity that is repeated each year the intervention is deployed
(2) Higher cost estimate for "Procurement" reflects wastage on drugs and diagnostics not previously accounted for
(3) Higher cost estimate for "Storage and distribution" is due to inclusion of storage and distribution costs at district level, only central level was costed previously
(4) "Training" now includes training of supervisors
(5) "Supervision" now includes supervision by regional, district, and health facility staff, only MACEPA supervision was costed previously

(6) Higher costs under “Implementation” include transportation and lodging allowance for hard to reach areas (as per protocol) during campaign rounds, printing of forms

File A1. Reference implementation scenarios detailing operational assumptions by intervention

- An Excel table that details by intervention resource lists and quantities of resources costed for each operational activity across all implementation stages (i.e. from the initial micro-planning on the new intervention to evaluation). The table offers a descriptive intervention narrative to aid in interpretation of the cost estimates derived here.
- The table along with all supplementary materials covered in Appendix A can be downloaded from Malar J: *https://malariajournal.biomedcentral.com/articles/10.1186/s12936-020-03405-3#Sec21*

File A2. Costing model inputs database

- An Excel table that contains resource lists, respective prices and quantities for each intervention (tabs RR to IRS) that serve as inputs to the costing models (Stata do-files) shared in Additional file 3. For each micro-input the table gives the reference value associated with the reference implementation scenario, minimum and maximum value of the parameter, a flag that denotes how the parameter was treated in sensitivity analysis (i.e. varied within the range or according to the multiplier), resource category grouping matching Fig. 2, parameter label, units, description, and source of data. Additionally, tab “sensitivity” gives multiplier range for each parameter and grouping. Tab “archetypes” gives values of operational and setting inputs by setting archetype.
- The table along with all supplementary materials covered in Appendix A can be downloaded from Malar J: *https://malariajournal.biomedcentral.com/articles/10.1186/s12936-020-03405-3#Sec21*

File A3. Costing models by intervention and scope

- The folder contains Stata do-files that detail how operational details as per Additional file 1, are combined with information on prices and quantities of resources collated in Additional file 2 to produce and estimate of intervention costs. The files can be run together with the datasets in Additional file 2 to reproduce estimates presented in the manuscript. The files can be used to also model alternative implementation of interventions or produce estimates for settings other than the reference.
- The table along with all supplementary materials covered in Appendix A can be downloaded from Malar J: *https://malariajournal.biomedcentral.com/articles/10.1186/s12936-020-03405-3#Sec21*

Appendix B. Supplementary files to Chapter 3: Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data

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File B1. Scenarios for capacity scale-up

Expanding cold chain storage

Based on the cold store assessment detailed above, allowances are made for additional cold chain equipment to meet the capacity required for the new EPI schedule including the RTS,S vaccine. We factor in, by distribution level, the cost of corresponding cold chain equipment including installation and supplementary items (i.e. thermometer, generator, freezer); the cost of cold chain equipment and related overheads are calculated on per cubic meter (/m3) per month basis and are multiplied by the required capacity and length of storage to estimate the total costs of resource expansion. These expenditures related to additional capacity are included in both average and marginal analyses.

Expanding labor

For purposes of this evaluation we consider labor to be fixed and while shortage of qualified medical staff is noted across the EPI levels in the three countries evaluated expansion of labor is not accommodated in this analysis. The assumption, however, could be easily relaxed. For settings where it is feasible to expand medical staff to accommodate the RTS,S, cost of a paper advertisement (1 month), review of candidates and subsequent interviews (1 work day), and a 5 day training could be costed proportional to the number of newly hired staff. Costs of these additional vaccinators or EPI officers are to be included in both average and marginal analyses.

Expanding transportation

Capacity to accommodate transportation of vaccines and supplies is evaluated by distribution level. Based on identified shortages, vehicles similar to those already in use by the EPI, at each administrative level are costed. Similarly to cold chain expansion, cost of vehicles is calculated to per cubic meter per kilometre (/m3/km) basis and scaled to accommodate identified capacity needs. That is, cold chain and transport costs are assumed to be continuous variables, and are not costed in natural units of vehicles, cold boxes, etc. Costs of these additional vehicles are included in both average and marginal analyses.

Expanding waste management

Additional incinerators at central, regional, and district levels to accommodate waste management of RTS,S and additional fuel for fire pits are costed in settings where expansions in waste management capacity are required.

File B2. Costing models by intervention and scope

- The folder contains an Excel workbook with all inputs needed to populate costing models for vaccine introduction by country.
- The table along with all supplementary materials covered in Appendix A can be downloaded from Malar J: *https://ars.els-cdn.com/content/image/1-s2.0-S0264410X15015224-mmc2.xlsx*

File B3. Cost functions by activity

Costs of vaccine introduction are captured by the following cost function:

$\boldsymbol{TC = F + M + E + O + P + S + T + I + G}$, where **(1)**

F is cost of introduction activities
M is cost of activities related to social mobilization and EIC
E is cost of training
O is cost of supervision
V is cost of procurement
P is cost of program management, monitoring and surveillance activities
S is cost of storage
T is cost of transportation
I is cost of immunization
G is cost of waste management

Total introduction costs (*F*) could be represented as follows:

$\boldsymbol{F = P + A + F + Tt + Ts + Tv + M,}$ where **(2)**

P is cost of activities related to planning vaccine introduction including mircoplanning, development of training and EIC materials
A represents expenditures related to cold-chain assessment
F revision of immunization cards and tally sheets
T_t captures expenditures related to training of trainers
T_s captures expenditures related to training of supervisors
T_v captures expenditures related to training of vaccinators
M captures expenditures related to social mobilization and IEC activities

Activities related to planning vaccine introduction (*P*) can be described by the following function:

$\boldsymbol{P = W + T + H + F + C + S}$, where **(2.1)**

W is wages including per-diems of EPI staff at all levels involved in planning activities
T is cost of transportation
H is hotel costs
F is cost of facility rental
C is cost of consumables
S is cost of stationaries

Wages of EPI workers (*W*) are described by the following function:

$\boldsymbol{W = \sum_{i=1}^{n} \frac{W_{1i}}{20} * d_{1i} + \left[\sum_{i=1}^{m} \left(\frac{W_{2i}}{20} + q_{2i}\right)\right] * s_2 * d_2}$, where **(2.1.1)**

W_{1i} is monthly wages of EPI officer *i* at central level

d_{1i} is number of days allocated for planning activities involving regional managers (i.e. workshops for planning and development of training and EIC materials)
W_{2i} is monthly wages of EPI officer *i* at regional level
q_{2i} is per-diem for EPI staff *i* at regional level
s_2 is number of regional stores
d_2 is number of days allocated for planning activities involving regional managers (i.e. workshops for planning and development of training and EIC materials)

In the paper we assumed that all central level staff in managerial positions (excluding custodial staff, drivers, etc.) as captured by the cMYP will spend 30 days planning the vaccine introduction (d_{1i}=30, for all i=1 to n). Further 3 1-day workshops with national and regional staff are assumed to be carried out for planning purposes (d_2 =3). We assume 2 regional level EPI representatives to take part in these planning meetings (i.e. one Regional Health Officer and one Medical Officer)(m=2).

Cost of transportation (*T*) for planning meetings for regional EPI staff is calculated as:

$\boldsymbol{T = W + V + F + M}$, where **(2.1.2)**

W is driver wages and per-diems
V is cost of vehicle
F is cost of fuel
M is cost of maintenance

Driver wages and per-diems (*W*) are calculated as:

$\boldsymbol{W = \left(\frac{w_2}{20} + q_2\right) * dd_2 * s_2}$, where **(2.1.2.1)**

w_2 is wages of drivers at regional level
q_2 is driver per-diems at regional level
s_2 is number of stores at regional level
dd_2 is number of workshops including regional managers

Vehicle operational cost (*V*) is in turn calculated as:

$\boldsymbol{V = \frac{M}{U} * D_2 * s_2 * dd_2}$, where **(2.1.2.2)**

M is cost of vehicle
U is vehicle ULY in km
D_2 is RT distance from regional store to central facility
s_2 is number of regional stores
dd_2 number of planning meetings

Fuel costs (*F*) are estimated as follows:

$\boldsymbol{F = f * C * D_2 * s_2 * dd_2}$, where **(2.1.2.3)**

f is cost of fuel per km
C is vehicle fuel consumption per km
D_2 is RT distance from regional store to central facility in km
s_2 is number of regional stores
dd_2 number of planning meetings

Maintenance costs (*M*) are assumed to be 15% of total fuel costs (*F*):

$$\boldsymbol{M = F *. 15} \quad \textbf{(2.1.2.4)}$$

Hotel costs (*H*) are estimated as:

$\boldsymbol{H = h * n_2 * s_2 * d_2 * dd_2}$, where **(2.1.3)**

h is hotel cost per night
n_2 is number of EPI officers per regional level attending the meetings
s_2 is number of regional stores
d_2 is number of days per workshop
dd_2 number of planning meetings

Facility rental costs (*F*) are calculated assuming 2m2/ per attendee:

$\boldsymbol{F = f * (n_1 + n_2 * s_2) * 2 * d_2 * dd_2}$, where **(2.1.4)**

f is facility rental per m2
n is number of EPI officers from central level participating in planning meetings
m is number of EPI staff per regional level participating in planning meetings
s_2 is number of regional stores
d_2 is number of days per workshop
dd_2 number of planning meetings

Cost of consumables (*C*) for planning meetings is estimated as:

$\boldsymbol{C = q * (n + m * s_2) * d_2 * dd_2}$, where **(2.1.5)**

q is cost of consumables per person (i.e. snacks, refreshments, etc.)
n is number of EPI officers from central level participating in planning meetings
m is number of EPI officers from regional level participating in planning meetings
s_2 is number of regional stores
d_2 is number of days per workshop
dd_2 number of planning meetings

In the paper we make an allowance for consumables equal to 1/3 of per-diem at central level ($q = \frac{q_1}{3}$).

Cost of stationaries (*S*) is calculated as:

$$\boldsymbol{S = (z + p) * (n + m * s_2) * dd_2}\text{, where} \quad \textbf{(2.1.6)}$$

z is cost per pens per person
p is cost of paper allowance per person
n is number of EPI officers from central level participating in planning meetings
m is number of EPI officers from regional level participating in planning meetings, per region
s_2 is number of regional stores
dd_2 number of planning meetings

Cost of cold chain assessment (*A*) is taken directly from cMYP document; no cost functions were defined for this component.

Cost of printing tally sheets (monthly/ 12 per year) and immunization cards (*P*) including a 25% buffer is calculated as:

$$\boldsymbol{F = (f_c * B + f_s * s_4 * 12) * 1.25}\text{, where} \quad \textbf{(2.1.7)}$$

f_c is cost of printing an immunization card
B is cohort size
f_s is cost of printing a tally sheet
s_4 is number of health facilities providing immunization

Training of trainers (T_t) is captured by the following cost function:

$$\boldsymbol{T_t = W + T + H + F + C + S + P}\text{, where} \quad \textbf{(2.2)}$$

W is wages including per-diems of staff trained
T is cost of transportation for trainers to central facility
H is hotel costs for trainer accommodations
F is facility rental costs
C is cost of consumables
S is cost of stationaries
P is cost of printed materials

Cost function for wages of trainers (*W*) is based on the assumption that medical staff from district levels are trained in this capacity at regional level by the regional staff and is calculated as follows:

$$\boldsymbol{W = \left[\sum_{i=1}^{n}\left(\frac{w_{3i}}{20} + q_{3i}\right) * s_3 + \sum_{i=1}^{m}\frac{W2i}{20} * s_2\right] * d_3}\text{, where} \quad \textbf{(2.2.1)}$$

k is number of trainers per district
w_3 is monthly wages of medical staff *i* at district level
q_3 is per-diem of medical staff *i* at district level
s_3 is number of district stores in a country
w_2 is monthly wages of medical staff *i* at regional level
q_2 is per-diem of medical staff *i* at regional level

s_2 is number of regional stores in a country
d_3 is number of days per workshop

In the paper we assume that 2 Public Health Nurses (or equivalent as defined by cMYP EPI district staff structure) per district are trained as trainers at regional level(k=2); training is conducted by the central EPI staff whose wages are covered under general planning activities (Equation 1.1.1). Training is carried out over 5 days (d_3=5).

T, H, F, C, and S are calculated following the cost functions represented by Equations 2.1.2-5 respectively. Quantities are updated with assumptions on number of for trainers at district for regional level and respective distances. Facility and consumables costs include both the central and district staff; central staff required to train district workers is assessed assuming 50 trainees per trainer.

Cost of printed materials (*P*) is estimated as follows:

$$\boldsymbol{P = f * n * (k * s_3 + \frac{k * s_3}{50})}\text{, where} \quad \textbf{(2.2.2)}$$

f is cost of printing per sheet (A4)
n is number of sheets in the training manual
k is number of trainees per district
s_3 is number of districts

Training of regional supervisors (T_s) is assumed to be carried out at central level and is captured by the following cost function:

$$\boldsymbol{Ts = W + T + H + F + C + S + P}\text{, where} \quad \textbf{(2.3)}$$

W is wages including per-diems of staff trained
T is cost of transportation for regional supervisors to central facility
H is hotel costs for supervisor accommodations
F is facility rental costs
C is cost of consumables
S is cost of stationaries
P is cost of printed materials

W, T, H, F, C, S, and P are calculated based on the cost functions as defined above; quantities and distances are adjusted to reflect the staff requirements and region to central stores distances.

Cost of training vaccinators (*Tv*) is captured by the following function:

$$\boldsymbol{Tv = W + T + F + C + S + P}\text{, where} \quad \textbf{(2.4)}$$

W is cost of EPI staff wages
T is cost of transportation to district facilities
F is cost of facility rental
C is cost of consumables
S is cost of stationaries

P is cost of printed materials

W, T, F, C, S, and *P* are described by functions detailed above. Assumptions on quantities are updated as per respective scenario.

In this paper we assume that training of health care workers involved in immunizations is held at district level. 5 workers are trained per central, regional and district facilities; 1 vaccinator for all other levels. Training is conducted by district EPI staff and lasts 1 day. We assume that informational booklets of 100 pages are printed and distributed to facilitate the training. Training is conducted the year of vaccine introduction, thereafter RTS,S is integrated into the routine EPI training and refresher courses- a fraction of these annual costs based on cMYP assessment is attributed to the RTS,S vaccine.

Total cost of EIC activities and social mobilization can be expressed as:

$\boldsymbol{M = L + S + R}$, where **(3)**

L is cost of launching ceremony at the central level
S is cost of community sensitization meetings at district levels
R is costs of advertising including TV and print media

Cost function describing activities and costs related to launching ceremonies (L) are defined based on the scenario detailed in Table1. Key inputs include speaker fees, band fees, volunteer per-diems, payments for support technical staff, facility rental, consumables for support staff, an allowance for miscellaneous expenses, and cost of printed media.

$\boldsymbol{L = W + F + C + A + P}$, where **(3.1)**

W is wages, speaker fees, volunteer per-diems
F is facility rental costs
C is cost of consumables
A is an allowance for miscellaneous expenses
P is cost of printed media

EPI wages, speaker fees, volunteer per-diems (*W*) and related labour costs are estimated as:

$\boldsymbol{W = \sum_{i=1}^{m} w_i * n_i * d_i}$, where **(3.1.1)**

i is unit of labour involved in launching ceremony
w_i is daily payment for services rendered
n_s is number of staff
d_i is number of days involved in preparation for or running the launching ceremony

F, C, and *P* are estimated as described by cost functions captured by Equations above updating quantity assumptions based on the relevant scenario.

In this paper we assume 5 external speakers to be presenting at the launching ceremony; 1 volunteer per 50 attendees; a band; and 10 technical workers to support the event. Involvement of central EPI workers is assumed to be costed under general planning allowance. Band fee taken to be equivalent to monthly wages of a Public Health Nurse. Assumptions regarding the number of attendees at the launching ceremony are made for each country based on cohort size in the capital. An allowance of 1,000 USD is assumed for miscellaneous expenditures. Cost of printed media is estimated assuming 2 printed sheets per attendee.

Expenditures related to community mobilization at district level (S) are defined following the scenario detailed in Table 1 in main text. Cost inputs include wages and per-diems for regional staff, speaker fees, hotel and transportation for regional staff, band fees, volunteer per-diems, facility rental, consumables, an allowance for miscellaneous expenses, and cost of printed media.

$$\boldsymbol{S = (W + H + T + f_b + n_v * f_v + F + C + A + P) * (s_3 - 1) * d_3}, \text{ where} \quad \textbf{(3.2)}$$

W is wages and per-diems for regional staff conducting EIC activities at regional level
H is hotel costs for supervisor accommodations
T is cost of transportation for regional supervisors to central facility
f_b is band fees
n_v is number of volunteers
f_v is volunteer per diems
F is facility rental costs
C is cost of consumables
A is an allowance for miscellaneous expenses
P is cost of printed materials
s_3 is number of district stores
d_3 is number of days over which EIC meetings take place in each district

In this paper we assume 3 regional EPI officers travelling to districts to conduct EIC related activities. Band fees are proxied with 50% of PHI monthly wages. Number of volunteers is based assuming 1 volunteer per 50 attendees, volunteer per-diems as based on PHI per-diems for outreach activities. Assumptions regarding the number of attendees at the district sensitization meetings are made for each country based on district cohort size (See Supplemental Information File S3). An allowance of 250 USD is assumed for miscellaneous expenditures. Cost of printed media is estimated assuming 2 printed sheets per attendee. We assume one 1-day meeting per district (d_3=1).

W, F, C, and P are estimated as described by cost functions described above updating quantity assumptions based on the relevant scenarios.

Cost of advertisement (R) is calculated as follows:

$$\boldsymbol{R = R_{tv} + R_r + R_p + P}, \text{ where} \quad \textbf{(3.3)}$$

R_{tv} is cost of TV advertisement
R_r is cost of radio segments
R_p is cost of advertisement in newspapers
P is cost of print media (i.e. posters, flyers, leaflets)

Cost of TV advertisement (R_{tv}) is described by a function:

$\boldsymbol{R_{tv} = f_{tv} * t_{tv} * n_{tv}}$, where **(3.3.1)**

f_{tv} is rate per minute of TV advertisement (loaded rate including cost of development, production)
t_{tv} is length of the segment
n_{tv} is number of segments per year

R_r, R_p is captured by the same function described above.

In this paper we assume length of TV and radio advertisements of 30 seconds (t_{tv}, t_r=.5). An intense campaign of 3 daily messages on national programs for the first 3 months(20 days/ month), the 2 daily messages for another 3 months, and once daily reminders through the end of the year. Thereafter IEC messages are delivered in the context of routine EPI communications. For advertisement in newspapers estimates are based on ¼ page segment to be run in 3 major outlets for one year.

Cost of print materials (*P*) is described by a function:

$\boldsymbol{P = f_p * s_4 * 1.25 + f_f * B * 1.25}$, where **(3.3.2)**

f_p is cost of print poster 1m by 1m
s_4 is number of health facilities
f_f is cost of printing a flyer(A4)
B is country birth cohort size

Cost of supervision (*O*) over vaccine introduction is described as:

$\boldsymbol{O = W + T}$, where **(5)**

W is wages of central, regional, and district staff involved in EPI supervisory capacity including per-diems

T is cost of transportation
Wages for supervisory activities related to the new vaccine are costed by first calculating the total cost of supervisory activities conducted by the EPI staff and then allocating a fraction of these costs to RTS,S. The assumption is that amount of time allocated to a given antigen for supervisory activities is proportional to the number of doses. The calculation is represented by the following function:

$\boldsymbol{W = \left[\sum_{l=1}^{e}\sum_{i=1}^{m}\left(\frac{W_{li}}{20} + q_{li}\right) * d_{li}\right] * \frac{n}{N}}$, where **(5.1)**

l is level of EPI system (i.e. central, regional, district)
i is EPI staff at level *l* involved in supervisory activities
W_{li} is monthly wages of EPI staff *i* at level *l* involved in supervisory activities
q_{li} is per-diem for EPI staff *i* at level *l* involved in supervisory activities
d_{li} is number of days EPI staff *i* at level *l* is conducting supervisory visits per year
n is number of doses in RTS,S schedule
N is number of vaccine doses in EPI schedule

T is estimated as described by the function detailed above; travel distances are assumed to be 100km per day RT; as with labour costs wages are allocated to RTS,S based on the ratio of number of doses required for RTS,S over total number of doses in new EPI schedule.

Cost of activities related to monitoring and general program management are captured by the following function:

$\boldsymbol{M = W + P + A}$, where **(6)**

W is wages of EPI staff at central, regional, district levels
P is cost of printing tally sheets and immunization cards
A is cost of post introduction evaluation

Wages for monitoring and program management (*W*) activities are calculated net of wages attributed to supervisory activities and allocated to RTS,S based on the ratio of number of doses required for RTS,S over total number of doses in new EPI schedule. The following function details this calculation:

$\boldsymbol{W = \left[\sum_{l=1}^{e}\sum_{i=1}^{m}(W_{li} - (\frac{W_{li}}{20} * \frac{d_{li}}{12})\right] * 12 * \frac{n}{N}}$, where **(6.1)**

l is level of EPI system (i.e. central, regional, district)
i is EPI staff at level *l* involved in supervisory activities
W_{li} is monthly wages of EPI staff *i* at level *l* involved in supervisory activities
d_{li} is number of days EPI staff *i* at level *l* is conducting supervisory visits per year
n is number of doses in RTS,S schedule
N is number of vaccine doses in EPI schedule

Cost of post-introduction evaluation (*A*) is obtained directly from cMYP; no cost functions are defined for this cost category.

We assume that after vaccine is rolled out activities related to social mobilization and IEC for RTS,S are integrated within the routine service provision. A proportion of annual budget is allocated to RTS,S.

We assume that after vaccine is rolled out RTS,S related training is integrated into training of new EPI staff and refresher courses. A proportion of annual budget is allocated to RTS,S.

Procurement of immunization supplies is described by the following function:

$\boldsymbol{V = \left[\sum_{c=1}^{n} f_c * n_c * \frac{1}{(1-W_c)}\right] * (1 + F) * B * C}$, where **(7)**

c is immunization supplies (i.e. vaccine, syringes, cotton, etc.)
f_c is cost of immunization supply c
n_c is number of units of immunization supplies c required per dose
w_c is wastage for immunization supply c
F is freight
B is birth cohort
C is proportion of birth cohort immunized; if multiple doses are required C is the sum of expected coverage for each dose

In this paper, given our focus on SSA countries we assume that immunization supplies are purchased through the UNICEF Supply Division; thus an additional UNICEF procurement fee is added.

Cost of cold and dry storage (*S*) for vaccines and immunization supplies is captured by the following formula:

$\boldsymbol{S = W + E + F}$, where **(8)**

W is wages of cold chain personnel across all storage levels
E is cost of cold chain equipment including maintenance and overheads
F is cost of facility including overheads

Wages of cold chain staff are calculated as:

$\boldsymbol{W = [\sum_{l=1}^{n} \sum_{i=1}^{m} w_{li} * n_{li} * a_l * s_l * p_l] * \frac{v}{V}}$, where **(8.1)**

l is level of storage facility (i.e. central, regional, district, etc.)
i is staff unit at storage facility at level *l*
w_{li} is monthly wages of staff *i* at storage facility level *l*
n_{li} is number of staff *i* at storage facility level *l*
a_l is number of months vaccines and immunization are stored at level *l*
s_l is number of stores at level *l*
p_l is facility usage for EPI related activities at level *l*
v is volume of RTS,S vaccine
V is total volume of all vaccines in EPI schedule

Cost of storage and related equipment (*E*) including maintenance (5%) and overheads is captured by the following cost function:

$$\boldsymbol{E = \sum_{l=1}^{m} \left[\left(E_l^c * v_l * 1.05 + \sum_{e=1}^{z} E_{le} * n_{le} * p_l * \frac{v}{V} * 1.05 + \sum_{i=1}^{q} C_{li} * n_{le} * f * t * p_l * \frac{v}{V} \right) * s_l * a_l \right]} \quad \textbf{(8.2)}$$

where
l is level of storage facility
E^c_l is annualized and discounted cost of cold chain equipment *c* at level *l* in m3
v_l is volume of vaccines stored at level *l* in m3
g_l is grossing factor for cold chain equipment used at store level *l*
e is type of supplementary equipment other than cold chain
E_{le} is annualized and discounted cost of equipment unit *e* used at store level *l*
n_{le} is number of equipment units *e* used at store level *l*
p_l is percent time equipment unit *e* is used for EPI at level *l*
v is volume of RTS,S vaccine
V is total volume of all vaccines in EPI schedule
i is type of equipment including cold chain used at store level *l*
C_{li} is energy consumption of equipment unit *i* used at level *l* (i.e. electricity, diesel)
f is cost per unit of energy source
t is length of operation per month

s_l is number of stores at level l
a_l is length of storage at store level *l*

Where v_l is calculated as:

$$\boldsymbol{v_l = \frac{v}{n} * \frac{1}{1-w} * b * g_l * B * C}, \text{ where} \quad \textbf{(8.2.1)}$$

v is volume per vaccine vial
n is number of doses per vial
w is vaccine wastage rate
b is bulking factor
g_l is grossing factor for cold chain storage at level l
B is cohort size
C is proportion of birth cohort immunized; if multiple doses are required C is the sum of expected coverage for each dose

In this paper, we made generic assumptions on types of cold chain and related equipment used at each store level; these are based on cohort size and expected volume of vaccines to be stored at each level. See Supplemental Information File S3 for country assumptions. Grossing factors are calculated for each type of cold chain equipment based on the dimensions specified for equipment selected. Additionally, cost of a power generator was added to each of the central, regional and district stores (1 unit per store); and one freezer at each of the district level stores. It was further assumed that cold chain equipment is powered with electricity; diesel is costed as source of power for the power generator.

Facility costs (*F*) are calculated for central, regional, and district levels and are represented by the following function:

$$\boldsymbol{F = \sum_{l=1}^{m}\left((v_l + vs_l)/h_l\right) * f_l * a_l}, \text{ where} \quad \textbf{(8.3)}$$

l is level of storage facility (i.e. central, regional, district, etc.)
v_l is volume of vaccines stored at level *l* in m3
vs_l is volume of immunization supplies stored at level *l* in m3
h_1 is height of the storage unit at store level *l*
f_1 is annualized and discounted cost of storage facility rental at level l per month per m2
a_1 is number of months supplies are stored at store level l

Where volume for dry storage of immunization supplies are computed following the basic function as outlined above; no grossing factors are assumed for dry storage.

Cost of transporting vaccines and immunization supplies from central levels to point of delivery can be represented as:

$$\boldsymbol{T = W + V + F + M + S}, \text{ where} \quad \textbf{(9)}$$

W is wages including per-diems of drivers
V is cost of vehicles including maintenance

F is cost of fuel
M is cost of vehicle maintenance
S is cost of cold boxes

Wages (*W*) of drivers and per-diems associated with transport of vaccines and immunization supplies are estimated via the following cost function:

$$\boldsymbol{W = \sum_{l=1}^{m} d_l * \left(\frac{W_l}{20} + q_l\right) * Z_l}, \text{ where} \quad \textbf{(9.1)}$$

l is level of storage facility (i.e. central, regional, district, etc.)
d_l is days spent delivering vaccines and immunization supplies by driver at level *l* per year
W_l is driver monthly wages at level *l*
q_l is driver per-diems at level *l*
Z is scaling factor

Where days spent delivering vaccines and immunization supplies (d_l) by driver at level *l* per year are calculated as:

$$\boldsymbol{d_l = \left(\frac{D_l}{dh} * n_l + s_l * n_l * t_l\right)/8}, \text{ where} \quad \textbf{(9.1.1)}$$

D_l is average distance travelled per round of delivery at level *l*
dh is average speed per hour
s_l is number of stores at level *l*
n_l is number of deliveries at level *l*
t_l is time in hours spent loading/unloading supplies per store

Scaling factor (Z_l) captures the share of vehicle carriage capacity taken up by the vaccine and is computed as:

$$\boldsymbol{Z_l = \left(\frac{v_l + vs_l}{s_l * n_l} * m\right)/vv_l}, \text{ where} \quad \textbf{(9.1.2)}$$

v_l is volume of vaccines stored at level *l* in m3
vs_l is volume of immunization supplies stored at level *l* in m3
s_l is number of stores at level *l*
n_l is number of deliveries at level *l*
m is number of stores per round of delivery at level l
vv_l is vehicle carriage capacity at level l
Vehicle costs (*V*) and cost of maintenance (*M*) are estimated by the costs function outlined above.

Cost of fuel (*F*) is calculated as per function:

$$\boldsymbol{F = \sum_{l=1}^{m} D_l * C_l * f * Z}, \text{ where} \quad \textbf{(9.2)}$$

l is level of storage facility (i.e. central, regional, district, etc.)
D_l is average distance travelled per round of delivery at level *l*
C_l is fuel consumption of vehicle operating at store level *l*
f is cost of fuel per litre
Z is scaling factor

Cost of cold boxes is added to regional and district distribution stores and is calculated including 20% replacement rate as follows:

$$\boldsymbol{S} = \sum_{\boldsymbol{l}=\mathbf{1}}^{\boldsymbol{m}} \frac{\boldsymbol{v_l}}{\boldsymbol{vb_l * s_l}} * \boldsymbol{f_l} * \mathbf{1.2} * \frac{\boldsymbol{v}}{\boldsymbol{V}}, \text{ where} \quad \textbf{(9.3)}$$

l is level of storage facility (i.e. central, regional, district, etc.)
v_l is volume of vaccines stored at level *l* in m3
vb_l is internal volume of cold boxes used at level *l* in m3
s_l is number of stores at level *l*
f_l is cost of cold box used at level *l*
v is volume of RTS,S vaccine
V is total volume of all vaccines in EPI schedule

Cost of an immunization is captured as a following function:

$$\boldsymbol{I} = \boldsymbol{W} + \boldsymbol{F} + \boldsymbol{S}, \text{ where} \quad \textbf{(10)}$$

W is cost of wages of medical stuff involved in immunization including outreach
F is cost of facility including overheads and furniture
S is cost of office supplies

Wages of immunization workers including fixed and outreach delivery are calculated as:

$$\boldsymbol{W} = \left[\frac{\boldsymbol{W}}{\boldsymbol{20 * h * 60}} * \boldsymbol{t_d} * \boldsymbol{B} * \boldsymbol{C} + \boldsymbol{q_4} * \boldsymbol{d_4} * \mathbf{12} * \frac{\boldsymbol{n}}{\boldsymbol{N}}\right] * \boldsymbol{s_4}, \text{ where} \quad \textbf{(10.1)}$$

W is monthly wages of immunization staff
h is number of hours worked per day
t_d if time to administer a dose in minutes
B is cohort size
C is proportion of birth cohort immunized; if multiple doses are required C is the sum of expected coverage for each dose
q_4 is immunization staff per-diem
d_4 is number of days per month staff conducts outreach
n is number of doses in RTS,S schedule
N is number of vaccine doses in EPI schedule
s_4 is number of health facilities providing immunization

Facility costs including overheads(10%) are estimated as follows:

$$\boldsymbol{F} = \left(\boldsymbol{f_f} * \boldsymbol{s_f} * \boldsymbol{p_{epi}} * \frac{\boldsymbol{n}}{\boldsymbol{N}}\right) * \mathbf{1.1} * \boldsymbol{s_4}, \text{ where} \quad \textbf{(10.2)}$$

f_f is annualized and discounted cost of facility per m2
s_f is square footage of an immunization office
p_{epi} is facility usage for EPI related activities
n is number of doses in RTS,S schedule
N is number of vaccine doses in EPI schedule

s_4 is number of health facilities providing immunization

Cost of supplies and office furnishings (S) are computed as:

$$\boldsymbol{S = \left[\sum_{f=1}^{n} U_f * n_f + \sum_{s=1}^{m} U_s * n_s\right] * p_{epi} * \frac{n}{N} * s_4}, \text{ where} \quad \textbf{(10.3)}$$

f is unit of furniture (i.e. stool, chair, etc.)
U_f is annualized and discounted cost per unit of furniture f
n_f is number of units of furniture f per immunization office
s is unit of stationaries (i.e. pens, paper etc.)
n_s is number of units of stationary s per immunization office
p_{epi} is facility usage for EPI related activities
n is number of doses in RTS,S schedule
N is number of vaccine doses in EPI schedule
s_4 is number of health facilities providing immunization

Cost of waste management are summarized by the function:

$$\boldsymbol{G = W + E + F}, \text{ where} \quad \textbf{(11)}$$

W is wages of technical staff operating the incinerator
E is cost of equipment including protective gear and maintenance and overheads
F is cost fuel

Wages of technical staff involved in waste management of immunization supplies are first attributed to EPI and then to RTS,S based on the total value of RTS,S in new immunization schedule and are calculated as follows:

$$\boldsymbol{W = [\sum_{l=1}^{e} W_l * 12 * s_l * p_l] * \frac{v}{V} * \frac{v_i}{v}}, \text{ where} \quad \textbf{(11.1)}$$

l is level of EPI facility
W_l is monthly wages of technical staff at facility level l
s_l is number of facilities at level l
p_l is percent of time spent of EPI activities at level l
v is volume of RTS,S vaccine
V is total volume of all vaccines in EPI schedule
v_i is volume of RTS,S incinerated

In this paper in the absence of detailed information we assumed that incinerators are used at central, regional, and district level facilities; at all other levels immunization supplies are discharged at fire pits.

Cost of incinerator and related equipment (*E*) is discounted and annualized and captured by the following function:

$$\boldsymbol{E = [\sum_{l=1}^{e} \sum_{c=1}^{n} (U_c + M + F) * s_l * p_l] * \frac{v}{V} * \frac{v_i}{v}}, \text{ where} \quad \textbf{(11.2)}$$

l is level of EPI facility with an incinerator
c is equipment (i.e. incinerator, bottle crusher, protective gear)

U_c is annualized and discounted cost of equipment *c*
M is equipment maintenance
F is equipment overheads
s_l is number of facilities at level l
p_l is percent of time spent of EPI activities at level l
v is volume of RTS,S vaccine
V is total volume of all vaccines in EPI schedule
v_i is volume of RTS,S incinerated

In this paper we cost an incinerator, bottle crasher, and protective gear for each facility equipped with an incinerator. We allocat 5% of equipment cost toward maintenance(M).

Cost of fuel (*F*) is calculated as follows:

$$\boldsymbol{F = f * Cf * 12 * (s4 - s1 - s2 - s3) * p_4 * \frac{v}{V}}, \text{ where} \quad \textbf{(11.4)}$$

f is cost of fuel per litre
C_f is fuel consumption per incinerator per month
s_1-s_4 is number of health facilities at each level
p_4 is proportion fire pit is used by EPI
V is total volume of all vaccines in EPI schedule
v_i is volume of RTS,S incinerated

In this paper we assume fuel consumption per month of 10l per facility (Cf=10). Proportion of time fire pit is used for EPI (p4) at lower levels is imputed based on time allocation for technical staff.

Table B1. Average annual *economic* cost of RTS,S immunization delivered in the 6 to 9 months schedule by country (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction[1]	167494	301400	513607	183233	410628	260915
Supervision	29941	178654	147950	213450	650896	251771
Monitoring	98428	158016	470528	197951	227203	66969
Training[2]	3084	7415	17447	4892	12256	9630
EIC[3]	54434	52963	53876	26361	62061	35383
Procurement	9903660	10679279	14591719	6447159	24677812	18322750
Storage	225522	280159	529596	246328	365121	532201
Transportation	74320	124292	303080	84534	378273	262421
Vaccination	359144	618568	2946024	519996	1970238	1232853
Waste Management	14711	25040	57725	27364	44795	37857
Total	10930737	12425787	19631552	7951267	28799284	21012750
Total Delivery[4]	1027077	1746508	5039832	1504108	4121471	2690000
Total Per Dose	6.68	7.04	8.14	7.47	7.06	6.94
Total Delivery Per Dose	0.63	0.99	2.09	1.41	1.01	0.89
Total Per FIC[5]	23.03	24.00	28.22	25.42	24.58	24.77

[1] Annualized and discounted economic cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.). See paper Table1 for details. [2] RTS,S fraction of costs for routine training activities conducted by the EPI program (assuming 10% annual turn-over); excluding training in advance of the new vaccine introduction costed under "Introduction". [3] RTS,S fraction of costs for routine EIC activities conducted by the EPI program; excluding expenditures related to initial information and incentivisation of the population training in advance of the new vaccine introduction costed under "Introduction". [4] Program costs net of vaccine and immunization supplies. [5] FIC is defined as a child that received 3 doses of the schedule.

Table B2. Average annual *financial* cost of RTS,S immunization delivered in the 6 to 9 months schedule by country (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction[1]	74906	132042	193107	72016	167019	110664
Supervision	1435	8584	7106	10260	31206	12163
Monitoring	8000	8000	8000	8000	8000	8000
Training[2]	0	0	0	0	0	0
EIC[3]	0	0	0	0	0	0
Procurement	9903660	10679279	14591719	6447159	24677812	18322750
Storage	204061	244579	414641	175518	262571	506407
Transportation	39225	30357	79547	30170	142293	102807
Vaccination	80235	103743	364297	17345	185542	270581
Waste Management	9925	8339	39792	7819	29449	30681
Total	10321447	11214923	15698209	6768287	25503892	19364054
Total Delivery[4]	417787	535644	1106490	321128	826080	1041303
Total Per Dose	6.31	6.36	6.51	6.35	6.26	6.40
Total Delivery Per Dose	0.26	0.30	0.46	0.30	0.20	0.34
Total Per FIC[5]	21.74	21.66	22.56	21.64	21.77	22.83

[1] Annualized financial cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.). See paper Table1 for details. [2] RTS,S fraction of costs for routine training activities conducted by the EPI program (assuming 10% annual turn-over); excluding training in advance of the new vaccine introduction costed under “Introduction”. [3] RTS,S fraction of costs for routine EIC activities conducted by the EPI program; excluding expenditures related to initial information and incentivisation of the population training in advance of the new vaccine introduction costed under “Introduction”. [4] Program costs net of vaccine and immunization supplies. [5] FIC is defined as a child that received 3 doses of the schedule.

Table B3. Average annual *economic* cost of RTS,S immunization delivered in the 6 to 9 months booster schedule by country (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction[1]	167494	301400	513607	183233	410628	260915
Supervision	40005	239950	198394	286226	871306	335695
Monitoring	123329	200329	600036	251138	288093	83051
Training[2]	3933	9506	22332	6262	15661	12256
EIC[3]	69423	67902	68961	33742	79300	45033
Procurement	12457572	13465178	18335080	8129821	30981478	22886980
Storage	278096	344984	646740	301969	446716	644744
Transportation	94405	157207	378992	106725	475822	325050
Vaccination	463789	806249	3820746	683676	2563441	1585290
Waste Management	18122	30803	70432	33521	54695	45825
Total	13716167	15623507	24655318	10016313	36187140	26224838
Total Delivery[4]	1258595	2158330	6320239	1886492	5205662	3337859
Total Per Dose	6.66	7.02	8.14	7.46	7.07	6.94
Total Delivery Per Dose	0.61	0.97	2.09	1.41	1.02	0.88
Total Per FIC[5]	36.12	37.72	44.30	40.03	38.61	38.64

[1] Annualized and discounted economic cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.). See paper Table1 for details. [2] RTS,S fraction of costs for routine training activities conducted by the EPI program (assuming 10% annual turn-over); excluding training in advance of the new vaccine introduction costed under “Introduction”. [3] RTS,S fraction of costs for routine EIC activities conducted by the EPI program; excluding expenditures related to initial information and incentivisation of the population training in advance of the new vaccine introduction costed under “Introduction”. [4] Program costs net of vaccine and immunization supplies. [5] FIC is defined as a child that received 4 doses of the schedule.

Table B4. Average annual *financial* cost of RTS,S immunization delivered in the 6 to 9 months booster schedule by country (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction[1]	74906	132042	193107	72016	167019	110664
Supervision	3659	22011	18191	26267	79748	30961
Monitoring	8000	8000	8000	8000	8000	8000
Training[2]	0	0	0	0	0	0
EIC[3]	0	0	0	0	0	0
Procurement	12457572	13465178	18335080	8129821	30981478	22886980
Storage	251392	300876	505929	215013	320624	612997
Transportation	50734	40028	102725	38906	183101	129179
Vaccination	102329	133004	466300	22201	237081	344375
Waste Management	12226	10258	48552	9578	35958	37138
Total	12960818	14111396	19677884	8521803	32013010	24160294
Total Delivery[4]	503246	646218	1342804	391982	1031532	1273314
Total Per Dose	6.30	6.34	6.50	6.35	6.25	6.39
Total Delivery Per Dose	0.25	0.29	0.44	0.29	0.20	0.34
Total Per FIC[5]	34.13	34.07	35.35	34.06	34.15	35.60

[1] Annualized financial cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.). See paper Table1 for details. [2] RTS,S fraction of costs for routine training activities conducted by the EPI program (assuming 10% annual turn-over); excluding training in advance of the new vaccine introduction costed under “Introduction”. [3] RTS,S fraction of costs for routine EIC activities conducted by the EPI program; excluding expenditures related to initial information and incentivisation of the population training in advance of the new vaccine introduction costed under “Introduction”. [4] Program costs net of vaccine and immunization supplies. [5] FIC is defined as a child that received 4 doses of the schedule.

Table B5. Average annual *economic* cost of RTS,S immunization delivered in the EPI schedule by country (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction[1]	167494	301400	513607	183233	410628	260915
Supervision	28516	170146	140905	203286	619901	239782
Monitoring	98428	158016	470528	197951	227203	66969
Training[2]	3084	7415	17447	4892	12256	9630
EIC[3]	54434	52963	53876	26361	62061	35383
Procurement	13204882	14239040	19455626	8596211	32903752	24430332
Storage	293093	362459	680541	316849	470787	681289
Transportation	100347	166382	401592	112884	505633	346021
Vaccination	382637	676571	3184340	595248	2184796	1314586
Waste Management	19094	32354	74094	35166	57607	48409
Total	14352008	16166747	24992554	10272081	37454624	27433314
Total Delivery[4]	1147126	1927707	5536929	1675870	4550874	3002983
Total Per Dose	6.58	6.87	7.78	7.23	6.89	6.80
Total Delivery Per Dose	0.53	0.82	1.72	1.18	0.84	0.74
Total Per FIC[5]	22.68	23.42	26.94	24.63	23.98	24.25

[1] Annualized and discounted economic cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.). See paper Table1 for details. [2] RTS,S fraction of costs for routine training activities conducted by the EPI program (assuming 10% annual turn-over); excluding training in advance of the new vaccine introduction costed under “Introduction”. [3] RTS,S fraction of costs for routine EIC activities conducted by the EPI program; excluding expenditures related to initial information and incentivisation of the population training in advance of the new vaccine introduction costed under “Introduction”. [4] Program costs net of vaccine and immunization supplies. [5] FIC is defined as a child that received 3 doses of the schedule.

Table B6. Average annual *financial* cost of RTS,S immunization delivered in the EPI schedule by country (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction[1]	74906	132042	193107	72016	167019	110664
Supervision	0	0	0	0	0	0
Monitoring	8000	8000	8000	8000	8000	8000
Training[2]	0	0	0	0	0	0
EIC[3]	0	0	0	0	0	0
Procurement	13204882	14239040	19455626	8596211	32903752	24430332
Storage	264874	316031	532236	225565	337701	647563
Transportation	54199	42827	109851	41382	195855	138154
Vaccination	80235	103743	364297	17345	185542	270581
Waste Management	12882	10774	51076	10048	37872	39232
Total	13699978	14852457	20714194	8970567	33835740	25644526
Total Delivery[4]	495096	613417	1258567	374356	931989	1214194
Total Per Dose	6.28	6.31	6.44	6.32	6.22	6.35
Total Delivery Per Dose	0.23	0.26	0.39	0.26	0.17	0.30
Total Per FIC[5]	21.65	21.51	22.33	21.51	21.66	22.67

[1] Annualized financial cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.). See paper Table1 for details. [2] RTS,S fraction of costs for routine training activities conducted by the EPI program (assuming 10% annual turn-over); excluding training in advance of the new vaccine introduction costed under “Introduction”. [3] RTS,S fraction of costs for routine EIC activities conducted by the EPI program; excluding expenditures related to initial information and incentivisation of the population training in advance of the new vaccine introduction costed under “Introduction”. [4] Program costs net of vaccine and immunization supplies. [5] FIC is defined as a child that received 3 doses of the schedule.

Table B7. Average annual *economic* cost of RTS,S immunization delivered in the EPI booster schedule by country (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction[1]	167494	301400	513607	183233	410628	260915
Supervision	38186	229043	189376	273216	831701	320436
Monitoring	123329	200329	600036	251138	288093	83051
Training[2]	3933	9506	22332	6262	15661	12256
EIC[3]	69423	67902	68961	33742	79300	45033
Procurement	16610096	17953570	24446774	10839762	41308640	30515972
Storage	359327	443320	824538	385376	571893	818530
Transportation	127765	210599	501610	142557	636308	427772
Vaccination	501418	899559	4201717	804756	2905881	1714530
Waste Management	23379	39519	89667	42730	69792	58096
Total	18024350	20354746	31458618	12962772	47117896	34256592
Total Delivery[4]	1414253	2401176	7011843	2123010	5809257	3740619
Total Per Dose	6.57	6.86	7.79	7.24	6.90	6.80
Total Delivery Per Dose	0.52	0.81	1.74	1.19	0.85	0.74
Total Per FIC[5]	35.60	36.85	42.39	38.86	37.70	37.86

[1] Annualized and discounted economic cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.). See paper Table1 for details. [2] RTS,S fraction of costs for routine training activities conducted by the EPI program (assuming 10% annual turn-over); excluding training in advance of the new vaccine introduction costed under “Introduction”. [3] RTS,S fraction of costs for routine EIC activities conducted by the EPI program; excluding expenditures related to initial information and incentivisation of the population training in advance of the new vaccine introduction costed under “Introduction”. [4] Program costs net of vaccine and immunization supplies. [5] FIC is defined as a child that received 4 doses of the schedule.

Table B8. Average annual *financial* cost of RTS,S immunization delivered in the EPI booster schedule by country (USD, 2013)

	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Introduction[1]	74906	132042	193107	72016	167019	110664
Supervision	0	0	0	0	0	0
Monitoring	8000	8000	8000	8000	8000	8000
Training[2]	0	0	0	0	0	0
EIC[3]	0	0	0	0	0	0
Procurement	13204882	14239040	19455626	8596211	32903752	24430332
Storage	264874	316031	532236	225565	337701	647563
Transportation	54199	42827	109851	41382	195855	138154
Vaccination	80235	103743	364297	17345	185542	270581
Waste Management	12882	10774	51076	10048	37872	39232
Total	13699978	14852457	20714194	8970567	33835740	25644526
Total Delivery[4]	495096	613417	1258567	374356	931989	1214194
Total Per Dose	6.28	6.31	6.44	6.32	6.22	6.35
Total Delivery Per Dose	0.23	0.26	0.39	0.26	0.17	0.30
Total Per FIC[5]	21.65	21.51	22.33	21.51	21.66	22.67

[1] Annualized financial cost of activities held in the introductory stage (micro-planning, cold chain evaluation, training, etc.). See paper Table1 for details. [2] RTS,S fraction of costs for routine training activities conducted by the EPI program (assuming 10% annual turn-over); excluding training in advance of the new vaccine introduction costed under “Introduction”. [3] RTS,S fraction of costs for routine EIC activities conducted by the EPI program; excluding expenditures related to initial information and incentivisation of the population training in advance of the new vaccine introduction costed under “Introduction”. [4] Program costs net of vaccine and immunization supplies. [5] FIC is defined as a child that received 4 doses of the schedule.

Table B9. Vaccine Volume Calculator

Vaccine	Presentation	Vaccine vol. (cm3/dose)	Diluent vol. (cm3/dose)	Wastage rate	Age	Doses	Temperature	Volume (m3)					
								Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
BCG	20	1.3	1.1	0.5	Birth	1	2 to 8C	3.19	3.76	5.88	2.49	9.18	7.26
OPV	20	2		0.25	Birth, 4, 8, 12 weeks	4	-15 to -20C	6.12	7.37	12.87	4.82	17.84	13.42
DTP	10	2.8		0.25	Birth, 4, 8, 12 weeks	3	2 to 8C	6.57	7.82	13.02	5.35	19.56	14.35
MCV	10	2.6	3.2	0.4	9 months	2	2 to 8C	10.23	13.06	26.45	8.25	35.18	24.32
PCV	1	12		0.05	12-15 months	3	2 to 8C	20.04	23.56	40.89	13.86	60.60	41.85
Rota	1	17.1		0.05	6 and 10 weeks	3	2 to 8C	31.70	24.45	41.84	17.19	59.55	0.00
HPV	2	5.7		0.05	9 to 13 years				44.68	72.31	29.55	106.35	74.92
YFV	10	2.6	4.9	0.4	9 months	1	3 to 8C	7.01	8.25	0.37	5.27		
TT	10	3.1		0.25	Female 15-49	2	2 to 8C	23.01	58.58	48.63	25.02	109.68	84.18
RTS,S EPI	2	4.84	4.84	0.25	4, 8, 12 weeks	3	2 to 8C	22.73	27.04	45.00	18.49	67.61	49.60
RTS,S EPI booster	2	4.84	4.84	0.25	4, 8, 12 weeks, 18 months	4	2 to 8C	28.59	34.09	56.54	23.32	84.88	61.95
RTS,S 5 to 17 months	2	4.84	4.84	0.25	6, 7.5,9 months	3	2 to 8C	17.05	20.28	33.75	13.87	50.71	37.20
RTS,S 5 to 17 months booster	2	4.84	4.84	0.25	6, 7.5,9, 17 months	4	2 to 8C	21.44	25.57	42.40	17.49	63.66	46.46
Net volume -20C								6.12	7.37	13.02	5.35	19.56	14.35
Net volume at +5 C								101.76	184.17	243.35	103.96	389.19	238.70
RTS,S percent increase in volume													
EPI								17.4%	12.4%	14.93%	14.47%	14.19%	16.39%
EPI booster								20.9%	15.1%	18.07%	17.58%	17.19%	19.67%
5 to 17 months								13.6%	9.6%	11.63%	11.26%	11.04%	12.82%
5 to 17 months booster								16.6%	11.8%	14.19%	13.79%	13.48%	15.51%

EPI schedule updated with planned vaccine introduction prior to RTS,S (tentatively in 2017); these include HPV, Rota, PCV, MCV2. HPV coverage is assumed to be 75% of DTP. Source: http://data.unicef.org/child-health/immunization (WUENIC, 2013 revision) (2013).

Appendix C. Supplementary files to Chapter 4: Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa

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File C1. Estimating the public health impact of RTS,S immunization

Methodology to evaluate the public health impact of the RTS,S immunization program is detailed in (1). Present analysis incorporates new data on malaria distribution made available with the release of MAP 2014 prevalence surfaces (2). These data replace MAP 2010 prevalence surfaces used in (1) and reflect the impact of scale-up of malaria control interventions and as a result lower prevalence of the disease across the African continent. Additionally, in this study, vaccine properties have been updated with the final results from the phase 3 trial that incorporated longer follow-up data (3). Compared to (1), the initial vaccine efficacy at third dose is higher (91.1% compared to 79.2% in (1) and half-life shorter (7.32 months compared to 1.12 years in (1). Differences in the underlying burden of the disease and, to a lesser extent, in estimated vaccine properties result in an overall lower predicted public health impact of the vaccine in this analysis compared to earlier analyses in (1).

To assess the impact of vaccine introduction a factorially designed experiment was constructed. It comprised different vaccine profiles, malaria transmission, and health system contexts, comprising a total of over 20,000 scenarios. It was implemented within the OpenMalaria simulation platform based on a population of 100,000 humans, 6 epidemiological models with varying assumptions on individual immunity, heterogeneity in transmission and co-morbidities, and 5 seeds to incorporate the uncertainty in predictions as a result of stochasticity.

Malaria burden estimates are based on EIR distributions computed from MAP 2014 prevalence surfaces (4). OpenMalaria modeled relationship between EIR, effective treatment, and prevalence was used to produce distribution of malaria exposure for given setting; these country level estimates reflect transmission at current level of malaria control interventions (5). The level of malaria transmission, control interventions, and the immunization rate were held constant throughout the evaluation period; no scale-up was assumed for the vaccine introduction. Population growth and demography were held constant.

Consistent with recommendations on impact and cost-effectiveness studies of pre-licensure vaccines adverse effects following the vaccination have not been incorporated.

Impact estimates were computed as weighted averages over all simulations, where the weights were determined as summarized in Table1.

Table C1. Factors varying among the simulations

Factor	Description	Method of determining weights
Model variants:	Six different epidemiological models of malaria (R0000, R0068, R0131, R0132, and R0133, R0670) (6)	Fit to field data (1;6;7)
Vaccine properties	Efficacy immediately after completion of vaccination schedule, half-life, half-life decay shape	Fitting to Phase III trial data(1;8)
Vaccine coverage	Proportion of children fully vaccinated (receiving all doses in the respective schedule)	Projections based on country DTP coverage levels from UNICEF(9)
Case management	Effective treatment of malaria infections in the population. For uncomplicated episodes this includes treatments with antimalarials other than first-line and treatments obtained from informal care providers. The metric adjusts for loss in efficacy due to poor adherence with drug regimen, drug quality, and resistance(10). Compliant treatments is assumed for severe disease, with generic assumptions in hospitalization rates(11).	Linear interpolation between simulations with pre-defined levels of access to effective care(1)
Transmission	Numbers of people exposed in eight different categories of the Entomological Inoculation Rate (EIR)	Representation of each country by a distribution of exposure based on the MAP 2014 posterior distributions of prevalence(2), translation of prevalence to EIR(4), and the GRUMP population model

Predictions of the number of malaria infections, uncomplicated malaria episodes, severe malaria episodes, malaria-related hospitalizations, direct and indirect malaria deaths were made for each country by time period both in the absence of and with an addition of the RTS,S program. Reported estimates reflect two main sources of uncertainty: structural and stochastic. Of the two, model structural uncertainty dominates. Assumptions on individual immunity, heterogeneity in transmission, and co-morbidities captured with the models have a somewhat different effect on the simulated population depending on distribution of transmission and health systems inputs. Thus, when we produce estimates of total impact (in the paper this would be total impact for countries with median transmission in a given range, group of countries eligible for GAVI support, and all 42 countries in SSA) the sum has a narrower range then the predicted range in either of the countries. Additionally, narrowing of prediction intervals for aggregate estimates is due to higher weight of most populous and highest burden countries for which predicted impact is estimated more precisely. We address parameter uncertainty concerning intervention impact (vaccine properties and programmatic implementation assumptions) with the sensitivity analysis.

File C2. Estimating cost of immunization

Program costs associated with RTS,S immunization were extrapolated from a recent micro-costing study (12); the latter prospectively estimated vaccine introduction costs deployed through routine outlets within the EPI system in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda. Costs estimated in the study refer to economic costs of the program and cover activities carried out in the introductory stage including training, development of IEC materials etc. as well routine activities related to procurement, distribution, monitoring, supervision, IEC, vaccination, and waste management. Costing accounts for longer immunization visits, higher intensity of supervision and IEC efforts for deployment modalities requiring visits outside of the routine schedule. For the vaccine schedule modeled in this study new visits will potentially be needed to administer 2nd and 4th doses .

Program costs for all countries were calculated based on median service delivery costs averaged across the 6 countries in (12); these amounted to $38·71 per FVC for the 4-dose 6-9 months schedule. In this analysis, in addition to health systems costs estimated in (12) we also included household expenditures related to the vaccination visit; for visits outside of the routine EPI schedule we added $0·40 and $0·20 for each new visit to account for cost of travel and consumables (13-17). Thus, the total direct societal cost of the program was estimated at $39·91 per FVC.

Table C2. Cost of RTS,S immunization per FVC by scope (2013, USD)

Country	Burkina Faso	Ghana	Kenya	Senegal	Tanzania	Uganda
Economic	36·25	37·91	44·49	40·20	38·71	38·71
Financial	34·46	34·57	35·87	34·49	34·42	35·82

Cost data from (12).

A range bounded by lowest financial cost assuming existing capacity and highest economic costs evaluated at zero spare capacity across the 6 countries were additionally considered in the sensitivity analysis.

File C3. Estimating cost of malaria case management

Malaria service delivery costing methodology follows a case management model described in (11). Costs were estimated by severity of illness. For uncomplicated episodes these include cost of medication, diagnosis, and non-medical expenditures at facility level. Cost of the first-line antimalarial(*Arthemeter-Lumefantrine* (*AL*)) according to (18) and another antimalarial mediation(*Sulfadoxine-Pyrimethamine* (*SP*)) to account for non-compliant treatment were drawn from the international price lists(19); these were calculated according to age and weight appropriate drug dosage as per medication (20) and were scaled to account for country specific levels of compliance with the recommended treatments and adherence to the regimen (10). We assume that at least half of the recommended drug dosage is administered for non-adherent cases and cost accordingly. Cost of diagnosis with an RDT is included based on country specific fraction of fever episodes tested. Service related expenditures including medical staff, facility charges etc. by level of health care facility were taken from the WHO-CHOICE(21;22) study and were weighted according to patterns in health seeking for fever estimated from the DHS(23-25) .

For severe episodes costs were estimated by health outcome; a weighted average cost per severe episode is reported. It is assumed that all severe cases for which care is sought are treated in inpatient hospital setting and that the treatment received is compliant with the international and national guidelines for management of severe illness (26). Cost of severe illness covers antimalarial drugs, diagnostics, maintenance therapy, commodities, and hospital “hotel” charges. The prior include intravenous artesunate and oral ACT regimens based on age and severity of illness in accordance with the country policy. Costs vary by outcome with drug and day-bed charges scaled by length of hospitalization. We assume inpatient stays that result in a recovery to last 4·5 days; stays associated with neurological sequilae – 10 days; and fatal episodes- expire within 2 days of hospitalization (27).

In addition, for episodes, both uncomplicated and severe, treated in the formal sector $0·40 and $0·20 were added to account for travel and consumables respectively (13-17).

Costs are expressed in 2013 USD.

Costs by country and severity of illness estimated following the methodology detailed above are shown in Appendix C, Table C4.

Table C3. Baseline, low and high values of parameters varied in sensitivity analysis

Parameter	Baseline	Low	High	Notes
Half-life	7·32 months	6 months	10·2 months	Upper and lower bounds of the 95th prediction interval (8)
Initial efficacy	91·1%	75%	99%	Upper and lower bounds of the 95th prediction interval (8)
Effective coverage	country	Decreased by 25%	Increased by 25%	
Immunization rate	75% country DTP coverage	Decreased by 25%	Increased by 25%	
Transmission	country	Transmission bins decreased by 50%	Transmission bins increased by 50%	(4)
Vaccine price per dose	$5	$2	$10	
Vaccine delivery cost per dose	$1·14	$0·28	$2·36	Lowest financial and highest economic costs across 6 countries were chosen as representative low and high values of vaccine delivery costs (12)
Discount rate	3%	0%	10%	
Time horizon	10 years	5 years	15 years	

Table C4. Summary of country inputs

	EIR[a]	*Pf*PR$_{2-10}$ (%)[b]	Health seeking (%)[c]	Effective coverage (%)[d]	Coverage at 4th dose (%)[e]	Cost per uncomplicated case (USD)	Cost per severe case (USD)	GDP per capita (USD)[f]	Government health care expenditures per capita (USD)[g]
Angola	2·58	7	57	49	53	10·0	238·8	5783	267
Benin*	3·45	23	57	30	43	2·1	60·7	805	37
Botswana	0·00	2	75	71	57	13·2	422·6	7411	397
Burkina Faso*	8·11	34	60	35	54	2·1	54·7	716	46
Burundi*	1·63	8	58	38	57	1·9	36·2	267	21
Cameroon*	1·87	15	55	26	52	2·1	80·3	1329	67
Central African Republic*	2·36	30	32	17	23	1·9	46·8	335	13
Chad*	0·43	6	36	10	28	0·6	59·5	1010	37
Comoros*	0·18	16	52	27	50	2·6	59·9	842	51
Congo	2·50	11	65	38	51	5·8	162·4	3167	131
Cote d`Ivoire*	6·60	38	55	25	46	2·2	74·0	1540	87
Democratic Republic of the Congo*	2·94	21	56	26	46	1·1	37·1	445	16
Djibouti	0·00	2	76	47	48	6·4	158·0	1668	137
Equatorial Guinea	4·02	31	68	38	9	22·7	1884·7	20581	714
Eritrea*	0·02	2	13	8	56	2·9	60·9	544	17
Ethiopia*	0·01	2	26	14	44	1·7	42·7	505	25
Gabon	3·82	15	67	40	46	14·4	598·3	10292	441
Ghana	4·42	25	53	31	56	2·3	58·1	1876	100
Guinea*	6·56	42	48	21	35	1·3	45·4	531	25
Guinea Bissau*	0·70	5	51	29	48	1·6	40·9	555	32
Kenya*	1·14	7	58	35	48	2·5	60·9	1238	45
Liberia*	8·62	29	77	42	41	1·6	38·4	453	44
Madagascar*	0·33	3	41	22	43	1·8	49·0	463	20
Malawi*	3·03	12	59	40	55	2·3	41·0	237	26
Mali*	6·81	45	40	20	43	1·6	46·5	726	53
Mauritania*	0·11	2	45	22	49	2·3	72·9	1300	48
Mozambique*	5·66	23	59	38	46	2·6	46·5	598	40
Namibia	0·50	3	63	44	52	8·2	231·7	5615	423
Niger*	3·52	15	62	39	41	2·2	43·6	431	27
Nigeria	4·97	26	84	32	34	1·7	87·7	2966	115
Rwanda*	1·04	3	66	54	59	2·7	48·7	639	71
Sao Tome and Principe*	3·53	7	72	54	58	4·0	77·2	1610	110

	EIR[a]	*Pf*PR$_{2-10}$ (%)[b]	Health seeking (%)[c]	Effective coverage (%)[d]	Coverage at 4th dose (%)[e]	Cost per uncomplicated case (USD)	Cost per severe case (USD)	GDP per capita (USD)[f]	Government health care expenditures per capita (USD)[g]
Senegal*	0·49	2	56	31	54	2·6	73·2	1047	46
Sierra Leone*	17·38	40	63	50	53	2·3	43·5	809	96
Somalia*	0·08	3	13	8	25	2·0	42·7	133	·
South Sudan*	0·43	9	16	8	29	3·4	86·9	1045	18
Sudan	0·14	2	39	25	56	3·3	86·9	1751	115
Tanzania*	1·76	5	77	46	56	2·1	49·4	927	49
The Gambia*	0·32	2	65	37	58	1·9	49·9	482	29
Togo*	6·53	37	58	32	51	2·0	54·7	636	54
Uganda*	8·90	13	84	66	47	2·7	50·7	657	59
Zambia	6·56	11	75	59	49	4·1	73·9	1845	93
Zimbabwe*	0·27	2	47	32	56	2·9	60·9	953	·

* Counties eligible for GAVI support (GNI <1580 USD); Nominal values are expressed in 2013 USD; [a] Population weighted median EIR based on 2014 estimates from MAP(4); [b] Population weighted median *Pf*PR$_{2-10}$ based on 2014 *estimates* from MAP(4); [c] Author tabulations based on country DHS data, 14 day recall; [d] Updated country estimates based on (10); [e] Projected from country DTP coverage(9) assumed 60% of country DTP3 coverage; [f, g] (28);

Table C5. Cumulative impact of RTS,S immunization: disease averted grouped by country levels of *Pf*PR$_{2-10}$

	Total events averted				Events averted per 100,000 FVC				Percent events averted			
	*Pf*PR$_{2-10}$			All countries	*Pf*PR$_{2-10}$			All countries	*Pf*PR$_{2-10}$			All countries
	<5%	5-10%	>10%		<5%	5-10%	>10%		<5%	5-10%	>10%	
Any	15751 (14583; 16918)	12989 (12251; 13727)	94458 (90322; 98594)	123198 (117300; 129096)	24688 [596-88931]	60281 [18418-139319]	99390 [42851-141970]	73501 [596-141970]	11·95 [5·35-16·16]	9·5 [4·56-12·60]	7·74 [1·28-11·39]	9·29 [1·28-16·16]
Uncomplicated	15333 (14202; 16463)	12673 (11956; 13391)	92380 (88327; 96433)	120386 (114623; 126149)	23997 [572-86945]	58782 [17952-136168]	97315 [41764-139126]	71694 [572-139126]	12·05 [5·37-16·34]	9·56 [4·58-12·72]	7·8 [1·29-11·45]	9·36 [1·29-16·34]
Severe	418 (378; 458)	316 (292; 339)	2078 (1956; 2200)	2812 (2635; 2989)	731 [19-2219]	1475 [466-3290]	2119 [992-3560]	1685 [19-3560]	9·6 [4·72-14·00]	7·26 [3·83-11·28]	5·77 [0·78-10·14]	7·12 [0·78-14·00]
Out-patient visits	8839 (8050; 9628)	5970 (5581; 6358)	51396 (48904; 53887)	66204 (62595; 69813)	9955 [169-61807]	27699 [5822-92075]	47561 [18026-95569]	34989 [169-95569]	11·98 [4·82-18·86]	9·58 [4·23-13·39]	7·62 [1·29-11·81]	9·14 [1·29-18·86]
In-patient visits	196 (177; 215)	150 (138; 161)	991 (928; 1054)	1337 (1247; 1426)	344 [8-1111]	693 [219-1680]	996 [453-1851]	792 [8-1851]	9·52 [4·43-14·84]	7·18 [3·60-11·22]	5·73 [0·79-10·17]	7·06 [0·79-14·84]
Direct deaths[a]	78 (70; 86)	64 (59; 69)	472 (442; 502)	614 (572; 657)	72 [1-243]	158 [39-370]	240 [84-410]	180 [1-410]	10·44 [4·26-16·36]	8·21 [3·96-12·03]	6·77 [0·90-10·73]	7·97 [0·90-16·36]
Deaths[b]	43 (38; 47)	34 (31; 37)	234 (218; 251)	311 (288; 334)	126 [3-500]	286 [92-703]	499 [170-761]	350 [3-761]	7·37 [1·41-11·62]	6·78 [3·05-9·42]	5·91 [0·95-8·51]	6·46 [0·95-11·62]
DALYs	4078 (3650; 4507)	3371 (3096; 3646)	24838 (23237; 26439)	32288 (30041; 34535)	6600 [156-26135]	15069 [4822-36946]	26211 [8937-40054]	18413 [156-40054]	7·39 [1·39-11·62]	6·83 [3·05-9·47]	5·95 [0·96-8·59]	6·5 [0·96-11·62]
Direct DALYs	2269 (2032; 2505)	1792 (1639; 1944)	12488 (11633; 13343)	16549 (15335; 17762)	3749 [52-12834]	8371 [2079-19646]	12780 [4541-21621]	9581 [52-21621]	10·53 [4·36-16·14]	8·34 [4·04-12·18]	6·91 [0·94-10·86]	8·1 [0·94-16·14]

Group totals for events averted and program costs cumulated over 10 years and all countries in the respective group are reported as averages and 95th percentile prediction intervals. Cumulative program output metrics per 100,000 FVC and cost-effectiveness ratios are reported as medians and min and max ranges of country median estimates averaged over uncertainty predictions from the model. Unless otherwise noted DALYs are estimated without age-weighting and discounting. [a] "Direct deaths" inlcude only deaths directly attributable to malaria. [b] "Deaths" inlcude malaria deaths attributable to malaria and deaths that occur with a co-mornbidity and malaria. Based on the sample of countries evaluated, vaccine and health systems assumptions, the relative contribution of health outcomes to DALYs is as follows: Uncomplicated cases contribute 0.64%, severe cases contribute 0.40%, direct malaria deaths contribute 49.66%, and indirect malaria deaths contribute 49.3%.

Table C6. Cumulative impact of RTS,S immunization: disease averted, costs, and cost-effectiveness by country

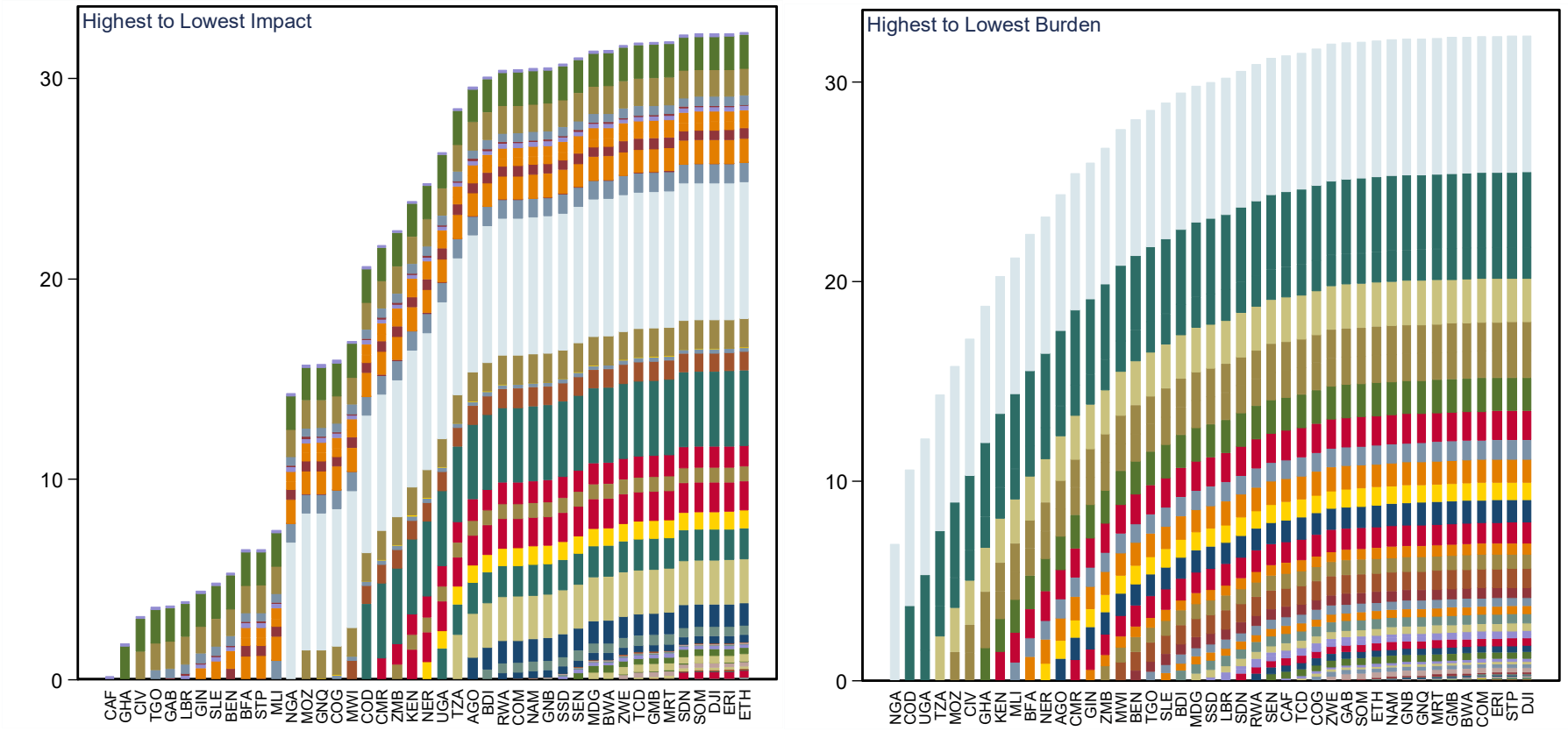
Country	Episodes averted per 100,000 FVC	Deaths[a] averted per 100,000 FVC	DALYs averted per 100,000 FVC	Total DALYs averted (thousands)	Total net costs[c] (millions)	Cost per DALY averted
Angola	65914 (45863;81948)	306 (164;438)	16071 (8610;23001)	1095 (587; 1568)	232 (231;234)	230 (147;398)
Benin	103152 (81443; 117721)	530 (351;662)	27825 (18417;34748)	507 (335;633)	63 (63; 63)	129 (100;188)
Botswana	39649 (6455;65233)	152 (5;312)	7969 (280;16304)	24 (1; 50)	10 (10; 11)	1389 (208;12519)
Burkina Faso	101320 (79692; 114361)	517 (333;625)	27249 (17559;32971)	1175 (757; 1422)	149 (149;149)	131 (105;197)
Burundi	61389 (46161;76103)	306 (188;441)	16025 (9831;23081)	495 (304;713)	108 (108;108)	231 (151;355)
Cameroon	80854 (65666;93314)	425 (292;550)	22306 (15306;28862)	1057 (726; 1368)	165 (164;165)	161 (120;227)
Central African Republic	112985 (94577; 121416)	620 (440;761)	32568 (23059;40054)	128 (91;158)	14 (14; 14)	109 (87;151)
Chad	21314 (18418;25935)	119 (92;157)	6195 (4822; 8202)	123 (96;163)	69 (69; 69)	572 (425;723)
Comoros	52961 (42851;60745)	278 (189;354)	14591 (9925;18569)	19 (13; 24)	5 (5;5)	247 (187;351)
Congo	88485 (67478; 106807)	441 (276;608)	23111 (14451;31874)	214 (134;295)	32 (32; 32)	156 (107;238)
Cote d`Ivoire	116795 (92143; 128817)	613 (409;742)	32246 (21500;39065)	1368 (912; 1657)	146 (146;147)	110 (88;161)
Democratic Republic of the Congo	81026 (65152;91087)	425 (289;526)	22339 (15168;27661)	3745 (2543; 4637)	583 (583;584)	160 (126;229)
Djibouti	8779 (4539;12591)	43 (18; 76)	2259 (948; 3991)	2 (1;4)	3 (3;3)	1858 (877; 3696)
Equatorial Guinea	95056 (74134; 107346)	474 (303;575)	24992 (15965;30312)	7 (5;9)	1 (1;1)	111 (83;175)
Eritrea	4024 (2748; 8554)	23 (15; 44)	1177 (773; 2300)	12 (8; 23)	36 (36; 36)	3252 (1522; 4532)
Ethiopia	1283 (596; 4271)	7 (3; 20)	356 (156; 1022)	52 (23;149)	511 (511;511)	12764 (3427;22448)

Country	Episodes averted per 100,000 FVC	Deaths[a] averted per 100,000 FVC	DALYs averted per 100,000 FVC	Total DALYs averted (thousands)	Total net costs[c] (millions)	Cost per DALY averted
Gabon	120427 (91968; 140075)	592 (368;752)	31118 (19358;39556)	75 (47; 96)	8 (7;8)	106 (78;165)
Ghana	120290 (95052; 135205)	618 (406;757)	32483 (21342;39874)	1654 (1087; 2031)	177 (176;177)	110 (87;163)
Guinea	104363 (84655; 116963)	568 (383;682)	29953 (20182;36008)	530 (357;637)	61 (61; 62)	119 (96;172)
Guinea Bissau	48876 (36838;62230)	258 (176;398)	13493 (9199;20828)	45 (31; 69)	12 (12; 12)	273 (168;380)
Kenya	68152 (52888;82002)	345 (223;471)	18119 (11668;24697)	1466 (944; 1998)	281 (281;282)	201 (141;298)
Liberia	120814 (93683; 136707)	583 (369;707)	30699 (19472;37274)	215 (136;261)	24 (24; 24)	117 (93;178)
Madagascar	29989 (23150;37149)	162 (109;252)	8468 (5722;13163)	345 (233;536)	142 (142;142)	430 (265;610)
Malawi	87742 (66491; 104933)	430 (267;581)	22569 (14016;30480)	938 (582; 1267)	144 (144;145)	162 (114;248)
Mali	89941 (73822; 100849)	492 (337;589)	25933 (17730;31102)	951 (650; 1141)	127 (127;127)	137 (111;196)
Mauritania	18655 (14087;24342)	101 (67;161)	5276 (3489; 8418)	37 (25; 59)	25 (25; 25)	695 (415; 1001)
Mozambique	96887 (75061; 109008)	483 (306;587)	25427 (16119;30955)	1434 (909; 1745)	195 (195;196)	141 (112;215)
Namibia	56640 (37884;73607)	275 (147;424)	14436 (7658;22210)	56 (30; 86)	13 (13; 13)	262 (154;452)
Niger	67707 (51969;78754)	333 (212;423)	17499 (11110;22260)	885 (562; 1126)	175 (175;175)	206 (155;312)
Nigeria	94195 (74431; 104940)	485 (316;591)	25551 (16645;31147)	6834 (4452; 8331)	923 (921;926)	140 (111;208)
Rwanda	64748 (32236;88931)	297 (108;500)	15566 (5642;26135)	339 (123;569)	76 (76; 76)	276 (133;620)
Sao Tome and Principe	114136 (77022; 139319)	511 (261;703)	26880 (13710;36946)	8 (4; 12)	1 (1;1)	139 (93;251)
Senegal	34228 (22603;47724)	181 (106;315)	9439 (5597;16463)	317 (188;553)	117 (117;117)	402 (212;624)
Sierra Leone	121928 (91709; 141970)	566 (346;686)	29909 (18286;36259)	374 (229;454)	43 (43; 43)	120 (95;190)

Country	Episodes averted per 100,000 FVC	Deaths[a] averted per 100,000 FVC	DALYs averted per 100,000 FVC	Total DALYs averted (thousands)	Total net costs[c] (millions)	Cost per DALY averted
Somalia	9168 (7430;14625)	52 (38; 75)	2690 (2006; 3929)	36 (27; 53)	47 (47; 47)	1340 (888; 1739)
South Sudan	44008 (39080;47765)	246 (197;320)	12865 (10308;16758)	183 (147;238)	50 (50; 50)	275 (208;338)
Sudan	15511 (10600;21716)	84 (51;148)	4375 (2666; 7742)	349 (212;617)	278 (278;278)	860 (451; 1311)
Tanzania	66852 (43241;87045)	320 (164;495)	16746 (8578;25894)	2199 (1126; 3400)	456 (456;457)	230 (134;406)
The Gambia	21282 (11084;33069)	112 (49;220)	5824 (2588;11489)	32 (14; 62)	19 (19; 19)	700 (303; 1348)
Togo	119343 (93429; 132324)	607 (399;734)	31938 (21006;38677)	452 (297;547)	49 (49; 49)	112 (89;165)
Uganda	87144 (57040; 106269)	326 (170;440)	17190 (8937;23176)	1537 (799; 2072)	308 (308;310)	217 (149;387)
Zambia	92502 (62986; 111661)	389 (207;515)	20464 (10894;27106)	739 (393;978)	124 (124;125)	181 (126;317)
Zimbabwe	27944 (18373;39218)	148 (88;261)	7724 (4615;13604)	234 (140;412)	106 (106;106)	493 (257;759)

Estimates represent country cumulative statistics at year 10 of the program averaged across uncertainty predictions from the model; 95th percentile prediction intervals are given in parantheses. DALYs are estimated without age-weighting and discounting. [a] inlcude direct malaria mortality and indirect mortality from malaria comorbidity. [b] inlcude only direct malaria related moratlity. [c] represent cumulative program costs minus any health savings resulting from averted malaria mortality and morbidity incurred by the health systems and patients; costs are discounted at 3%. Nominal values expressed in 2013 USD.

Figure C1. Cumulative impact of RTS,S vaccination: total DALYs averted by country



The figures illustrate total predicted impact of RTS,S vaccination cumulated over 10 years and countries; the latter are cumulated sequentially by effectiveness and total burden averted. On the left countries are ranked highest to lowest by predicted effectiveness (DALYs averted per 100,000 FVC). Starting with Central African Republic, where of the 43 countries evaluated vaccine averts most DALYs per program output (32,568 DALYs averted per 100,000 FVC), each consecutive bar shows the sum of DALYs averted by the vaccine in Central African Republic and next highest effectiveness countries. On the right countries are ranked by total baseline malaria burden highest to lowest (total number of DALYs). Starting with Nigeria- highest burden country in SSA- each consecutive bar shows the sum of DALYs averted by the vaccine in Nigeria and next highest burden countries. X-axis labels refer to the next highest impact/ burden country over which vaccine`s impact is cumulated. For both figures the last bar shows the total burden averted across the 43 countries. Colors within the bar represent burden averted in a particular country.

Table C7. Case management, program costs and cumulative predicted cost-effectiveness of RTS,S immunization: Health systems perspective

	*Pf*PR$_{2-10}$				GAVI eligible	All countries
	<5%	**5-10%**	**10-40%**	**>40%**		
Cost per uncomplicated case (USD)	3.3 [1.14-12.60]	3.01 [0.45-9.42]	3.58 [0.65-22.40]	1.02 [0.89-1.16]	1.7 [0.45-3.43]	3.28 [0.45-22.40]
Cost per severe case (USD)	101.66 [39.64-421.32]	85.71 [34.93-237.50]	178.57 [35.80-1883.40]	44.68 [44.09-45.27]	52.97 [34.93-85.63]	132.18 [34.93-1883.40]
Cost per FVC (USD)	38.71	38.71	38.71	38.71	38.71	38.71
DALYs averted /100,000 FVC	6006 [156-26135]	15289 [4822-36946]	25949 [8937-40054]	28402 [17730-36008]	18050 [156-40054]	18413 [156-40054]
Total net program costs (millions)[c]	1354 (1354; 1354)	1162 (1161; 1163)	3414 (3413; 3416)	4182 (4180; 4183)	1749 (1747; 1750)	5930 (5927; 5933)
$/ DALY averted	564 [129-21773]	219 [90-702]	126 [76-376]	186 [84-21773]	170 [76-12143]	182 [76-21773]
$/ Direct DALY averted	965 [263-65499]	395 [169-1628]	259 [142-741]	358 [156-65499]	325 [142-8476]	350 [142-65499]
$/ Discounted DALY averted	1106 [254-42290]	431 [177-1376]	248 [149-737]	366 [166-42290]	334 [149-22596]	359 [149-42290]
$/ Discounted direct DALY averted	1879 [517-129806]	773 [333-3193]	509 [279-1449]	704 [306-129806]	638 [279-16589]	687 [279-129806]

Group totals for events averted and program costs are reported as averages and 95th percentile prediction intervals cumulated over 10 years and across all countries in the respective group. Cumulative program output metrics per 100,000 FVC and cost-effectiveness ratios are reported as medians and min and max range of country median estimates averaged over uncertainty predictions from the model. Unless otherwise noted DALYs are estimated without age-weighting and discounting. [a] "Total deaths" inlcude malaria deaths attributable to malaria and deaths that occur with a co-mornbidity and malaria. [b] "Total direct deaths" inlcude only deaths directly attributable to malaria. [c] "Total net program costs" represent cumulative program costs minus any health savings resulting from averted malaria mortality and morbidity incurred by the health systems; costs are discounted at 3%. Nominal values expressed in 2013 USD.

Table C8. Sensitivity analysis over range of vaccine properties and country specific inputs: predicted DALYs averted per 100,000 FVC and ICER by scenario and by country levels of *Pf*PR$_{2-10}$

	Description	DALYs averted per 100,000 FVC				Cost per DALY averted			
		*Pf*PR$_{2-10}$			All countries	*Pf*PR$_{2-10}$			All countries
		<5%	5-10%	>10%		<5%	5-10%	>10%	
0	Baseline	6600	15069	25360	18050	529	227	127	191
		[156-26135]	[4822-36946]	[15774-29831]	[156-40054]	[133-22445]	[91-723]	[115-219]	[85-22445]
1	Transmission bins increased by 50%	10368	19304	27250	20376	332	181	125	170
		[2383-19344]	[10090-30131]	[17403-37134]	[2383-37134]	[180-1469]	[113-345]	[89-200]	[89-1469]
2	Transmission bins decreased by 50%	5133	14412	24677	16075	698	240	138	216
		[205-13394]	[4884-24786]	[13049-30450]	[205-30450]	[261-17093]	[139-714]	[111-267]	[111-17093]
3	Immunization rate increased by 25%	9388	23117	35320	24968	379	150	95	139
		[497-21507]	[10179-36981]	[20093-44647]	[497-44647]	[162-7047]	[92-342]	[70-173]	[70-7047]
4	Immunization rate decreased by 25%	5281	12456	19868	13540	675	275	170	256
		[280-12097]	[4819-20802]	[11302-25192]	[280-25192]	[289-12528]	[166-724]	[134-309]	[134-12528]
5	Vaccine price $10 per dose	6600	15069	25360	18050	923	378	232	350
		[156-26135]	[4822-36946]	[15774-29831]	[156-40054]	[395-17124]	[227-989]	[188-422]	[188-17124]
6	Vaccine price $2 per dose	6600	15069	25360	18050	256	101	64	97
		[156-26135]	[4822-36946]	[15774-29831]	[156-40054]	[109-4758]	[61-275]	[37-117]	[37-4758]
7	Cost of vaccine delivery $2.36 per dose	6600	15069	25360	18050	580	236	145	220
		[156-26135]	[4822-36946]	[15774-29831]	[156-40054]	[248-10757]	[142-621]	[114-265]	[114-10757]
8	Cost of vaccine delivery $0.28 per dose	6600	15069	25360	18050	452	183	113	171
		[156-26135]	[4822-36946]	[15774-29831]	[156-40054]	[193-8386]	[110-484]	[86-206]	[86-8386]
9	Discount rate 10%	6600	15069	25360	18050	387	156	97	145
		[156-26135]	[4822-36946]	[15774-29831]	[156-40054]	[166-7207]	[94-413]	[75-177]	[75-7207]
10	Discount rate 0%	6600	15069	25360	18050	578	235	145	220

	Description	DALYs averted per 100,000 FVC				Cost per DALY averted			
		*Pf*PR$_{2-10}$			All countries	*Pf*PR$_{2-10}$			All countries
		<5%	5-10%	>10%		<5%	5-10%	>10%	
		[156-26135]	[4822-36946]	[15774-29831]	[156-40054]	[246-10708]	[141-621]	[112-264]	[112-10708]
11	Time horizon 15 years	7836	17230	25797	18042	422	187	121	177
		[449-17144]	[6822-27731]	[15181-33756]	[449-33756]	[190-7269]	[115-475]	[90-213]	[90-7269]
12	Time horizon 5 years	5505	14378	24505	16008	696	258	149	234
		[284-13063]	[5232-24883]	[13063-30360]	[284-30360]	[287-13244]	[149-718]	[121-287]	[121-13244]
13	Vaccine half-life 10.2 months	8297	19447	31102	21168	429	175	108	164
		[446-18849]	[7564-32499]	[17672-39438]	[446-39438]	[185-7856]	[105-461]	[83-197]	[83-7856]
14	Vaccine half-life 6 months	6495	15373	24485	16699	549	222	138	207
		[341-14948]	[5931-25665]	[13938-31046]	[341-31046]	[233-10271]	[134-588]	[106-250]	[106-10271]
15	Vaccine initial efficacy 99%	7397	17568	28226	19145	482	194	119	181
		[390-16991]	[6783-29411]	[15960-35666]	[390-35666]	[205-8984]	[116-514]	[91-218]	[91-8984]
16	Vaccine initial efficacy 75%	5970	13895	21671	14956	597	248	156	232
		[318-13552]	[5408-22937]	[12528-27722]	[318-27722]	[258-11020]	[150-645]	[121-278]	[121-11020]
17	Vaccine half-life 10.2 months and initial efficacy 99%	9721	22756	36590	24829	366	149	92	139
		[526-21993]	[8885-38026]	[20728-46353]	[526-46353]	[159-6654]	[90-392]	[70-168]	[70-6654]
18	Vaccine half-life 6 months and Vaccine initial efficacy 75%	4869	11479	18004	12405	732	299	188	279
		[253-11229]	[4424-19100]	[10371-22983]	[253-22983]	[311-13831]	[180-788]	[146-336]	[146-13831]
19	Vaccine half-life 10.2 months and initial efficacy 99% and immunization rate increased by 25%	12961	31652	48786	34295	274	110	69	101
		[702-29324]	[14074-50701]	[27637-61352]	[702-61352]	[119-4990]	[67-248]	[47-126]	[47-4990]
20	Vaccine half-life 6 months and Vaccine initial efficacy 75%	3652	8610	13503	9303	976	400	250	373

	Description	DALYs averted per 100,000 FVC				Cost per DALY averted			
		*Pf*PR$_{2-10}$			All countries	*Pf*PR$_{2-10}$			All countries
		<5%	5-10%	>10%		<5%	5-10%	>10%	
	and Immunization rate decreased by 25%								
		[190-8422]	[3318-14325]	[7778-17237]	[190-17237]	[415-18441]	[241-1051]	[199-449]	[199-18441]

Estimates represent medians of country median estimates within the group, range [min-max] reported in parenthesis below; Nominal values are expressed in 2013 USD;

Appendix D. Supplementary files to Chapter 5: State of inequality in malaria intervention coverage in Sub-Saharan African countries

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Table D1. Country name, ISO3 label, *PfPR*$_{2-10}$, and DHS/MIS survey corresponding to 2015* year label by country

Country	ISO3	*Pf*PR$_{2-10}$*	Survey year(s)	DHS file	Year label
Angola	AGO	0.066419	2011	AOXX62FL	2015
Benin	BEN	0.226732	2011-2012	BJXX61FL	2015
Burkina Faso	BFA	0.339542	2014	BFXX70FL	2015
Burundi	BDI	0.076145	2012-2013	BUXX6HFL	2015
Cameroon	CMR	0.1459	2011	CMXX61FL	2015
Chad	TCD	0.062353	2014-2015	TDXX71FL	2015
Comoros	COM	0.164316	2012	KMXX61FL	2015
Congo	COG	0.11469	2011-2012	CGXX60FL	2015
Congo, Democratic Republic	COD	0.209264	2013-2014	CDXX61FL	2015
Cote d'Ivoire	CIV	0.381616	2011-2012	CIXX62FL	2015
Gabon	GAB	0.151068	2012	GAXX60FL	2015
Ghana	GHA	0.250699	2014	GHXX72FL	2015
Guinea	GIN	0.421519	2012	GNXX62FL	2015
Kenya	KEN	0.0689	2015	KEXX7HFL	2015
Liberia	LBR	0.292958	2013	LBXX6AFL	2015
Madagascar	MDG	0.032263	2016	MDXX71FL	2015
Malawi	MWI	0.121212	2015-2016	MWXX7HFL	2015
Mali	MLI	0.454885	2012-2013	MLXX6HFL	2015
Mozambique	MOZ	0.231735	2011	MZXX62FL	2015
Namibia	NAM	0.030788	2013	NMXX61FL	2015
Niger	NER	0.15034	2012	NIXX61FL	2015
Nigeria	NGA	0.259483	2013	NGXX6AFL	2015
Rwanda	RWA	0.025569	2014-2015	RWXX70FL	2015
Senegal	SEN	0.024716	2014	SNXX70FL	2015
Sierra Leone	SLE	0.398516	2013	SLXX61FL	2015
Tanzania	TZA	0.050974	2015-2016	TZXX7HFL	2015
Togo	TGO	0.367213	2013-2014	TGXX61FL	2015
Uganda	UGA	0.12953	2014-2015	UGXX72FL	2015
Zambia	ZMB	0.10741	2013-2014	ZMXX61FL	2015
Zimbabwe	ZWE	0.024222	2015	ZWXX70FL	2015

XX refers to DHS/MIS recode files as follows: KR files were used to estimate fever prevalence, health seeking and treatment for fever among children under the age of 5; PR files were used to estimate proportion of population that slept under an ITN the night prior to the survey and malaria prevalence among children under the age of 5; IR files were used to estimate SP uptake during the most recent pregnancy; HR files were used for estimates of ITN and IRS coverage; WI files were used to obtain asset-wealth index score data for surveys collected prior to 2002. * Country mean malaria parasite prevalence among children aged between 2 and 10 (*Pf*PR2-10) is based on 2015 MAP estimates from (16). *MAP* Malaria Atlas Project, *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey

Table D2. Country name, ISO3 label, and DHS/MIS survey corresponding to 2005, 2010 and 2015* year labels by country

Country	ISO3	Survey year(s)	DHS file	Year label
Angola	AGO	2006	AOXX51FL	2005
Angola	AGO	2011	AOXX62FL	2010
Benin	BEN	2006	BJXX51FL	2005
Benin	BEN	2011-2012	BJXX61FL	2010
Burkina Faso	BFA	2003	BFXX43FL	2005
Burkina Faso	BFA	2010	BFXX62FL	2010
Burkina Faso	BFA	2014	BFXX70FL	2015
Cameroon	CMR	2004	CMXX44FL	2005
Cameroon	CMR	2011	CMXX61FL	2010
Chad	TCD	2004	TDXX41FL	2005
Chad	TCD	2014-2015	TDXX71FL	2015
Congo	COG	2005	CGXX51FL	2005
Congo	COG	2011-2012	CGXX60FL	2010
Democratic Republic of the Congo	COD	2007	CDXX50FL	2010
Democratic Republic of the Congo	COD	2013-2014	CDXX61FL	2015
Cote d'Ivoire	CIV	2005	CIXX50FL	2005
Cote d'Ivoire	CIV	2011-2012	CIXX62FL	2010
Ghana	GHA	2003	GHXX4BFL	2005
Ghana	GHA	2008	GHXX5AFL	2010
Ghana	GHA	2014	GHXX72FL	2015
Guinea	GIN	2005	GNXX52FL	2005
Guinea	GIN	2012	GNXX62FL	2010
Kenya	KEN	2003	KEXX42FL	2005
Kenya	KEN	2008-2009	KEXX52FL	2010
Kenya	KEN	2015	KEXX7HFL	2015
Liberia	LBR	2006-2007	LBXX51FL	2005
Liberia	LBR	2011	LBXX61FL	2010
Liberia	LBR	2013	LBXX6AFL	2015
Madagascar	MDG	2003-2004	MDXX41FL	2005
Madagascar	MDG	2011	MDXX61FL	2010
Madagascar	MDG	2016	MDXX71FL	2015
Malawi	MWI	2004	MWXX4DFL	2005
Malawi	MWI	2010	MWXX61FL	2010
Malawi	MWI	2015-2016	MWXX7HFL	2015
Mali	MLI	2006	MLXX53FL	2005
Mali	MLI	2012-2013	MLXX6HFL	2010
Mozambique	MOZ	2003-2004	MZXX41FL	2005
Mozambique	MOZ	2011	MZXX62FL	2010
Namibia	NAM	2006-2007	NMXX51FL	2010
Namibia	NAM	2013	NMXX61FL	2015
Niger	NER	2006	NIXX51FL	2005
Niger	NER	2012	NIXX61FL	2010
Nigeria	NGA	2003	NGXX4BFL	2005
Nigeria	NGA	2008	NGXX53FL	2010
Nigeria	NGA	2013	NGXX6AFL	2015

Country	ISO3	Survey year(s)	DHS file	Year label
Rwanda	RWA	2005	RWXX53FL	2005
Rwanda	RWA	2010-2011	RWXX61FL	2010
Rwanda	RWA	2014-2015	RWXX70FL	2015
Senegal	SEN	2005	SNXX4HFL	2005
Senegal	SEN	2010-2011	SNXX61FL	2010
Senegal	SEN	2014	SNXX70FL	2015
Sierra Leone	SLE	2008	SLXX51FL	2010
Sierra Leone	SLE	2013	SLXX61FL	2015
Tanzania	TZA	2004-2005	TZXX4IFL	2005
Tanzania	TZA	2009-2010	TZXX63FL	2010
Tanzania	TZA	2015-2016	TZXX7HFL	2015
Uganda	UGA	2006	UGXX52FL	2005
Uganda	UGA	2011	UGXX60FL	2010
Uganda	UGA	2014-2015	UGXX72FL	2015
Zambia	ZMB	2007	ZMXX51FL	2010
Zambia	ZMB	2013-2014	ZMXX61FL	2015
Zimbabwe	ZWE	2005-2006	ZWXX52FL	2005
Zimbabwe	ZWE	2010-2011	ZWXX62FL	2010
Zimbabwe	ZWE	2015	ZWXX70FL	2015

XX refers to DHS/MIS recode files as follows: KR files were used to estimate fever prevalence, health seeking and treatment for fever among children under the age of 5; PR files were used to estimate proportion of population that slept under an ITN the night prior to the survey and malaria prevalence among children under the age of 5; IR files were used to estimate SP uptake during the most recent pregnancy; HR files were used for estimates of ITN and IRS coverage; WI files were used to obtain asset-wealth index score data for surveys collected prior to 2002. *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey

Table D3. Distribution of households with at least one ITN for every two persons in 2015*

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Angola	0.064 (0.055 to 0.072)	0.030 (0.020 to 0.040)	0.079 (0.062 to 0.095)	0.049 (0.029 to 0.068)	2.629 (1.601 to 3.657)	0.049 (0.035 to 0.064)	0.065 (0.041 to 0.089)
Benin	0.446 (0.434 to 0.458)	0.425 (0.404 to 0.446)	0.516 (0.491 to 0.541)	0.091 (0.059 to 0.124)	1.215 (1.132 to 1.298)	0.071 (0.045 to 0.097)	0.221 (0.152 to 0.290)
Burkina Faso	0.492 (0.476 to 0.507)	0.411 (0.371 to 0.450)	0.583 (0.552 to 0.614)	0.172 (0.122 to 0.223)	1.419 (1.262 to 1.576)	0.142 (0.104 to 0.181)	0.354 (0.261 to 0.446)
Burundi	0.255 (0.230 to 0.280)	0.207 (0.172 to 0.242)	0.309 (0.273 to 0.345)	0.102 (0.055 to 0.148)	1.492 (1.206 to 1.778)	0.076 (0.041 to 0.111)	0.546 (0.367 to 0.725)
Cameroon	0.045 (0.041 to 0.049)	0.036 (0.024 to 0.048)	0.063 (0.054 to 0.071)	0.026 (0.012 to 0.041)	1.730 (1.100 to 2.359)	0.022 (0.012 to 0.033)	0.060 (0.031 to 0.089)
Chad	0.280 (0.270 to 0.291)	0.295 (0.274 to 0.316)	0.350 (0.327 to 0.372)	0.055 (0.023 to 0.086)	1.186 (1.070 to 1.302)	0.019 (-0.005 to 0.043)	0.231 (0.159 to 0.303)
Comoros	0.254 (0.230 to 0.277)	0.186 (0.154 to 0.219)	0.321 (0.277 to 0.364)	0.134 (0.081 to 0.187)	1.719 (1.352 to 2.086)	0.117 (0.077 to 0.157)	0.281 (0.193 to 0.370)
Congo	0.111 (0.100 to 0.122)	0.174 (0.152 to 0.196)	0.084 (0.066 to 0.103)	-0.090 (-0.118 to -0.061)	0.485 (0.362 to 0.609)	-0.069 (-0.091 to -0.048)	-0.119 (-0.153 to -0.084)
Congo, Democratic Republic	0.254 (0.238 to 0.269)	0.233 (0.207 to 0.260)	0.237 (0.208 to 0.267)	0.004 (-0.035 to 0.044)	1.018 (0.847 to 1.189)	0.020 (-0.012 to 0.051)	-0.012 (-0.085 to 0.062)
Cote d'Ivoire	0.317 (0.299 to 0.335)	0.345 (0.304 to 0.385)	0.280 (0.242 to 0.319)	-0.064 (-0.120 to -0.008)	0.814 (0.666 to 0.962)	-0.045 (-0.088 to -0.003)	-0.135 (-0.236 to -0.034)
Gabon	0.145 (0.134 to 0.156)	0.213 (0.193 to 0.232)	0.064 (0.046 to 0.083)	-0.148 (-0.175 to -0.121)	0.303 (0.210 to 0.396)	-0.112 (-0.134 to -0.089)	-0.231 (-0.273 to -0.189)
Ghana	0.452 (0.436 to 0.469)	0.426 (0.396 to 0.456)	0.411 (0.375 to 0.447)	-0.015 (-0.062 to 0.032)	0.965 (0.857 to 1.074)	-0.052 (-0.089 to -0.016)	-0.130 (-0.250 to -0.009)
Guinea	0.097 (0.087 to 0.107)	0.085 (0.067 to 0.102)	0.076 (0.060 to 0.093)	-0.008 (-0.033 to 0.016)	0.901 (0.629 to 1.173)	0.004 (-0.016 to 0.024)	-0.008 (-0.054 to 0.037)
Kenya	0.400 (0.367 to 0.434)	0.258 (0.214 to 0.303)	0.531 (0.470 to 0.592)	0.272 (0.196 to 0.349)	2.054 (1.624 to 2.484)	0.213 (0.153 to 0.273)	0.550 (0.426 to 0.674)
Liberia	0.221 (0.204 to 0.239)	0.227 (0.198 to 0.257)	0.187 (0.157 to 0.217)	-0.040 (-0.082 to 0.002)	0.823 (0.653 to 0.993)	-0.052 (-0.088 to -0.015)	-0.121 (-0.197 to -0.045)
Madagascar	0.444 (0.420 to 0.468)	0.422 (0.386 to 0.458)	0.456 (0.408 to 0.504)	0.034 (-0.026 to 0.094)	1.082 (0.935 to 1.228)	0.032 (-0.013 to 0.078)	0.086 (-0.064 to 0.236)
Malawi	0.235 (0.224 to 0.245)	0.153 (0.139 to 0.167)	0.383 (0.363 to 0.402)	0.230 (0.206 to 0.254)	2.502 (2.241 to 2.763)	0.170 (0.153 to 0.186)	0.481 (0.424 to 0.538)
Mali	0.418 (0.402 to 0.435)	0.370 (0.336 to 0.405)	0.438 (0.407 to 0.469)	0.068 (0.023 to 0.113)	1.183 (1.048 to 1.318)	0.046 (0.012 to 0.081)	0.106 (0.002 to 0.210)
Mozambique	0.226 (0.211 to 0.241)	0.169 (0.143 to 0.196)	0.278 (0.252 to 0.303)	0.108 (0.071 to 0.146)	1.639 (1.337 to 1.941)	0.090 (0.061 to 0.119)	0.168 (0.109 to 0.228)
Namibia	0.120 (0.110 to 0.130)	0.149 (0.123 to 0.175)	0.068 (0.048 to 0.088)	-0.081 (-0.114 to -0.048)	0.458 (0.301 to 0.615)	-0.068 (-0.093 to -0.044)	-0.123 (-0.163 to -0.084)

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Niger	0.166 (0.156 to 0.177)	0.107 (0.091 to 0.123)	0.262 (0.241 to 0.283)	0.155 (0.129 to 0.181)	2.451 (2.041 to 2.861)	0.124 (0.105 to 0.144)	0.545 (0.458 to 0.633)
Nigeria	0.221 (0.210 to 0.232)	0.208 (0.181 to 0.236)	0.199 (0.183 to 0.216)	-0.009 (-0.041 to 0.023)	0.956 (0.807 to 1.104)	-0.017 (-0.041 to 0.007)	-0.045 (-0.098 to 0.009)
Rwanda	0.426 (0.409 to 0.442)	0.307 (0.284 to 0.329)	0.601 (0.571 to 0.630)	0.294 (0.258 to 0.330)	1.959 (1.791 to 2.127)	0.227 (0.201 to 0.254)	0.600 (0.544 to 0.656)
Senegal	0.363 (0.331 to 0.395)	0.338 (0.295 to 0.381)	0.308 (0.234 to 0.382)	-0.030 (-0.116 to 0.056)	0.911 (0.661 to 1.161)	-0.047 (-0.119 to 0.025)	-0.080 (-0.214 to 0.054)
Sierra Leone	0.149 (0.140 to 0.159)	0.155 (0.136 to 0.173)	0.157 (0.136 to 0.179)	0.003 (-0.025 to 0.031)	1.018 (0.833 to 1.202)	0.008 (-0.013 to 0.030)	0.081 (-0.002 to 0.164)
Tanzania	0.388 (0.373 to 0.402)	0.279 (0.247 to 0.311)	0.428 (0.400 to 0.457)	0.149 (0.106 to 0.193)	1.536 (1.329 to 1.743)	0.102 (0.068 to 0.136)	0.219 (0.118 to 0.319)
Togo	0.329 (0.313 to 0.346)	0.272 (0.245 to 0.299)	0.325 (0.293 to 0.358)	0.054 (0.012 to 0.096)	1.197 (1.029 to 1.365)	0.009 (-0.024 to 0.043)	0.016 (-0.085 to 0.117)
Uganda	0.623 (0.600 to 0.645)	0.618 (0.575 to 0.662)	0.622 (0.580 to 0.664)	0.004 (-0.058 to 0.065)	1.006 (0.905 to 1.106)	0.001 (-0.050 to 0.051)	0.018 (-0.103 to 0.138)
Zambia	0.274 (0.262 to 0.285)	0.248 (0.228 to 0.267)	0.329 (0.298 to 0.360)	0.082 (0.045 to 0.118)	1.329 (1.166 to 1.493)	0.061 (0.033 to 0.088)	0.225 (0.132 to 0.317)
Zimbabwe	0.264 (0.244 to 0.284)	0.268 (0.234 to 0.303)	0.204 (0.172 to 0.235)	-0.065 (-0.111 to -0.020)	0.758 (0.610 to 0.906)	-0.068 (-0.104 to -0.032)	-0.176 (-0.250 to -0.103)

For each country population weighted and adjusted for survey design estimate of the statistic characterizing the level and distribution of the respective malaria intervention coverage indictor is reported in each column. 95% confidence intervals are reported in the parentheses below the estimate. Q1 and Q5 denote respectively the lowest and highest asset-wealth quintiles. CIX was implemented with *conindex* command in Stata SE 14. SII was computed on individual data; estimates represent the difference in the predicted probabilities of the respective coverage indicator evaluated at highest and lowest values of the asset-wealth ranking variable (1 and 0) computed as marginal effects following probit estimation. For details of statistics evaluated refer to text and methodological guidance in [29]. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *SII* Slope Index of Inequality

Table D4. Distribution of population that slept under an ITN last night in 2015*

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Angola	0.189 (0.172 to 0.206)	0.100 (0.077 to 0.122)	0.173 (0.153 to 0.194)	0.073 (0.043 to 0.104)	1.737 (1.298 to 2.177)	0.073 (0.045 to 0.102)	0.092 (0.049 to 0.134)
Benin	0.627 (0.616 to 0.638)	0.613 (0.591 to 0.635)	0.655 (0.635 to 0.676)	0.042 (0.012 to 0.072)	1.068 (1.017 to 1.119)	0.021 (-0.002 to 0.044)	0.054 (-0.010 to 0.118)
Burkina Faso	0.670 (0.655 to 0.685)	0.637 (0.606 to 0.668)	0.610 (0.578 to 0.643)	-0.026 (-0.072 to 0.019)	0.958 (0.889 to 1.028)	-0.014 (-0.050 to 0.023)	-0.159 (-0.271 to -0.048)
Burundi	0.486 (0.451 to 0.521)	0.351 (0.306 to 0.395)	0.575 (0.528 to 0.622)	0.224 (0.170 to 0.279)	1.640 (1.426 to 1.854)	0.168 (0.125 to 0.211)	0.596 (0.475 to 0.717)
Cameroon	0.076 (0.071 to 0.082)	0.045 (0.036 to 0.054)	0.099 (0.087 to 0.111)	0.054 (0.038 to 0.069)	2.178 (1.670 to 2.685)	0.040 (0.028 to 0.051)	0.086 (0.056 to 0.117)
Chad	0.217 (0.204 to 0.230)	0.208 (0.184 to 0.233)	0.318 (0.292 to 0.343)	0.110 (0.075 to 0.145)	1.527 (1.311 to 1.743)	0.059 (0.030 to 0.088)	0.381 (0.306 to 0.456)
Comoros	0.384 (0.363 to 0.405)	0.339 (0.302 to 0.377)	0.396 (0.353 to 0.438)	0.056 (0.000 to 0.112)	1.165 (0.989 to 1.341)	0.058 (0.016 to 0.100)	0.145 (0.044 to 0.246)
Congo	0.261 (0.244 to 0.277)	0.370 (0.339 to 0.401)	0.174 (0.146 to 0.203)	-0.196 (-0.237 to -0.154)	0.471 (0.385 to 0.557)	-0.157 (-0.189 to -0.125)	-0.275 (-0.326 to -0.224)
Congo, Democratic Republic	0.502 (0.480 to 0.524)	0.421 (0.384 to 0.458)	0.455 (0.415 to 0.495)	0.034 (-0.021 to 0.088)	1.080 (0.947 to 1.214)	0.035 (-0.010 to 0.080)	-0.038 (-0.132 to 0.056)
Cote d'Ivoire	0.333 (0.313 to 0.352)	0.426 (0.383 to 0.469)	0.218 (0.185 to 0.252)	-0.208 (-0.262 to -0.154)	0.512 (0.418 to 0.606)	-0.169 (-0.214 to -0.124)	-0.375 (-0.448 to -0.303)
Gabon	0.267 (0.250 to 0.284)	0.318 (0.296 to 0.339)	0.116 (0.092 to 0.139)	-0.202 (-0.235 to -0.169)	0.364 (0.284 to 0.444)	-0.167 (-0.198 to -0.136)	-0.324 (-0.384 to -0.265)
Ghana	0.357 (0.339 to 0.374)	0.463 (0.425 to 0.501)	0.181 (0.159 to 0.202)	-0.282 (-0.326 to -0.239)	0.390 (0.334 to 0.447)	-0.267 (-0.303 to -0.231)	-0.703 (-0.777 to -0.629)
Guinea	0.189 (0.176 to 0.202)	0.190 (0.160 to 0.220)	0.141 (0.119 to 0.162)	-0.049 (-0.086 to -0.012)	0.741 (0.579 to 0.904)	-0.030 (-0.058 to -0.002)	-0.094 (-0.158 to -0.031)
Kenya	0.476 (0.442 to 0.510)	0.345 (0.290 to 0.400)	0.539 (0.463 to 0.615)	0.194 (0.099 to 0.288)	1.562 (1.226 to 1.897)	0.140 (0.066 to 0.213)	0.381 (0.209 to 0.553)
Liberia	0.317 (0.295 to 0.340)	0.311 (0.279 to 0.342)	0.217 (0.175 to 0.258)	-0.094 (-0.146 to -0.042)	0.697 (0.546 to 0.848)	-0.094 (-0.141 to -0.046)	-0.232 (-0.330 to -0.134)
Madagascar	0.682 (0.658 to 0.706)	0.791 (0.767 to 0.814)	0.604 (0.553 to 0.655)	-0.187 (-0.244 to -0.129)	0.764 (0.694 to 0.834)	-0.151 (-0.195 to -0.108)	-0.436 (-0.581 to -0.291)
Malawi	0.339 (0.327 to 0.351)	0.249 (0.230 to 0.268)	0.451 (0.428 to 0.475)	0.203 (0.174 to 0.231)	1.815 (1.654 to 1.975)	0.149 (0.128 to 0.170)	0.355 (0.285 to 0.425)
Mali	0.605 (0.591 to 0.620)	0.563 (0.533 to 0.593)	0.590 (0.563 to 0.617)	0.027 (-0.013 to 0.068)	1.049 (0.975 to 1.122)	0.024 (-0.008 to 0.055)	-0.053 (-0.148 to 0.043)
Mozambique	0.295 (0.280 to 0.309)	0.262 (0.230 to 0.294)	0.335 (0.307 to 0.363)	0.073 (0.030 to 0.116)	1.278 (1.087 to 1.469)	0.056 (0.023 to 0.090)	0.112 (0.050 to 0.175)
Namibia	0.039 (0.034 to 0.045)	0.060 (0.043 to 0.076)	0.014 (0.008 to 0.020)	-0.046 (-0.063 to -0.029)	0.232 (0.112 to 0.352)	-0.039 (-0.051 to -0.026)	-0.064 (-0.081 to -0.047)

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Niger	0.138 (0.125 to 0.151)	0.064 (0.052 to 0.077)	0.239 (0.214 to 0.263)	0.174 (0.147 to 0.201)	3.702 (2.908 to4.496)	0.144 (0.123 to 0.164)	0.533 (0.426 to 0.640)
Nigeria	0.129 (0.120 to 0.139)	0.094 (0.076 to 0.113)	0.120 (0.109 to 0.131)	0.025 (0.004 to 0.047)	1.267 (0.995 to 1.539)	0.011 (-0.008 to 0.031)	0.014 (-0.029 to 0.058)
Rwanda	0.614 (0.597 to 0.631)	0.472 (0.445 to 0.500)	0.736 (0.710 to 0.762)	0.263 (0.227 to 0.299)	1.557 (1.456 to 1.658)	0.218 (0.191 to 0.244)	0.457 (0.397 to 0.517)
Senegal	0.404 (0.367 to 0.441)	0.368 (0.304 to 0.432)	0.317 (0.226 to 0.409)	-0.051 (-0.163 to 0.061)	0.862 (0.570 to 1.154)	-0.047 (-0.131 to 0.037)	-0.103 (-0.266 to 0.059)
Sierra Leone	0.418 (0.400 to 0.436)	0.440 (0.412 to 0.469)	0.286 (0.258 to 0.314)	-0.154 (-0.195 to -0.114)	0.649 (0.573 to 0.725)	-0.103 (-0.136 to -0.071)	-0.410 (-0.477 to -0.342)
Tanzania	0.490 (0.475 to 0.506)	0.441 (0.402 to 0.481)	0.528 (0.495 to 0.561)	0.087 (0.034 to 0.139)	1.196 (1.064 to 1.329)	0.069 (0.029 to 0.110)	0.158 (0.046 to 0.269)
Togo	0.336 (0.321 to 0.352)	0.360 (0.330 to 0.389)	0.280 (0.256 to 0.305)	-0.080 (-0.118 to -0.041)	0.778 (0.685 to 0.872)	-0.082 (-0.113 to -0.051)	-0.207 (-0.284 to -0.131)
Uganda	0.686 (0.666 to 0.705)	0.723 (0.688 to 0.759)	0.638 (0.596 to 0.680)	-0.085 (-0.142 to -0.029)	0.882 (0.807 to 0.957)	-0.085 (-0.128 to -0.042)	-0.190 (-0.305 to -0.075)
Zambia	0.349 (0.336 to 0.362)	0.347 (0.325 to 0.369)	0.344 (0.315 to 0.373)	-0.003 (-0.040 to 0.033)	0.990 (0.885 to 1.095)	-0.022 (-0.051 to 0.006)	-0.054 (-0.136 to 0.029)
Zimbabwe	0.085 (0.075 to 0.096)	0.098 (0.078 to 0.117)	0.066 (0.052 to 0.079)	-0.032 (-0.056 to -0.008)	0.672 (0.477 to 0.867)	-0.034 (-0.054 to -0.014)	-0.072 (-0.109 to -0.034)

For each country population weighted and adjusted for survey design estimate of the statistic characterizing the level and distribution of the respective malaria intervention coverage indictor is reported in each column. 95% confidence intervals are reported in the parentheses below the estimate. Q1 and Q5 denote respectively the lowest and highest asset-wealth quintiles. CIX was implemented with *conindex* command in Stata SE 14. SII was computed on individual data; estimates represent the difference in the predicted probabilities of the respective coverage indicator evaluated at highest and lowest values of the asset-wealth ranking variable (1 and 0) computed as marginal effects following probit estimation. For details of statistics evaluated refer to text and methodological guidance in [29]. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *SII* Slope Index of Inequality

Table D5. Distribution of households with IRS in the last 12 months in 2015*

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Angola							
Benin	0.060 (0.052 to 0.069)	0.124 (0.100 to 0.148)	0.030 (0.019 to 0.041)	-0.094 (-0.121 to -0.068)	0.241 (0.142 to 0.340)	-0.074 (-0.094 to -0.053)	-0.186 (-0.253 to -0.118)
Burkina Faso	0.004 (0.002 to 0.006)	0.000 (0.000 to 0.000)	0.009 (0.003 to 0.016)	0.009 (0.003 to 0.016)		0.007 (0.002 to 0.013)	0.042 (-0.009 to 0.093)
Burundi	0.053 (0.025 to 0.081)	0.082 (0.033 to 0.132)	0.016 (0.005 to 0.026)	-0.067 (-0.115 to -0.018)	0.189 (0.035 to 0.343)	-0.052 (-0.090 to -0.014)	-0.286 (-0.558 to -0.014)
Cameroon	0.013 (0.010 to 0.016)	0.002 (0.000 to 0.004)	0.033 (0.025 to 0.042)	0.031 (0.022 to 0.040)	16.464 (1.072 to 31.856)	0.028 (0.022 to 0.035)	0.133 (0.091 to 0.175)
Chad	0.004 (0.003 to 0.006)	0.001 (0.000 to 0.003)	0.010 (0.007 to 0.014)	0.009 (0.005 to 0.013)	7.687 (-0.234 to 15.609)	0.007 (0.004 to 0.010)	0.053 (0.020 to 0.086)
Comoros	0.043 (0.037 to 0.049)	0.094 (0.073 to 0.114)	0.018 (0.010 to 0.026)	-0.075 (-0.099 to -0.051)	0.197 (0.094 to 0.300)	-0.063 (-0.080 to -0.046)	-0.186 (-0.248 to -0.124)
Congo							
Congo, Democratic Republic							
Cote d'Ivoire	0.015 (0.006 to 0.023)	0.009 (-0.005 to 0.023)	0.030 (0.016 to 0.044)	0.021 (0.004 to 0.039)	3.454 (-2.037 to8.946)	0.018 (0.007 to 0.030)	0.081 (0.002 to 0.160)
Gabon	0.042 (0.033 to 0.052)	0.005 (0.002 to 0.007)	0.100 (0.071 to 0.129)	0.095 (0.066 to 0.124)	20.826 (8.650 to 33.002)	0.072 (0.051 to 0.094)	0.191 (0.130 to 0.252)
Ghana	0.097 (0.073 to 0.121)	0.292 (0.216 to 0.369)	0.055 (0.031 to 0.079)	-0.237 (-0.317 to -0.157)	0.188 (0.093 to 0.283)	-0.134 (-0.187 to -0.081)	-0.628 (-0.849 to -0.406)
Guinea	0.017 (0.005 to 0.030)	0.005 (-0.001 to 0.012)	0.036 (0.020 to 0.052)	0.030 (0.013 to 0.048)	6.482 (-1.828 to 14.792)	0.025 (0.012 to 0.037)	0.060 (0.013 to 0.108)
Kenya							
Liberia	0.107 (0.076 to 0.137)	0.169 (0.112 to 0.225)	0.049 (0.029 to 0.069)	-0.120 (-0.180 to -0.060)	0.289 (0.134 to 0.444)	-0.102 (-0.157 to -0.048)	-0.182 (-0.268 to -0.095)
Madagascar	0.087 (0.065 to 0.109)	0.086 (0.052 to 0.121)	0.061 (0.040 to 0.082)	-0.025 (-0.065 to 0.014)	0.704 (0.341 to 1.068)	-0.023 (-0.058 to 0.012)	-0.113 (-0.207 to -0.019)
Malawi	0.049 (0.039 to 0.060)	0.045 (0.033 to 0.057)	0.052 (0.037 to 0.067)	0.007 (-0.010 to 0.025)	1.161 (0.747 to 1.575)	0.002 (-0.012 to 0.015)	0.005 (-0.034 to 0.044)
Mali	0.062 (0.046 to 0.078)	0.058 (0.037 to 0.079)	0.057 (0.042 to 0.071)	-0.002 (-0.027 to 0.024)	0.975 (0.548 to 1.401)	-0.003 (-0.025 to 0.018)	0.041 (-0.058 to 0.139)
Mozambique	0.185 (0.164 to 0.205)	0.143 (0.099 to 0.187)	0.301 (0.276 to 0.326)	0.158 (0.108 to 0.208)	2.105 (1.434 to 2.775)	0.133 (0.092 to 0.174)	0.321 (0.242 to 0.400)
Namibia	0.155 (0.141 to 0.169)	0.313 (0.277 to 0.348)	0.030 (0.021 to 0.038)	-0.283 (-0.320 to -0.246)	0.094 (0.064 to 0.125)	-0.224 (-0.254 to -0.193)	-0.331 (-0.372 to -0.289)
Niger	0.005 (0.003 to 0.006)	0.001 (-0.001 to 0.003)	0.015 (0.010 to 0.021)	0.014 (0.008 to 0.020)	11.421 (-5.643 to 28.484)	0.010 (0.006 to 0.014)	0.233 (0.130 to 0.337)
Nigeria	0.017 (0.011 to 0.023)	0.012 (-0.000 to 0.024)	0.021 (0.014 to 0.028)	0.009 (-0.005 to 0.023)	1.767 (-0.125 to 3.658)	0.010 (-0.001 to 0.022)	0.027 (-0.001 to 0.056)

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Rwanda							
Senegal	0.087 (0.059 to 0.115)	0.150 (0.091 to 0.209)	0.071 (0.042 to 0.100)	-0.079 (-0.143 to -0.014)	0.474 (0.212 to 0.735)	-0.062 (-0.112 to -0.011)	-0.103 (-0.192 to -0.014)
Sierra Leone	0.048 (0.031 to 0.065)	0.035 (0.015 to 0.054)	0.069 (0.050 to 0.088)	0.034 (0.007 to 0.061)	1.996 (0.751 to 3.240)	0.024 (0.001 to 0.047)	0.168 (-0.000 to 0.336)
Tanzania	0.055 (0.046 to 0.064)	0.039 (0.021 to 0.057)	0.061 (0.046 to 0.075)	0.022 (-0.002 to 0.046)	1.563 (0.728 to 2.399)	0.009 (-0.011 to 0.029)	0.025 (-0.031 to 0.081)
Togo							
Uganda	0.049 (0.032 to 0.066)	0.123 (0.073 to 0.173)	0.014 (0.004 to 0.023)	-0.110 (-0.162 to -0.057)	0.109 (0.013 to 0.206)	-0.087 (-0.129 to -0.046)	-0.182 (-0.294 to -0.069)
Zambia	0.284 (0.266 to 0.303)	0.227 (0.195 to 0.259)	0.348 (0.308 to 0.387)	0.120 (0.069 to 0.171)	1.530 (1.252 to 1.808)	0.098 (0.059 to 0.138)	0.285 (0.153 to 0.418)
Zimbabwe	0.213 (0.179 to 0.248)	0.376 (0.315 to 0.437)	0.087 (0.030 to 0.143)	-0.290 (-0.372 to -0.208)	0.230 (0.076 to 0.384)	-0.261 (-0.327 to -0.195)	-0.433 (-0.524 to -0.342)

For each country population weighted and adjusted for survey design estimate of the statistic characterizing the level and distribution of the respective malaria intervention coverage indictor is reported in each column. 95% confidence intervals are reported in the parentheses below the estimate. Q1 and Q5 denote respectively the lowest and highest asset-wealth quintiles. CIX was implemented with *conindex* command in Stata SE 14. SII was computed on individual data; estimates represent the difference in the predicted probabilities of the respective coverage indicator evaluated at highest and lowest values of the asset-wealth ranking variable (1 and 0) computed as marginal effects following probit estimation. For details of statistics evaluated refer to text and methodological guidance in [29]. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *SII* Slope Index of Inequality

Table D6. Distribution of women that received at least 3 doses of SP during an ANC visit during their most recent pregnancy in 2015*

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Angola	0.079 (0.067 to 0.091)	0.017 (0.004 to 0.030)	0.171 (0.126 to 0.215)	0.154 (0.108 to 0.200)	10.126 (2.093 to 18.159)	0.131 (0.104 to 0.158)	0.231 (0.178 to 0.284)
Benin	0.139 (0.126 to 0.152)	0.098 (0.078 to 0.118)	0.207 (0.173 to 0.241)	0.109 (0.069 to 0.149)	2.112 (1.556 to 2.668)	0.083 (0.053 to 0.113)	0.240 (0.149 to 0.331)
Burkina Faso							
Burundi							
Cameroon	0.115 (0.103 to 0.127)	0.065 (0.047 to 0.084)	0.190 (0.156 to 0.224)	0.124 (0.086 to 0.163)	2.895 (1.925 to 3.866)	0.088 (0.062 to 0.114)	0.239 (0.156 to 0.321)
Chad	0.076 (0.065 to 0.086)	0.055 (0.040 to 0.070)	0.151 (0.121 to 0.181)	0.096 (0.062 to 0.129)	2.752 (1.820 to 3.684)	0.055 (0.032 to 0.077)	0.294 (0.186 to 0.403)
Comoros	0.101 (0.080 to 0.123)	0.080 (0.040 to 0.120)	0.114 (0.058 to 0.170)	0.034 (-0.036 to 0.103)	1.423 (0.414 to 2.433)	0.012 (-0.040 to 0.064)	0.041 (-0.090 to 0.172)
Congo	0.105 (0.089 to 0.120)	0.089 (0.073 to 0.105)	0.095 (0.052 to 0.138)	0.006 (-0.040 to 0.051)	1.063 (0.549 to 1.577)	0.006 (-0.023 to 0.035)	0.004 (-0.056 to 0.065)
Congo, Democratic Republic	0.054 (0.043 to 0.064)	0.046 (0.029 to 0.063)	0.059 (0.035 to 0.084)	0.014 (-0.016 to 0.043)	1.294 (0.587 to 2.000)	0.016 (-0.005 to 0.037)	0.028 (-0.037 to 0.093)
Cote d'Ivoire	0.066 (0.054 to 0.079)	0.054 (0.035 to 0.072)	0.100 (0.064 to 0.136)	0.046 (0.006 to 0.086)	1.862 (0.942 to 2.783)	0.032 (0.004 to 0.060)	0.108 (0.003 to 0.213)
Gabon	0.063 (0.045 to 0.081)	0.049 (0.034 to 0.065)	0.066 (0.014 to 0.117)	0.016 (-0.037 to 0.069)	1.327 (0.217 to 2.437)	0.005 (-0.032 to 0.042)	0.012 (-0.067 to 0.091)
Ghana	0.385 (0.352 to 0.418)	0.366 (0.294 to 0.438)	0.507 (0.447 to 0.566)	0.140 (0.047 to 0.234)	1.384 (1.067 to 1.701)	0.080 (0.010 to 0.150)	0.229 (0.045 to 0.413)
Guinea	0.094 (0.080 to 0.109)	0.045 (0.028 to 0.062)	0.150 (0.116 to 0.184)	0.105 (0.067 to 0.142)	3.320 (1.863 to4.777)	0.090 (0.062 to 0.117)	0.208 (0.138 to 0.278)
Kenya	0.240 (0.203 to 0.277)	0.259 (0.190 to 0.327)	0.261 (0.154 to 0.367)	0.002 (-0.123 to 0.128)	1.009 (0.522 to 1.496)	-0.002 (-0.093 to 0.089)	0.032 (-0.204 to 0.267)
Liberia	0.172 (0.149 to 0.195)	0.172 (0.140 to 0.203)	0.127 (0.083 to 0.172)	-0.044 (-0.099 to 0.010)	0.741 (0.450 to 1.033)	-0.039 (-0.085 to 0.006)	-0.111 (-0.211 to -0.012)
Madagascar	0.101 (0.085 to 0.117)	0.087 (0.063 to 0.111)	0.113 (0.073 to 0.153)	0.026 (-0.019 to 0.071)	1.299 (0.740 to 1.858)	0.032 (-0.000 to 0.063)	0.071 (-0.074 to 0.216)
Malawi	0.304 (0.289 to 0.319)	0.306 (0.277 to 0.335)	0.288 (0.247 to 0.330)	-0.018 (-0.069 to 0.033)	0.942 (0.779 to 1.106)	0.008 (-0.028 to 0.045)	-0.003 (-0.100 to 0.094)
Mali	0.108 (0.092 to 0.123)	0.054 (0.034 to 0.074)	0.224 (0.183 to 0.265)	0.170 (0.124 to 0.216)	4.125 (2.440 to5.810)	0.134 (0.101 to 0.167)	0.592 (0.452 to 0.731)
Mozambique	0.094 (0.082 to 0.107)	0.072 (0.049 to 0.095)	0.122 (0.094 to 0.150)	0.049 (0.013 to 0.086)	1.686 (1.007 to 2.365)	0.051 (0.024 to 0.078)	0.101 (0.036 to 0.166)
Namibia	0.033 (0.023 to 0.042)	0.035 (0.016 to 0.054)	0.015 (0.001 to 0.031)	-0.020 (-0.044 to 0.005)	0.442 (-0.052 to 0.936)	-0.001 (-0.020 to 0.017)	-0.010 (-0.045 to 0.024)
Niger	0.086 (0.073 to 0.099)	0.059 (0.040 to 0.078)	0.135 (0.105 to 0.165)	0.076 (0.041 to 0.111)	2.280 (1.401 to 3.160)	0.049 (0.024 to 0.075)	0.239 (0.081 to 0.397)

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Nigeria	0.058 (0.050 to 0.066)	0.025 (0.017 to 0.032)	0.063 (0.049 to 0.076)	0.038 (0.022 to 0.054)	2.546 (1.604 to 3.489)	0.040 (0.027 to 0.053)	0.083 (0.049 to 0.118)
Rwanda							
Senegal	0.034 (0.022 to 0.046)	0.025 (0.013 to 0.037)	0.011 (-0.005 to 0.027)	-0.014 (-0.034 to 0.006)	0.443 (-0.220 to 1.105)	0.004 (-0.015 to 0.023)	0.001 (-0.038 to 0.041)
Sierra Leone	0.201 (0.175 to 0.227)	0.169 (0.138 to 0.201)	0.153 (0.109 to 0.197)	-0.016 (-0.070 to 0.037)	0.903 (0.596 to 1.211)	0.002 (-0.037 to 0.040)	-0.130 (-0.272 to 0.012)
Tanzania	0.078 (0.067 to 0.090)	0.055 (0.037 to 0.074)	0.130 (0.101 to 0.159)	0.074 (0.040 to 0.109)	2.345 (1.394 to 3.296)	0.049 (0.023 to 0.076)	0.191 (0.083 to 0.299)
Togo	0.190 (0.167 to 0.213)	0.103 (0.070 to 0.135)	0.321 (0.264 to 0.377)	0.218 (0.153 to 0.283)	3.118 (1.985 to4.250)	0.183 (0.133 to 0.233)	0.600 (0.449 to 0.750)
Uganda	0.252 (0.223 to 0.281)	0.230 (0.182 to 0.279)	0.268 (0.210 to 0.326)	0.038 (-0.044 to 0.119)	1.164 (0.785 to 1.542)	0.020 (-0.041 to 0.081)	0.031 (-0.141 to 0.204)
Zambia	0.496 (0.476 to 0.516)	0.419 (0.385 to 0.454)	0.643 (0.598 to 0.689)	0.224 (0.167 to 0.281)	1.534 (1.368 to 1.699)	0.166 (0.126 to 0.207)	0.456 (0.374 to 0.539)
Zimbabwe	0.079 (0.067 to 0.091)	0.017 (0.004 to 0.030)	0.171 (0.126 to 0.215)	0.154 (0.108 to 0.200)	10.126 (2.093 to 18.159)	0.131 (0.104 to 0.158)	0.231 (0.178 to 0.284)

For each country population weighted and adjusted for survey design estimate of the statistic characterizing the level and distribution of the respective malaria intervention coverage indictor is reported in each column. 95% confidence intervals are reported in the parentheses below the estimate. Q1 and Q5 denote respectively the lowest and highest asset-wealth quintiles. CIX was implemented with *conindex* command in Stata SE 14. SII was computed on individual data; estimates represent the difference in the predicted probabilities of the respective coverage indicator evaluated at highest and lowest values of the asset-wealth ranking variable (1 and 0) computed as marginal effects following probit estimation. For details of statistics evaluated refer to text and methodological guidance in [29]. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *SII* Slope Index of Inequality

Table D7. Distribution of children under five with fever that sought care at a formal provider in 2015*

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Angola	0.557 (0.522 to 0.593)	0.404 (0.310 to 0.498)	0.767 (0.724 to 0.811)	0.363 (0.260 to 0.467)	1.899 (1.444 to 2.353)	0.292 (0.204 to 0.379)	0.405 (0.307 to 0.504)
Benin	0.386 (0.355 to 0.418)	0.276 (0.207 to 0.346)	0.472 (0.407 to 0.538)	0.196 (0.100 to 0.291)	1.707 (1.217 to 2.197)	0.141 (0.071 to 0.210)	0.329 (0.165 to 0.493)
Burkina Faso	0.586 (0.556 to 0.616)	0.444 (0.384 to 0.504)	0.620 (0.544 to 0.696)	0.176 (0.079 to 0.273)	1.396 (1.142 to 1.651)	0.166 (0.089 to 0.243)	0.255 (-0.034 to 0.544)
Burundi	0.542 (0.512 to 0.573)	0.560 (0.505 to 0.615)	0.564 (0.484 to 0.643)	0.004 (-0.095 to 0.102)	1.006 (0.830 to 1.183)	0.007 (-0.062 to 0.075)	0.086 (-0.118 to 0.290)
Cameroon	0.270 (0.243 to 0.298)	0.115 (0.085 to 0.146)	0.430 (0.373 to 0.487)	0.315 (0.250 to 0.379)	3.724 (2.630 to4.819)	0.261 (0.212 to 0.309)	0.555 (0.453 to 0.656)
Chad	0.231 (0.206 to 0.257)	0.136 (0.098 to 0.173)	0.369 (0.324 to 0.414)	0.233 (0.174 to 0.292)	2.719 (1.888 to 3.551)	0.182 (0.138 to 0.225)	0.571 (0.448 to 0.695)
Comoros	0.447 (0.389 to 0.504)	0.405 (0.293 to 0.516)	0.495 (0.371 to 0.618)	0.090 (-0.070 to 0.250)	1.223 (0.785 to 1.661)	0.117 (-0.001 to 0.234)	0.255 (-0.006 to 0.516)
Congo	0.466 (0.423 to 0.510)	0.403 (0.361 to 0.444)	0.610 (0.516 to 0.703)	0.207 (0.104 to 0.310)	1.515 (1.234 to 1.795)	0.129 (0.056 to 0.201)	0.244 (0.118 to 0.371)
Congo, Democratic Republic	0.398 (0.373 to 0.424)	0.374 (0.331 to 0.417)	0.415 (0.354 to 0.477)	0.041 (-0.034 to 0.116)	1.110 (0.902 to 1.318)	0.019 (-0.033 to 0.071)	0.133 (-0.015 to 0.281)
Cote d'Ivoire	0.338 (0.306 to 0.370)	0.216 (0.145 to 0.287)	0.514 (0.437 to 0.592)	0.298 (0.192 to 0.404)	2.378 (1.513 to 3.242)	0.198 (0.123 to 0.273)	0.489 (0.326 to 0.653)
Gabon	0.502 (0.439 to 0.566)	0.444 (0.378 to 0.511)	0.579 (0.377 to 0.781)	0.134 (-0.074 to 0.343)	1.303 (0.820 to 1.785)	0.068 (-0.067 to 0.202)	0.153 (-0.139 to 0.444)
Ghana	0.559 (0.511 to 0.607)	0.551 (0.474 to 0.628)	0.540 (0.411 to 0.669)	-0.011 (-0.161 to 0.139)	0.980 (0.709 to 1.252)	0.007 (-0.100 to 0.114)	-0.045 (-0.358 to 0.267)
Guinea	0.334 (0.299 to 0.369)	0.206 (0.152 to 0.261)	0.595 (0.504 to 0.687)	0.389 (0.282 to 0.495)	2.882 (1.999 to 3.766)	0.265 (0.198 to 0.332)	0.564 (0.444 to 0.683)
Kenya	0.656 (0.618 to 0.693)	0.582 (0.507 to 0.658)	0.738 (0.660 to 0.817)	0.156 (0.045 to 0.267)	1.268 (1.051 to 1.485)	0.111 (0.032 to 0.190)	0.300 (0.108 to 0.491)
Liberia	0.574 (0.535 to 0.613)	0.506 (0.454 to 0.559)	0.622 (0.490 to 0.754)	0.116 (-0.029 to 0.261)	1.229 (0.932 to 1.526)	0.099 (0.014 to 0.184)	0.241 (0.032 to 0.449)
Madagascar	0.521 (0.476 to 0.567)	0.504 (0.436 to 0.573)	0.562 (0.422 to 0.703)	0.058 (-0.098 to 0.214)	1.115 (0.798 to 1.431)	0.061 (-0.041 to 0.163)	0.197 (-0.176 to 0.570)
Malawi	0.614 (0.593 to 0.634)	0.602 (0.566 to 0.639)	0.607 (0.557 to 0.657)	0.005 (-0.055 to 0.064)	1.008 (0.908 to 1.107)	0.000 (-0.041 to 0.042)	-0.023 (-0.159 to 0.112)
Mali	0.291 (0.247 to 0.335)	0.181 (0.098 to 0.263)	0.548 (0.472 to 0.623)	0.367 (0.255 to 0.479)	3.034 (1.583 to4.485)	0.224 (0.140 to 0.308)	0.773 (0.678 to 0.867)
Mozambique	0.587 (0.549 to 0.626)	0.538 (0.465 to 0.610)	0.687 (0.609 to 0.766)	0.150 (0.043 to 0.257)	1.278 (1.052 to 1.504)	0.178 (0.105 to 0.252)	0.328 (0.200 to 0.456)
Namibia	0.586 (0.546 to 0.627)	0.570 (0.492 to 0.649)	0.568 (0.470 to 0.666)	-0.003 (-0.128 to 0.123)	0.995 (0.775 to 1.215)	-0.002 (-0.092 to 0.088)	-0.021 (-0.184 to 0.142)

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Niger	0.508 (0.470 to 0.546)	0.409 (0.331 to 0.487)	0.616 (0.556 to 0.676)	0.207 (0.109 to 0.305)	1.505 (1.184 to 1.826)	0.135 (0.062 to 0.208)	0.359 (0.184 to 0.533)
Nigeria	0.315 (0.290 to 0.339)	0.252 (0.209 to 0.295)	0.436 (0.374 to 0.499)	0.184 (0.108 to 0.260)	1.729 (1.345 to 2.114)	0.137 (0.084 to 0.190)	0.341 (0.223 to 0.459)
Rwanda	0.492 (0.462 to 0.522)	0.386 (0.331 to 0.440)	0.624 (0.562 to 0.687)	0.239 (0.156 to 0.322)	1.619 (1.337 to 1.900)	0.182 (0.120 to 0.243)	0.465 (0.335 to 0.596)
Senegal	0.458 (0.398 to 0.518)	0.442 (0.357 to 0.528)	0.564 (0.377 to 0.752)	0.122 (-0.084 to 0.328)	1.275 (0.785 to 1.765)	0.072 (-0.086 to 0.229)	0.130 (-0.172 to 0.432)
Sierra Leone	0.656 (0.626 to 0.686)	0.652 (0.600 to 0.704)	0.564 (0.494 to 0.633)	-0.088 (-0.175 to -0.001)	0.865 (0.738 to 0.992)	-0.034 (-0.096 to 0.029)	-0.230 (-0.456 to -0.005)
Tanzania	0.660 (0.628 to 0.691)	0.560 (0.498 to 0.621)	0.795 (0.733 to 0.856)	0.235 (0.147 to 0.323)	1.420 (1.227 to 1.613)	0.199 (0.134 to 0.265)	0.478 (0.359 to 0.597)
Togo	0.389 (0.351 to 0.427)	0.362 (0.300 to 0.425)	0.563 (0.484 to 0.643)	0.201 (0.100 to 0.302)	1.555 (1.208 to 1.901)	0.130 (0.051 to 0.209)	0.554 (0.366 to 0.743)
Uganda	0.762 (0.724 to 0.801)	0.701 (0.642 to 0.759)	0.844 (0.768 to 0.920)	0.143 (0.049 to 0.237)	1.205 (1.059 to 1.350)	0.123 (0.057 to 0.190)	0.276 (0.120 to 0.432)
Zambia	0.719 (0.696 to 0.742)	0.686 (0.641 to 0.730)	0.752 (0.687 to 0.818)	0.066 (-0.013 to 0.145)	1.096 (0.977 to 1.215)	0.050 (-0.001 to 0.101)	0.119 (0.008 to 0.231)
Zimbabwe	0.451 (0.401 to 0.500)	0.419 (0.334 to 0.504)	0.605 (0.514 to 0.695)	0.186 (0.061 to 0.310)	1.443 (1.078 to 1.808)	0.153 (0.055 to 0.252)	0.374 (0.176 to 0.572)

For each country population weighted and adjusted for survey design estimate of the statistic characterizing the level and distribution of the respective malaria intervention coverage indictor is reported in each column. 95% confidence intervals are reported in the parentheses below the estimate. Q1 and Q5 denote respectively the lowest and highest asset-wealth quintiles. CIX was implemented with *conindex* command in Stata SE 14. SII was computed on individual data; estimates represent the difference in the predicted probabilities of the respective coverage indicator evaluated at highest and lowest values of the asset-wealth ranking variable (1 and 0) computed as marginal effects following probit estimation. For details of statistics evaluated refer to text and methodological guidance in [29]. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *SII* Slope Index of Inequality

Table D8. Distribution of children under five with fever that were treated with an antimalarial medication in 2015*

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Angola	0.283 (0.248 to 0.318)	0.181 (0.072 to 0.290)	0.519 (0.465 to 0.573)	0.338 (0.216 to 0.460)	2.865 (1.111 to4.620)	0.268 (0.163 to 0.373)	0.420 (0.295 to 0.544)
Benin	0.384 (0.350 to 0.417)	0.267 (0.198 to 0.337)	0.444 (0.361 to 0.527)	0.176 (0.069 to 0.284)	1.660 (1.132 to 2.188)	0.104 (0.025 to 0.184)	0.236 (0.035 to 0.438)
Burkina Faso	0.492 (0.462 to 0.521)	0.361 (0.313 to 0.409)	0.563 (0.465 to 0.661)	0.202 (0.093 to 0.311)	1.558 (1.217 to 1.899)	0.192 (0.125 to 0.260)	0.422 (0.224 to 0.620)
Burundi	0.255 (0.222 to 0.287)	0.290 (0.243 to 0.338)	0.244 (0.171 to 0.317)	-0.047 (-0.130 to 0.037)	0.840 (0.564 to 1.115)	-0.038 (-0.102 to 0.027)	-0.158 (-0.337 to 0.021)
Cameroon	0.231 (0.207 to 0.256)	0.066 (0.040 to 0.093)	0.317 (0.259 to 0.374)	0.250 (0.187 to 0.314)	4.781 (2.685 to6.878)	0.236 (0.192 to 0.281)	0.481 (0.371 to 0.591)
Chad	0.269 (0.235 to 0.303)	0.226 (0.175 to 0.278)	0.315 (0.266 to 0.365)	0.089 (0.017 to 0.161)	1.394 (1.007 to 1.780)	0.065 (0.013 to 0.118)	0.212 (0.031 to 0.392)
Comoros	0.267 (0.219 to 0.316)	0.164 (0.081 to 0.248)	0.332 (0.192 to 0.471)	0.167 (0.007 to 0.327)	2.016 (0.706 to 3.325)	0.108 (-0.008 to 0.223)	0.264 (0.002 to 0.525)
Congo	0.139 (0.118 to 0.159)	0.122 (0.096 to 0.147)	0.152 (0.085 to 0.219)	0.030 (-0.042 to 0.102)	1.247 (0.637 to 1.857)	0.030 (-0.017 to 0.077)	0.047 (-0.043 to 0.138)
Congo, Democratic Republic	0.292 (0.268 to 0.316)	0.225 (0.179 to 0.270)	0.433 (0.372 to 0.494)	0.208 (0.133 to 0.284)	1.928 (1.455 to 2.401)	0.156 (0.104 to 0.208)	0.448 (0.319 to 0.577)
Cote d'Ivoire	0.175 (0.146 to 0.204)	0.103 (0.062 to 0.145)	0.280 (0.210 to 0.350)	0.177 (0.095 to 0.258)	2.708 (1.432 to 3.985)	0.128 (0.074 to 0.182)	0.330 (0.150 to 0.509)
Gabon	0.259 (0.207 to 0.312)	0.189 (0.149 to 0.230)	0.280 (0.169 to 0.392)	0.091 (-0.025 to 0.207)	1.480 (0.829 to 2.131)	0.104 (0.033 to 0.175)	0.201 (0.049 to 0.354)
Ghana	0.485 (0.439 to 0.532)	0.414 (0.336 to 0.492)	0.529 (0.392 to 0.665)	0.115 (-0.043 to 0.272)	1.277 (0.869 to 1.686)	0.089 (-0.022 to 0.200)	0.223 (-0.089 to 0.536)
Guinea	0.281 (0.250 to 0.312)	0.224 (0.171 to 0.276)	0.328 (0.252 to 0.403)	0.104 (0.012 to 0.196)	1.465 (0.985 to 1.946)	0.108 (0.047 to 0.170)	0.189 (0.057 to 0.320)
Kenya	0.271 (0.228 to 0.314)	0.197 (0.145 to 0.250)	0.196 (0.132 to 0.261)	-0.001 (-0.084 to 0.082)	0.996 (0.575 to 1.416)	0.025 (-0.050 to 0.100)	0.005 (-0.190 to 0.199)
Liberia	0.557 (0.523 to 0.591)	0.518 (0.470 to 0.567)	0.575 (0.435 to 0.715)	0.057 (-0.091 to 0.205)	1.110 (0.820 to 1.399)	0.034 (-0.052 to 0.121)	0.083 (-0.147 to 0.313)
Madagascar	0.101 (0.073 to 0.129)	0.101 (0.048 to 0.155)	0.027 (0.004 to 0.050)	-0.075 (-0.133 to -0.016)	0.264 (-0.004 to 0.532)	-0.039 (-0.090 to 0.011)	-0.185 (-0.321 to -0.049)
Malawi	0.376 (0.354 to 0.398)	0.404 (0.364 to 0.445)	0.251 (0.206 to 0.297)	-0.153 (-0.215 to -0.092)	0.621 (0.492 to 0.751)	-0.093 (-0.138 to -0.048)	-0.316 (-0.416 to -0.216)
Mali	0.226 (0.184 to 0.267)	0.189 (0.109 to 0.268)	0.284 (0.209 to 0.359)	0.095 (-0.014 to 0.205)	1.505 (0.756 to 2.254)	0.070 (-0.005 to 0.145)	0.270 (-0.018 to 0.558)
Mozambique	0.299 (0.264 to 0.334)	0.361 (0.275 to 0.447)	0.171 (0.094 to 0.247)	-0.190 (-0.305 to -0.075)	0.473 (0.233 to 0.713)	-0.100 (-0.179 to -0.021)	-0.246 (-0.363 to -0.128)
Namibia	0.084 (0.059 to 0.110)	0.120 (0.062 to 0.177)	0.044 (0.002 to 0.086)	-0.076 (-0.147 to -0.005)	0.366 (-0.028 to 0.759)	-0.030 (-0.082 to 0.021)	-0.060 (-0.142 to 0.023)

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Niger	0.192 (0.165 to 0.219)	0.105 (0.063 to 0.147)	0.309 (0.240 to 0.377)	0.203 (0.123 to 0.284)	2.934 (1.590 to4.277)	0.143 (0.088 to 0.198)	0.579 (0.355 to 0.804)
Nigeria	0.327 (0.303 to 0.352)	0.221 (0.184 to 0.258)	0.475 (0.406 to 0.544)	0.254 (0.175 to 0.332)	2.145 (1.670 to 2.620)	0.217 (0.167 to 0.267)	0.481 (0.368 to 0.594)
Rwanda	0.112 (0.090 to 0.134)	0.110 (0.076 to 0.144)	0.061 (0.014 to 0.108)	-0.049 (-0.107 to 0.010)	0.558 (0.094 to 1.021)	-0.036 (-0.075 to 0.003)	-0.151 (-0.226 to -0.076)
Senegal	0.067 (0.027 to 0.107)	0.050 (0.022 to 0.078)	0.148 (0.007 to 0.289)	0.098 (-0.047 to 0.242)	2.956 (-0.321 to6.233)	0.080 (-0.022 to 0.181)	0.176 (-0.060 to 0.412)
Sierra Leone	0.483 (0.450 to 0.517)	0.493 (0.429 to 0.556)	0.441 (0.379 to 0.503)	-0.052 (-0.141 to 0.037)	0.895 (0.724 to 1.066)	-0.006 (-0.074 to 0.062)	-0.088 (-0.316 to 0.141)
Tanzania	0.511 (0.480 to 0.542)	0.555 (0.487 to 0.623)	0.432 (0.367 to 0.497)	-0.123 (-0.216 to -0.030)	0.779 (0.629 to 0.928)	-0.121 (-0.186 to -0.055)	-0.329 (-0.497 to -0.161)
Togo	0.183 (0.153 to 0.213)	0.219 (0.155 to 0.283)	0.210 (0.138 to 0.282)	-0.009 (-0.105 to 0.088)	0.960 (0.526 to 1.394)	-0.016 (-0.087 to 0.054)	0.030 (-0.200 to 0.260)
Uganda	0.770 (0.739 to 0.800)	0.754 (0.711 to 0.797)	0.789 (0.711 to 0.868)	0.035 (-0.057 to 0.126)	1.046 (0.923 to 1.169)	0.008 (-0.055 to 0.072)	-0.022 (-0.216 to 0.172)
Zambia	0.398 (0.371 to 0.426)	0.456 (0.408 to 0.504)	0.234 (0.171 to 0.297)	-0.222 (-0.301 to -0.144)	0.513 (0.366 to 0.660)	-0.184 (-0.237 to -0.132)	-0.408 (-0.493 to -0.324)
Zimbabwe	0.010 (0.002 to 0.017)	0.003 (-0.003 to 0.009)	0.028 (-0.000 to 0.055)	0.025 (-0.004 to 0.053)	9.176 (-11.110 to 29.462)	0.017 (-0.000 to 0.034)	0.079 (-0.049 to 0.207)

For each country population weighted and adjusted for survey design estimate of the statistic characterizing the level and distribution of the respective malaria intervention coverage indictor is reported in each column. 95% confidence intervals are reported in the parentheses below the estimate. Q1 and Q5 denote respectively the lowest and highest asset-wealth quintiles. CIX was implemented with *conindex* command in Stata SE 14. SII was computed on individual data; estimates represent the difference in the predicted probabilities of the respective coverage indicator evaluated at highest and lowest values of the asset-wealth ranking variable (1 and 0) computed as marginal effects following probit estimation. For details of statistics evaluated refer to text and methodological guidance in [29]. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *SII* Slope Index of Inequality

Table D9. Distribution of children under five with fever that were treated with first-line antimalarial medication in 2015*

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Angola	0.217 (0.188 to 0.245)	0.082 (0.051 to 0.114)	0.442 (0.385 to 0.500)	0.360 (0.294 to 0.426)	5.371 (3.202 to7.539)	0.275 (0.232 to 0.318)	0.419 (0.346 to 0.492)
Benin	0.123 (0.100 to 0.146)	0.055 (0.023 to 0.087)	0.143 (0.083 to 0.203)	0.088 (0.020 to 0.156)	2.598 (0.739 to4.456)	0.059 (0.005 to 0.113)	0.130 (-0.028 to 0.287)
Burkina Faso	0.137 (0.118 to 0.157)	0.077 (0.056 to 0.099)	0.173 (0.118 to 0.228)	0.095 (0.036 to 0.155)	2.231 (1.290 to 3.173)	0.097 (0.055 to 0.139)	0.260 (0.048 to 0.471)
Burundi	0.180 (0.153 to 0.206)	0.200 (0.157 to 0.243)	0.159 (0.093 to 0.225)	-0.041 (-0.118 to 0.036)	0.795 (0.431 to 1.159)	-0.026 (-0.076 to 0.024)	-0.181 (-0.312 to -0.051)
Cameroon	0.061 (0.048 to 0.073)	0.010 (0.002 to 0.019)	0.111 (0.067 to 0.155)	0.101 (0.056 to 0.146)	10.762 (0.914 to 20.610)	0.091 (0.065 to 0.118)	0.272 (0.168 to 0.377)
Chad	0.027 (0.019 to 0.035)	0.017 (0.002 to 0.031)	0.067 (0.041 to 0.093)	0.050 (0.020 to 0.080)	4.016 (0.205 to7.827)	0.041 (0.021 to 0.062)	0.259 (0.117 to 0.400)
Comoros	0.043 (0.010 to 0.076)	0.003 (-0.003 to 0.009)	0.095 (-0.032 to 0.222)	0.092 (-0.035 to 0.219)	31.843 (-44.24 to 107.929)	0.066 (-0.018 to 0.151)	0.175 (-0.074 to 0.423)
Congo	0.051 (0.036 to 0.066)	0.014 (0.006 to 0.022)	0.094 (0.044 to 0.145)	0.080 (0.029 to 0.131)	6.656 (1.500 to 11.811)	0.064 (0.030 to 0.098)	0.144 (0.057 to 0.231)
Congo, Democratic Republic	0.056 (0.042 to 0.069)	0.059 (0.030 to 0.088)	0.069 (0.042 to 0.097)	0.010 (-0.030 to 0.050)	1.172 (0.427 to 1.917)	-0.004 (-0.030 to 0.023)	0.023 (-0.051 to 0.096)
Cote d'Ivoire	0.031 (0.017 to 0.044)	0.018 (-0.004 to 0.041)	0.052 (0.014 to 0.091)	0.034 (-0.011 to 0.078)	2.857 (-1.213 to 6.926)	0.021 (-0.005 to 0.047)	0.046 (-0.050 to 0.141)
Gabon	0.088 (0.061 to 0.114)	0.033 (0.016 to 0.051)	0.148 (0.065 to 0.232)	0.115 (0.030 to 0.200)	4.456 (1.052 to7.860)	0.083 (0.026 to 0.139)	0.194 (0.064 to 0.325)
Ghana	0.379 (0.334 to 0.425)	0.309 (0.236 to 0.383)	0.419 (0.282 to 0.557)	0.110 (-0.047 to 0.267)	1.355 (0.803 to 1.908)	0.076 (-0.035 to 0.188)	0.212 (-0.101 to 0.526)
Guinea	0.014 (0.007 to 0.020)	0.019 (0.003 to 0.035)	0.020 (0.001 to 0.038)	0.001 (-0.024 to 0.025)	1.030 (-0.279 to 2.339)	0.010 (-0.008 to 0.028)	0.033 (-0.017 to 0.083)
Kenya	0.248 (0.207 to 0.290)	0.165 (0.115 to 0.216)	0.173 (0.110 to 0.236)	0.008 (-0.074 to 0.089)	1.046 (0.545 to 1.547)	0.040 (-0.033 to 0.112)	0.047 (-0.146 to 0.241)
Liberia	0.239 (0.202 to 0.276)	0.257 (0.210 to 0.305)	0.204 (0.111 to 0.297)	-0.053 (-0.157 to 0.051)	0.794 (0.406 to 1.182)	-0.059 (-0.134 to 0.017)	-0.143 (-0.311 to 0.026)
Madagascar	0.017 (0.007 to 0.028)	0.003 (-0.003 to 0.009)	0.011 (-0.008 to 0.030)	0.008 (-0.012 to 0.027)	3.505 (-5.453 to 12.462)	0.001 (-0.016 to 0.018)	-0.001 (-0.085 to 0.083)
Malawi	0.345 (0.323 to 0.367)	0.383 (0.343 to 0.424)	0.217 (0.175 to 0.259)	-0.167 (-0.226 to -0.108)	0.566 (0.440 to 0.692)	-0.105 (-0.148 to -0.061)	-0.345 (-0.420 to -0.270)
Mali	0.043 (0.027 to 0.059)	0.051 (0.009 to 0.093)	0.054 (0.009 to 0.100)	0.004 (-0.059 to 0.066)	1.072 (-0.199 to 2.343)	-0.001 (-0.042 to 0.040)	0.065 (-0.171 to 0.302)
Mozambique	0.179 (0.147 to 0.211)	0.220 (0.141 to 0.299)	0.082 (0.040 to 0.124)	-0.138 (-0.227 to -0.049)	0.373 (0.141 to 0.604)	-0.083 (-0.146 to -0.019)	-0.181 (-0.265 to -0.096)

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Namibia	0.038 (0.019 to 0.057)	0.083 (0.034 to 0.132)	0.000 (0.000 to 0.000)	-0.083 (-0.132 to -0.034)	0.000 (0.000 to 0.000)	-0.047 (-0.081 to -0.013)	-0.073 (-0.119 to -0.026)
Niger	0.153 (0.129 to 0.176)	0.074 (0.041 to 0.107)	0.250 (0.187 to 0.313)	0.176 (0.105 to 0.248)	3.379 (1.642 to 5.116)	0.133 (0.083 to 0.182)	0.546 (0.300 to 0.792)
Nigeria	0.060 (0.049 to 0.070)	0.036 (0.023 to 0.049)	0.104 (0.074 to 0.134)	0.068 (0.035 to 0.101)	2.857 (1.546 to 4.168)	0.058 (0.036 to 0.081)	0.156 (0.094 to 0.217)
Rwanda	0.112 (0.090 to 0.134)	0.110 (0.076 to 0.144)	0.061 (0.014 to 0.108)	-0.049 (-0.107 to 0.010)	0.558 (0.094 to 1.021)	-0.036 (-0.075 to 0.003)	-0.151 (-0.226 to -0.076)
Senegal	0.007 (0.002 to 0.012)	0.022 (0.004 to 0.040)	0.001 (-0.001 to 0.003)	-0.021 (-0.039 to -0.003)	0.043 (-0.051 to 0.137)	-0.019 (-0.034 to -0.003)	-0.037 (-0.083 to 0.008)
Sierra Leone	0.372 (0.335 to 0.409)	0.412 (0.345 to 0.480)	0.306 (0.256 to 0.357)	-0.106 (-0.191 to -0.021)	0.743 (0.569 to 0.916)	-0.040 (-0.108 to 0.028)	-0.162 (-0.348 to 0.024)
Tanzania	0.434 (0.402 to 0.466)	0.507 (0.440 to 0.574)	0.320 (0.256 to 0.385)	-0.187 (-0.280 to -0.094)	0.631 (0.480 to 0.783)	-0.180 (-0.248 to -0.113)	-0.455 (-0.603 to -0.307)
Togo	0.090 (0.072 to 0.109)	0.073 (0.040 to 0.107)	0.108 (0.058 to 0.157)	0.034 (-0.026 to 0.094)	1.462 (0.512 to 2.413)	0.022 (-0.020 to 0.064)	0.051 (-0.108 to 0.209)
Uganda	0.667 (0.630 to 0.703)	0.684 (0.633 to 0.736)	0.574 (0.445 to 0.702)	-0.110 (-0.251 to 0.030)	0.839 (0.638 to 1.039)	-0.064 (-0.149 to 0.022)	-0.294 (-0.568 to -0.021)
Zambia	0.360 (0.333 to 0.387)	0.428 (0.381 to 0.476)	0.172 (0.113 to 0.231)	-0.257 (-0.332 to -0.181)	0.401 (0.257 to 0.546)	-0.209 (-0.260 to -0.158)	-0.428 (-0.495 to -0.361)
Zimbabwe	0.004 (-0.001 to 0.009)	0.003 (-0.003 to 0.009)	0.002 (-0.002 to 0.007)	-0.001 (-0.008 to 0.007)	0.733 (-1.308 to 2.774)	-0.000 (-0.005 to 0.005)	-0.003 (-0.013 to 0.007)

For each country population weighted and adjusted for survey design estimate of the statistic characterizing the level and distribution of the respective malaria intervention coverage indictor is reported in each column. 95% confidence intervals are reported in the parentheses below the estimate. Q1 and Q5 denote respectively the lowest and highest asset-wealth quintiles. CIX was implemented with *conindex* command in Stata SE 14. SII was computed on individual data; estimates represent the difference in the predicted probabilities of the respective coverage indicator evaluated at highest and lowest values of the asset-wealth ranking variable (1 and 0) computed as marginal effects following probit estimation. For details of statistics evaluated refer to text and methodological guidance in [29]. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Appendix D, Tables D1-D2). *CIX* Concentration Index, *SII* Slope Index of Inequality Index.

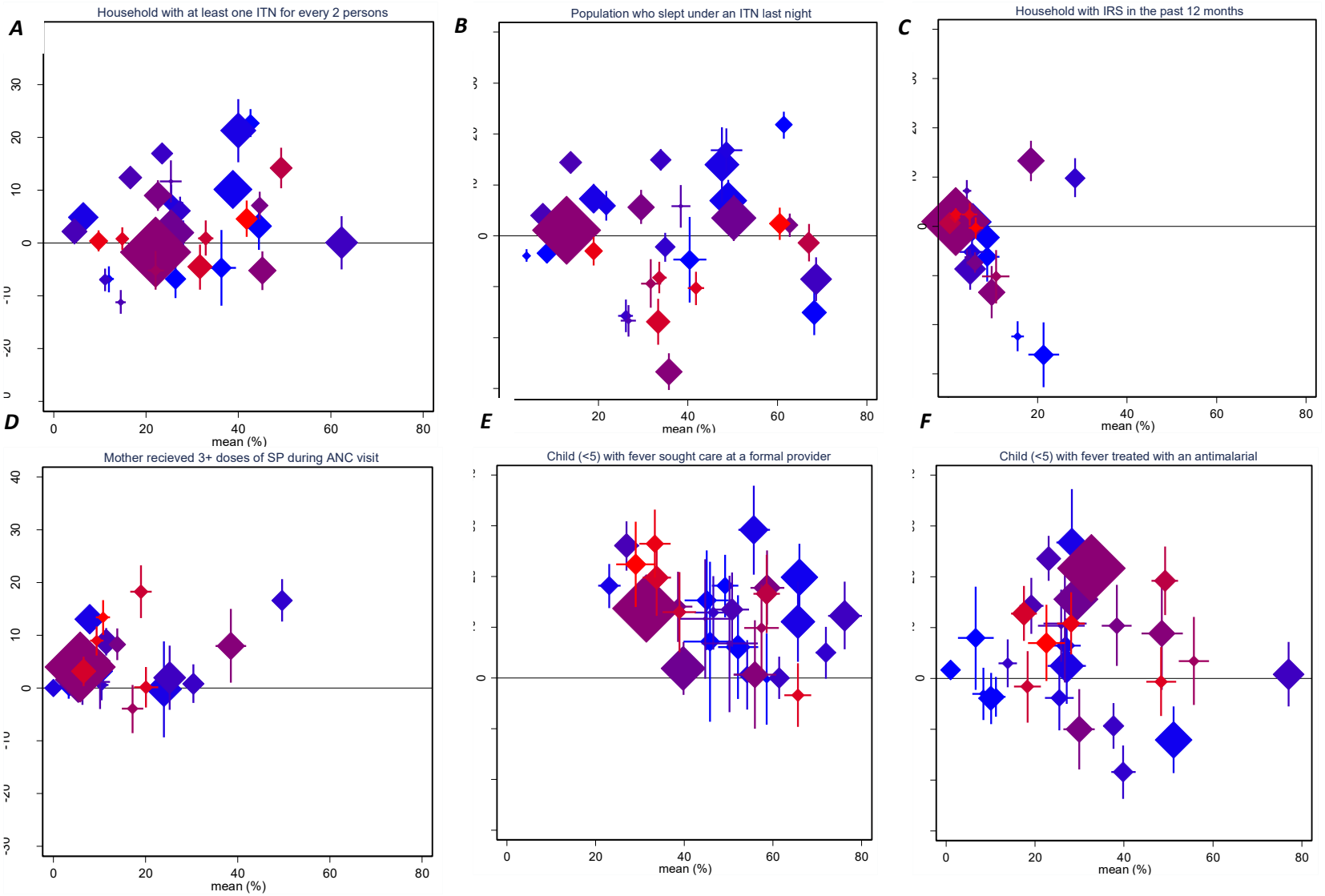

Figure D1. Level and degree of asset-wealth inequality in distribution of malaria intervention coverage indicators in Sub-Saharan African countries in 2015*

For each country concentration index (CIX) of the indicator is plotted against population mean; whiskers denote the 95% confidence interval of the estimate. Country marker size is weighted with population size. Marker color code changing from bright blue to bright red refers to country mean malaria prevalence based on 2015 MAP estimates (corresponding values are given in appendix table S2). *A* illustrates CIX and country mean for proportion of households with at least one ITN for every two person in the house. *B* illustrates CIX and country mean for proportion of population that slept under an ITN the night prior to the survey. *C* illustrates CIX and country mean for proportion of households residing in dwellings that have been sprayed within the last 12 months. *D* illustrates CIX and country mean and CIX for proportion of women that received at least 3 doses of SP at an ANC visit during their most recent pregnancy. *E* illustrates CIX and country mean for proportion of children under the age of five with fever sought care at a formal provider. *F* illustrates CIX and country mean for proportion of children under the age of five with fever that were treated with an antimalarial medication. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Additional file D1). *CIX* Concentration Index, *MAP* Malaria Atlas Project, *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey.

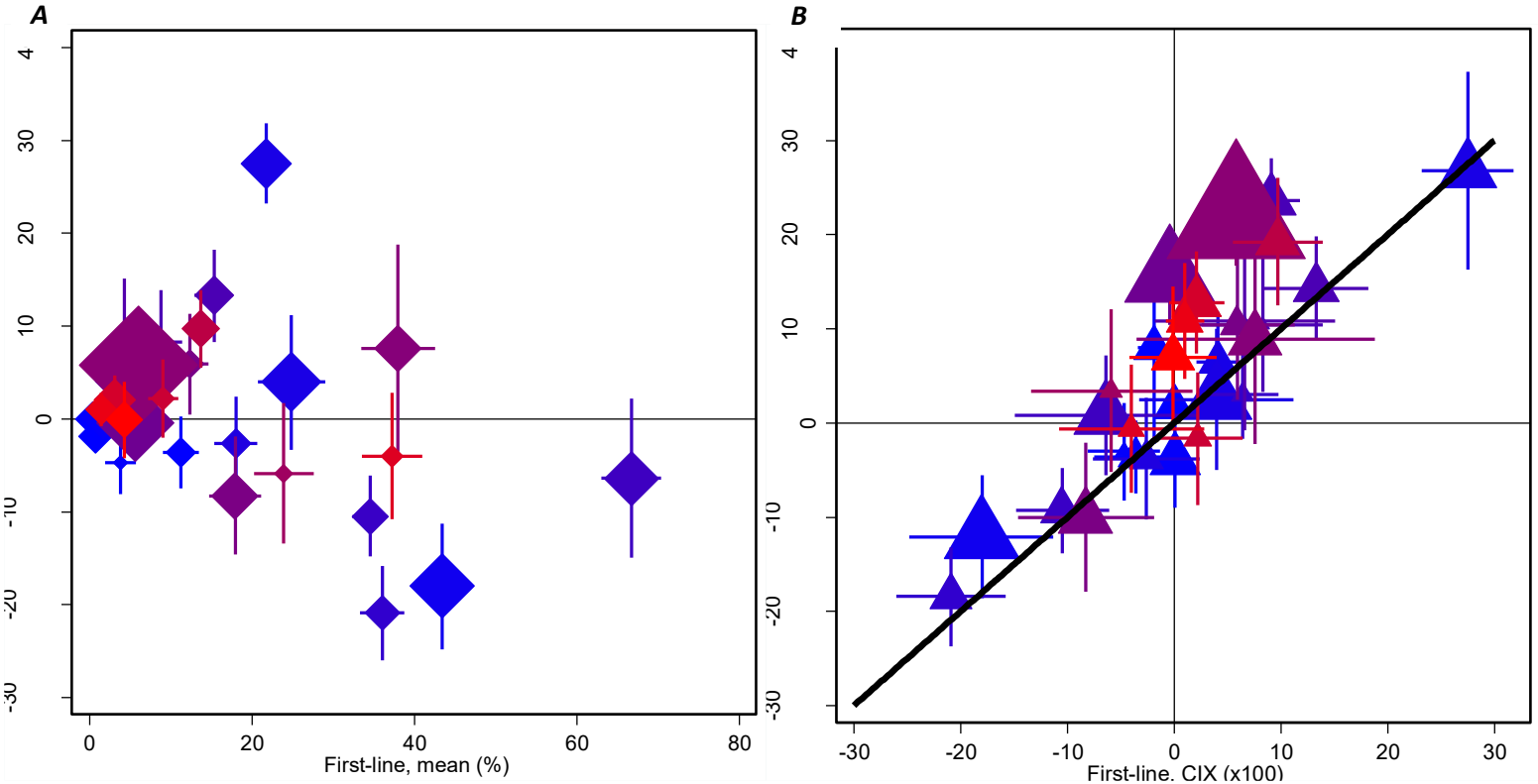

Figure D2. Distribution of first-line antimalarial medication across asset-wealth index among children under five with fever in Sub-Saharan African countries in 2015*

A country concentration index (CIX) for receipt of first-line antimalarial medication for fever among children under the age of five is plotted against population mean. *B* country CIX for antimalarial treatment is plotted against CIX for receipt of country first-line antimalarial medication for children under the age of five with fever. Whiskers denote the 95% confidence interval of the estimate. Country marker size is weighted with population size. Marker color code changing from bright blue to bright red refers to country mean malaria prevalence based on 2015 MAP estimates (corresponding values are given in Additional file 1). *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (country list and year of data collection are detailed in Additional file D1). *CIX* Concentration Index, *MAP* Malaria Atlas Project, *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey.

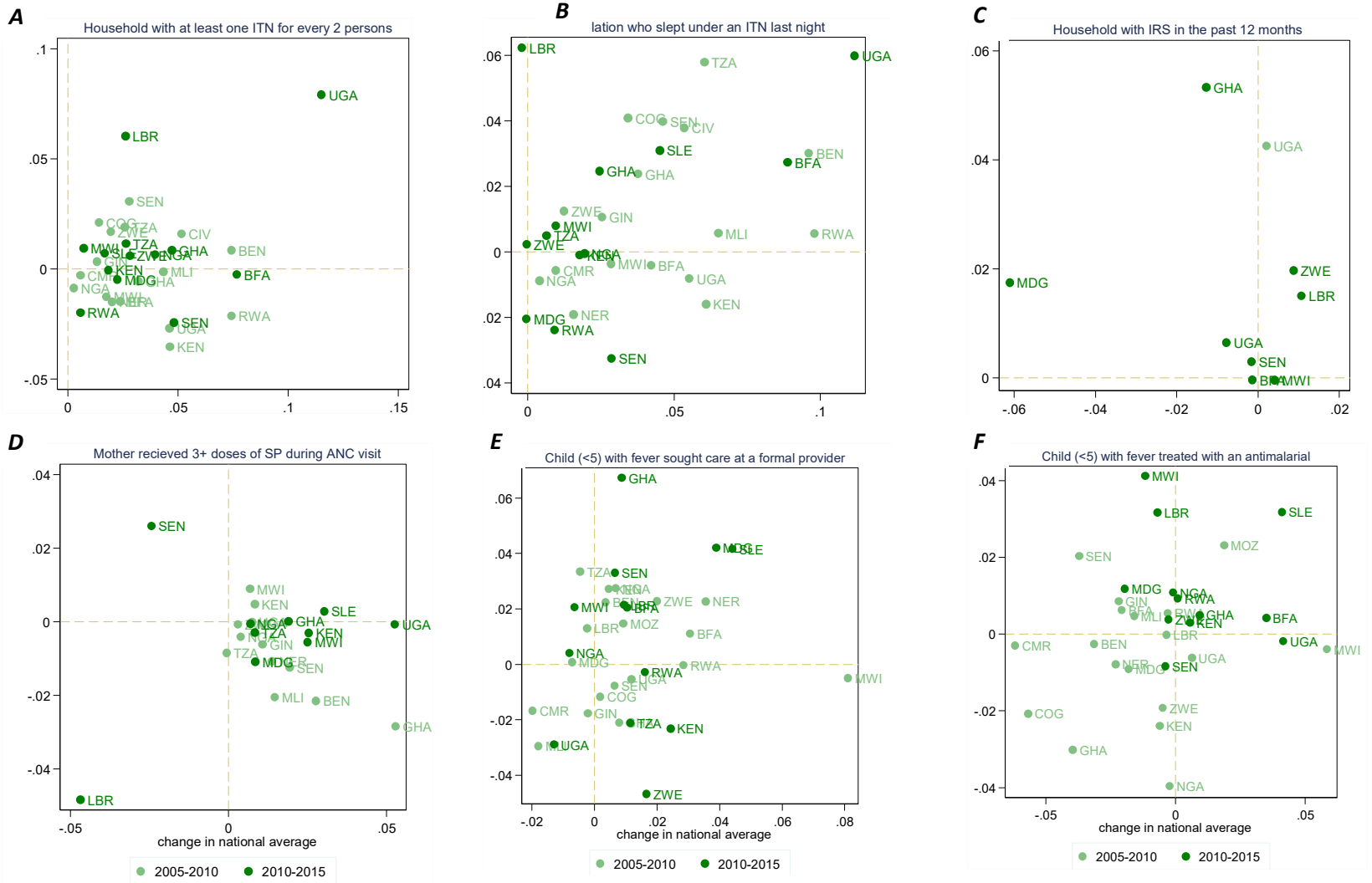

Figure D3. Changes in distribution of malaria intervention coverage indicators by asset-wealth in Sub-Saharan African countries from 2005 to 2015*

A illustrates for each country the difference in average annual change in the proportion of households with at least one ITN for every two person (defacto) in the house in the lowest asset-wealth quintile and that of the highest (annual absolute excess change) against average annual change in the population (percentage points). B illustrates for each

country the difference in average annual change in the proportion of population that slept under an ITN the night prior to the survey in the lowest asset-wealth quintile and that of the highest (annual absolute excess change) against average annual change in the population (percentage points). C illustrates for each country the difference in average annual change in the proportion of households in dwelling that have been sprayed within the last 12 months in the lowest asset-wealth quintile and that of the highest (annual absolute excess change) against average annual change in the population (percentage points). D illustrates for each country the difference in average annual change in the proportion of women that received at least 3 doses of SP at an ANC visit during their most recent pregnancy in the lowest asset-wealth quintile and that of the highest (annual absolute excess change) against average annual change in the population (percentage points). E illustrates for each country the difference in average annual change in the proportion of children under the age of five with fever sought care at a formal provider (2 weeks recall) in the lowest asset-wealth quintile and that of the highest (annual absolute excess change) against average annual change in the population (percentage points). F illustrates for each country the difference in average annual change in the proportion of children under the age of five with fever that were treated with an antimalarial medication in the lowest asset-wealth quintile and that of the highest (annual absolute excess change) against average annual change in the population (percentage points). *Data drawn from a subset of countries with repeated DHS/MIS conducted between 2005 and 2015 (country list, ISO3 code, and years of data collection detailed in Additional file D1). DHS Demographic and Health Surveys, MIS Malaria Indicator Survey.

Table D10. Distribution of malaria prevalence across asset-wealth quintiles in Sub-Saharan African countries in 2015*

Country	Total	Q1	Q5	Difference Q5-Q1	Ratio Q5:Q1	CIX	SII
Benin	0.135 (0.097 to 0.173)	0.213 (0.140 to 0.285)	0.015 (0.000 to 0.029)	-0.198 (-0.272 to -0.124)	0.069 (-0.002 to 0.140)	-0.192 (-0.254 to -0.130)	-0.271 (-0.346 to -0.197)
Burkina Faso	0.248 (0.229 to 0.267)	0.389 (0.344 to 0.433)	0.049 (0.030 to 0.068)	-0.340 (-0.388 to -0.292)	0.126 (0.075 to 0.177)	-0.273 (-0.311 to -0.234)	-0.719 (-0.784 to -0.654)
Burundi	0.614 (0.590 to 0.638)	0.666 (0.629 to 0.703)	0.261 (0.197 to 0.325)	-0.404 (-0.477 to -0.331)	0.393 (0.295 to 0.491)	-0.267 (-0.316 to -0.218)	-0.833 (-0.880 to -0.786)
Congo, Democratic Republic	0.128 (0.101 to 0.155)	0.197 (0.146 to 0.248)	0.048 (0.026 to 0.071)	-0.149 (-0.201 to -0.096)	0.245 (0.123 to 0.367)	-0.109 (-0.147 to -0.071)	-0.590 (-0.783 to -0.396)
Cote d'Ivoire	0.308 (0.278 to 0.338)	0.333 (0.292 to 0.375)	0.146 (0.111 to 0.182)	-0.187 (-0.242 to -0.132)	0.438 (0.319 to 0.558)	-0.118 (-0.169 to -0.067)	-0.360 (-0.431 to -0.290)
Ghana	0.415 (0.384 to 0.446)	0.573 (0.521 to 0.625)	0.122 (0.086 to 0.158)	-0.451 (-0.514 to -0.389)	0.213 (0.148 to 0.278)	-0.372 (-0.430 to -0.315)	-0.677 (-0.730 to -0.624)
Guinea	0.364 (0.331 to 0.396)	0.600 (0.533 to 0.668)	0.060 (0.020 to 0.100)	-0.540 (-0.619 to -0.462)	0.100 (0.032 to 0.168)	-0.490 (-0.550 to -0.431)	-0.976 (-0.998 to -0.954)
Kenya	0.469 (0.433 to 0.505)	0.653 (0.601 to 0.704)	0.061 (0.024 to 0.097)	-0.592 (-0.655 to -0.528)	0.093 (0.037 to 0.150)	-0.415 (-0.469 to -0.360)	-0.889 (-0.942 to -0.837)
Madagascar	0.091 (0.070 to 0.111)	0.096 (0.060 to 0.132)	0.019 (-0.004 to 0.042)	-0.077 (-0.120 to -0.034)	0.197 (-0.056 to 0.449)	-0.070 (-0.107 to -0.032)	-0.172 (-0.270 to -0.075)
Mali	0.051 (0.032 to 0.070)	0.109 (0.069 to 0.150)	0.001 (-0.000 to 0.002)	-0.108 (-0.149 to -0.068)	0.009 (-0.002 to 0.021)	-0.088 (-0.120 to -0.056)	-0.483 (-0.657 to -0.309)
Mozambique	0.472 (0.443 to 0.502)	0.640 (0.597 to 0.683)	0.103 (0.075 to 0.130)	-0.538 (-0.590 to -0.485)	0.160 (0.116 to 0.205)	-0.413 (-0.461 to -0.366)	-0.688 (-0.722 to -0.655)
Rwanda	0.383 (0.352 to 0.414)	0.550 (0.495 to 0.606)	0.056 (0.035 to 0.078)	-0.494 (-0.552 to -0.436)	0.102 (0.063 to 0.142)	-0.384 (-0.435 to -0.333)	-0.601 (-0.646 to -0.557)
Senegal	0.078 (0.065 to 0.092)	0.127 (0.100 to 0.154)	0.013 (0.001 to 0.025)	-0.113 (-0.142 to -0.084)	0.106 (0.010 to 0.202)	-0.094 (-0.119 to -0.068)	-0.242 (-0.316 to -0.168)
Tanzania	0.011 (0.005 to 0.017)	0.031 (0.013 to 0.049)	0.000 (-0.000 to 0.001)	-0.031 (-0.049 to -0.013)	0.005 (-0.005 to 0.015)	-0.027 (-0.042 to -0.013)	-0.076 (-0.126 to -0.026)
Togo	0.145 (0.125 to 0.164)	0.226 (0.186 to 0.266)	0.010 (0.003 to 0.018)	-0.216 (-0.256 to -0.175)	0.046 (0.013 to 0.078)	-0.189 (-0.224 to -0.153)	-0.543 (-0.629 to -0.457)
Uganda	0.380 (0.348 to 0.412)	0.515 (0.458 to 0.573)	0.095 (0.062 to 0.127)	-0.420 (-0.487 to -0.354)	0.184 (0.118 to 0.250)	-0.380 (-0.435 to -0.326)	-0.770 (-0.829 to -0.711)

RDT confirmed malaria prevalence in children aged 6 to 59 months assessed in a representative sub-sample of the DHS/MIS surveyed population. 95% confidence intervals are reported in the parentheses below the estimate. Q1 and Q5 denote respectively the lowest and highest asset-wealth quintiles. CIX was implemented with conindex command in Stata SE 14. SII was computed on individual data; estimates represent the difference in the predicted probabilities of the respective coverage indicator evaluated at highest and lowest values of the asset-wealth ranking variable (1 and 0) computed as marginal effects following probit estimation. For details of statistics evaluated refer to text and methodological guidance in [29]. *Data drawn from a subset of countries with DHS/MIS conducted after 2010 (year of data collection detailed in Additional file D1). *RDT* Rapid Diagnostic Test, *CIX* Concentration Index, *SII* Slope Index of Inequality, *DHS* Demographic and Health Survey, *MIS* Malaria Indicator Survey.