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Cost-Effectiveness of Indoor Residual Spraying for Malaria Prevention in a Region with High Insecticide-Treated Bed Net Coverage

By

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By

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2013

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Abstract

Cost-Effectiveness of Indoor Residual Spraying for Malaria Prevention
in a Region with High Insecticide-Treated Bed Net Coverage
By Rachel Stelmach

The Tanzania National Malaria Control Program (NMCP) has reduced the burden of malaria in mainland Tanzania, but resource constraints threaten its capacity to maintain and expand its achievements. This thesis presents a decision-tree cost-effectiveness analysis of an indoor residual spraying (IRS) program combined with an insecticide-treated bed net (ITN) distribution program, compared to ITN distribution alone. The primary outcome of interest is the expected economic cost to society per case of malaria averted in children in mainland Tanzania under the age of 5. IRS data are drawn from campaigns in northwest Tanzania between 2008 and 2012; all other data are drawn from published literature. Through one-way sensitivity analyses, probabilistic sensitivity analysis, and scenario analyses, the effects of variations in insecticide resistance, the malaria parasitemia prevalence rate, and IRS tactics are also examined. In the base case, the combination of ITN distribution and IRS is expected to be more expensive and more effective than the ITN-only intervention (incremental cost per case averted (ICER): $152.36). Important drivers of variability in cost per case averted are the number of IRS rounds required, insecticide costs for IRS, the ITN usage rate, the prevalence of parasitemia, and the probability that an infected child develops symptoms. Compared to blanket spraying, targeted spraying is expected to lead to a higher number of malaria cases per person targeted (between 0.211 and 0.256 versus between 0.050 and 0.076), but the cost per case averted is expected to be lower (ICER: $41.70). In a scenario of increasing pyrethroid resistance, the expected cost per case averted is expected to be higher than in the base case (ICER: $192.12). The NMCP should pursue blanket IRS spraying only in the northern and southern regions, which have the highest prevalence of malaria. If the cost per case averted of blanket spraying exceeds the NMCP's willingness to pay, targeted spraying provides a valid alternative, but it will probably lead to a higher incidence of malaria. A malaria program that employs multiple methods of prevention and control will improve the cost-effectiveness of all its interventions.

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Chapter 1: Introduction

1.1 Introduction and Rationale

Malaria, an infectious disease transmitted primarily by mosquito bites, causes disability and death in 97 countries throughout the world. The World Health Organization (WHO) estimates that in 2012 approximately 207 million people suffered a case of malaria, of which 627,000 died. Of these deaths, approximately 90% occurred in sub-Saharan Africa (WHO Global Malaria Programme [GMP], 2013). Beyond the direct effects of malaria morbidity and mortality, malaria creates many indirect consequences, including a reduction of the labor force due to illnesses of workers and their families, an increase of negative birth outcomes, and a hindrance of education due to school absenteeism and to cognitive impairment due to severe anemia (Chima, Goodman, & Mills, 2003). If these indirect costs affect much of the population, malaria can hamper the economic growth of entire nations.

Tanzania has suffered under a massive burden of malaria: in 2000, 24% of deaths of Tanzanian children under the age of five were directly attributable to malaria (Roll Back Malaria Partnership [RBM], 2012). Since then, however, international and domestic interest in malaria prevention and control has increased. Between 2003 and 2010, the malaria prevention and control program in mainland Tanzania received about $450 million in external funding (RBM, 2012). This money supports multiple anti-malaria efforts: the promotion of effective case management, the provision of prophylactic treatment for pregnant women (IPTp), the indoor residual spraying (IRS) of insecticides to kill mosquitoes, and the distribution of insecticide-treated bed nets (ITNs) to stop mosquitoes from biting sleeping people (Tanzania Malaria Impact Evaluation Research Group, 2012).

These programs have brought about a significant decline in the prevalence of malaria infections among all age groups. Since their inception, under-five child mortality has declined by 45%, from 148 deaths per 1000 live births in 1999 to 81 per 1000 live births in 2010, and the prevalence of severe childhood anemia has declined by 50%, from 11% in 2004-2005 to 5.5% in 2010 (RBM, 2012). The Tanzania National Malaria Control Program (NMCP) and its partners have made great progress in reducing the burden of malaria and its effects since the late 1990s, but since they have not yet interrupted malaria transmission throughout Tanzania, the malaria programs must continue to receive support. Without constant vigilance, their gains could erode or even reverse.

1.2 Problem statement

The current global interest in malaria does not represent the world's first large-scale attempt to combat the disease, and prior programs offer important lessons for those hoping for a sustainable reduction in the malaria burden. In the 1940s and 1950s, the discovery of the usefulness of dichlorodiphenyltrichloroethane (DDT) as a residual insecticide—that is, as a chemical that lingers on a surface for an extended period of time while retaining its insecticidal properties—prompted a global plan to eradicate malaria. Guided by WHO and other international organizations, countries spent vast amounts of resources trying to stop malaria within their borders. In some countries, these efforts succeeded; in others, after years of hard work, the control programs fell into disorder, and malaria returned to previous levels of transmission (Mabaso, Sharp, & Lengeler, 2004; Webb Jr, 2011). In the majority of countries where malaria rebounded, a collapse of prevention and control programs preceded the resurgence, often due to by a lack of financial support for those programs. Insecticide resistance,

which necessitates the use of ever more-expensive pesticides, further stressed malaria control budgets (Cohen et al., 2012).

The scarcity of available resources means that knowing that an intervention prevents malaria is insufficient: program designers must also compare the intervention with other potential interventions. At minimum, they need to know the efficacy and potential costs of each intervention they consider. They should also examine the effectiveness of each intervention in their context and how that effectiveness might change if the intervention is combined with others. Furthermore, since governments often fund malaria control programs, calculations should include costs incurred by citizens and not by the program itself. Improving the detail and specificity of cost and effect estimates should improve the resulting decisions.

In mainland Tanzania, the government's malaria control efforts work: coverage rates of prevention and treatment interventions have risen, and important malaria indicators have fallen. There is less evidence, however, regarding which of the NMCP's interventions drive these gains, and still less describing the relative cost-effectiveness of the different interventions alone or in combination. Investing in all possible interventions without regard to their cost-effectiveness could waste resources due to the duplication of efforts. At worst, if some of the interventions produce antagonistic effects or if the available budget stretches too thin for adequate implementation of the interventions, indiscriminate investment could worsen the malaria situation. On the other hand, failing to explore potential interventions could undermine the effectiveness of the malaria prevention and control program.

Economic analyses can provide the type of evidence described above. By understanding the relative costs and effects of potential programs, policy makers can create smarter, more sustainable malaria programming, maintain previous achievements, and use scarce resources in

the best possible manner. As insecticide resistance increases, along with its inherent negative effects on costs and efficacy, cost-effectiveness analyses will increase in importance.

In mainland Tanzania, the NMCP should examine the costs and benefits of IRS programs; how these costs and benefits compare to those of other anti-malaria interventions, particularly ITNs; and how changes in context, including changes in malaria transmission and in insecticide resistance, affect these costs and benefits.

1.3 Purpose statement

This thesis examines the costs and health outcomes of IRS in combination with ITN distribution in mainland Tanzania. Through sensitivity and scenario analyses, it accounts for the potential effects of insecticide resistance, different strategies of IRS, and intra-country variations in malaria prevalence.

1.4 Research questions

- What is the expected cost per case of malaria averted by conducting both an IRS program and an ITN distribution program in mainland Tanzania, compared to conducting only an ITN distribution program?
- How might *variations in malaria prevalence* change the expected cost per case of malaria averted by conducting both an IRS program and an ITN distribution program in mainland Tanzania, compared to conducting only an ITN distribution program?
- How might *variations in IRS strategy* change the expected cost per case of malaria averted by conducting both an IRS program and an ITN distribution program in mainland Tanzania, compared to conducting only an ITN distribution program?

- How might *variations in insecticide resistance* change the expected cost per case of malaria averted by conducting both an IRS program and an ITN distribution program in mainland Tanzania, compared to conducting only an ITN distribution program?

1.5 Significance statement

At the time of writing, the NMCP is drafting its next medium-term strategic plan for malaria control and prevention. Furthermore, the current round of funding for IRS through the United State President's Malaria Initiative (PMI) ends in 2015, though it is likely to be renewed. The district governments, which direct public health decisions in Tanzania, have expressed strong reservations about funding future IRS campaigns and have cited the cost of insecticides as particularly "insuperable" (Akim, Govere, Gruber, & Ngasala, 2014). In regions that conduct IRS, resource constraints rather epidemiology already drive programmatic decisions, particularly in the shift from blanket IRS, in which all structures in a region receive spraying, to targeted IRS, in which only "hot spots" receive spraying (Akim et al., 2014; RBM, 2012).

Although IRS has proven effective in the past, considerations of its cost and its effectiveness relative to other proven interventions call its place in Tanzania's current vector control program into question. This cost-effectiveness study will provide the NMCP with additional information to guide its decision on the future of IRS in mainland Tanzania.

1.6 Definition of terms

- General terms
    - "Tanzania" refers to mainland Tanzania. Although Zanzibar is politically united with the mainland, its experience with malaria is different. In particular, its malaria control program has access to more resources than does that of the mainland. As such, Zanzibar is excluded from the analyses within this paper.

- "Parasitemia" refers to a state in which the malaria parasite appears in a person's blood. It differs from a case of malaria, which in this thesis refers to a person who is infected with the malaria parasite and displays signs or symptoms of malaria.

- Interventions
  - "Case management" encompasses diagnostic methods and treatment regimens for malaria.
  - "Intermittent preventive treatment" (IPT) involves the provision of anti-malarial drugs to individuals considered at risk for malaria infection regardless of their infection status.
    - "IPTp" refers to IPT in pregnant women.
    - "IPTi" refers to IPT in infants, meaning children 12 months of age or younger.
    - "IPTc" refers to IPT in children, meaning children 5 years of age or younger.
  - "Insecticide treated nets" (ITNs) refers to nets that have been treated with an insecticide and are hung over people's beds while the person is asleep. ITN refers both to standard ITNs and to LLINs.
    - "Long-lasting insecticide-treated nets" (LLINs) refers to ITNs with formulations that endure longer than standard ITNs.
  - "Indoor residual spraying" (IRS) refers to the application of a chemical insecticide to the walls of dwelling places with the expectation that the chemical will kill insects for several months.
    - "Blanket IRS" refers to spraying all structures within a geographic region.

    - "Targeted IRS" refers to spraying only some structures within a geographic region, usually in response to an outbreak or epidemic.

- Analyses
    - "Cost studies" and "cost analyses" consider only the costs of interventions. Any outcomes considered involve measures of coverage, such as number of persons protected, and do not include any considerations of efficacy or effectiveness.
    - "Effectiveness studies" and "effectiveness analyses" consider only the health outcomes of interventions.
    - "Cost-effectiveness studies" and "cost-effectiveness analyses" combine considerations of interventions' costs with considerations of their health outcomes, such as cases of malaria averted. If they use some measure of life years as their outcome, they are technically "cost-utility analyses," but this paper will only use the umbrella term "cost-effectiveness."
    - "Cost-benefit studies" combine considerations of interventions' costs with considerations of their outcomes, with costs and outcomes reported in the same unit of currency.
    - "Disability-adjusted life years" (DALYs) represent years of life with an adjustment for quality of life. A measure of 0 DALYs represents perfect health, and 1 DALY represents death. In general, DALYs are presented in terms of DALYs averted by an intervention.

- Outcomes
    - “Cost per case averted” and “incremental cost per case averted” both refer to the additional amount spent on an intervention in order to prevent an additional case of malaria, when compared to another intervention.

Chapter 2: Comprehensive Review of the Literature

2.1 Introduction

This literature review contains four parts: an overview of malaria in Tanzania; a history and description of malaria prevention and control in Tanzania; a detailed discussion of IRS for malaria control, including a discussion of lessons learned from prior IRS campaigns; and a review of economic analyses of interventions for malaria prevention and control, with a particular focus on economic analyses of IRS. The review concludes with an evaluation of the available cost-effectiveness evidence and an identification of the knowledge gaps that this study endeavors to fill.

2.2 Malaria in Tanzania

In mainland Tanzania, 93% of the population lives at risk for malaria infection (Akim et al., 2014). Of the geographic regions with malaria transmission, approximately 20% have unstable seasonal malaria transmission during rainy seasons, 20% have malaria transmission all year with spikes during rainy seasons, and 60% have stable transmission patterns throughout the year. All of Tanzania experiences a rainy season between March and May, and northern and western Tanzania experience a second rainy season between November and January (Akim et al., 2014; Tanzania Malaria Impact Evaluation Research Group, 2012; Tanzania Ministry of Health and Social Welfare [MOHSW], 2003).

45 species of *Anopheles* mosquitoes, the primary malaria vector, have been recorded in Tanzania; of these, 11 have been implicated in malaria transmission (Kigadye, Nkwengulila, Magesa, & Abdulla, 2010). The primary malaria vectors in Tanzania are *Anopheles gambiae*, which predominates in humid coastal regions; *An. arabiensis*, which predominates in dry and semi-arid regions; and *An. funestus*, which is the least common of the three (Akim et al., 2014;

Kabula et al., 2012; Kigadye et al., 2010; Russell et al., 2013). The species' geographic distribution reflects their different behaviors, including breeding habits and feeding patterns; these differences are discussed in greater detail in the section on insecticide resistance. Generally, mosquito vectors tend to exist in greater numbers at lower altitudes, near coastal regions, and during periods of higher levels of rainfall (Drakeley et al., 2005).

The overall prevalence of malaria parasitemia in Tanzania was 9.5% in 2011, but the prevalence of malaria varies within the country according to the factors listed above. It is highest in the coastal districts of the northern and southern regions, which border Lake Victoria and the Indian Ocean, respectively. Some districts that border Lake Nyasa in the southwest and Lake Tanganyika in the west also experience a higher-than-average prevalence rate of malaria. The highest regional prevalence, 41.1% in 2008, occurred in the northern region of Kagera. The lowest prevalence rates of malaria occur in the central regions, which have a higher elevation and more arid climates. In 2008, Arusha region reported the lowest prevalence, 0.4%. (Akim et al., 2014).

Approximately 75% of Tanzania's population lives in a rural environment, particularly in the northern and southern highlands and the regions near Lake Victoria (Tanzania Malaria Impact Evaluation Research Group, 2012). The primary urban center is the capital, Dar es Salaam, in the southeast. Dar es Salaam residents experience malaria transmission throughout the year with spikes during the two annual rainy seasons (De Castro et al., 2004). Malaria incidence and prevalence rates are generally lower in Dar es Salaam than in the surrounding rural regions: in 2002-04, between 0.8% and 10% of urban regional school children tested positive for malaria parasites, depending on season and sampling methods (De Castro et al., 2004; Geissbühler et al., 2009; Wang et al., 2006).

Malaria in children under the age of five excites particular concern, as that age group faces the highest risk of morbidity and mortality due to malaria. In 2000, before the current round of anti-malaria programs, approximately 24% of under-five mortality in Tanzania was directly attributable to malaria infections, with an additional 12-24% indirectly attributable to malaria via the exacerbation of chronic anemia or other illnesses (Tanzania Malaria Impact Evaluation Research Group, 2012). In the 2011-12 Tanzania HIV/AIDS and Malaria Indicator survey (MIS), between 4% and 9% of all children tested positive for the malaria parasite, with the former estimate using diagnoses by microscopy and the latter by rapid diagnostic test (RDT). The geographic distribution of infection mirrored that of all-ages malaria, and prevalence increased with age, from 2.1%/3.5% among those aged 6 to 8 months to 5.7%/11.7% among those aged 48-59 months (Tanzania Commission for AIDS, Zanzibar AIDS Commission, National Bureau of Statistics, Office of Chief Government Statistician, & ICF International, 2013).

2.3 Tanzania Malaria Control Strategies

This section begins with a description of the history of malaria programs in Tanzania. It then discusses the malaria control strategies endorsed by the NMCP: case detection and management through disease surveillance and health care systems, IPTp at public health service points, distribution and promotion of LLINs, and IRS (Tanzania Commission for AIDS et al., 2013).

2.3.1 History of malaria programs in Tanzania. Between 1885 and 1919, Tanzania, then called Tanganyika, fell under German colonial rule. In 1899, the German colonial government initiated larva control measures, including draining standing water and pouring kerosene into stagnant water, in Dar es Salaam and Kilwa (RBM, 2012). This era also saw

limited attempts to prevent contact with malarial mosquitoes through improving housing design and implementing usage of woven cotton bed nets (Makundi, Mboera, Malebo, & Kitua, 2007). Malaria treatment using quinine was often restricted to colonial officials and their families, but intermittent compulsory mass quinine administrations were conducted in the entire population (RBM, 2012; Yhdego & Majura, 1988).

After World War I, the British Empire took control of Tanganyika as a British protectorate. The British continued many of the larvicidal programs begun by the Germans, including those in Dar es Salaam, and expanded them into the surrounding countryside. The increased availability of DDT and other insecticides for the control of indoor-resting mosquitoes in the 1940s and 1950s inspired IRS campaigns in many countries, including Tanzania, through the Global Eradication Programme of Malaria, which was established in 1955 (Mabaso et al., 2004). The Pare-Taveta scheme, a three-year project in the Pare region of Tanzania, demonstrated the effectiveness of IRS for reducing populations of anopheline mosquitoes. The project essentially interrupted malaria transmission in the region, although some seasonal malaria cases remained (Pringle, 1967). After the project ended, mosquito populations rebounded within five years to pre-spraying levels, but the wider availability of chloroquine as an antimalarial treatment prevented malaria prevalence from rebounding as dramatically (Draper, Lelijveld, Matola, & White, 1972; Pringle, 1967; RBM, 2012).

After Tanzania achieved independence in 1961, its anti-malaria programs collapsed (Makundi et al., 2007). Insecticide spraying, larval control efforts, and disease surveillance programs all ceased (RBM, 2012). Governmental decentralization in 1972 further reduced the coordination between and the funding for malaria programs. In 1974, WHO and the Tanzanian Ministry of Health attempted to launch a national malaria control program centered around

larviciding, insecticide spraying, and provision of prophylactic treatment, but the program collapsed in 1975 due to financial, technical, and administrative problems (Yhdego & Majura, 1988). General economic problems plagued Tanzania in the 1980s, as they did many other sub-Saharan African countries. The government of Tanzania reduced its overall spending, including its spending on malaria programs, which led to a deterioration of health infrastructure and drug distribution systems, a decrease in salaries and motivation for health care workers, and inadequate supervision and management of surviving programs (Tanzania MOHSW, 2003).

In the mid-1990s, attention turned to reforming the Tanzanian health care system. A general health sector reform was proposed in 1994 and enacted in 1999-2002 (Tanzania MOHSW, 2003). The NCMP was founded in 1995 as a part of the Directorate of Preventive Services of the Mainland Ministry of Health and Social Welfare; a separate Zanzibar Malaria Control Programme (ZMCP) handles malaria programs for Zanzibar under the Zanzibar Ministry of Health. The NMCP and ZMCP separately lead, implement, and set targets for anti-malarial efforts, and they each coordinate the efforts of academic, research, non-governmental, and private partners in their respective regions (Akim et al., 2014; RBM, 2012). The decentralized structure of Tanzania's health system means that individual districts control prioritization and funding for all health programs within their borders, including anti-malaria programs (RBM, 2012). Tanzania was one of the first countries involved in the Roll Back Malaria (RBM) partnership in 1998, and it was instrumental in the creation of both the 1997 Harare Declaration and the 2000 Abuja Declaration (RBM, 2012; Tanzania MOHSW, 2003).

Malaria prevention and control programs in Tanzania have undergone several cycles in the past century in which anti-malaria programs succeeded in temporarily reducing negative malaria outcomes, but then those programs ended, and mosquitoes and the malaria they transmit

returned. A 1998 review of anti-malaria efforts in Tanzania found several recurrent challenges: insecticide and larvicide resistance, increased environmental concerns about the repeated use of insecticides and the subsequent slowdown in development of new insecticides, increased costs of insecticides, lukewarm public participation and support, and the scale of mosquito breeding sites. Above all, a lack of sustainable access to financial, human, and other resources has hamstrung otherwise viable programs. Although Tanzania currently receives more international support for its anti-malaria campaigns than ever in its history, the pre-RBM concerns remain incredibly important for today's programs.

Under the National Malaria Medium-Term Strategic Plan 2008-2013, the goal for mainland Tanzania was an 80% reduction in malaria burden from 2008 levels. The successor plan remains in draft, but it is expected that the mainland goal will continue to be prevention and control rather than elimination (Akim et al., 2014).

The next subsections will describe recent anti-malaria interventions in Tanzania, including their structure, their current status, and the challenges for their future.

2.3.2 Case detection and management. Adequate case management reduces the negative effects of malaria infections for those who fall ill; it can also prevent transmission of the malaria parasite to new hosts by reducing the number of people with active malaria infections. Changes in the recommended treatment regimen are primarily driven by changes in malaria parasites' susceptibility to various drugs. Resistance to chloroquine, the recommended first-line drug from 1970 to 2001, first appeared in Tanzania in 1978. Between 1997 and 1999, approximately half of children who received an appropriate dose of chloroquine experienced treatment failure after two weeks. To overcome this resistance, the Tanzanian government designated sulphdoxine-pyrimethamine (SP) the first-line antimalarial in 2001 and banned the

use of chloroquine. Unfortunately, the malaria parasites' resistance to SP grew so rapidly that in 2006, the government changed its recommendation once again to artemisinin combination therapy (ACT) using artemetherlumefantrine (ALu) as the first line drug and quinine as the second-line drug (RBM, 2012; Tanzania Malaria Impact Evaluation Research Group, 2012).

Even the most efficacious drugs, however, cannot reduce the burden of malaria unless people receive them. Treatment-seeking behavior in Tanzania has remained relatively constant over the past decade, with only about 60% of children with fevers seeking formal treatment (RBM, 2012). A Global Fund initiative begun in 2006 provides rapid diagnostic tests (RDTs) at public health facilities in about half the country, though evidence remains mixed as to whether these RDTs improve the accurate diagnosis and appropriate treatment of malaria (RBM, 2012). Since malaria has received so much attention as the most important febrile disease in Tanzania and because a provider's failing to catch a case of malaria is seen as "indefensible," almost all of the children who seek treatment for fever receive some sort of antimalarial drug (Chandler et al., 2008). Of the children who seek treatment, however, only about one third—or 20% of all children with fevers—receive the recommended antimalarial within 24 hours of the onset of fever (RBM, 2012). People who self-define their illness as a general fever rather than malaria, who initially seek out traditional medicine, or who do not attend a health facility are less likely to receive a timely dose of the correct antimalarial drug (Hetzel et al., 2008).

Further compounding the problems due to poor treatment-seeking behavior have been logistical failings leading to shortages and stock outs of ALu. In 2007 and 2008, there were no national-level shortages of ALu, but procurement delays in early 2009 led to increasingly widespread stock outs in late 2009 and throughout 2010. Prices have also remained high relative to the prices of other antimalarials, which further limits access to ACTs. Emergency

procurements have largely filled the gaps, but more procurement reforms are expected in the new medium-term malaria program (Tanzania Malaria Impact Evaluation Research Group, 2012).

Instead of seeking formal treatment for malaria-like symptoms as soon as they develop, people often pursue self-care through over-the-counter painkillers, neem tree roots and leaves, or cold baths or showers. They seek formal treatment only if their symptoms persist or worsen (Hetzel et al., 2008; Metta, Haisma, Kessy, Hutter, & Bailey, 2014). Aside from the attribution of malaria symptoms to tiredness or to other illnesses, people may opt for home care if they find health care facilities too expensive or staffed with unhelpful workers. The recent changes in drug recommendations have also introduced uncertainty as to the efficacy of Western medicine and increased a preference for the old monotherapies, which are perceived as having a simpler dosing schedule, and for local herbs, which are generally low-cost or free and are perceived as having few to no side effects (Metta et al., 2014; Rutta et al., 2011). Unfortunately, when large proportions of the population opt for self-care—including taking antimalarials without a prescription—over being prescribed ACT, the delays in appropriate treatment can increase complications and contribute to the development of drug-resistant malaria (Metta et al., 2014).

In order to improve access to and use of ACT, the Tanzanian government has offered subsidized and free ALu at public and mission health facilities since 2006. To reach the 35% of individuals who seek care through private providers, the government also runs a program in partnership with the Global Fund to accredit private outlets to distribute ACT. Staff at these "ADDO" facilities receive training in drug dispensing, case management, pharmaceutical management, and business practices (RBM, 2012). The ADDOs have increased the use of ACTs and decreased the use of SP, though their effectiveness has varied across districts (Rutta et al., 2011).

The 2013 goals for case management in children under 5 years of age were for 80% of children with fever to receive appropriate treatment within 24 hours of fever onset and for 80% of children diagnosed with uncomplicated malaria to be treated in health facilities and to have their malaria appropriately managed (RBM, 2012). It is uncertain what the next medium-term goals for case management will include.

2.3.3 Intermittent preventive treatment in pregnancy (IPTp). Malaria infections pose particularly high risks for pregnant women and their newborn children. Contracting malaria increases the risk of maternal anemia and hypertension, premature delivery, intrauterine growth retardation, low birth weight, stillbirth, and perinatal death. These risks are especially great during a woman's first and second pregnancies, the second and third trimesters of each pregnancy, and during every pregnancy of an HIV-positive woman (Tanzania Malaria Impact Evaluation Research Group, 2012). Infants whose mother experienced a malaria infection during their gestation are more susceptible to increased parasitemia and clinical malaria, especially if their mother had multiple prior pregnancies (Harrington, Morrison, Fried, & Duffy, 2013). As such, an important component of reducing morbidity and mortality due to malaria is reducing cases of malaria during pregnancy.

In addition to the interventions that protect all individuals, such as LLINs, WHO also recommends IPTp. Pregnant women receive two prophylactic doses of some anti-malarial—in Tanzania as in many sub-Saharan African countries, SP—beginning in the second trimester, with the doses at least four weeks apart (Tanzania Malaria Impact Evaluation Research Group, 2012). In Tanzania, routine antenatal care involves IPTp.

The 2013 goal for IPTp coverage was for 80% of pregnant women to have received a full course—i.e., two doses—of IPTp during their most recent pregnancy that resulted in a live birth.

Unfortunately, the IPTp coverage rate has remained well below this goal. In 2010, approximately 60% of pregnant women received a first dose of IPTp, compared to 50% in 2004; only 26% received both doses, compared to 21% in 2004 (Tanzania Malaria Impact Evaluation Research Group, 2012; RBM, 2012). This shortfall occurs despite the fact that over 90% of women in mainland Tanzania attend formal antenatal clinics (ANCs) (Tanzania Malaria Impact Evaluation Research Group, 2012).

According to a review of qualitative studies on IPTp in Tanzania, the lack of IPTp utilization is related to both maternal choice and the practices of the ANCs. Some women fear side effects that they associate with IPTp, including miscarriage, larger infant birth weight that complicates delivery, mouth sores, fatigue, fever, and rashes. Some also report that the costs associated with travel to the clinics are too high, even with the cost of IPTp being subsidized or covered. Clinic staff struggle with SP stock outs, a lack of resources such as clean water and cups, and confusion born of sometimes-conflicting guidelines from multiple stakeholders (Mubyazi & Bloch, 2014; Pell, Straus, Andrew, Meñaca, & Pool, 2011). Worse yet, drug resistance to SP is quite high in many regions of Tanzania, and there is evidence that IPTp with SP in areas of high drug resistance does not reduce the odds of maternal malaria, low birth weight, or maternal anemia and may in fact increase the odds of severe malaria in infants (Harrington et al., 2013).

Despite strong support from the government of Tanzania and relatively high ANC attendance rates, IPTp coverage remains low, and the efficacy of SP as a prophylactic in areas of SP drug resistance is questionable. It remains to be seen how the new medium-term strategic plan will address these shortcomings over the next five years.

2.3.4 Insecticide-treated bed nets (ITNs). In Tanzania's most recent wave of anti-malaria programs, which began in the late 1980s, ITNs and LLINs have proven the NMCP's most successful malaria prevention tool. ITNs began limited use in Tanzania in the late 1980s, and their usage expanded in the 1990s (Tanzania Malaria Impact Evaluation Research Group, 2012). A pilot social marketing distribution scheme, the KINECT project, began in 1996 in the Kilombero Valley region of southeast Tanzania (RBM, 2012). Social marketing uses commercial marketing techniques to promote goods sold without profit being the primary motivation. In the case of KINECT, social marketing efforts were supported by an initial subsidy of 25% of the purchasing costs of nets and a 90% subsidy of the purchasing costs of net re-treatment kits. Health workers, shopkeepers, religious leaders, and village government staff sold the products (Minja et al., 2001; Schellenberg et al., 2001). KINECT reduced the incidence rate of malaria, the prevalence rate of malaria, and the overall mortality rate in children in the Kilombero valley (Schellenberg et al., 2001). After KINECT's success, the Tanzanian government began its first nation-wide ITN distribution campaign in 2000 (RBM, 2012).

In 2004, in order to encourage ITN ownership among women of childbearing age, the Tanzanian government began the Tanzania National Voucher Scheme (TNVS). The TNVS provides women with vouchers for a subsidized ITN during their first ANC visit at a public health facility; the women then redeem the vouchers at private distributors after a small "top-up" payment (RBM, 2012). The vouchers for pregnant women are funded by the Global Fund, and a 2006 expansion of the TNVS funded by the United States President's Malaria Initiative (PMI) allowed for additional vouchers for infants (Hanson et al., 2009).

On top of the TNVS, the Tanzanian government has also organized several "catch-up" campaigns in which LLINs have been distributed for free. In 2008, concerned that ITN coverage

remained too low among children under the age of five, it launched such a campaign with support from the World Bank, PMI, Malaria No More, the United Nations Children's Fund (UNICEF), World Vision Switzerland, the United Kingdom Department for International Development (DFID), the Swiss Agency for Development and Cooperation (SDC), and other partners (Bonner et al., 2011). Between 2008 and 2010, this campaign distributed 8.7 million LLINs to children under the age of five, and ITN ownership among households with at least one children under five years old reached 80% (RBM, 2012). The catch-up programs became even more ambitious in 2011, with a coverage target of at least one LLIN in every sleeping space. To this end, the government distributed over 17 million free LLINs to households that did not yet own any LLINs (Tanzania Malaria Impact Evaluation Research Group, 2012). ITN and LLIN ownership increased significantly after this campaign, but the education and behavior change components of the intervention were somewhat less effective, and ITN usage increased less dramatically (Ruhago, Mujinja, & Norheim, 2011; West et al., 2012).

The 2013 targets for ITN ownership were for 90% of households to own at least one ITN and for 80% to own at least two ITNs. For usage, it was hoped that 80% of pregnant women and 80% of children under five would use ITNs each night. In 2010, the date of the most recent national malaria survey, 63% of households owned at least one ITN, which represents a significant increase from 2004/5, when only about 23% of households did so. Furthermore, 64% of all children under the age of five and 56% of pregnant women reported sleeping under an ITN the night before the survey, which is more than twice as much as in 2007 (RBM, 2012). ITN use tends to be highest among infants, children aged 1-4, and women of childbearing age and lowest among women over age 50, children aged 5-14, and adult men (Tsuang, Lines, & Hanson, 2010). Beyond demographic and socioeconomic characteristics, important factors that drive non-use of

ITNs include features of house design, including the bother of having a net in a room in which people sleep but also perform daytime activities, and climactic factors such as season and temperature (Dunn, Le Mare, & Makungu, 2011; Koenker et al., 2012). Strong private domestic manufacturing and distribution networks provide Tanzania with a steady supply of ITNs, and effective consensus building allows Tanzania to organize unified and successful national ITN campaigns. ITNs are therefore likely to remain a key component of Tanzania's malaria campaign for the foreseeable future (de Savigny et al., 2012).

Unfortunately, ITNs and LLINs can only protect against mosquitoes that enter sleeping spaces. Consistent ITN usage in a region may interrupt indoor mosquitoes biting at night, but outdoor biting during the day will continue (Russell et al., 2011). As *An. gambiae* and *An. funestus* have proven more flexible regarding these kinds of behavior shifts, regions with high ITN coverage may see shifts in dominant mosquito vector species from high levels of *An. arabiensis* to higher levels of *An. gambiae* and *An. funestus* (Kitau et al., 2012). These remaining mosquitoes may prove less susceptible to ITNs or other insecticide-based prevention programs, such as IRS (Russell et al., 2011). Even with successful ITN programs, therefore, other malaria prevention and control campaigns must continue.

2.3.5 Indoor residual spraying (IRS). Indoor residual spraying with pesticides is the final component in the government of Tanzania's fight against malaria; it is covered in detail in the next section.

2.4 IRS

This section discusses IRS as an intervention, including its components, the theory behind its use, its effectiveness when used alone, and its effectiveness when used in combination with other interventions. Then follows a discussion of programmatic concerns for developing

and maintaining a successful IRS campaign, including resource constraints, insecticide resistance, and community acceptance. This discussion includes considerations of campaigns in other countries in sub-Saharan Africa. The section then concludes with a description of the current state of IRS interventions in mainland Tanzania.

2.4.1 Description of IRS. IRS is currently recommended for mosquito vector control in 88 countries, including 40 in the WHO Africa Region (GMP, 2013). A round of IRS involves spraying the walls of buildings, particularly dwelling places, with a long-lasting insecticide. After a mosquito takes a blood meal, it rests on the walls of the dwelling and absorbs the insecticide. The goal of IRS is not directly to prevent mosquito bites but rather to kill female mosquitoes before the malaria parasite has a chance to develop and to be spread to more humans. It can also reduce the overall longevity of the mosquito population, thereby reducing the probability of a mosquito becoming infected. Such a "mass effect" of mosquito mortality requires a high level of coverage, sometimes cited as between 85-90%. Some insecticides, such as DDT, also produce a repellent effect that discourages the mosquitoes from entering sprayed dwelling places (Coosemans & Carnevale, 1995; Pluess, Tanser, Lengeler, & Sharp, 2010).

An ideal insecticide for IRS is highly toxic to mosquitoes for several months after application, not toxic to people or domestic animals, stable in tropical environments, and unlikely to contaminate the environment. Furthermore, it should not quickly induce insecticide resistance in anopheline mosquitoes. On top of these technical concerns, it also needs to be affordable for sustained application over many rounds of spraying (Coosemans & Carnevale, 1995). Depending on the seasonality of transmission and the type of insecticide used, IRS needs to be repeated one to three times every year.

There are currently 12 types of insecticides approved by WHO for use in IRS; each falls into one of four classes. Chlorinated hydrocarbons, including DDT, provide the longest-lasting effects—over six months of protection—and are generally the least expensive. Environmental and health concerns, insecticide resistance, and its tendency to act as a repellent have, however, rendered DDT considerably less popular than during its peak from the 1940s through the 1970s (Cameron, 2010; Coosemans & Carnevale, 1995; Oxborough et al., 2014). DDT is not currently used for IRS in Tanzania. Another common class of insecticides approved for IRS is the pyrethroids, which includes lambda-cyhalothrin (ICON), which was used for IRS activities in Tanzania until 2010. As a class, pyrethroids offer between 3-8 months of protection at a relatively low cost, and they present a low risk of adverse effects for humans and household animals. Unfortunately, they are also the only insecticides approved by the WHO Pesticide Evaluation Scheme (WHOPES) for use in LLINs, and pyrethroid resistance is becoming a major problem in sub-Saharan Africa, including in Tanzania (Oxborough et al., 2014; West et al., 2014). Organophosphorous insecticides offer 2-3 months of protection, but most insecticides of this class have undesirable characteristics, including relatively high levels of toxicity to humans (Coosemans & Carnevale, 1995). The class of insecticides currently used for IRS in Tanzania is therefore the carbamates, specifically bendiocarb (West et al., 2014). Bendiocarb costs more per unit than the pyrethroids, and some studies suggest that it poses a higher risk of toxicity to mammals, including humans, although there have not yet been any serious adverse effects reported due to IRS with bendiocarb (Coosemans & Carnevale, 1995; West et al., 2014). The primary reason for choosing bendiocarb over other pesticides is its high level of efficacy against pyrethroid-resistant mosquitoes, which is of particular concern in regions with high usage levels

of pyrethroid-treated LLINs, such as most of Tanzania (Coosemans & Carnevale, 1995; West et al., 2014).

2.4.2 Effectiveness of IRS. IRS, especially IRS using DDT, has "a long and distinguished history in malaria control" (Pluess et al., 2010). During the 1950s and 1960s, time-limited IRS campaigns greatly reduced or even eliminated malaria as a public health problem in parts of Asia, Russia, Europe, and Latin America. As described above in the section on the history of malaria campaigns in Tanzania, it also formed the backbone of previous malaria control efforts in Tanzania. In the most recent wave of malaria programs, it continues to perform an important role for many countries. Recent studies in several sub-Saharan countries—including but not limited to Benin, Botswana, Madagascar, Malawi, South Africa, and Uganda—report a significant improvement in malaria indicators after beginning IRS campaigns, even after controlling for LLIN coverage and socioeconomic factors (Brutus et al., 2001; Bukirwa et al., 2009; Maharaj et al., 2012; R. Ossè et al., 2012; Simon et al., 2013; Skarbinski et al., 2012). Additionally, recent evidence from Tanzania, Benin, and other countries suggests that malaria indicators rebound if IRS is halted or scaled back without adequate precautions (Akim et al., 2014; R. A. Ossè et al., 2013).

A recent meta-regression analysis found a mean reduction of 62% in malaria prevalence after implementation of IRS (risk ratio (RR): 0.38; 95% confidence interval (CI): 0.31, 0.46)), though the authors noted significant heterogeneity in their findings. They state that IRS appears to be most effective in regions that begin with a high malaria prevalence, that conduct several rounds of spraying, that use DDT, and that are not fighting *Plasmodium falicparum* malaria (Kim, Fedak, & Kramer, 2012).

Unfortunately, and slightly paradoxically, the evident success of IRS has undermined the quality of evidence available regarding its effectiveness. In the 1940s and 1950s, the benefits of IRS with DDT seemed so obvious that program implementers spent little time quantifying the effects of their programs (Pluess et al., 2010). A lack of baseline epidemiological data and a de-valuation of malaria research during those decades also undermined attempts to measure the campaigns' effects. As the elimination campaigns deteriorated in the 1960s, so too did many surveillance systems, which further undermined any available monitoring data (Nájera, González-Silva, & Alonso, 2011). In studies of modern IRS campaigns, authors often only provide longitudinal information on a single region without providing a valid counterfactual (Pluess et al., 2010). Studies that provide a counterfactual often contain important flaws, relying on a single year of data, which may understate the effect of IRS in high-transmission regions, or operating in a region with a history of IRS (K. Kolaczinski, Kolaczinski, Kilian, & Meek, 2007; Pluess et al., 2010). The most recent Cochrane review of IRS concluded, therefore, that although IRS does reduce malaria transmission and improve health outcomes, quantifying the effects of IRS is only possible at the local level (Pluess et al., 2010).

2.4.3 Combining IRS and ITNs. As described above, the distribution of ITNs and LLINs is the centerpiece of the most recent wave of malaria control programs in mainland Tanzania. Throughout the country, a large proportion of the population own and use LLINs each night. Any proposed IRS campaign in Tanzania must therefore consider the combined effects of IRS and ITNs.

In theoretical descriptions and mathematical models, IRS and ITNs display a complex relationship. At first glance, it appears that the interventions should have additive effects. Both interventions kill mosquitoes using pesticides, but they do so at different stages of the

transmission cycle: ITNs intercept mosquitoes in the process of seeking out hosts, while IRS targets who have already bitten a host and are resting while digesting their meal (Okumu & Moore, 2011; Yakob, Dunning, & Yan, 2011). The coverage with one of the interventions can also compensate for less-than-ideal coverage with the other. For example, ITNs can continue to work after the IRS pesticide has degraded, and IRS can compensate for worn-out ITNs (Okumu & Moore, 2011; West et al., 2014). Unfortunately, IRS and ITNs can also undermine each other. If the pesticide used in IRS repels mosquitoes from houses, the mosquitoes will not contact the ITNs while feeding, and if mosquitoes do not feed indoors due to ITNs, they will not contact the treated walls while resting (Yakob et al., 2011). These negative effects increase with insecticides with high repellent effects, such as DDT, and decrease with insecticides without repellent effects, such as bendiocarb (Okumu, Kiware, Moore, & Killeen, 2013; Yakob et al., 2011).

The practical evidence is as conflicting as the theoretical, due in part to the weaknesses of the IRS evidence base described in the previous section. A 2009 systematic review found eight observational studies comparing the combined effects of IRS and ITNs with either IRS or ITNs alone. Of these, five reported a significant protective effect of the combination when compared to either intervention alone, but three showed no significant effect. The review authors concluded that a significant protective effect probably exists when the interventions are delivered together, but that the observational nature of the studies and the conflicting nature of their findings precluded a meta-analysis of that effect (Kleinschmidt et al., 2009). Recent observational studies have reinforced this ambiguity, with some finding a significant protective effect of combining IRS and ITNs (Bradley et al., 2012; Hamel et al., 2011) and some not (Protopopoff et al., 2008; Temu, Coleman, Abilio, & Kleinschmidt, 2012).

A 2013 analysis of demographic and health surveys (DHS) and MIS from 17 countries in sub-Saharan Africa found that the combination of IRS and ITNs was associated with a significant reduction in parasitemia in regions with moderate malaria transmission risk compared no intervention (Odds ratio (OR): 0.47, 95% confidence interval (CI) 0.33, 0.63, $p < 0.0001$). Furthermore, this risk reduction was significantly greater than the risk reduction of either intervention alone ($p = 0.02$). In regions with high or low malaria transmission risk (parasite prevalence rate either between 40% and 100% or between 0% and 5%), however, the combined effects of the interventions did not differ significantly from those of the individual interventions (Fullman, Burstein, Lim, Medlin, & Gakidou, 2013).

A cluster-randomized controlled trial (CRT) published in 2014 specifically examines the combination of IRS and ITNs in the Lake Zone of Tanzania. All clusters in the study received LLINs through the 2011 universal catch-up campaign and received IRS with ICON in 2011. The authors then compare an intervention arm that also received two rounds of IRS with bendiocarb in 2011/12 with a control arm that received no IRS during 2011/12. They found that the intervention arm reported significantly lower levels of parasitemia two months after the second round of spraying (OR: 0.48, 95%CI: 0.15, 0.75; $p = 0.009$), but that this effect faded by six months after the second round of spraying (OR: 0.48, 95%CI: 0.18, 1.24; $p = 0.127$). This fade is unsurprising, as bendiocarb loses its effectiveness 3-5 months after spraying (West et al., 2014). While this CRT provides good evidence that the combination of IRS and ITNs makes sense in the Lake Zone of Tanzania, it relies on a single year of data in a region with a history of receiving IRS, which undermines its generalizability to a potential long-term expansion of IRS.

Based on the current evidence, the effects of combining IRS and ITNs/LLINs are uncertain and dependent on local factors, including the type of pesticide used and the baseline

malaria prevalence. In mainland Tanzania, which experiences a moderate to high malaria prevalence rate and uses bendiocarb for IRS, the evidence suggests that adding IRS to an area of relatively high ITN coverage will improve malaria and health outcomes. Due to the flaws in the data outlined above and the aforementioned uncertainty, however, this conclusion is tenuous and will require sensitivity testing inmodels predicting the combined effects of the interventions.

2.4.4 Current IRS in Tanzania. Although several previous Tanzanian anti-malaria campaigns consisted primarily of IRS campaigns, IRS has only played a small part in the most recent wave of anti-malaria programs in mainland Tanzania. The first re-introduction of IRS began with targeted spraying in 2007 to control outbreaks in Muleba and Karagwe districts, part of the Lake Zone in northwest Tanzania. In both regions, IRS dramatically reduced key malaria indicators between 2007 and 2010. Muleba saw malaria-related admissions decrease by 84% (incidence rate (IR): 124 per 1,000 person years (PY) to 23 per 1,000 PY) and child mortality decrease by 89% (IR: 42 per 10,000 PY to 5 per 10,000 PY); Karagwe saw a 78% decrease in confirmed malaria cases as a percentage of clinic admissions, from 23% to 5% (RBM, 2012). In 2009, IRS spread to additional districts; by 2011, sixteen districts in three regions conducted blanket IRS, and two additional districts conducted targeted IRS (Colaço, Yevstigneyeva, & Lalji, 2014; RBM, 2012). In 2012, budget constraints drove the Tanzania Vector Control Scale Project (TVCSP) to switch to targeted spraying only in all 19 districts. The current IRS strategy involves two rounds per year of bendiocarb spraying at no charge to residents (Akim et al., 2014; Colaço et al., 2014; RBM, 2012).

There is some evidence that the switch to targeted instead of blanket IRS has increased the region's vulnerability to malaria epidemics and that this risk is intensified by reduced levels of adult immunity to the malaria parasite due to several years of successful malaria control

(Akim et al., 2014). It is important to note, however, that during important outbreaks, including one in Muleba in 2011, ACT stock outs, drug resistance, and low reported bed net use also contributed to the spike in malaria incidence (RBM, 2012).

The coverage goal for 2013 was to have IRS scaled up to cover 60 districts and 50% of the national population (RBM, 2012). Coverage has fallen short of this goal, and it remains to be seen how IRS will factor into the next medium-term Tanzania malaria control plan.

2.4.5 Lessons learned from prior IRS campaigns. This subsection discusses important programmatic and technical lessons from IRS-centric malaria control programs, including the Global Malaria Eradication Programme (GMEP) in the 1940s and 1950s. It begins with a discussion of factors that improve the chances of success for malaria control programs. It then discusses five key factors that have tended to undermine IRS programs and that continue to pose challenges to Tanzania's current malaria control strategy: resource constraints, a lack of epidemiologic data, insecticide resistance, adverse effects of exposure to pesticides, and wavering community acceptance of IRS.

2.4.5.1 Components of successful programs. The requirements for a successful IRS program closely resemble those for almost any public health program. A solid epidemiological understanding of the disease within the specific country's context and strong surveillance capacity can help the country to develop the best plan possible with its available resources and to monitor and evaluate the program's activities and progress (K. Kolaczinski et al., 2007; Mabaso et al., 2004; RTI International, 2014). Good infrastructure, including physical infrastructure for transporting spraying teams and financial infrastructure for transferring funds, and strong logistical support can allow teams to carry out their work as efficiently as possible. Well-trained and well-supervised spraying teams can carry out operations with maximum efficiency and

effectiveness (K. Kolaczinski et al., 2007). International cooperation, both with international funders and with neighboring countries, can increase available resources and prevent cross-border transmission from undermining progress (Maharaj et al., 2012; Simon et al., 2013).

As IRS is often run on a national scale and funded at least in part by national governments, national socioeconomic and health system structures also play a part in helping IRS to succeed. A strong health-care system allows for effective case management and IPT, as well as for the distribution of LLINs, both of which reinforce the successes of an IRS campaign (K. Kolaczinski et al., 2007). Sustained political commitment to malaria control even as the malaria burden declines can ensure that funding does not disappear before malaria does (Blumberg, Frean, & Moonasar, 2014). Finally, the country's overall economic prosperity underpins the availability of funding for malaria control campaigns and for the many systems that ensure their success (Mabaso et al., 2004).

Unfortunately, as will be seen in the next several sections, getting all of these pieces together in a sustainable fashion is extremely difficult.

2.4.5.2 Resource constraints. As always in public policy, finding the money to finance IRS is often the most challenging and yet most crucial aspect of program development; it is also the most likely to undermine an IRS program. Even in best-case scenarios, IRS requires funding to be sustained over many years because it requires an influx of money each time spraying occurs (Coosemans & Carnevale, 1995; Nájera et al., 2011). The high recurrent costs of IRS can reduce its attractiveness for long-term malaria control.

In a systematic review of 75 malaria resurgence events in 61 countries between 1930 and 2004, over half (39/75, 52%) were driven by the weakening of malaria control programs due to a lack of resources. Often, the drawdown in funds was due in part to the success of the program:

malaria burden declined, political attention shifted elsewhere, and the money went with it (Cohen et al., 2012). Sometimes, a lack of perceived programmatic effectiveness drove away funding, especially if the low effectiveness was combined with rising costs, including increases in pesticide costs (Nájera et al., 2011; RTI International, 2014). As seen in Tanzania's recent shift from blanket to targeted spraying, the availability of funding can drive programmatic decisions toward what is seen as affordable rather than what is ideal (Akim et al., 2014; Colaço et al., 2014). In settings with limited resources—that is, in almost all realistic public policy settings—context-specific cost and effectiveness data are crucial for making the best possible use of limited funds.

2.4.5.3 Lack of epidemiological data. As with any large-scale public health campaign, an IRS campaign requires good baseline data both for program design and targeting and for monitoring and evaluation. In Cameroon in the 1950s, failure to account for epidemiological variation within the country meant that the IRS campaign succeeded in the forested south, where it was accompanied by sprays of the forest itself, but failed in the northern savannah regions (Carnevale & Mouchet, 2001). Lack of data also undermined Liberia's ability to focus its IRS campaign, which contributed to its deterioration and to the erosion of the gains from the program (Webb Jr, 2011). Sadly, poor data is not only a feature of the programs begun just after World War II. PMI's initial IRS efforts in Angola in the 2000s relied on incomplete administrative data without laboratory confirmations; malaria was probably not even a public health problem in the region during that dry year (Somandjinga, Lluberas, & Jobin, 2009).

Mainland Tanzania maintains a relatively strong malaria surveillance system. Malaria indicator surveys are conducted every four years, and 21 sentinel sites monitor insecticide resistance (Akim et al., 2014). Surveillance data plus monitoring and evaluation data from prior

campaigns must be used to inform the development of the next medium-term strategic malaria control plan.

2.4.5.4 Insecticide resistance. Insecticide resistance, by which chemicals used in malaria prevention through IRS or ITNs lose their capacity to kill vector mosquitoes, is a crucial problem with pesticide-based vector control efforts, and it is increasing in importance over time. As with any form of drug resistance, insecticide resistance develops when susceptible organisms die and leave behind only the organisms not susceptible to the compound in question. These resistant organisms then reproduce and pass on the adaptation that allowed them to survive.

Physiological resistance takes the form of a genetic mutation that either alters the target receptor or enzyme in the mosquito so that the insecticide can no longer interfere with it or, more commonly, allows the mosquito's enzymes to break down the insecticide before it has a toxic effect (Sokhna, Ndiath, & Rogier, 2013). The former pathway also allows for the development of cross-resistance, as the alteration in the target complex blocks all insecticides that would interfere with that complex (Sokhna et al., 2013). In Tanzania, resistance levels vary by region, but resistance to ICON, permethrin, DDT, and bendiocarb have all appeared to varying extents (Akim et al., 2014). As mentioned above, bendiocarb is the current insecticide used for IRS. Bendiocarb works well in regions with high pyrethroid resistance (Akogbeto, Padonou, Bankole, Gazard, & Gbedjissi, 2011), but vector mosquitoes in Tanzania already display some resistance to bendiocarb. Physiological resistance to insecticides will continue to be an important consideration for the NMCP in future IRS campaigns.

Behavioral resistance, which develops in a similar fashion to physiological resistance except that the adaptive change is behavioral rather than genetic, also reduces the effectiveness of IRS. As a general rule, anopheline mosquito vectors feed indoors—known as endophagy or

endophilic behavior—and at night, and therefore IRS and ITNs can reduce their population size. Unfortunately, mosquitoes can change their preferred feeding and resting patterns to avoid IRS and ITN exposure. These behavioral shifts can involve changing preferred hosts, with cattle often being an important substitute; beginning to feed earlier in the evening before people go to bed under ITNs; or shifting toward daytime feeding and exophagy, an outdoor feeding habit (Mahande, Mosha, Mahande, & Kweka, 2007; Reddy et al., 2011). All of these changes reduce the vectors' exposure to the pesticides used in IRS and ITNs and thereby reduce the effectiveness of those interventions.

Due to differing capacities for developing behavioral and physiological resistance, different species of anopheline mosquitoes display different capacities to adapt to IRS and ITN campaigns. In mainland Tanzania, *An. funestus* and *An. arabiensis* tend to be more variable in their feeding and resting behaviors than *An. gambiae*, which makes them less susceptible to insecticide-based interventions (Kreppel, Maliti, & Ferguson, 2012; Lwetoijera et al., 2014; Mahande et al., 2007). In southern Tanzania, both *An. arabiensis* and *An. funestus* appear to have shifted to exophilic feeding resting behavior and to have begun feeding earlier in the day in response to high LLIN coverage (Lwetoijera et al., 2014; Mahande et al., 2007). After the introduction of IRS, *An. gambiae* populations tend either to crash, leaving *An. arabiensis* and *An. funestus* as the most important vector species, or to develop physiological resistance (Lwetoijera et al., 2014).

To prevent insecticide resistance, the Global Plan for Insecticide Resistance Management suggests rotating the insecticides used for malaria control, monitoring for insecticide resistance at fixed points, and avoiding the use of pyrethroids for IRS if ITNs are an important malaria control measure (Akim et al., 2014; Steinhardt et al., 2013). The last point is an important

advantage of IRS over LLINs: IRS programs have four classes of pesticides available for use, while LLINs may only contain pyrethroids (Pluess et al., 2010). 21 sentinel sites monitor insecticide resistance in mainland Tanzania. They report quarterly and annually to the districts, the NMCP, and international partners (Akim et al., 2014). It was due to the data gathered at these sites that IRS with ICON was ended in favor of IRS with bendiocarb; they will continue to be crucial sources of data for detecting insecticide resistance in the future.

2.4.5.5 Potential side effects of IRS. As with any pesticide use, concerns exist about possible adverse side effects due to exposure to pesticides via IRS. Much of the concern focuses on DDT (Bouwman, Becker, & Schutte, 1994; Channa, Röllin, Nøst, Odland, & Sandanger, 2012; Manaca et al., 2012; Van Dyk, Bouwman, Barnhoorn, & Bornman, 2010; Wassie, Spanoghe, Tessema, & Steurbaut, 2012), and since DDT has been used for IRS for much longer than any other pesticide, most studies examining the potential long-term effects of exposure to insecticide through IRS focus on DDT (Aneck-Hahn, Schulenburg, Bornman, Farias, & de Jager, 2007; Cocco et al., 1997). No serious side effects of exposure to bendiocarb through IRS have been reported, but the short time in which bendiocarb has been used for IRS has precluded any meaningful assessment of long-term effects of exposure (West et al., 2014).

2.4.5.6 Lack of community acceptance. Since IRS requires that residents allow spray teams into their homes, the success of an IRS campaign requires community acceptance. A qualitative study in the Lake Zone region of Tanzania assessed residents' thoughts and feelings on IRS and the motivations for their decision to either accept or reject participation in the campaign (Kaufman, Rweyemamu, Koenker, & Macha, 2012). The majority of those interviewed saw IRS as an important public good for protecting people—particularly pregnant women and children—against malaria. A commonality among those who refused IRS was a

feeling of a lack of knowledge about the intervention. They expressed confusion that IRS can kill mosquitoes while leaving other pest populations unscathed, and they feared side effects including itching, stomach upset, or damage to internal or sexual organs. Participants suggested increasing focus on education campaigns and hiring trustworthy, well-trained, and well-supervised spraying teams (Kaufman et al., 2012).

One key negative side effect of IRS that can decrease the acceptability of IRS is the apparent increase of bedbug, flea, and lice infestations after spraying (Akim et al., 2014; Kaufman et al., 2012; Mng'ong'o et al., 2011). In Suriname, IRS appeared to increase the cockroach population to the point that the cockroaches began to attack crops and children (Kaufman et al., 2012). Non-mosquito pest insects appear to have developed resistance at least to pyrethroids in Tanzania, though their resistance status regarding other pesticides remains unknown (Akim et al., 2014). If a person feels that the negative mental and physical health effects of an infestation with these insects outweighs the potential positive effects of malaria prevention, he or she might reject the next round of IRS (Akim et al., 2014).

Qualitative studies such as the one carried out in northern Tanzania are important for capturing community members' opinions, especially if they are supplemented with quantitative data on coverage and epidemiological trends. Equally important as the collection of data, however, is the use of that data to address the communities' concerns. For Tanzania in particular, program designers should place a greater emphasis on the education component of IRS campaigns and craft operation plans and budgets reflect this emphasis.

2.5 Economic Analyses

This section discusses the available cost-effectiveness evidence related to the NMCP interventions described above. It begins with an overview of the cost-effectiveness of case

management, IPT, and ITNs. Then follows a comprehensive overview of published economic studies related to IRS, including cost studies, cost-effectiveness studies, and computer models.

2.5.1 Case management. Two important components of case management are diagnosis and treatment. A 2011 systematic review, which examined all English-language literature published between 2000-2010 related to the cost-effectiveness of malaria prevention interventions, found that ACT was consistently more cost-effective than other antimalarials (White, Conteh, Cibulskis, & Ghani, 2011). This finding suggests that the disadvantage of drug resistance to older antimalarials, such as SP and chloroquine, outweighs their advantage of relatively lower costs (Goodman & Mills, 1999).

The 2011 review also found that the cost-effectiveness of diagnostic procedures—clinical observation, microscopy, and RDTs—varied too much by setting and "diagnostic throughput" for any one of these methods to be consistently preferable to the others (White et al., 2011). Overall, in the six diagnosis and treatment studies examined, the cost of treating uncomplicated malaria appeared to be affected primarily by personnel and training costs (mean 29%, range 10-78%) and by treatment and diagnostic costs (mean 11%, range 1-80%) (White et al., 2011).

2.5.2 IPT. Prophylactic treatment of malaria among key risk groups, namely pregnant women and their young children, appears to be cost-effective relative to other anti-malaria interventions (Goodman & Mills, 1999). The 2011 systematic review cited above includes 7 cost studies and 9 cost-effectiveness studies that examined IPTi, IPTc, or IPTp. In 2009 dollars, the financial cost per person protected is lowest for infants (median $0.60, range: $0.48 - $1.08), higher for pregnant women (median $2.06, range: $0.47 - $3.36), and highest for children (median $4.03, range: $1.25-$11.80). Overall, the median cost to the provider per disability adjusted life year (DALY) averted by IPT is $24 (range: $1.08-$44.24) (White et al., 2011).

Variability in these costs is primarily driven by drug costs and by personnel costs, with iPTi displaying relatively more sensitivity to drug costs than IPTc or IPTp (White et al., 2011).

2.5.3 ITNs. ITNs, which have a reputation for high levels of efficacy and effectiveness over a long period of time, have a related reputation of being one of the most cost-effective malaria prevention interventions available (Goodman & Mills, 1999). Unfortunately, as often happens with interventions that seem self-evidently to work well at a low cost, cost-effectiveness analyses are neglected in favor of adequacy evaluations. When costs are analyzed, they are most often compared to coverage, as in cost per person protected, rather than to direct health outcomes, as in cases of malaria averted. In 2000, the lack of credible evidence prompted a systematic review team to publish guidelines for cost-effectiveness studies of ITNs; their guidelines apply to cost-effectiveness reviews of many malaria prevention programs and this thesis' methods follow them as much as possible (J. Kolaczinski & Hanson, 2006).

Fortunately, after publication of those guidelines, more studies have been published; unfortunately, the findings of those studies display great heterogeneity. In the 2011 systematic review cited above, the cost of ITN programs for a year's protection appears relatively stable across time and location, with a median standardized financial cost per person protected of $2.20 (range: $0.88 - $9.54) in 2009 United States dollars (USD). Cost-effectiveness studies of ITNs, however, are far less conclusive, with the median cost to the provider being $27 per DALY averted (range: $8.15-$110). The width of the range suggests that, as for many interventions, the context of the intervention matters. For ITNs in particular, one key factor that can dramatically affect program costs is whether participants must purchase their nets at full cost or can receive them for free or at a lower cost from the program, since nets represent a mean of 63% of costs to ITN programs (range: 12-92%) (White et al., 2011). Of the preventive malaria interventions,

people's willingness to pay is generally highest for ITNs. Coverage and effectiveness might therefore be relatively stable whether individuals buy their own nets and have them treated through the program or receive treated nets from the program (Trapero-Bertran, Mistry, Shen, & Fox-Rushby, 2013). If that is the case, if a cost-effectiveness study takes the provider perspective, a program in which participants buy their own nets will look much more cost-effective than a program that purchases the nets for its participants. This difference is part of what prompted the recommendation in the 2006 methods review that economic analyses of ITNs use the societal perspective whenever possible (J. Kolaczinski & Hanson, 2006).

2.5.4 IRS. As with the evidence on the effectiveness of IRS, the evidence on the cost-effectiveness of IRS is mixed. This section presents the results of a review of the published and grey literature, which included searches of MEDLINE, EMBASE, Web of Science, the Cochrane Library, and Econlit as well as searches of included studies' bibliographies and communications with staff members of RTI International. This section first discusses evidence available from 9 cost studies, which present intermediate outcomes such as cost per structure sprayed or cost per person protected. It then discusses evidence available from 6 cost-effectiveness studies, which present health outcomes such as cost per malaria case averted or cost per DALY averted. It concludes by discussing evidence available from 6 computer simulations of cost, cost-effectiveness, or cost-benefit models.

2.5.4.1 Cost studies. Cost studies provide an important counterpart to the effectiveness studies described above. They include no estimates of health outcomes, and if they compare interventions, their authors implicitly or explicitly assume that they provide equivalent health effects at equivalent levels of coverage. This review covers 9 cost studies on IRS: 5 conducted in sub-Saharan Africa, 3 in south-east Asia, and 1 in South America. Six of them compare IRS with

ITNs (Curtis, Maxwell, Finch, & Njunwa, 1998; Guyatt, Kinnear, Burini, & Snow, 2002; Kere & Kere, 1992; Konradsen et al., 1999; Kroeger, Ayala, & Lara, 2002; Verlé, Lieu, Kongs, Van Der Stuyft, & Coosemans, 1999); two compare different formulations for IRS within a single context (Konradsen et al., 1999; Mills, 1992); and two discuss overall programmatic costs for countries' IRS programs supported by PMI (Abbott & Johns, 2013; Sine, Colaco, & Frawley, 2011). All but one of them use the provider perspective for their cost calculations; the other takes the societal perspective (Konradsen et al., 1999). Two of the studies taking the provider perspective present participants' costs but do not factor them into their overall calculations for IRS (Guyatt, Kinnear, et al., 2002; Mills, 1992).

Of the studies that compare ITNs with IRS, two found that IRS is less expensive per person protected, while four found that ITNs are less expensive person protected. In general, studies in which only one round of IRS is required find the cost per person protected to be lower than studies in which two rounds are required, often to the point that, in terms of cost per person protected, one round of IRS is cheaper than ITNs but two rounds are more expensive. DDT is generally the cheapest chemical available for IRS, followed by malathion and ICON; programs that have to change formulations due to drug resistance generally see their cost per person protected increase. In the analysis of PMI-supported IRS campaigns, a threshold affect in terms of cost per structure sprayed occurs when a program's scale reaches approximately 150,000 structures sprayed. Where more than 150,000 structures are sprayed, mean cost per structure sprayed is less than or equal to $15 (2010 USD); when fewer than 150,000 structures are sprayed, mean cost per structure sprayed is greater than or equal to $20 (Sine et al., 2011).

Consistently, the most important driver of costs per person protected for both ITN and IRS programs is the cost of insecticides, though IRS program costs display relatively more

sensitivity to insecticide costs (Abbott & Johns, 2013; Guyatt, Kinnear, et al., 2002; Kroeger et al., 2002; Sine et al., 2011; Verlé et al., 1999). Since insecticide costs generally increase when programs face insecticide resistance, conducting thorough sensitivity analyses for insecticide costs is important when attempting to describe the potential costs of an IRS program. Other important costs are the costs of spray operations, including the equipment and personnel, and the costs of full-time local staff (Abbott & Johns, 2013; Guyatt, Kinnear, et al., 2002; Sine et al., 2011).

2.5.4.2 Cost-effectiveness studies. Cost-effectiveness studies go a step beyond cost studies: instead of assuming that the interventions in question provide equivalent effectiveness at equivalent levels of coverage, they include health outcomes in their measures of effect. These comparisons allow program designers and policy makers to compare programs with different intermediate outputs, including different malaria programs if the outcome is cases of malaria averted or different health programs if the outcome is DALYs averted. Of the 6 cost-effectiveness studies, 3 examine IRS in comparison with ITNs (Bhatia, Fox-Rushby, & Mills, 2004; Goodman et al., 2001; Kamolratanakul, Butraporn, Prasittisuk, Prasittisuk, & Indaratna, 2001), while 3 consider IRS versus some other standard of prevention and so are not discussed in this review (Conteh, Sharp, Streat, Barreto, & Konar, 2004; Xu et al., 2002; J. O. Yukich et al., 2008). 3 use data from Asia, while 3 examine data from sub-Saharan Africa. Similarly to the cost studies, only one study takes the societal perspective (Bhatia et al., 2004), with the other five taking the provider perspective.

In the studies that compare IRS and ITNs, ITNs generally appear to be more cost-effective than IRS. A study in KwaZulu-Natal, South Africa found that in its base case, ITNs are generally more expensive but also more effective in terms of malaria cases averted. In a best-

case scenario analysis, it found that when nets and treatments are as cheap as possible, with a useful net life of 6 years, and a high initial distribution of nets, ITNs dominate IRS. That is, ITNs are expected to be both cheaper and more effective than IRS (Goodman et al., 2001). A study in India, which uses the societal perspective, also found that in its base case ITNs are significantly cheaper per case averted than IRS. It notes, however, that a switch from deltamethrin to synthetic pyrethroids for IRS and ITNs causes the confidence intervals for the incremental cost-effectiveness ratios (ICERs) for the two programs to overlap, suggesting that their cost-effectiveness measures are then equivalent (Bhatia et al., 2004). A final study in Thailand likewise found ITNs to be more cost-effective than IRS, though the study provides neither confidence intervals around its estimates nor sensitivity analyses of its results (Kamolratanakul et al., 2001).

In all studies that conducted sensitivity analyses on their findings, the primary driver of changes in cost estimates was the type of insecticide used for IRS. Other important considerations were the cost and useful life of nets (in studies that examined ITNs), personnel requirements, the number of structures sprayed per day, and the number of rounds of IRS required (Bhatia et al., 2004; Conteh et al., 2004; Goodman et al., 2001; Xu et al., 2002; J. O. Yukich et al., 2008).

2.5.4.3 Models. Cost-effectiveness models allow policy makers to consider how evidence might translate to their context and to audition programmatic options without the risks of real-world experiments. They must, however, accept the limitations of using data from one setting to attempt to predict outcomes in another setting. This review discusses 6 economic models that describe the implications of various aspects of IRS. 3 models examine the chemicals used in IRS, with DDT being of particular concern (Blankespoor, Dasgupta, Lagnaoui, & Roy, 2012;

Pedercini, Movilla Blanco, & Kopainsky, 2011; Walker, 2000); 2 models describe the economics of several malaria prevention and control programs, including IRS (Goodman, Coleman, & Mills, 1999; Morel, Lauer, & Evans, 2005); and 1 model analyzes the importance of malaria transmission rates to the cost-effectiveness of malaria control (Worrall, Connor, & Thomson, 2008). 4 are specific to IRS in sub-Saharan Africa, while 2 have a global scope. As in the other economic analyses presented here, the majority of models take the provider's perspective, with only two taking the societal perspective (Blankespoor et al., 2012; Goodman et al., 1999)

According to the models that examine different chemicals for use in IRS, DDT generally appears to be the cheapest available pesticide, but the negative health and economic impacts of using DDT might outweigh its positive effects. In a costing model from a World Bank working paper that examines the cost per structure sprayed for various pesticides, DDT is cheaper than almost all other WHO-approved formulations. The authors note, however, that the costs of other pesticides appear to be falling over time compared to DDT and that not all countries will pay the same fair market price for the same pesticide (Walker, 2000). Another working paper from the World Bank examines the costs and health effects of DDT use for IRS. It concludes that in some countries, the gains from improving malaria outcomes using DDT might be offset by negative consequences of DDT exposure, but in countries with high malaria endemicity, the health improvements from preventing malaria through IRS with DDT might outweigh the negative consequences (Blankespoor et al., 2012). The final model examining DDT uses cost-benefit analyses and systems theory to predict the effects of phasing out DDT use on gross domestic product (GDP). It describes the interactive effects of health, population dynamics, education, productivity, and malaria conditions in order to create a 40-year prediction of the economic effects of DDT use or non-use. The authors conclude that direct costs are higher for IRS without

DDT than for IRS with DDT, but that continuing use of DDT for IRS and rapidly phasing out use of DDT for IRS do not differ significantly in terms of the resultant yearly gain in GDP. They also note that DDT use for IRS appears less attractive in countries where agricultural exports form an important portion of GDP, as such countries would be more affected by a loss of agricultural exports due to DDT resistance (Pedercini et al., 2011).

The two models that examine IRS in comparison with other interventions both employ cost-effectiveness models with DALYs averted as the outcome. One, which discusses IRS with ICON, only accounts for IRS' protective effect in infants less than 12 months of age. The authors conclude that in low-income countries—in which category Tanzania is included—cost-effectiveness of IRS varies significantly by the number of rounds conducted, with the cost per DALY averted of two rounds per year being nearly twice as great as the cost per DALY averted for a single annual round. They note that their cost-effectiveness estimates change in response to the cost of insecticides, but the change is very small. Also, in high-income countries with lower baseline mortality due to malaria, the cost per DALY averted is expected to be much higher. ITNs and IRS are predicted to be of comparable cost per DALY averted (Goodman et al., 1999). The creators of the other model conclude that ITNs are significantly more cost-effective than IRS in terms of cost per DALY averted, but errors in their calculations prevent a nuanced interpretation of the drivers of those costs (Morel et al., 2005).

Finally, one model compares the cost per case prevented through IRS at different rates of malaria transmission. The authors find that the cost per case averted is extremely attractive in years of medium, high, or epidemic rates of malaria transmission, but that the cost per case averted becomes nearly 100 times greater in years of low transmission. They suggest that a prediction of upcoming malaria transmission rates through an electronic monitoring system

might allow programs to adjust their scale to ensure adequate coverage in years of high transmission and to prevent wasting resources in years of low transmission (Worrall et al., 2008).

2.6 Discussion of Available Evidence

The available evidence suggests that IRS can provide cost-effective malaria prevention, but its degree of cost-effectiveness varies across contexts. The type of pesticide used is crucial for both the cost and effectiveness estimates of an IRS campaign. Aside from direct differences in the cost of pesticides, the different lengths of time for which the pesticide remains effective may require different numbers of rounds of spraying each year, which alters the cost of IRS.

Most of the above studies take the provider perspective. While this perspective allows malaria program designers to consider how IRS might fit into their budgets, it does not permit governments to consider the overall effects that their policies might have on their citizens. Furthermore, it can make comparing estimates across studies difficult if not all programs purchase the same categories of goods, with the purchase cost of ITNs being a particularly important category that can be excluded if participants purchase their own nets. Since programs purchase the majority of inputs for IRS campaigns, using the provider perspective might be adequate in most cases, but in a comparison with ITNs, using only the provider perspective might bias results in favor of ITNs.

In general, the economic studies listed above consider interventions one at a time. Since countries frequently implement multiple interventions, however, a more meaningful comparison would include scenarios that consider combinations of interventions.

The available studies rarely consider differences between programs operating under endemic versus epidemic malaria conditions. Unfortunately, the cost and efficacy data for IRS and ITNs in epidemic situations are lacking, with much of the information being anecdotal rather

than systematic. Without these input data, meaningful cost-effectiveness analyses of IRS in epidemic settings are impossible (Worrall, Rietveld, & Delacollette, 2004).

Finally, from a technical standpoint, many of the included studies have serious flaws or omissions, particularly in how they handle the uncertainty surrounding their estimates. Almost all of the included studies describe their limitations and assumptions, but few provide measures of the uncertainty surrounding their estimates through confidence limits for point estimates or through sensitivity analyses on important variables. Since the evidence around IRS programs is often contradictory and always context-specific, studies that present only point estimates of their measures of cost or effectiveness can overstate the strength of their findings.

In response to the gaps highlighted above, this thesis focuses on a programmatically relevant combination of interventions, with both costs and effects considered from a societal perspective. A series of sensitivity and scenario analyses illuminate important drivers of variability and uncertainty in the findings. The IRS data include multiple pesticide formulations, thereby allowing for sensitivity analyses related to this important factor. The next chapter describes the methods of data collection and analysis as well as the results of the study.

Chapter 3: Project Contents

3.1 Methodology

3.1.1 Introduction. This section describes the parameters included in the decision tree model used for analysis. It describes the setting and population assumed for the model, the overall research design, the process used to develop the model, the procedures and instruments used to gather the data, the methods of data analysis, and ethical considerations. It ends with a discussion of the limitations and delimitations of this study.

3.1.2 Population and Sample. This thesis addresses malaria among residents of mainland Tanzania who are under the age of five years old. The data on malaria prevalence, treatment-seeking behaviors, and malaria prevention activities of Tanzanian residents in other age groups were inadequate for an analysis of malaria among all residents (Tanzania Commission for AIDS et al., 2013). This restriction will cause an underestimate of the effectiveness of both interventions in question, as both ITN use and IRS prevent malaria among individuals over five years of age.

The cost and coverage data for IRS were collected from IRS campaigns conducted in mainland Tanzania with support from RTI International between 2008 and 2012. The cost data for ITN campaigns and the effectiveness data were gathered from reviews and literature published between 2000 and 2014, with all data drawn from sub-Saharan Africa. The cost of illness data were taken from a study that presents the Tanzania-specific societal costs of cases of malaria of varying degrees of severity (Sicuri, Vieta, Lindner, Constenla, & Sauboin, 2013). The process of gathering these data is described below under “Instruments.”

3.1.3 Research design. This thesis uses decision-tree analysis using TreeAge software to examine the questions outlined in the introduction. A decision tree begins with a single decision

node representing two possible interventions. Here, the interventions being compared are ITNs alone and a combination of IRS with ITNs. Each intervention branch contains a series of chance nodes representing the probability of two intermediate outcomes; each node also contains an interval estimate around the point probability estimate. The chance nodes lead to a series of final cost outcomes and effectiveness outcomes presented at the terminal nodes, each of which also has interval estimates around its point estimates.

The cost and outcome values of each terminal node are multiplied by the overall probability of reaching that terminal node, and this process is "rolled back" through the decision tree until a single expected cost and a single expected effectiveness are determined for each intervention at the initial decision node. These are compared to produce an incremental cost-effectiveness ratio (ICER) that describes the expected cost per unit of an outcome, such as a case of malaria prevented. When the effectiveness outcome is undesirable, as is a case of malaria, a negative ICER suggests that one of the two interventions is more expensive but more effective than the other. The choice between the two interventions then requires a judgment call based on the policy maker's willingness to pay for the improved outcome. A positive ICER suggests that one intervention "dominates" the other: that is, that one is both cheaper and more effective than the other. In such a case, the dominant intervention should always be chosen. Through multiple iterations of the model that vary the probability at each chance node and the various potential costs at each terminal node according to a defined probability distribution, a 95% confidence region can be developed to show how much the ICER varies due to chance.

3.1.4 Procedures. The decision tree was designed based on important intermediate outcomes identified during the literature review as associated with variability in the costs and/or

effectiveness of IRS and ITN programs. Please see Appendix I for images of the tree and a description of its parameters.

The probabilities and distributions at each chance node were drawn from the published literature as cited below. Malaria cases averted were chosen as the health outcome over DALYs or other quality of life measures because the programmatic decision being evaluated involves the allocation of malaria funds, not the allocation of public health or other government funds. As such, the clear outcome of cost per malaria case averted will provide sufficient information for the NMCP and other stakeholders to evaluate these interventions. Using cost per DALY averted would add complexity and necessitate assumptions with little support from real-world data.

As the NMCP is a governmental program, cost data were gathered from a societal perspective. Costs to the agency running the campaigns were gathered from RTI International expenditure reports and the published literature. The costs of a case of malaria to society were estimated from published data specific to Tanzania. The time frame and the analytic horizon for this study are both one calendar year.

All expenses were entered into the RTI International expenditure reports in USD according to the exchange rate during the month in which they were recorded. Where cost data were drawn from published literature, all included studies reported their costing in USD, and so reported USD costs were used. In accordance with WHO cost-effectiveness guidelines, all costs were converted to 2011 USD using the United States GDP deflator (Tan-Torres Edejer et al., 2003; U.S. Department of Commerce Bureau of Economic Analysis, 2015).

The costs of LLINs were annualized over their expected useful life—3 years at baseline, varied between 1 and 5 years in sensitivity analyses—at a standard baseline discount rate of 3%. Other capital costs were likewise annualized over their expected useful life. Controversy persists

over the appropriateness of a 3% discount rate, and so to check the robustness of the findings to changes in this assumption, the discount rate was varied between 0% and 5% in sensitivity analyses (Tan-Torres Edejer et al., 2003).

3.1.5 Instruments. This section describes the procedures for collecting and synthesizing the cost and effectiveness data used in the decision-tree analysis. It begins with discussing the data collection process for the Tanzania IRS program, the only primary data used in this analysis. It continues with a description of the process of gathering ITN programmatic cost data, malaria costs of illness, and effectiveness data from the published literature.

3.1.5.1 IRS cost data As stated above, the only primary data used in this thesis are the cost data from the program implementer's perspective. All expenditure data for the IRS campaign at each regional office were entered electronically at the time of expenditure. These data were sent to the central office in Dar es Salaam, where they were checked for errors and compiled into a report each month. Each monthly report was sent to RTI International headquarters in North Carolina, where it was entered into Cognos software.

The values of in-kind contributions, including governmental support and water contributions from households, were estimated during in-person interviews with district, regional, and national government officials. These estimates were reviewed by RTI International staff members who supported the spray operations and by regional health officers. Please see Appendix II for the instrument used during the interviews. When the RTI International staff members' estimates were lower than those of the government officials, the arithmetic mean of the estimates was used (Colaço et al., 2014).

All IRS cost data were collapsed into five broad categories in an Excel file: spray operations, spray operations commodities, local administration, in-kind contributions from the

government and community members, and short-term technical assistance (STTA) and US- and Nairobi-based support services. The components of each of these categories are displayed in Table 1. As none of the ITN programs included in the analysis considered international support in their costing, all STTA and US- or Nairobi-based costs were excluded from the analyses.

The costs of each of the component categories were recorded for each year of spraying. During the spray campaigns, spray teams tracked the number of people reported to live in each household sprayed. The average number of people per household each year was then multiplied by the number of structures sprayed to estimate the number of people protected. Each component category's cost was divided by the number of people protected each year to determine the cost per person protected of each component category for each year. As noted above, the US GDP inflator was used to adjust the costs to 2011 USD. Expected useful lives were determined for capital expenditures by discussion with Tanzania-based RTI International staff and by standard estimates from the literature.

2011 was selected as the baseline costing year because it reflects the first year of bendiocarb use and so the first year in which multiple rounds of spraying were required. Since resistance to single-spray insecticides is likely to continue to increase, it is reasonable to assume that bendiocarb and other insecticides that require multiple rounds of spraying will be used in the future. As spraying had already been conducted for three years prior to 2011, the costs of IRS in 2011 should reflect the costs of an established program, rather than the start-up

Table 1: IRS cost categories

Category	Components	Notes
Spray operations	Planning and logistics assessment activities	
	Environmental compliance	Includes soak pit construction, waste storage, and waste disposal
	Training of spray operators	
	Information, education, and communication (IEC) and community mobilization	
	Warehousing	
	Short-term labor	Includes only seasonal labor directly tied to the spraying itself (e.g. spray operators, IEC mobilizers, field supervisors, and data entry clerks)
	Transportation	Includes only transportation directly tied to the spraying itself (i.e. transporting spray operators between villages)
	Other spray costs	Includes medical costs (pregnancy tests for spray operators, first aid), mop-up operations, post-spray meetings, and monitoring and evaluation activities
Spray operations commodities	Insecticide	
	Spray equipment and equipment repair kits	
	Personal protective equipment (PPE)	
	Shipping	
Local administration	Office leases, utilities, and maintenance	
	Office furniture, equipment, and supplies	
	Communication	
	Travel and transportation	Includes all transportation not directly tied to spray operations
	Local labor	Includes all long-term staff based in Tanzania employed by RTI International, as distinct from short-term staff hired only for spray operations
	Other local administration costs	
In-kind contributions	Warehouse space	Government-provided warehouse space
	Office space	Government-provided office space
	Government vehicles	
	Fuel for government vehicles	
	Government labor costs	
	Water usage at households	Used to hydrate insecticide sachets during spray operations
Short-term technical assistance and US costs	U.S.- and Nairobi-based support services	Not included in analysis
	U.S.- and Nairobi-based labor	Not included in analysis
	Lodging, per diems, and other expenses related to international travel to Tanzania	Not included in analysis

costs of a new program. 2012 was not selected as the baseline year because the strategic shift from blanket to targeted spraying during that year could render the effectiveness data used in this study inaccurate, as they were derived from blanket spraying campaigns. The minimum and

maximum values used for sensitivity analysis reflect the lowest and highest reported costs per person protected for each category.

In order to allow for sensitivity analyses of the number of rounds of testing, a separate variable representing the number of rounds of spraying was created with a baseline value of 2 and a range of 1 to 2. All costs directly associated with spraying—that is, all spray operations costs, plus the costs of insecticide, shipping costs of spray commodities, and water usage at households—were multiplied by the number of rounds of spraying. This total was added to the total of all other IRS costs to determine the total costs per person of IRS spraying.

3.1.5.2 ITN cost data. The baseline ITN program is the TNVS, which is described in the literature review. Briefly, the TNVS is a national program to promote ITN ownership for pregnant women and their infants through subsidized vouchers distributed through ANCs. The economic cost data for the TNVS were extracted from Mulligan, Yukich, and Hanson (2008) for all categories except for net costs. In order to reflect current net costs, an important driver of variability in ITN distribution costs, an estimate of 2014 LLIN prices in Tanzania was obtained from Tanzania-based RTI International staff. The minimum and maximum LLIN costs used in the sensitivity analyses reflect the minimum and maximum 2014 global costs of LLINs reported by UNICEF (United Nations Children's Fund (UNICEF), 2014). The categories for the TNVS cost data are presented in Table 2. As described above, the cost of the ITNs was annualized at a baseline value of three years of useful life at a baseline 3% discount rate.

Table 2: ITN cost categories

Category	Components	Notes
Net distribution operations	Planning and logistics assessment activities	
	Training distributors	
	Information, education, and communication (IEC) and community mobilization	
	Warehousing	Includes storage of nets
	Short-term labor	Includes only labor tied directly to the distribution of nets; if net distributors were volunteers, includes an economic valuation of their time
	Transportation	Includes only transportation directly tied to the transportation of nets
Net distribution commodities	Nets	LLINs come impregnated with insecticide, and so costs of insecticides are included in the costs of the net
	Voucher production	Only recorded if a voucher-based distribution scheme
Local administration	Office leases, utilities, and maintenance	Includes recurrent costs associated with running an office, less labor costs
	Office furniture, equipment, and supplies	Includes capital costs associated with running an office
	Local labor	Includes all long-term local staff, as distinct from short-term staff or volunteers hired only for net distribution and related activities

In order to reflect potential differences in costs of ITN distribution due to varying distribution strategies, a review of published costing studies for ITN/LLIN distribution was consulted (White et al., 2011), with additional searches of MEDLINE, EMBASE, Web of Science, and EconLit conducted to capture studies published after the review's time frame. Costs per net distributed were extracted according to the categories used in the Mulligan et al. study from all studies that report costs of ITN/LLIN distribution programs. Studies differed widely in their categorization of costs. In order to avoid recording expenses twice, where categorizations were unclear or did not match with the Mulligan et al. categorizations, the costs for that category were not recorded. Economic costs, which account for the annualization of capital purchases and for the value of volunteers' time, were preferentially extracted over financial costs. After

conversion to 2011 dollars, the minimum and maximum non-zero costs were used as the bounds for the sensitivity analyses. The only exception to this process was the voucher costs, for which the minimum cost was set to zero to reflect a non-voucher-based distribution system.

As described in the literature review, the mainland Tanzania NMCP tends to operate with multiple international partners, with each partner focusing on a small portion of the overall malaria program. It seems likely that in regions with both IRS and ITNs, a separate administrative structure would direct each program. The IRS plus ITN arm of the decision tree therefore includes separate local administration costs for each program.

The cost per net distributed was calculated by adding up the costs from each category. In line with standard assumptions in Tanzania, it was assumed that each net protected 2 people (Tanzania Commission for AIDS et al., 2013). A new variable was created representing the number of people protected by a single net, with a baseline value of 2 and a range of 1 to 3 people. The cost per net distributed was divided by this new variable to determine the total cost of ITN distribution per person protected.

3.1.5.3 Malaria cost of illness data. The estimates of the cost of a case of malaria were drawn from a study examining the costs to society of a case of malaria in a child under the age of 5 in Tanzania (Sicuri et al., 2013). The components considered in the costs of illness are presented in Table 3.

Table 3: Cost of illness components

Category	Components	Notes
Household costs	Direct household costs	Includes costs of traveling to clinic, costs of hospitalization, costs of treatment, and user fees
	Indirect household costs	Includes caregivers' reported loss of productivity during the entire malaria episode
Health system costs	Recurrent costs	Includes drugs and personnel
	Capital costs	Includes equipment and building space
	Costs of complications	Includes blood transfusions for severe anemia, anti-seizure/anticonvulsant therapies for cerebral malaria, and rehabilitation costs post-discharge for neurological sequelae

The study presents costs for uncomplicated malaria, defined as malaria not requiring hospitalization; malaria with severe anemia; cerebral malaria, most commonly malaria accompanied by coma; and cerebral malaria with neurological sequelae. Uncomplicated malaria costs in Tanzania were used as the baseline for the cost of a case of malaria without complications. As there are no confidence limits presented around this point, the costs were varied by 50% in either direction for the sensitivity analyses. The cost of a case of malaria with complications was calculated using the method from the original article as the mean cost of a case with complications. The minimum value for sensitivity analysis was a case of malaria with severe anemia; the maximum value was a case of cerebral malaria with neurological sequelae.

3.1.5.4 Effectiveness data. This section describes the process of gathering and synthesizing the probabilities at each chance node in the tree in the order that they appear in the tree: the probability of receiving IRS in the dwelling, the probability of correctly using an ITN, the probability of malaria infection given no intervention, the reduction in the risk of malaria infection with each intervention or combination of interventions, the probability of an infected child developing symptoms, the probability that a symptomatic child seeks treatment, the probability that the treatment fails, and the probability that a symptomatic child develops complications due to malaria.

The probability of receiving IRS in the dwelling was drawn from reported coverage rates in recent spraying campaigns in mainland Tanzania, with the baseline being the mean reported level and the minimum and maximum reflecting the reported range (Akim et al., 2014; West et al., 2014). The probability of correctly using an ITN was drawn from the most recent MIS conducted in Tanzania. The baseline value is the mean 2011-12 mainland rate. The minimum value reflects the lowest regional usage rate, while the maximum reflects the highest (Tanzania

Commission for AIDS et al., 2013). As described in the literature review, there is little evidence regarding the association between electing to receive IRS and using an ITN, and the evidence available is contradictory. As such, receiving IRS and using an ITN were treated as independent variables.

As with the probability of correctly using an ITN, the population prevalence of malaria parasitemia was drawn from the most recent MIS conducted in Tanzania. The baseline value is the mean 2011-12 mainland rate. The minimum value reflects the lowest regional usage rate, while the maximum reflects the highest (Tanzania Commission for AIDS et al., 2013). The probability of parasitemia for each branch was calculated by multiplying the parasitemia rate by the risk reduction appropriate for the branch's intervention or interventions. The reduction of risk due to receiving IRS, using an ITN, or a combination of the two, was drawn from a study of MIS data from 17 sub-Saharan African countries (Fullman et al., 2013). The risk reductions used reflect those of a medium-transmission setting—a parasite rate of $Pf\text{PR}_{2\text{-}10}$ between 5% and 40%—which describes much of mainland Tanzania. The estimates of risk reduction may not apply to regions with the lower parasitemia rates included in this thesis. In the original study, however, the confidence intervals around the risk reduction in low transmission settings, with $Pf\text{PR}_{2\text{-}10}$ between 0% and 5%, contain the confidence intervals for the same interventions in the medium-transmission setting.

The probability that a child infected with the malaria parasite actually develops symptoms of malaria is uncertain. The baseline rate was taken from a one-year follow-up study in Uganda (Njama-Meya, Kamya, & Dorsey, 2004). The maximum rate assumes all infections will eventually lead to malaria, as is suggested by a study in Dar es Salaam that reports no asymptomatic malaria cases among school children (Strøm, Tellevik, Fataki, Langeland, &

Blomberg, 2013). The assumption of all cases of malaria eventually becoming symptomatic also reflects personal communications from malaria experts. The minimum rate is the lowest calculable rate in the literature, drawn from a cross-sectional study in Mozambique (Mabunda, Aponte, Tiago, & Alonso, 2009).

The probability of seeking formal treatment is also drawn from the most recent MIS conducted in Tanzania. The baseline value is the average 2011-12 mainland rate. The minimum value reflects the lowest regional usage rate, while the maximum reflects the highest.

The probability of treatment failure, defined as a relapse of the same malaria infection with confirmation by polymerase chain reaction testing (PCR) within 28 days of the start of treatment, is drawn from the literature. The baseline represents the PCR-corrected failure rate using ALu in mainland Tanzania, while the maximum represents treatment failure after using a monotherapy of Amodiaquine (Mutabingwa et al., 2005). The minimum represents perfectly effective treatment, as recorded in a study using ALu in northeastern Tanzania, in which all apparent treatment failures were novel infections (Shayo et al., 2014).

The probability of developing complicated malaria is drawn from a follow-up study in children aged 1-4 in Tanzania, with the range reflecting the confidence limits of the estimate (Gonçalves et al., 2014). This study assumes that the probability of developing complicated malaria does not change whether the child receives no formal treatment or whether the child receives formal treatment but the treatment fails. The published literature neither confirms nor contradicts this assumption. It is further assumed that if a child receives treatment for the initial infection and that treatment fails, the child will receive treatment for the second infection. In the interests of not having the tree continue into eternity, the second round of treatment is assumed to be the final round. The second round of treatment could also fail, of course, but the probability

of reaching that point is small enough that it would have little influence on the overall cost-effectiveness estimates.

3.1.6 Plans for data analysis. The primary outcome of interest for this study is the ICER comparing IRS and ITN usage together versus ITN usage alone. Tornado diagrams were used to determine the most parsimonious combination of variables that explain at least 95% of the variability in the expected costs and in the expected number of cases. They were also examined for any additional variables that display a threshold effect on the costs and effects—that is, variables whose ranges include values at which the preferred intervention changes. One-way sensitivity analyses of the effects of varying these parameters over their ranges on the expected costs, cases, and cost per case averted for each arm were then performed.

Of the parameters used for one-way sensitivity analyses, those whose variation affects the expected cost per case averted were set to vary over their distributions through a series of 10,000 iterations of the decision tree to generate the 95% confidence field for the ICER. Parameters that only affect expected costs or cases expected without affecting the expected cost per case averted were held at their baseline value. Count variables were defined as triangular. A log normal distribution was assumed around the baseline value for cost estimates based on the values collected, with the limits of the observed ranges taken as the 95% confidence limits of the distribution. A beta distribution was assumed for probabilities, with α and β determined by visually examining distributions in R Studio to find values that give the appropriate expected value and a distribution that appears to fall within the appropriate range. All other parameters were held at their baseline level.

A best-case and worst-case scenario analysis was also conducted in which the variables selected from the tornado diagram were set to the levels that made the combined intervention

appear as good and as bad as possible, respectively, when compared to ITNs alone. “Best” and “worst” were assessed in terms of expected cost per case averted from the combined intervention. If variations in the parameter do not result in any changes in the expected cost per case averted, then the value that provides the highest or lowest cost for the combined intervention was selected. Finally, if varying the parameter changes neither the expected cost per case averted nor the expected cost of the intervention, the value that provides the highest or lowest expected number of cases of malaria was selected. All parameters not identified in the tornado diagrams were held at their base case level.

In order to assess the potential effects of differing levels of malaria prevalence on the ICER, the probability of exposure to malaria—described using prevalence of parasitemia—was used in one-way sensitivity analyses.

The potential effects of differing levels of IRS coverage and IRS strategy were assessed through scenario analyses in which the coverage rates and the effectiveness of IRS were shifted to their minimum plausible levels.

Finally, the potential effects of changes in insecticide characteristics were assessed using a sensitivity analysis and a scenario analysis. The sensitivity analysis describes the potential effects of variations in the cost of insecticides on the ICER of the two intervention arms. It represents a scenario in which the efficacy of the pesticides remains unchanged in mainland Tanzania but the global price for pesticides varies. The scenario analysis describes a potential increase in pyrethroid resistance. The expected effectiveness of ITNs was decreased to its lowest plausible value, and the maximum cost estimates from two annual rounds of IRS with bendiocarb were used. All other parameters were held at their base case values.

3.1.7 Ethical considerations. The only primary data analyzed in this thesis are cost data with no links to identifiable individuals. All outcome data were drawn from published literature and hence are secondary data. As such, this thesis does not constitute human subjects research; Emory IRB approval was not required.

3.1.8 Limitations and delimitations. This model only considers a single year of the intervention. As such, it cannot describe the potential cost savings of a long-term malaria program that reduces the prevalence of parasitemia. Unfortunately, as described in the literature review section, the effectiveness data that would allow a multi-year analysis do not exist; extrapolating the available single-year effectiveness data into a multi-year model would involve an unacceptable amount of guesswork. IRS requires spraying at least once each year and so generates relatively high recurrent costs; ITN distribution, conversely, requires only one net for several years' protection and so generates relatively high capital costs. A focus on single-year costs rather than multiple-year costs might bias the results in favor of a combination of IRS and ITN programs versus ITNs alone. The annualization of the cost of an ITN over its usable life should mitigate this concern.

Also, the model only compares a combination of IRS and ITN distribution versus ITN distribution alone, this study cannot evaluate an IRS-only intervention. As mentioned in the literature review, however, ITNs serve as the centerpiece of Tanzania's malaria control program; it is extremely unlikely that the NMCP would halt ITN distribution completely in favor of an IRS-only strategy.

Although the various sensitivity and scenario analyses attempt to show how the results might apply across mainland Tanzania, the most recent cost and outcome data are specific to the

IRS campaigns in northwest Tanzania. It is possible that differences in malaria control programs within Tanzania might render this generalization invalid.

As with any model, although the cost and effectiveness estimates presented reflect the best data available, the model can only generate probabilities, not certainties. Factors exogenous to the model could influence its outcomes. For example, the accessibility and type of malaria testing available might increase the chances that a person with parasitemia learns that they have it and so increase the probability that they seek treatment. This would increase costs in the short term, but with a longer analytic horizon, prompt testing and effective treatment could lower the transmission rate within the population and so reduce both cases and costs over time.

This model excludes potential costs to agriculture and deleterious health effects due to the spraying of pesticides within homes. This is a potential downside of IRS spraying, but the long-term effects of spraying with bendiocarb are uncertain. Most studies examining the long-term effects of insecticide-based vector control focus on DDT, and most studies describing the relationship between malaria and agriculture focus on productivity losses due to illness (Asenso-Okyere, Asante, Tarekegn, & Andam, 2011). The data are insufficient to include these considerations in the model, but NMCP staff should weigh the balance of decreased illness and the potential long-term costs of pesticide use.

3.2 Results

3.2.1 Values. Values for the probabilities, their ranges for one-way sensitivity analyses, and their sources are shown in Table 4.

Non-annualized values for costs, their sources, and their ranges are shown in Table 5. All costs are presented in terms of person protected except for ITN costs, which are presented in terms of net distributed so that the number of people protected per net can be varied in sensitivity analysis.

Table 4: Probability values

Description	Baseline	Minimum	Maximum	Source(s)
Probability receive IRS in dwelling	0.908	0.840	0.947	(Akim et al., 2014; West et al., 2014)
Probability correctly use an ITN	0.745	0.587	0.889	(Tanzania Commission for AIDS et al., 2013)
Probability develop parasitemia, given no intervention	0.095	0.000	0.318	(Fullman et al., 2013; Tanzania Commission for AIDS et al., 2013)
Risk reduction of parasitemia with ITN use	0.130	0.030	0.220	(Fullman et al., 2013)
Risk reduction of parasitemia with IRS use	0.200	0.030	0.340	(Fullman et al., 2013)
Risk reduction of parasitemia with IRS and ITN use	0.530	0.370	0.670	(Fullman et al., 2013)
Probability develop malaria symptoms	0.890	0.117	1.000	(Mabunda et al., 2009; Njama-Meya et al., 2004; Strøm et al., 2013)
Probability seek formal treatment	0.776	0.481	0.946	(Tanzania Commission for AIDS et al., 2013)
Probability that treatment fails (continue to test positive for the *same* malaria infection with PCR correction)	0.027	0.000	0.485	(Mutabingwa et al., 2005; Shayo et al., 2014; Tanzania Commission for AIDS et al., 2013)
Probability develop complicated malaria	0.157	0.104	0.233	(Gonçalves et al., 2014)

Table 5: Non-annualized cost values (2011 USD)

Description	Baseline	Minimum	Maximum	Source(s)
5a. IRS				
Planning and logistics assessment activities	$0.02	$0.02	$0.26	RTI International expense reports
Environmental compliance	$0.00	$0.00	$0.02	RTI International expense reports
Training	$0.27	$0.14	$0.27	RTI International expense reports
IEC and community mobilization	$0.09	$0.07	$0.23	RTI International expense reports
Short-term labor	$0.45	$0.40	$0.61	RTI International expense reports
Transportation	$0.33	$0.29	$0.50	RTI International expense reports
Other spray operations costs	$0.44	$0.05	$0.44	RTI International expense reports
Insecticide	$0.43	$0.34	$0.84	RTI International expense reports
Spray equipment and equipment repair kits	$0.00	$0.00	$0.15	RTI International expense reports
Personal protective equipment (PPE)	$0.04	$0.00	$0.11	RTI International expense reports
Shipping	$0.06	$0.04	$0.07	RTI International expense reports
Office leases, utilities, maintenance	$0.04	$0.03	$0.07	RTI International expense reports
Office furniture, equipment, supplies	$0.01	$0.01	$0.16	RTI International expense reports
Communication	$0.02	$0.02	$0.02	RTI International expense reports
Travel and transportation	$0.03	$0.03	$0.09	RTI International expense reports
Vehicle purchase	$0.00	$0.00	$0.06	RTI International expense reports
Local labor	$0.26	$0.07	$0.45	RTI International expense reports
Other local administration	$0.02	$0.02	$0.04	RTI International expense reports
Warehouse space	$0.01	$0.01	$0.03	RTI International expense reports
Office space	$0.00	$0.00	$0.01	RTI International expense reports
Government vehicles	$0.00	$0.00	$0.01	RTI International expense reports
Fuel for government vehicles	$0.00	$0.00	$0.00	RTI International expense reports
Government labor costs	$0.02	$0.02	$0.05	RTI International expense reports
Water usage at households	$0.04	$0.03	$0.05	RTI International expense reports

Description	Baseline	Minimum	Maximum	Source(s)
5b. ITNs				
Planning and logistics assessment activities	$0.02	$0.02	$0.81	(Guyatt, Corlett, Robinson, Ochola, & Snow, 2002; Guyatt, Kinnear, et al., 2002; Mulligan, Yukich, & Hanson, 2008; White et al., 2011)
Training distributors	$0.49	$0.01	$1.52	(Guyatt, Corlett, et al., 2002; Guyatt, Kinnear, et al., 2002; Mulligan et al., 2008; White et al., 2011; J. Yukich, Mulligan, Tediosi, Hanson, & Lengeler, 2007)
IEC and community mobilization	$1.29	$0.04	$2.16	(Grabowsky et al., 2005; Mulligan et al., 2008; White et al., 2011; J. Yukich, McGuire, et al., 2007)
Warehousing/storage of nets	$0.12	$0.01	$0.30	(J. H. Kolaczinski et al., 2010; Mulligan et al., 2008; White et al., 2011)
Distributors' labor	$0.05	$0.01	$1.95	(Becker-Dreps et al., 2009; Goodman et al., 2001; Mulligan et al., 2008; White et al., 2011)
Transportation	$0.42	$0.05	$3.16	(J. H. Kolaczinski et al., 2010; Mulligan et al., 2008; White et al., 2011)
Nets	$3.36	$2.50	$4.80	(UNICEF, 2014), personal communication
Printing vouchers	$0.20	$0.01	$0.20	(Mulligan et al., 2008; White et al., 2011; J. Yukich, Mulligan, et al., 2007)
Office leases, utilities, maintenance	$0.27	$0.00	$0.27	(J. H. Kolaczinski et al., 2010; Mulligan et al., 2008; White et al., 2011)
Office furniture, equipment, supplies	$0.01	$0.01	$0.07	(De Allegri et al., 2010; Mulligan et al., 2008; White et al., 2011)
Administration/other staff labor (not net distribution)	$2.04	$0.04	$12.65	(Goodman et al., 2001; J. H. Kolaczinski et al., 2010; Mulligan et al., 2008; White et al., 2011)
5c. Cost of illness				
Uncomplicated malaria	$5.36	$2.68	$8.03	(Sicuri et al., 2013)
Severe malaria	$74.36	$39.53	$141.87	(Sicuri et al., 2013)

Estimated values—including useful lives for annualization, number of IRS rounds required, number of people covered by a single net, and the discount rate—are displayed with their sources and ranges in Table 6.

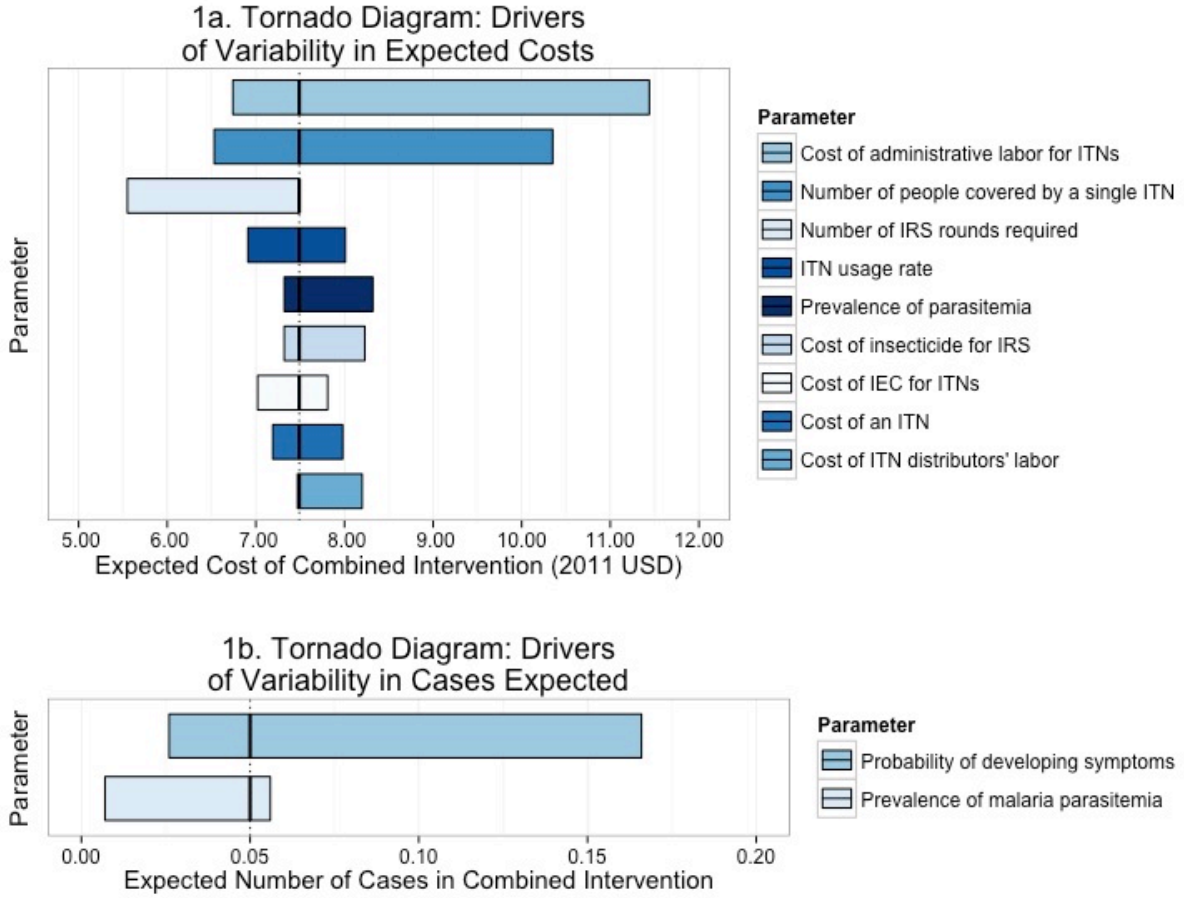
3.2.2 Base case. With all parameters set at baseline values, the combined intervention of IRS and ITNs is more expensive but more effective than ITNs alone. The expected cost of the ITN intervention alone is $3.41 per person targeted, with an expected 0.076 cases of malaria; the expected cost of the combined IRS and ITN intervention is $7.49 per person targeted, with an expected 0.050 cases of malaria. The baseline ICER is -$152.36. That is, when compared to ITN distribution alone, the expected cost per case of malaria averted by combining IRS with ITN distribution is $152.36.

The tornado diagrams describing the variability in expected costs and cases for the model are displayed in Figure 1. The width of each bar in the tornado diagram represents the degree of variability in the outcome explained by the parameter; parameters are listed by the proportion of variability they explain in descending order. The dark line in each bar represents the base-case values.

Table 6: Other estimated values

Description	Baseline	Minimum	Maximum	Source(s)
6a. Useful lives (years)				
Soak pits	3	1	5	(Sine et al., 2011)
Spray equipment	5	1	10	(Sine et al., 2011)
PPE	3	1	4	(Sine et al., 2011)
Office furniture, equipment, and supplies	3	1	5	(Sine et al., 2011)
Vehicle	5	4	6	(Sine et al., 2011)
Net	3	1	5	(UNICEF, 2014), personal communication
6b. Rounds and coverage estimates				
Number of rounds of IRS required	2	1	2	(Colaço et al., 2014)
Number of people covered by a single net	2	1	3	(Tanzania Commission for AIDS et al., 2013)
6c. Discount rate				
Discount rate	0.03	0	0.05	(Tan-Torres Edejer et al., 2003)

Figure 1: Tornado diagrams



As shown in Figure 1a, the primary drivers of variability in costs from the IRS portion were the number of IRS rounds required and the costs of insecticides; from the ITN portion, primary drivers of variability in costs were the cost of a net, the number of people protected by a single net, the cost of distributor labor, the cost of staff labor, the cost of IEC, and the prevalence of ITN usage; and from the tree as a whole, a primary driver of variability in costs was the prevalence of parasitemia in the population. Together, these variables accounted for over 95% of the variability in costs. For effectiveness, shown in Figure 1b, the prevalence of parasitemia and the probability that an infected child develops symptomatic malaria together explained over 98% of the variability in effectiveness. No parameters caused a threshold effect in either expected

costs or expected cases. The next section displays the results of one-way sensitivity analyses on these variables.

3.2.3 One-way sensitivity analyses.

3.2.3.1 IRS-only parameters. Two parameters were identified for sensitivity analysis that directly affect only the IRS portion of the IRS and ITN combination arm: the number of rounds required and the costs of insecticides for IRS. Both of these variables affect the expected cost of the combination arm without affecting the expected cost of the ITN-only arm. Neither parameter has any effect on the expected number of cases in either arm. They both affect the cost per case averted for the combined arm versus the ITN-only arm.

Figures 2 and 3 show the expected cost per person targeted, the expected number of cases of malaria per person targeted, and the incremental cost per case averted over the range of these parameters. In these figures, as in all such figures that follow in this section, the ITN-only intervention is presented using green triangles and the IRS-only intervention is presented using blue circles. The x-axes display the range of the parameter being analyzed in one-way sensitivity analysis. The y-axis differs for each chart shown: for the expected cost charts—Figures 2a and 3a—and the expected cases chart—Figures 2b and 3b, the y-axis represents the expected costs or cases at the corresponding parameter value. For the cost-effectiveness charts—Figures 2c and 3c—the y-axis represents the incremental cost per case averted when compared to the ITN-only arm at the corresponding parameter value. As the cheaper comparison group, the ITN-only arm will always have an incremental cost per case averted of $0.00. For the IRS and ITN arm, a larger number on the y-axis represents a larger cost per case averted.

Figure 2: Sensitivity analyses on number of IRS rounds required

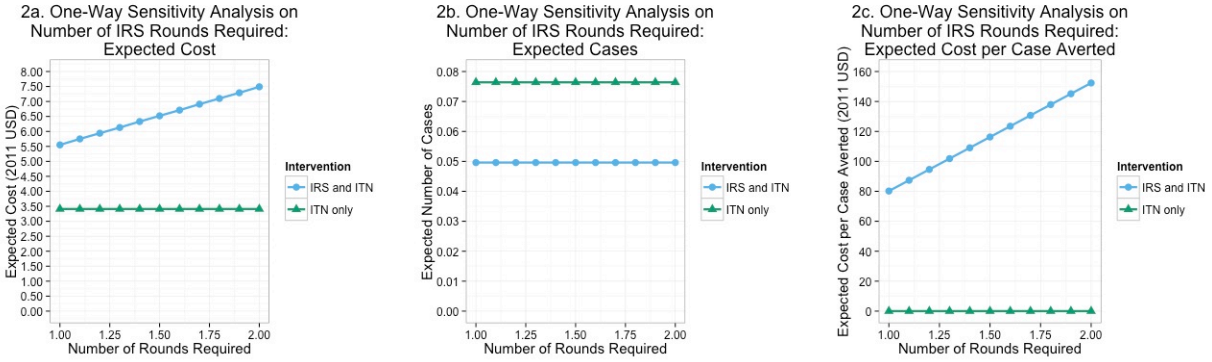
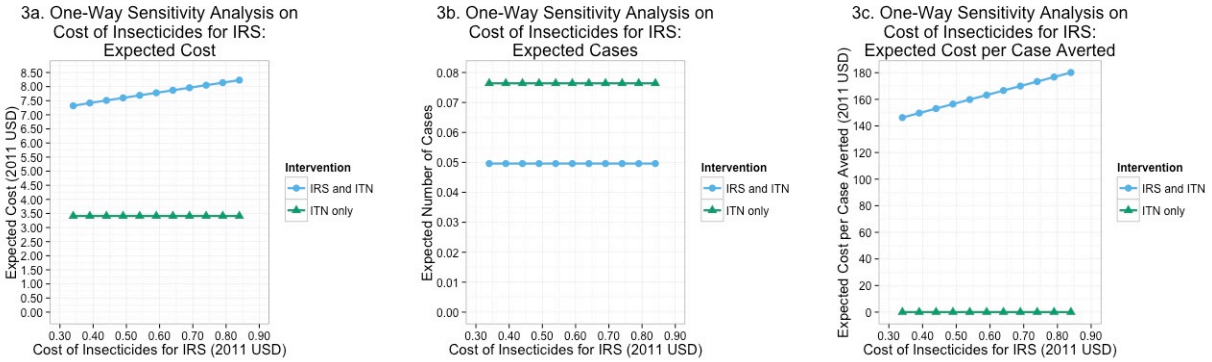


Figure 3: Sensitivity analyses on cost of insecticides for IRS



As the number of rounds required increases from 1 to 2, the expected cost of the combined intervention increases linearly from $5.55 to $7.49 while the expected cost of the ITN intervention remains constant. No change occurs in the expected number of cases over the range of this parameter. Driven by changes in costs, as the number of rounds increases, the expected cost per case averted increases from $80.18 to $152.36.

As the cost of insecticides increases, the expected cost of the combined intervention arm increases linearly from $7.32 to $8.23 while the expected cost of the ITN intervention remains constant. No change occurs in the expected number of cases over the range of this parameter. As the cost of insecticides increases, the expected cost per case averted increases linearly from $146.26 to $180.15.

3.2.3.2 ITN cost parameters. The degree of variability in the ITN cost estimates drives the expected cost of the ITN-only intervention and the ITN portion of the combined intervention to vary greatly. Since, however, variability in these costs causes parallel changes in the two arms' expected costs and causes no changes in the number of cases expected for either arm, none of these parameters alter the incremental cost per case averted, which is the primary outcome measure of this study. The one-way sensitivity analyses on the number of people covered by a single net and on the cost of a net are provided in Figures 4 and 5.

As the number of people covered by a single net increases, the expected costs of the interventions decline at the same rate, with the rate of decline diminishing as the number of people increases. The expected cost of the ITN-only intervention declines from $6.27 to $2.45, and that of the combined intervention declines from $10.35 to $6.53. As the cost of nets

Figure 4: Sensitivity analyses on number of people covered per ITN

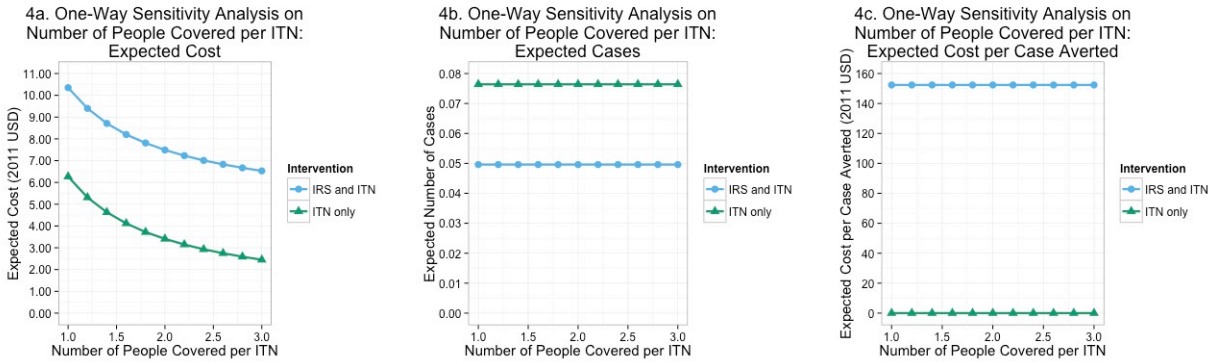
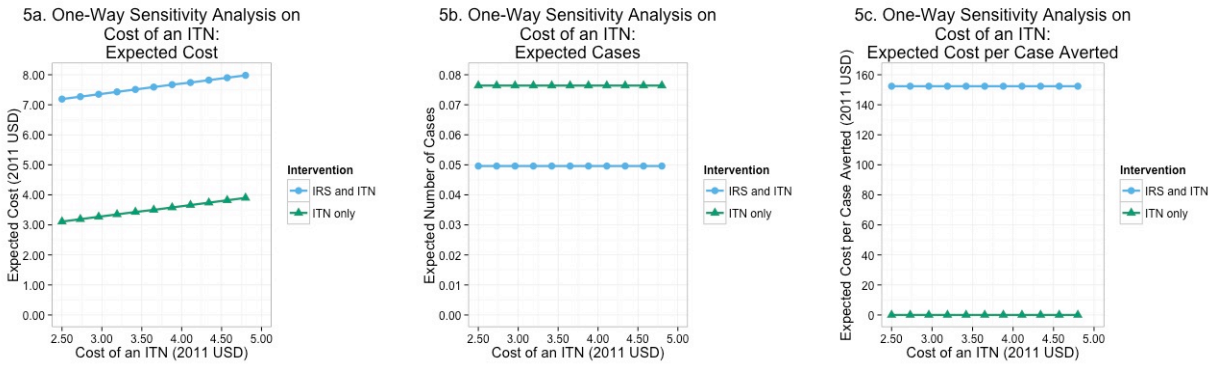


Figure 5: Sensitivity analyses on cost of an ITN

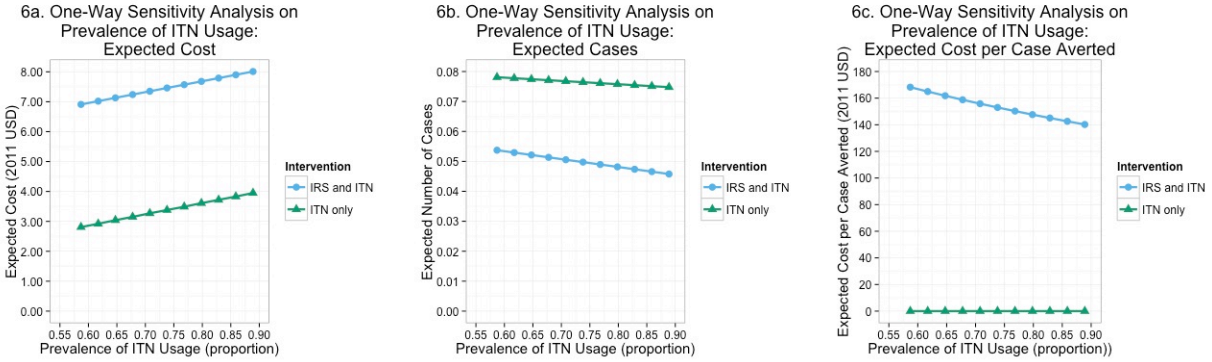


increases, the expected cost of the interventions increases linearly, with the ITN-only intervention increasing from $3.11 to $3.90 and the combined intervention increasing from $7.19 to $7.98. Both parameters drive parallel changes in expected costs in each arm and have no effect on the expected number of cases for either arm; therefore, they have no effect on the expected cost per case averted. The charts and interpretation for variations in IEC costs, administration and staff labor costs, and net distributors' labor costs are similar to those for variations in net costs. They appear in full in Appendix III.

3.2.3.3 Probability parameters. Three probability parameters were identified as driving variability in the model's outcomes: the prevalence of correct ITN usage, the population prevalence of parasitemia, and the probability that an infected person develops symptoms of malaria. All three of these parameters affect the expected costs and expected number of cases in both arms, and their variability drives changes in the expected cost per case averted.

Figure 6 shows the results of the one-way sensitivity analyses of ITN usage rates. As the rate of ITN usage increases, the expected cost of each arm increases linearly at the same rate, with the combined arm's expected cost increasing from $6.91 to $8.01, and the ITN-only arm's expected cost increasing from $2.81 to $3.95. At the same time, the expected number of cases in each arm decreases linearly, with the decrease being steeper in the combined ITN and IRS arm—from 0.054 cases to 0.046 cases—than in the ITN-only arm—from 0.078 cases to 0.075 cases. Together, these changes in the expected costs and cases for each arm cause the incremental cost per case averted by the combined arm versus the ITN-only arm to decrease linearly as the rate of correct usage of ITNs increases, from $168.24 per case averted to $140.20 per case averted.

Figure 6: Sensitivity analyses on prevalence of ITN usage



Figures 7 and 8 show the one-way sensitivity analyses on the prevalence of parasitemia in the population and on the probability that a child infected with the malaria parasite will develop symptomatic malaria. As shown in Figures 7a and 8a, as the values of these parameters increase, the expected cost of each arm increases linearly, with a more dramatic increase in the ITN-only arm. As the prevalence of parasitemia increases, the ITN-only arm's expected cost increases from $3.15 to $4.68, and the combined intervention arm's expected cost increases from $7.32 to $8.32. As the probability of symptoms increases, the ITN-only arm's expected cost increases from $2.93 to $3.47, and the combined invention arm's expected cost increases from $7.18 to $7.53.

Figure 7: Sensitivity analyses on probability of developing symptoms

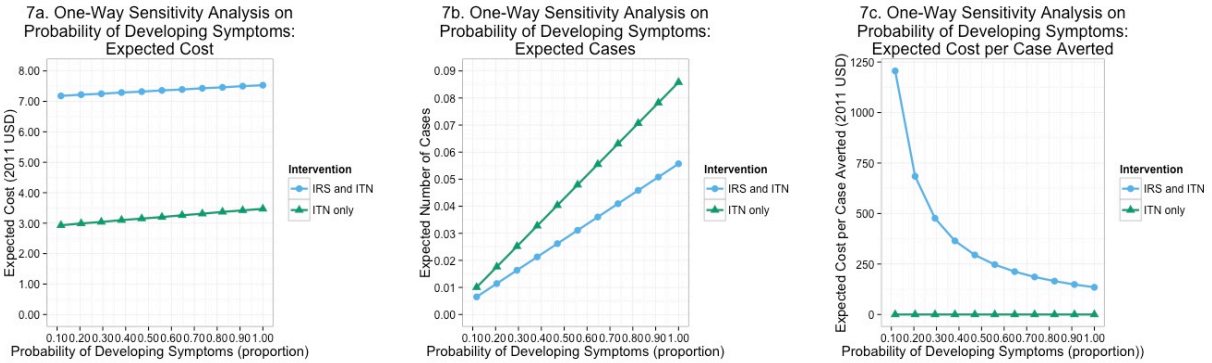
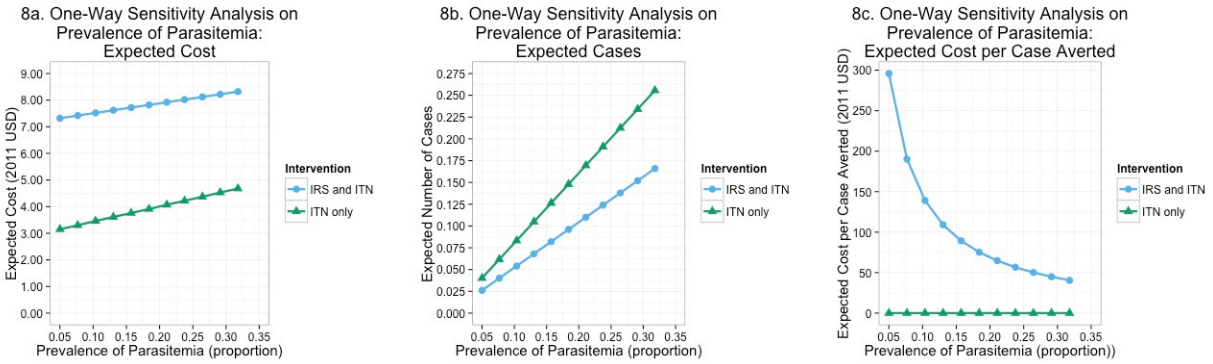


Figure 8: Sensitivity analyses on prevalence of parasitemia



Also, as shown in Figures 7b and 8b, as the values of these parameters increase, the expected number of cases increases linearly in each arm, with the increase being steeper in the ITN-only arm. As the prevalence of parasitemia increases, the expected number of cases increases from 0.040 cases to 0.256 cases in the ITN-only arm and from 0.026 cases to 0.0116 cases in the combined arm. As the probability of developing symptoms increases, the expected number of cases rises from 0.010 cases to 0.086 cases in the ITN-only arm and from 0.007 cases to 0.056 cases in the combined arm.

Together, these changes in the expected costs and cases for each arm drive the expected incremental cost per case averted by the combined arm versus the ITN-only arm to decrease as these parameters' values increase, with the rate of decrease slowing at higher prevalence rates. As shown in Figure 7c, as the prevalence rate of parasitemia increases, the expected cost per case averted declines from $295.89 to $40.53. As shown in Figure 8c, as the probability that an infected child develops symptoms increases, the expected cost per case averted declines from $1,205.98 to $134.82.

3.2.4 Probabilistic sensitivity analysis. The values used for probabilistic sensitivity analysis (PSA) are displayed in Table 7.

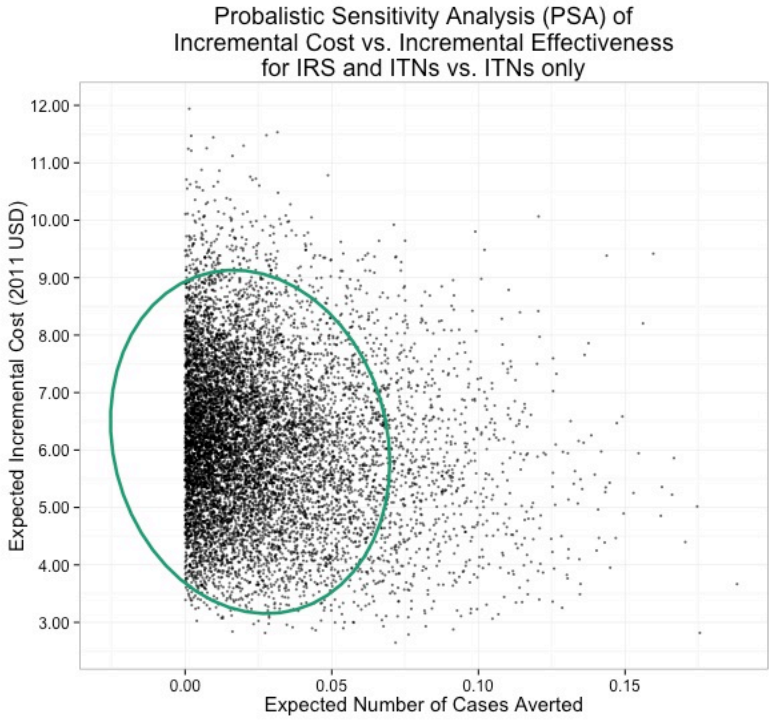
The results of the PSA in terms of the incremental cost per case averted are presented in Figure 9. Each iteration is represented by a single point; darker regions on the scatterplot show coordinates representing a higher number of iterations. The x-axis values represent the expected number of cases averted by implementing the IRS and ITN intervention instead of the ITN-only intervention per person targeted. The y-axis values represent the expected incremental cost of implementing the combined intervention instead of the ITN-only intervention. Note that the y-axis does not represent the cost per case averted, which would be calculated for each iteration by dividing the y-axis value by the x-axis value. The green ellipse in the figure represents the range in which 95% of the iterations fall, the equivalent of a 95% confidence range.

Table 7: Input values for probabilistic sensitivity analysis

Label	Expected Value	Minimum	Maximum	Distribution	Additional Parameters*
Number of IRS rounds required	2	1	3	Triangular	2.000
Cost of insecticide for IRS	$0.43	$0.34	$0.84	Log Normal	$0.22
Probability correctly use an ITN	0.745	0.587	0.889	Beta	74.5, 25.5
Probability develop malaria	0.890	0.117	1.000	Beta	2.67, 0.33
Probability of parasitemia, given no intervention	0.095	0.000	0.318	Beta	0.95, 9.15

*Additional parameters are mode for triangular distributions; standard deviation for log normal distributions; and α, β for beta distributions.

Figure 9: Probabilistic sensitivity analysis of incremental cost versus incremental effectiveness for IRS and ITNs versus ITNs only



Since all values are greater than zero in all cases, the combined intervention is always more expensive but more effective than the ITN-only intervention. The median expected incremental cost is $9.48 (95% confidence range: $6.98, $12.57), and the median expected number of cases averted is 0.035 cases (95% confidence range: 0.001, 0.175).

3.2.5 Scenario: best- and worst-case. Best- and worst-case values for the parameters described in the above one-way sensitivity analyses are displayed in Table 8.

Table 8: Input values for best- and worst-case scenario analyses

Label	Best Case	Worst Case
Number of IRS rounds required	1	2
Insecticide for IRS	$0.34	$0.84
Administration/other staff labor (not net distribution)	$0.04	$12.65
IEC for ITNs	$0.04	$2.16
ITN distributors' labor	$0.01	$1.95
Number of people covered by a single net	3	1
Unit cost of a net	$2.50	$4.80
Probability correctly use an ITN	0.889	0.587
Probability develop malaria	1.000	0.117
Probability of parasitemia, given no intervention	0.318	0.050

In the best-case scenario, both intervention arms have a lower expected cost and a higher expected number of malaria cases than in the base case. The expected cost of the ITN intervention alone is $3.07 per person in the target population, with an expected 0.281 cases of malaria; the expected cost of the combined IRS and ITN intervention is $4.55 per person in the target population, with an expected 0.172 cases of malaria. The best-case ICER is -$13.58. That is, when compared to ITN distribution alone, the expected cost per case of malaria averted by combining IRS with ITN distribution has a best-case value of $13.58.

In the worst-case scenario, both intervention arms have a higher expected cost and a lower expected number of malaria cases than in the base case. The expected cost of the ITN intervention alone is $13.18 per person in the target population, with an expected 0.005 cases of malaria; the expected cost of the combined IRS and ITN intervention is $17.42 per person in the target population, with an expected 0.004 cases of malaria. The worst-case ICER is -$2,516.41. That is, when compared to ITN distribution alone, the expected cost per case of malaria averted by combining IRS with ITN distribution has a worst-case value of $2,516.41.

3.2.6 Scenario: targeted spraying. The parameters adjusted for this scenario analysis are presented with their values in Table 9. The assumptions underpinning each choice of value are also given. In all cases, the most conservative plausible values were selected; they will tend to understate the benefits of adding targeted IRS spraying to existing ITN distribution. All other parameters are held at their baseline values as displayed in tables 4-6.

Table 9: Input values for targeted spraying scenario analysis

Label	Scenario Value	Notes
Number of IRS rounds required	1	Assume only target each house once per year
Probability of parasitemia, given no intervention	0.318	Assume focus only on regions with high prevalence of malaria; maximum regional prevalence
Probability receive IRS in dwelling	0.85	Reflects TVCSP target for IRS
Risk reduction of parasitemia with IRS use	0.030	Assume loss of efficacy due to lack of spillover effect; minimum risk reduction
Risk reduction of parasitemia with IRS and ITN use	0.370	Assume loss of efficacy due to lack of spillover effect; minimum risk reduction

In this scenario, the expected cost for each intervention arm is lower than in the base case, and the expected number of cases of malaria is higher. The ITN-only intervention has an expected cost of $4.68 and an expected 0.256 cases per person in the target population, while the IRS and ITN intervention has an expected cost of $6.55 and an expected 0.211 cases per person in the target population. The ICER for this scenario is -$41.70. That is, in the scenario analysis of targeted spraying, the expected cost per case of malaria prevented is $41.70.

3.2.7 Scenario: increased pyrethroid resistance. The parameters adjusted for this scenario analysis are presented with their values in Table 10. The assumptions underpinning each choice of value are also given. All other parameters are held at their baseline values as displayed in tables 4-6.

Table 10: Values for increased pyrethroid resistance scenario analysis

Label	Scenario Value	Notes
Risk reduction of parasitemia with ITN use	0.030	Assume loss of ITN efficacy to minimum level
Risk reduction of parasitemia with IRS and ITN use	0.370	Assume loss of ITN efficacy to minimum level
Cost of insecticide for IRS	$0.64	Reflects 2012 costs of bendiocarb

In this scenario, the expected cost for each intervention arm is higher than in the base case, as is the expected number of cases of malaria. The ITN-only intervention has an expected cost of $3.45 and an expected 0.083 cases per person in the target population, while the IRS and ITN intervention has an expected cost of $7.94 and an expected 0.059 cases per person in the target population. The ICER for this scenario is -$192.12. That is, in the scenario analysis of increased pyrethroid resistance, the expected cost per case of malaria prevented is $192.12.

Chapter 4: Discussion, Conclusion, and Recommendations

4.1 Discussion

4.1.1 Baseline findings. In all iterations of all scenarios examined using this model, the combination of IRS and ITNs is more effective but more expensive than ITN distribution alone. This finding makes sense, as the combined intervention arm includes the costs of ITN distribution, and the study on which the risk reductions were based found that the combination of IRS and ITNs resulted in a greater reduction in infection risk than did ITNs alone (Fullman et al., 2013). As described in the literature review, some uncertainty remains regarding the true effects on risk reduction due to combining these interventions: if IRS repels mosquitoes from the household, the mosquitoes might never come into contact with the ITNs, which would undermine the effectiveness of the ITNs (Yakob et al., 2011). However, bendiocarb, the insecticide of choice for IRS in mainland Tanzania, has very little repellent effect when compared to other IRS chemicals, which renders this deleterious effect unlikely (Okumu et al., 2013; Yakob et al., 2011). The finding that the combined interventions result in a reduction of expected cases when compared to either intervention alone also aligns with the most recent Cochrane review on the subject (Kleinschmidt et al., 2009).

ITN distribution is likely to remain the foundation of malaria control in Tanzania, and the NMCP will continue to use multiple channels of distribution in order to reach as many residents as possible (de Savigny et al., 2012). In order to account for the diversity of possible distribution methods, the studies used to generate ranges for the costs of ITN distribution included—among other variations—distribution of subsidized and free nets; distribution through ANCs, community groups, and the private sector; and stand-alone ITN programs and ITN programs integrated with vaccination campaigns (White et al., 2011). Any parameters that affect only the

cost of the ITN portion of the interventions make no difference, however, in the expected cost per case averted by choosing the combined intervention. Together, these facts suggest that the results of this model can apply to any region with an ITN distribution program, regardless of the mode of distribution.

In the base case scenario, which reflects a uniform implementation of IRS throughout the country, if the NMCP's willingness to pay to avert a case of malaria is greater than or equal to $152.36, then they should include an IRS component on top of their ITN distribution programs. This value exceeds the cost per case averted of the single interventions described in the most recent review of cost-effectiveness studies for malaria prevention and control, in which the expected societal cost per case averted by each intervention was less than $50 (White et al., 2011). The broad variability in expected cost per case averted shown in the PSA and the best/worst case scenario analysis suggests, however, that while a uniform introduction of IRS across all of mainland Tanzania would be unwise, IRS might prove useful under certain conditions. The one-way and scenario analyses highlight important factors to consider before deciding whether to implement the combined intervention; the next several subsections discuss these factors and their implications for the desirability of IRS in different circumstances.

4.1.2 Prevalence of malaria. In regions with low malaria parasitemia prevalence, such as the central region of Tanzania, the expected cost per case averted from the combined intervention versus the ITN-only intervention is almost two times as great as in the baseline scenario. Conversely, in regions with high malaria prevalence, such as the northwest and southeast of Tanzania, the expected cost per case averted is only about one third as great as in the baseline scenario. These findings affirm the wisdom of the NMCP's current IRS roll-out strategy, which has focused primarily on the regions with the highest prevalence of malaria

(Colaço et al., 2014; RBM, 2012). If IRS continues in Tanzania, it should occur in the northern and southern regions of the country; it should expand to central Tanzania.

4.1.3 Insecticide costs and resistance. The effects of variations in the costs of insecticides for IRS and the scenario of increasing pyrethroid resistance were explored in a one-way sensitivity analysis and a scenario analysis. The cost of insecticide is a driving factor of variability in the expected cost of the IRS and ITN combination arm and in the expected cost per case averted by choosing the combined intervention. More important, however, is the consideration of increasing pyrethroid resistance. In this scenario, the cost of insecticide was increased to reflect the actual costs of bendiocarb in 2012, and it was assumed that only shorter-lasting insecticides such as bendiocarb would retain their efficacy, thereby requiring two rounds of spraying. An increase in pyrethroid resistance could drive up global demand for bendiocarb and similar insecticides, thereby increasing the expected cost and expected cost per case averted of the combined intervention arm even further. The decline in efficacy of ITNs would also decrease the add-on effect of combining IRS and ITNs. Together, these effects suggest that as pyrethroid resistance increases, the expected cost per case averted of the combined interventions versus the ITN-only intervention will increase, even as the efficacy of ITNs declines. In such a scenario, the importance of non-insecticide-based malaria prevention and control efforts, namely case management and IPT, would increase.

Here, it is important to consider the implications of the one-way sensitivity analysis of ITN usage rates. As the prevalence of ITN usage increases, the expected cost per case averted by the combined intervention decreases. That is, as the coverage of one component of malaria control improves, the overall cost-effectiveness of the program improves. Even as pyrethroid resistance increases, therefore, sustaining and increasing ITN coverage should remain an

important component of the Tanzanian NMCP's programs. Strengths in one intervention can compensate for weaknesses the others, and weaknesses in one intervention can undermine the gains of the others. A combination of multiple interventions that tackle different aspects of malaria prevention and control is likely to be preferable to any single intervention (Tanzania Commission for AIDS et al., 2013).

4.1.4 Targeted spraying. In the scenario analysis, targeted spraying for IRS leads to more expected cases than in the baseline blanket-spraying scenario, but the expected cost per case averted decreases by 73% from the base case scenario. These findings suggest that the switch in strategy from blanket to targeted spraying, which was driven by budget constraints, will indeed reduce the overall costs of the IRS program (Akim et al., 2014; Colaço et al., 2014; RBM, 2012). In terms of cases of malaria, however, such a strategy leaves the population more vulnerable to malaria epidemics than would blanket spraying. This finding mirrors the actual outbreak in Muleba after the switch in IRS strategy, though other gaps in the malaria control program might have contributed to that outbreak (Akim et al., 2014). Choosing to switch from blanketed to targeted spraying involves, however, switching from a proactive strategy in which spraying occurs before outbreaks to a reactive strategy in which spraying occurs in response to outbreaks, and the savings in terms of dollars will probably require payment in terms of illness.

If budget constraints make blanket IRS infeasible, however, these findings suggest that targeted IRS would be preferable to no IRS at all in regions with a high prevalence of malaria, such as the north and south of Tanzania. Again, a well-rounded malaria control program could compensate for weaknesses in any single intervention; this statement is particularly likely to be true if the NMCP endorses a less-expensive but less-effective strategy—like targeted spraying—for one of the interventions.

4.1.5 Strengths and weaknesses. This paper uses primary data drawn from five years of IRS campaigns in mainland Tanzania, which allows the study to examine a practical policy question in a specific environment. The health outcome of cost per malaria case averted is well-supported by the literature and understandable by policy makers at the Tanzanian NCMP. As suggested by Kolaczinski and Hanson (2006), costing took a societal perspective, thereby capturing the widest possible array of costs, and economic costs were considered over financial costs. Finally, the many scenario and sensitivity analyses presented should allow policy makers to examine the effects of the assumptions underlying the model and to adapt the country-wide baseline findings to local settings.

In making the model as specific to the Tanzanian context as possible, however, some generalizability to other contexts may have been lost. The model also only accounts for two of the possible combinations of interventions for an NMCP: it does not consider IRS as a stand-alone intervention, nor does it consider other interventions such as case management or IPT. ITNs appear in both arms due to ITN distribution's status as a cornerstone of Tanzania's malaria control programs. In a country with less well-developed ITN distribution programs, this study's comparison would likely prove less useful, as it sheds little light on the cost-effectiveness of IRS as a stand-alone intervention. Furthermore, the choice to use malaria cases averted rather than DALYs averted or dollars saved means that these findings are limited to use within NMCP budget decisions, as they cannot be compared to programs with non-malaria outcomes.

From a technical perspective, this study is limited by the fact that ITN data were drawn from the published literature rather than collected in the same manner as the IRS data. Furthermore, the system used to record the costs of the IRS program did not allow for an

ingredients approach to costing, which is the preferred method of costing for economic studies due to its ease of use for generalizing the findings (J. Kolaczinski & Hanson, 2006).

4.1.6 Suggestions for future research. The parameter which describes the probability that an infected individual will develop symptoms of malaria explains approximately 11% of the variability in expected cases, the second-most out of any variable. Unfortunately, the empirical data on this probability's value remains inconclusive. Many national health surveys present the prevalence of parasitemia as the prevalence of malaria without any consideration of asymptomatic cases. Since populations likely experience a non-zero rate of asymptomatic infections, future studies should examine the probability that an infected person will develop symptoms of malaria.

As noted above, this study addresses a series of research questions specific to the Tanzanian context. Applying a similar decision-tree cost-effectiveness model to other malaria control programs in other contexts would inform evidence-based policy making, especially where real-world evidence of cost-effectiveness remains weak or conflicting. Within Tanzania, a more comprehensive cost-effectiveness study of all the NMCP's programs should be conducted, as it could enhance the NMCP's capacity to build the most cost-effective malaria prevention and control program possible.

Due to a lack of empirical evidence, this study excludes the potential long-term environmental, agricultural, and health effects of spraying bendiocarb for IRS. Without these data, any consideration of the costs of IRS is incomplete. Rigorous studies must be conducted on these long-term effects. A malaria control program that prevents malaria but undermines local agriculture or increases adverse reactions to insecticides could harm society overall.

4.2 Conclusion and recommendations.

This decision-tree analysis suggests that implementing IRS in an area with high ITN coverage will be more expensive than ITN distribution alone, but it will also reduce the number of cases of malaria in the region. As neither branch of the decision tree dominated the other in any scenario, the NMCP must consider the local context and its own willingness to pay to avert a single case of malaria when making its decision. Based on these findings, implementing IRS in the central region of Tanzania, which has an extremely low prevalence of malaria parasitemia, is not recommended. Continuing blanket IRS in the northern and southern regions of Tanzania, however, would be more cost-effective in terms of cost per case averted than would a nation-wide IRS campaign. If the NMCP and its partners have the financial capacity to do so, they should implement blanket IRS in the regions with the highest prevalence of malaria but should not expand to regions with lower prevalence rates.

If the NMCP lacks sufficient financial capacity for blanket spraying, targeted spraying provides an attractive alternative based on cost per case of malaria averted. Although discussions of the political desirability of reducing malaria cases to their lowest possible prevalence exceed the scope of this paper, the NMCP should weigh the importance of saving money with the potential negative repercussions of increasing malaria epidemics by choosing targeted spraying. Compared to blanket spraying throughout Tanzania, targeted spraying does, however, reduce the expected cost per case averted by about 73%. If the NMCP finds that the expected cost per case averted of blanket spraying exceeds its willingness to pay, it could still continue targeted spraying in high-prevalence regions.

Beyond evaluating the cost-effectiveness of the combination of IRS and ITN distribution, this paper also highlights the importance of a well-rounded malaria prevention and control

program. When ITN usage rates increase in the model, the expected cost per case averted by the combined intervention declines; when pyrethroid resistance undermines the effectiveness of ITNs, the expected cost per case averted by the combined intervention rises. If the latter scenario comes to pass, as seems likely, malaria control through case management, IPT, improved testing, and other non-insecticide-based interventions will only grow in importance. In choosing a package of malaria prevention and control programs, therefore, the NMCP and its partners should attack malaria through multiple intervention: the strength of one program can compensate for weaknesses in and reinforce the strengths of other programs.

Appendix I: Decision tree

Due to the size of the decision tree, it is presented in two portions. Figure A1 contains the beginning of the tree with the decision node (the blue square) representing the two intervention arms and the intervention-related probabilities at each chance node (the green circles). At each label node, represented by the jagged line, the tree continues with the branches shown in Figure A2, which contains the malaria illness and treatment probabilities as well as the cost and effectiveness outcomes at the terminal nodes (the red triangles). Figure A2 specifically represents the continuation of the branch in which the person receives both IRS and an ITN.

Each branch is labeled with a single probability, each of which is defined in Table A1. The probability of not having the event described at the chance node is represented by the # label and is calculated as 1 minus the probability of the event. Each chance event represented by a

Figure A1: Partial decision tree 1

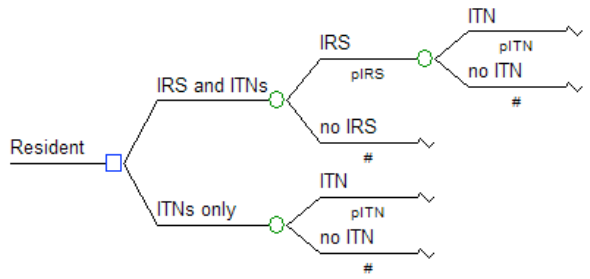
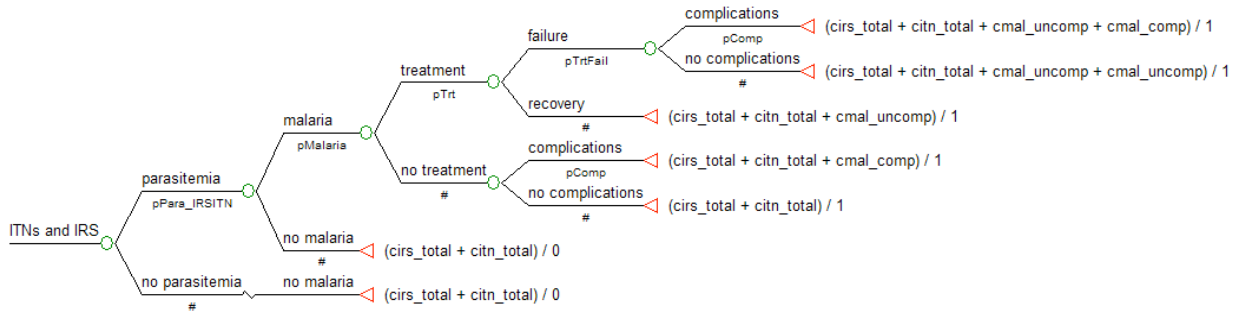


Figure A2: Partial decision tree 2



probability node might have an associated cost, an associated outcome, or both. At each terminal node, the costs and outcomes associated with each preceding probability node are added together. The costs are presented at the terminal node before the slash, and the malaria outcome is presented after the slash, with 1 representing a case of malaria 0 representing no malaria.

In this tree, first, the resident either receives IRS or does not. Then, she either uses an ITN or does not. Next, she is either infected with the malaria parasite or she is not. The probability of infection is dependent on which combination of interventions she receives. If she is not infected, she develops no malaria and the branch ends. If she is infected, then she might develop symptomatic malaria; if she does not, the branch ends. If she develops symptomatic malaria, she might seek and receive formal treatment; if she does not, she might or might not develop complicated malaria, and then the branches end. If she seeks treatment, it might fail; if it does not fail, the branch ends. If the treatment fails, it is assumed that she will seek treatment a second time for the new symptoms, whether they are symptoms of complicated malaria or not; in either case, the branch ends after this second round of treatment.

Table A1: Decision tree parameters

Probability parameter	**Associated event**	**Associated cost**	**Associated malaria outcome**
pIRS	Receive IRS in the home	cirs_total	—
pITN	Correctly use an ITN	citn_total	—
pPara_IRSITN	Develop parasitemia, in the arm with IRS and ITN usage	—	—
pMalaria	Develop symptomatic malaria	—	1
pTrt	Seek formal treatment	cmal_uncomp	—
pTrtFail	Treatment fails	—	—
pComp	Develop complications	cmal_comp	—
	Do not develop complications after treatment failure	cmal_uncomp	—
	Do not develop complications after receiving no treatment	—	—

Appendix II: In-kind contributions: Data collection instrument

Information Collection Instrument for
Estimating in-kind contributions to IRS in Tanzania

Interview date: _____ Interview location: _____

Persons interviewed: _____ Interviewer: _____

_____

Level of data captured: ☐ National ☐ Regional ☐ District – Name of District: _____

Government-owned Warehouses/Storage Facilities (regional or district level only)

	2008	2009
1. Were any warehouses or storage facilities owned by this (national/regional/district) government provided to RTI to store insecticide, equipment, PPE or solid waste materials related to spray operations ….	in 2008? ☐ Yes ☐ No (skip to 12)	in 2009? ☐ Yes ☐ No (skip to 12)
2. How many of these storage facilities were provided for RTI-supported spray operations ….	in 2008? _____ (no.)	in 2008? _____ (no.)

	Warehouse 1	Warehouse 2	Warehouse 3	Warehouse 4
3. Where were these storage facilities or warehouses located?	_____	_____	_____	_____
4. Was the storage facility in ____ used to store IRS materials …	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N
5. Approximately how many square meters of space was used to store IRS goods in the storage facility at _____ …	in 2008? _____ sq m in 2009? _____ sq m	in 2008? _____ sq m in 2009? _____ sq m	in 2008? _____ sq m in 2009? _____ sq m	in 2008? _____ sq m in 2009? _____ sq m
6. Was this space used in used for the entire year …	in 2008? ☐ Yes (go to 8) ☐ No in 2009? ☐ Yes (go to 8) ☐ No	in 2008? ☐ Yes (go to 8) ☐ No in 2009? ☐ Yes (go to 8) ☐ No	in 2008? ☐ Yes (go to 8) ☐ No in 2009? ☐ Yes (go to 8) ☐ No	in 2008? ☐ Yes (go to 8) ☐ No in 2009? ☐ Yes (go to 8) ☐ No
7. For how many days was this storage facility used for IRS goods …	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in2009? _____ days	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days
Notes				

	Warehouse 1	Warehouse 2	Warehouse 3	Warehouse 4
8. Did RTI pay any amount for use of the warehouse space at _____ …	in 2008? ☐ Yes ☐ No (go to 11) in 2009? ☐ Yes ☐ No (go to 11)	in 2008? ☐ Yes ☐ No (go to 11) in 2009? ☐ Yes ☐ No (go to 11)	in 2008? ☐ Yes ☐ No (go to 11) in 2009? ☐ Yes ☐ No (go to 11)	in 2008? ☐ Yes ☐ No (go to 11) in 2009? ☐ Yes ☐ No (go to 11)
9. How much did RTI pay …	In 2008? _____ Tsh In 2009? _____ Tsh	In 2008? _____ Tsh In 2009? _____ Tsh	In 2008? _____ Tsh In 2009? _____ Tsh	In 2008? _____ Tsh In 2009? _____ Tsh
10. Was the amount RTI paid in (2008/2009) a fair market price for the space used to store IRS goods in _____ or was it less than the fair market price?	in 2008? ☐ Yes (go to 12) ☐ Less in 2009? ☐ Yes (go to 12) ☐ Less	in 2008? ☐ Yes (go to 12) ☐ Less in 2009? ☐ Yes (go to 12) ☐ Less	in 2008? ☐ Yes (go to 12) ☐ Less in 2009? ☐ Yes (go to 12) ☐ Less	in 2008? ☐ Yes (go to 12) ☐ Less in 2009? ☐ Yes (go to 12) ☐ Less
11. What was the estimated fair market value of this space used to store IRS goods …	in 2008? Tsh _____ in 2009? Tsh _____	in 2008? Tsh _____ in 2009? Tsh _____	in 2008? Tsh _____ in 2009? Tsh _____	in 2008? Tsh _____ in 2009? Tsh _____
Notes:				

Sub-storage space, IRS sites

	2008	2009
12. Were any storage facilities provided at the sub-district or community level, often referred to IRS sites, including space to store insecticide, equipment, and PPE, and as a washing area to support spray operations …	in 2008? ☐ Yes ☐ No (skip to 18)	in 2009? ☐ Yes ☐ No (skip to 18)
13. How many of these storage facilities were provided for spray operations …	in 2008? _____ (no.)	in 2008? _____ (no.)
14. For how many days were each of these IRS site and the sub-storage facilities used for IRS …	in 2008? _____ (no. of days)	in 2009? _____ (no. of days)
15. Did RTI pay the fair market price for any of these IRS and sub-storage spaces …	in 2008? ☐ Yes, for all (go to 18) ☐ Yes for some ☐ No, for none (go to 17)	in 2009? ☐ Yes, for all (go to 18) ☐ Yes for some ☐ No, for none (go to 17)
16. For how many of the IRS site/sub-storage space did RTI pay a fair market price …	in 2008? _____ (no.)	in 2009? _____ (no.)
17. What is the fair market value of monthly rent for the average IRS site/sub-storage space used …	in 2008? _____ (Tsh)	in 2009? _____ (Tsh)
Notes:		

Office Space

	2008	2009
18. Was office space provided to any RTI staff working on IRS?	☐ Yes ☐ No (go to 24)	☐ Yes ☐ No (go to 24)

	Office 1	**Office 2**	**Office 3**	**Office 4**
19. Where were these offices located?	_____	_____	_____	_____
20. Approximately how large, in square meters, was the space RTI staff used?	_____ sq m	_____ sq m	_____ sq m	_____ sq m
21. Was this space used …	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N
22. For how many days or months did RTI use this space …	in 2008? _____ (days/months) in 2009? _____ (day/months)	in 2008? _____ (days/months) in 2009? _____ (day/months)	in 2008? _____ (days/months) in 2009? _____ (day/months)	in 2008? _____ (days/months) in 2009? _____ (day/months)
23. If RTI were to have rented similar space in the same location, what would be likely cost have been?	Tsh _____/month	Tsh _____/month	Tsh _____/month	Tsh _____/month
Notes:				

Transportation – Vehicles and Fuel

	Planning	Logistics Assessment	IEC, community mobilization	IRS operations	Post-IRS evaluation and follow-up
24. Were any regional/ district vehicles not belonging to RTI used to provide _____ support to IRS?	☐ 2008 Y/N ☐ 2009 Y/N	☐ 2008 Y/N ☐ 2009 Y/N	☐ 2008 Y/N ☐ 2009 Y/N	☐ 2008 Y/N ☐ 2009 Y/N	☐ 2008 Y/N ☐ 2009 Y/N
25. How many kilometers were traveled in those non-RTI vehicles were related to IRS _____ …	in 2008? _____ km in 2009? _____ km	in 2008? _____ km in 2009? _____ km	in 2008? _____ km in 2009? _____ km	in 2008? _____ km in 2009? _____ km	in 2008? _____ km in 2009? _____ km
	(If respondents are unable to provide a number of KMs for any of these functions, go to 26 for that function. For functions for which respondents provided a number of KMs, skip to 29.)				
26. For how many days were your vehicles used to support IRS _____ …	in 2008? ____ days in 2009? ____ days	in 2008? ____ days in 2009? ____ days	in 2008? ____ days in 2009? ____ days	in 2008? ____ days in 2009? ____ days	in 2008? ____ days in 2009? ____ days
Notes					
27. On average, for each day when your vehicle was used how many KMs did	in 2008? _____ km in 2009? _____ km	in 2008? _____ km in 2009? _____ km	in 2008? _____ km in 2009? _____ km	in 2008? _____ km in 2009? _____ km	in 2008? _____ km in 2009? _____ km

	Planning	Logistics Assessment	IEC, community mobilization	IRS operations	Post-IRS evaluation and follow-up
the vehicle travel, …					
28. One the average day when your vehicle was used, how many vehicles were used …	in 2008? _____ vehicles in 2009? _____ vehicles	in 2008? _____ vehicles in 2009? _____ vehicles	in 2008? _____ vehicles in 2009? _____ vehicles	in 2008? _____ vehicles in 2009? _____ vehicles	in 2008? _____ vehicles in 2009? _____ vehicles
29. During use of your vehicles for IRS _____, did your organization provide the fuel or was the fuel paid for by RTI…	in 2008? ☐ Us ☐ RTI (go to 31) in 2009? ☐ Us ☐ RTI (go to 31)	in 2008? ☐ Us ☐ RTI (go to 31) in 2009? ☐ Us ☐ RTI (go to 31)	in 2008? ☐ Us ☐ RTI (go to 31) in 2009? ☐ Us ☐ RTI (go to 31)	in 2008? ☐ Us ☐ RTI (go to 31) in 2009? ☐ Us ☐ RTI (go to 31)	in 2008? ☐ Us ☐ RTI (go to 31) in 2009? ☐ Us ☐ RTI (go to 31)
Notes:					

	Planning	Logistics Assessment	IEC, community mobilization	IRS operations	Post-IRS evaluation and follow-up
30. What is the average number of kilometers these vehicles travel per liter of fuel?	_____ km/liter	_____ km/liter	_____ km/liter	_____ km/liter	_____ km/liter
Notes:					

Labor services

	Malaria Focal Person	Storekeeper	District Medical Officer	Data Clerk	Health Education Officer
31. Did the ____ provide support to IRS, either during planning, operations or evaluation phases …	in 2008? ☐ Y/N (If "no" go to 36) in 2009? ☐ Y/N (if "no" go to 36)	in 2008? ☐ Y/N (If "no" go to 36) in 2009? ☐ Y/N (if "no" go to 36)	in 2008? ☐ Y/N (If "no" go to 36) in 2009? ☐ Y/N (if "no" go to 36)	in 2008? ☐ Y/N (If "no" go to 36) in 2009? ☐ Y/N (if "no" go to 36)	in 2008? ☐ Y/N (If "no" go to 36) in 2009? ☐ Y/N (if "no" go to 36)
32. For approximately how many days during did the ____ work to support IRS …	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days

	Malaria Focal Person	Storekeeper	District Medical Officer	Data Clerk	Health Education Officer
33. Were these full work days or partial work days …	in 2008? ☐ Full (go to 35) ☐ Partial in 2009? ☐ Full (go to 35) ☐ Partial	in 2008? ☐ Full (go to 35) ☐ Partial in 2009? ☐ Full (go to 35) ☐ Partial	in 2008? ☐ Full (go to 35) ☐ Partial in 2009? ☐ Full (go to 35) ☐ Partial	in 2008? ☐ Full (go to 35) ☐ Partial in 2009? ☐ Full (go to 35) ☐ Partial	in 2008? ☐ Full (go to 35) ☐ Partial in 2009? ☐ Full (go to 35) ☐ Partial
34. On average, how many hours per days did the ___ work while supporting the IRS cycle …	in 2008? _____ hours/day in 2009? _____ hours/day	in 2008? _____ hours/day in 2009? _____ hours/day	in 2008? _____ hours/day in 2009? _____ hours/day	in 2008? _____ hours/day in 2009? _____ hours/day	in 2008? _____ hours/day in 2009? _____ hours/day
35. During the IRS cycle, did the ___ continue to draw her/his salary?	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N
Notes:					

	Ward Executive Officers	Village Executive Officers
36. Did the ____ provide support to IRS, either during planning, operations or evaluation phases …	in 2008? ☐ Y/N (If "no" go to 40) in 2009? ☐ Y/N (if "no" go to 40)	in 2008? ☐ Y/N (If "no" go to 40) in 2009? ☐ Y/N (if "no" go to 40)
37. For approximately how many days during did the ____ work to support IRS …	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days
38. Were these full work days or partial work days …	in 2008? ☐ Full (go to 40) ☐ Partial in 2009? ☐ Full (go to 40) ☐ Partial	in 2008? ☐ Full (go to 40) ☐ Partial in 2009? ☐ Full (go to 40) ☐ Partial
39. On average, how many hours per days did the ___ work while supporting the IRS cycle …	in 2008? _____ hours/day in 2009? _____ hours/day	in 2008? _____ hours/day in 2009? _____ hours/day
Notes:		

40. Did any other (regional/district) staff provide support during IRS planning, operations or evaluation …	in 2008? ☐ Yes ☐ No	in 2009? ☐ Yes ☐ No
If respondents answered "yes" for either 2008 or 2009, proceed to 41. If respondents answered "no" for both 2008 and 2009, skip to 47.		

	_____	_____	_____	_____
41. Please name the positions of the other staff that provided support during the IRS cycles in either 2008 or 2009.	(Write the name of the first position named by the respondent above in the header cell of this column.)	(Write the name of the second position named by the respondent above in the header cell of this column.)	(Write the name of the third position named by the respondent above in the header cell of this column.)	(Write the name of the fourth position named by the respondent above in the header cell of this column.)
42. Did the ____ provide support to IRS, either during planning, operations or evaluation phases …	in 2008? ☐ Y/N (If "no" go to 47) in 2009? ☐ Y/N (if "no" go to 47)	in 2008? ☐ Y/N (If "no" go to 47) in 2009? ☐ Y/N (if "no" go to 47)	in 2008? ☐ Y/N (If "no" go to 47) in 2009? ☐ Y/N (if "no" go to 47)	in 2008? ☐ Y/N (If "no" go to 47) in 2009? ☐ Y/N (if "no" go to 47)
Notes:				
43. For approximately how many days during did the ____ work to support IRS …	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days	in 2008? _____ days in 2009? _____ days

	_____	_____	_____	_____
44. Were these full work days or partial work days …	in 2008? ☐ Full (go to 46) ☐ Partial in 2009? ☐ Full (go to 46) ☐ Partial	in 2008? ☐ Full (go to 46) ☐ Partial in 2009? ☐ Full (go to 46) ☐ Partial	in 2008? ☐ Full (go to 46) ☐ Partial in 2009? ☐ Full (go to 46) ☐ Partial	in 2008? ☐ Full (go to 46) ☐ Partial in 2009? ☐ Full (go to 46) ☐ Partial
45. On average, how many hours per days did the ___ work while supporting the IRS cycle …	in 2008? _____ hours/day in 2009? ____ hours/day	in 2008? _____ hours/day in 2009? ____ hours/day	in 2008? ____ hours/day in 2009? ____ hours/day	in 2008? ____ hours/day in 2009? ____ hours/day
46. During the IRS cycle, did the ___ continue to draw her/his salary?	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N	in 2008? ☐ Y/N in 2009? ☐ Y/N

Other goods or services

	2008	2009
47. Did households provide water to spray operation teams on the day that their houses were sprayed …	in 2008? ☐ Yes ☐ No (go to 50)	in 2009? ☐ Yes ☐ No (go to 50)
48. How much water did each household provide for spraying conducted in their house …	in 2008? _____ liters	in 2009? _____ liters
49. What was the value of the water provided …	in 2008? _____ Tsh	in 2009? _____ Tsh
50. Were any other goods or services provided by the (regional/district) government or by communities to support IRS …	in 2008? ☐ Yes ☐ No (complete interview)	in 2009? ☐ Yes ☐ No (complete interview)
51. What else was provided?	in 2008? _____	in 2009? _____
52. What was the value of ____ provided …	in 2008? _____ Tsh	in 2009? _____ Tsh
Notes:		

Appendix III: Additional sensitivity analyses

As in the results section, in all of the figures in this appendix, the ITN-only intervention is represented using green triangles and the IRS-only intervention is represented using blue circles. The x-axes display the range of the parameter being analyzed in the one-way sensitivity analyses. The y-axis differs for each chart shown: for the expected cost charts and the expected cases charts, the y-axis represents the expected costs or cases at the corresponding parameter value. For the cost-effectiveness charts, the y-axis represents the incremental cost per case averted when compared to the ITN-only arm at the corresponding parameter value. As the cheaper comparison group, the ITN-only arm will always have an incremental cost per case averted of $0.00. For the IRS plus ITN arm, a larger number on the y-axis represents a larger cost per case averted.

As shown in Figure A3, as the cost of IEC increases, the expected cost of each intervention increases linearly, with the ITN-only intervention increasing from $2.94 to $3.73 and the combined intervention increasing from $7.02 to $7.81. Variations in this parameter have no effect on the expected number of cases or expected cost per case averted.

As shown in Figure A4, as the cost of net distributors' labor increases, the expected cost of each intervention increases linearly, with the ITN-only intervention increasing from $3.39 to

Figure A3: Sensitivity analyses on cost of ITN distributors' labor

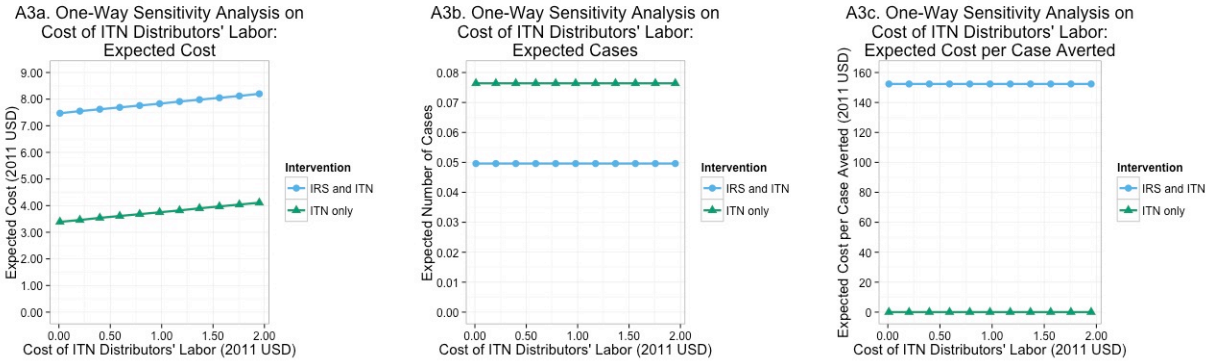
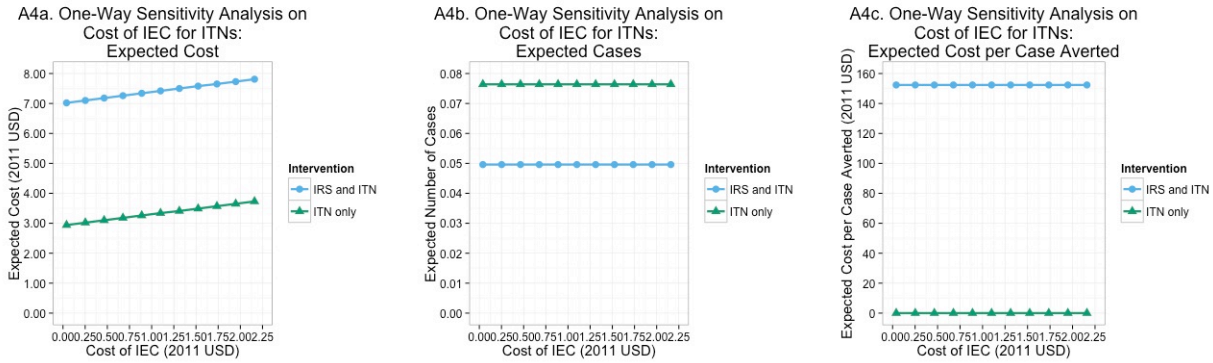


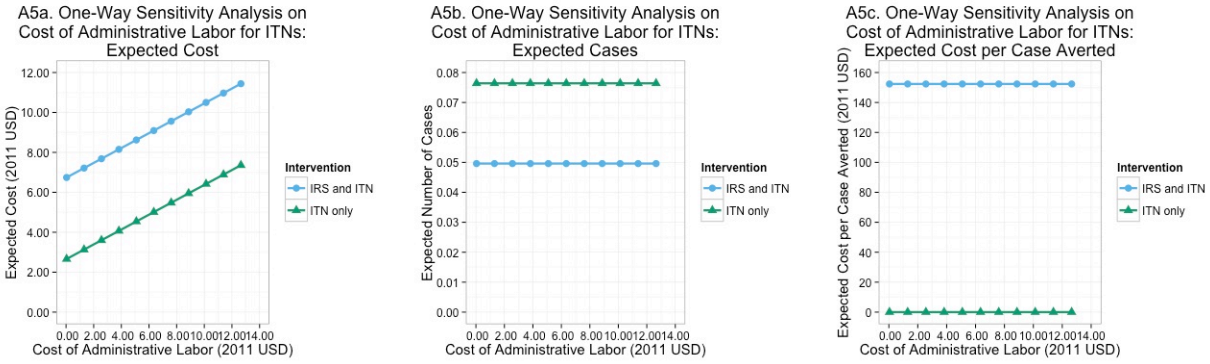
Figure A4: Sensitivity analyses on cost of IEC for ITNs



$4.11 and the combined intervention increasing from $7.47 to $8.20. Variations in this parameter have no effect on the expected number of cases or expected cost per case averted.

As shown in Figure A5, as the cost of administrative and other staff labor increases, the expected costs of each intervention increases linearly, with the ITN-only intervention increasing from $2.70 to $7.40 and the combined intervention increasing from $6.70 to $11.40. Variations in this parameter have no effect on the expected number of cases or expected cost per case averted.

Figure A5: Sensitivity analyses on cost of administrative labor for ITNs



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