Economic evaluation of malaria prevention in Ethiopia:

Economic burden, equity, and cost-effectiveness analysis of malaria prevention in south-central Ethiopia

Alemayehu Hailu

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Author: Alemayehu Hailu

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Scientific environment

The Ph.D. candidate was housed in Centre for International Health in the Department of Global Public Health and Primary Care at the faculty of Medicine, University of Bergen. Professor Bjarne Robberstad — as the main supervisor, and Professor Bernt Lindtjørn and Associate Professor Wakgari Deressa — as co-supervisors provided guidance throughout the Ph.D. period. This research was conducted as part of a large-scale randomized controlled trial project in Ethiopia — *MalTrials*. The *MalTrials* is Norwegian Research Council funded project, and was a joint multi-disciplinary collaboration of researchers from Norwegian institutions (Centre for International Health at the University of Bergen and Norwegian University of Life Sciences) and Ethiopian institutions (School of Public Health and Aklilu Lema institute of Pathobiology at Addis Ababa University, and School of Public and Environmental Health at Hawassa University).

Dedication

I dedicate this academic work and express my respect in memory of my late older brother **Tesfahun Desalegne Hailu** for your enormous pure Love and care in those beautiful days**.** You encouraged and showed me the light of education in my early days of schooling.

I am also grateful to my late brother **Solomon Desalegne**. We lost you due to cerebral malaria while serving the people would live free from malaria.

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Pure Love to your pure souls in heaven.

I am proud of my brothers and sisters: Fantayenesh Desalegne, Almaz Desalegne, Addisu Desalegne, and Lema Desalegne. Your Love, encouragement, and support motivated me to always dream big and achieve more.

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Alemayehu Desalegne Hailu
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Summary

Background: Despite remarkable efforts in the global fight against malaria and achievements in the reduction of morbidity and mortality in the last decade, the disease remains to be a huge challenge to the health systems of malaria-endemic low-income countries in Africa and in all corners of the globe. Beyond the wide range of consensus on the disease burden and prioritization of malaria, the available evidence on the economic burden of malaria in Ethiopia is scanty. No clear evidence yet exists about the additional resources required for a combined implementation of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) with respect to the added protection afforded. In addition, little is known about the prevailing status of LLINs and IRS across different levels of wealth strata.

Objectives: The aims of this thesis were to estimate the economic burden of malaria; to evaluate the cost-effectiveness of a combined implementation malaria prevention interventions (LLINs and IRS); and analyse the distributional (equity) implications of the interventions in the Adami Tullu district, south-central Ethiopia.

Methods: Studies included in this thesis were conducted from 2014 - 2016 in the Adami Tullu district of Oromia Region, in south-central Ethiopia as part of and partly in conjunction with the *MalTrials* project. We conducted a cost of illness using 190 malaria patients in the first study. In Paper II, we carried out a combination of trial-based and literature-based cost-effectiveness analysis using Markov modelling. In the third study, using a cross-sectional data from 6069 households we did an inequality analysis of ownership of LLINs and IRS status. The principal component analysis technique was used for ranking households based on socioeconomic position. We measured the inequality in LLINs and IRS using concentration indices and concentration curve (Paper I&III).

Results: The median cost of malaria per episode to the household was USD 5.06 (IQR: 2.98 – 8.10) and the direct cost was significantly higher among the poor. The trial-based analysis had shown that the routine practice dominates both the combined intervention and

singleton intervention while the literature-based analysis had indicated that combined intervention had an Incremental Cost-Effectiveness Ratio of USD 1403 per DALY averted. Immediately before we started the trial, the LLIN ownership was 11.6% and IRS coverage was 72.5%. We found a concentration index of 0.0627 for LLINs and - 0.0383 for the IRS. Inequality in LLIN ownership was mainly associated with a variability in a housing situation, the size of the household, and access to mass media and telecommunication service.

Conclusions: The economic burden of malaria to the rural households in Ethiopia is huge—mainly to the poor. Based on the trial-based cost-effectiveness analysis, we conclude that the combination of LLINs and IRS is not likely to be a cost-effective option compared with singleton intervention. However, based on the literature-based analysis, the combined intervention had potential to be a cost-effective alternative at 3 times GDP per capita per DALY averted. Furthermore, the ownership of LLIN was very low and significantly pro-rich, while IRS status was equitable across socioeconomic strata.

Key-words: Economic Evaluation; Malaria; Malaria Prevention; LLIN; IRS; Cost-effectiveness; Ethiopia

List of original papers

This thesis is based on the following three papers, which are referred to the text by their roman numerals.

Paper I:

Hailu A, Lindtjørn B, Deressa W, Gari T, Loha E, Robberstad B. Economic burden of malaria and predictors of cost variability to rural households in south-central Ethiopia. PLOS ONE 2017. https://doi.org/10.1371/journal.pone.0185315

Paper II:

Hailu A, Lindtjørn B, Deressa W, Gari T, Loha E, Robberstad B. Cost-effectiveness of combined intervention of LLIN and IRS compared with each intervention alone for malaria prevention in Ethiopia. (Under review in Cost Effectiveness and Resource Allocation Journal)

Paper III:

Hailu A, Lindtjørn B, Deressa W, Gari T, Loha E, Robberstad B. Equity in long-lasting insecticidal nets and indoor residual spraying for malaria prevention in a rural South Central Ethiopia. Malaria Journal 2016; 15:366. https://doi.org/10.1186/s12936-016-1425-0

Abbreviations

ACT	Artemisinin-based Combination Therapy
API	Annual Parasite Incidence
CEA	Cost-effectiveness analysis
CEAC	Cost Effectiveness Acceptability Curve
DALY	Disability Adjusted Life Year
ETB	Ethiopian Birr
FMoH	Federal Ministry of Health
GDP	Gross Domestic Product
ICER	Incremental Cost-Effectiveness Ratio
IQR	Inter-Quartile Range
IRS	Indoor Residual Spraying
ITN	Insecticidal Treated Nets
LLIN	Long Lasting Insecticidal Nets
MDG	Millennium Development Goal
MIS	Malaria Indicator Survey
NMCP	National Malaria Control Program
OOP	Out of Pocket Expenditure
PCR	Polymerase Chain Reaction
PHCU	Primary Health Care Unit
PSA	Probabilistic Sensitivity Analysis
PYO	Person Years of Observation
RCT	Randomized Controlled Trial
SD	Standard Deviation
SDG	Sustainable Development Goal
SE	Standard Error
USD	US Dollar
WHO	World Health Organization
WTP	Willingness to Pay

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Chapter I: Introduction

1.1. General overview of malaria

Malaria is an ancient complex disease (1), which may result in a wide variety of manifestations — ranging from very mild symptoms to severe disease and even death. Malaria can be categorized as uncomplicated or severe (complicated). The clinical symptoms associated with malaria are fever, headaches, body aches, chills, rigors sweats, nausea, vomiting, and malaise. In severe forms, it may be manifested with prostration, respiratory distress, severe anemia, and/or impaired consciousness (2).

Malaria is caused by a single cell protozoan parasites belonging to the genus *Plasmodium*. While there are more than 100 species of *Plasmodium* specious, only four of them are known to cause malaria infection in human: *P.falciparum, P.vivax, P.ovale,* and *P.malariae*. *Plasmodium falciparum* is the dominant malaria parasite in Africa and globally which causes most of the severe forms and deaths; while *P.vivax* is the second most significant species and is the most prevalent in South-east Asia and Latin America. Later in 1965, *P.knowlesi* has been recognized to be a cause of zoonotic malaria in humans (3).

The *Plasmodium* spread from one human being to another by the bite of female anopheles mosquito. The Anopheles mosquito thrive in warm and humid climates and uses swampy stagnant water ponds for a breading site (4-6). Various anopheles species have been found to be the vectors in different parts of the world. The dominant vectors are *An. Gambiae, An. arabiensis* and *An. funestus* in Africa; *An. freeborni* in Latin America. However, in Aisa-Pacific region various, more than 16, anopheles specious co-dominates (7).

Malaria is an acute febrile illness with an incubation period of about 10 - 15 days. However, in some of the cases, it may remain asymptomatic and the parasite may stay in the liver for a long time. Malaria can be effectively treated and cured if diagnosed and treated promptly (8-10). The existing first-line treatment is chloroquine for *P.vivax* and *P.ovale* while

artemisinin-based combination therapy (ACT) is recommended for treatment of *P.falciparum*. Primaquine can be used to treat liver-stage parasites of *P.vivax* (2).

1.2. Malaria burden: globally and in Africa

Malaria is widely spread globally and puts approximately half of the world population at risk in more than 90 countries and territories around the globe (11). According to the World Health Organization (WHO) World Malaria Reports, there were 211 million of malaria cases in 2015 (12), and 216 million cases in 2016 (11). Each year, malaria accounts for about 445,000 deaths, and about 70% of those deaths were among under-five children.

The African region continues to bear the largest share of the global malaria burden. About 90% of cases and 91% of malaria deaths occurred in Africa. Fifteen countries carried the 80% of the global malaria burden — all but one are in Africa (Figure 1) (11). When it comes to the global trend of morbidity and mortality from malaria, in the last 15 years, substantial improvement has been documented. However, since 2014 the trend has started to level-off — and in some regions it is reversed (11).

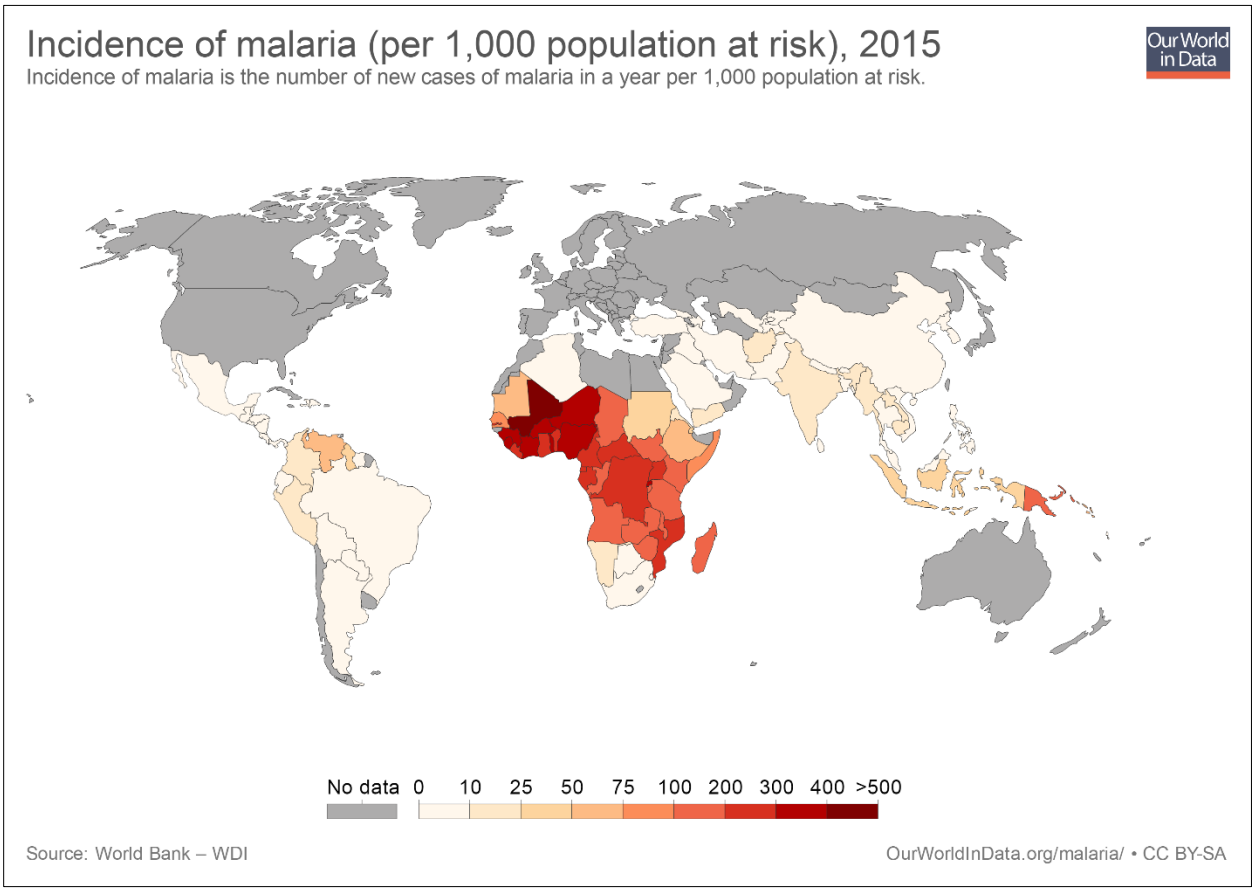


Figure 1: World Malaria Map, malaria incidence per 1,000 population at risk, 2015

1.3. Overview of Ethiopia

Without the knowledge of the context in Ethiopian health system and the country at large, it is impossible to truly understand either the malaria situation in Ethiopia or the implications of the finding in the studies. Ethiopia is the second most populous country in Africa with a total population of about 105 million (13). Administratively Ethiopia is divided into nine regional states and two chartered cities (Addis Ababa and Dire Dawa). The regions are divided in to Zones and Districts. The districts are further divided in to *Kebeles*[1]. Despite promising economic growth attained in the last two decades (14), by far Ethiopia is one of the countries with worst health and development indicators (15). This is

[1] *Kebele* is lowest administrative unit in Ethiopia, which on average contains populations of 5,000 people or about 1000 households. Each *Kebele* is further divided into *Zones* and *Gares.* A *Gare* contains about 40 – 50 close neighbouring households. In this study, *Gares* are considered as cluster units. For each *Kebele*, there is one Health Post.

largely due to preventable infectious diseases and nutritional deficiencies. Malaria along with lower respiratory infection and diarrhoea was one of the top-three-causes of DALY in 2010 (16). Recent evidence also depicts that the magnitude of non-communicable diseases is rising in Ethiopia (17).

About 85% of the population lives in rural areas and their livelihood is mainly dependent on subsistent agriculture. Poverty, low education levels, inadequate access to clean water, lack of sanitation facilities, and poor access to quality health care characterise rural Ethiopia (18); and this viciously contributed to the high burden of disease in the country. The country's per capita income is only USD 861 (14), which is substantially below the average for the region. Nearly a quarter of the population is estimated to be below the poverty line (18). The summary of major health and development indicator for Ethiopia is presented in Table 1.

Ethiopian Health Systems and National Malaria Control Program

According to National Health Sector Transformation Plan (HSTP) (19), the Ethiopia health care delivery system, in general, is organized into a three-tier system. The first, at a district level, is Primary Health Care Unit (PHCU). The PHCU comprise one primary hospital, which would serve for a population of about 60 to 100 thousand, about four health centres (each to serve for population 15 to 25 thousand), about five health posts are attached to each health centres (each health post to serve for 3 to 5 thousand of population). The second level comprise general hospitals, each would serve for a population of 1 to 1.5 million, while the third level comprise specialized hospital each would serve 3.5 to 5 million population. One level of care is connected to the next level with a referral system.

In line with the Sustainable Development Goals, the Ethiopian Ministry of Health has envisioned to see — a malaria free Ethiopia. To materialize this vision, the Ethiopian government is working under the National Malaria Control Program (NMCP) (20), setting

three ambitious goals to be realized by 2020: achieve near zero malaria deaths[2], reduce malaria cases by 75% from the 2013 baseline and eliminate malaria from selected low-transmission areas. The NMCP has mandates to facilitate and develop all malaria prevention, control, and treatment policy and strategy in Ethiopia; to monitor the implementation of the interventions; and to evaluate its impact. The NMCP also has emphasised the need for providing high quality, equitable, and effective malaria control services and scaling up the prevention interventions to all populations at risk.

Table 1: Major socioeconomic, health, and demographic indicators of Ethiopia.

Indicators	Value	Source
Total population in million (2017)	105	(13)
Real GDP growth rate (2016)	8 %	(14)
GDP per capita in current USD (2017)	861	(14)
Nominal exchange rate- Birr/USD (2015)	20.45	(21)
Consumer Prices (2016)	7.3%	(22)
Proportion of population in absolute poverty (2015/16)	23.5%	(18)
Human development index rank (2016)	174	(23)
Life expectancy at birth, years (Male- Female) (2015)	62.8 - 66.8	(15)
Health expenditure per capita in USD (2013/14)	28.65	(24)
% of out-of-pocket expenditure from total health expenditure (2013/14)	33%	(24)
Under-five mortality rate per 1000 live birth (2016)	58.4	(15)
Infant mortality per 1000 live birth (2015)	59.3	(15)
Maternal mortality ratios (2015)	353	(15)
Malaria annual parasite incidence (API)[3] 2015	58	(15)
Malaria point prevalence (2015)	1.5%	(25)

[2] Near zero death meant that no more than 1 confirmed malaria death per 100,000 population at risk per annum.

[3] Annual parasite incidence (API) is the number of malaria cases per 1,000 population at risk per year (mid-year population). The API measure the risk of infection in the area. The API is often used for comparing the risk of malaria infection between districts, provinces, and countries.

1.4. Malaria in Ethiopia

Malaria is one of the major public health problems in Ethiopia. It particularly affects vulnerable groups such as children and pregnant women (26). Records from the Ethiopian Federal Ministry of Health (FMoH) reveal that more than 75% of the total landmass of Ethiopia is malarious and about 68% of the population is living in areas at risk of malaria (27). For the year 2016, the WHO estimates more than 2.5 million cases and about 5,000 deaths in Ethiopia while about 1.7 million microscopically confirmed cases and 510 deaths were actually reported[4] (11). According to the 2015 Malaria Indicator Survey (MIS) for all-age population living in areas less than 2000 meters above sea level, the malaria parasite prevalence was 0.5% by microscopic blood-slide examination and 1.2 by RDT. (28). A model-based estimate by Deribew et al, (29) also produced significantly low number of malaria deaths compared with the WHO estimate for Ethiopia (11). Several recent empirical studies from all corners of the country (5, 30-40) show that malaria is still one of the leading health problems in Ethiopia. The disease is also one of the leading cause of inpatient admission and cause of hospital death (41).

Malaria is also one of the top causes of outpatient visits and inpatient admission in Oromia Region (41, 42). For example, a recent study from East *Shewa* Zone report that, of those suspected cases – presented with fever at the health centres, about a quarter (25%) of them were microscopically confirmed malaria positive cases (33). In Adami Tullu District, where we conducted the current project, an annual malaria incidence of about 24 per 1,000 population at risk was reported (30, 43).

The epidemiologic profile of malaria in Ethiopia is characterised by the following four peculiar features compare with other African countries (26). First, seasonal variability of malaria transmission in Ethiopia is high while it is perineal in most other African countries.

[4] The huge discrepancy in the number of malaria cases and death reported by the FMoH of Ethiopia and the WHO estimate might be due to the difference in the estimation methods applied. The report from FMoH was based on routine health facility records while the estimate by WHO uses verbal autopsy and model-based estimation technique.

The incidence peaks bi-annually immediately following the beginning of the rainy seasons from September to December and from April to May (26). The transmission depends on altitude and rainfall. Malaria epidemics are relatively frequent (26).

The second distinctive feature is that malaria transmission in Ethiopia is low and unstable while it is high and stable elsewhere. Third, the major malaria vector in Ethiopia (mosquito specious) is *An. arabiensis* while *An. gambiae* is dominant in most other places. *An. pharoensis, An. funestus* and *An. nili* also play a minor role in the transmission of malaria in Ethiopia (27). Fourth, in addition to *P.falciparum* — the dominant specious which account for about 60% of the total malaria cases in Ethiopia — the contribution of *P.vivax* (about 40%) is substantial in Ethiopia, unlike in other places in Africa *P.vivax* is rare (11).

Recently, the National Malaria Control Program (NMCP) in Ethiopia stratified (Figure 2) the districts into four groups based on the Annual Parasite Incidence (API): malaria free (API = 0), low (API < 5), moderate (API ≥ 5 & < 100), and high (API ≥ 100). Most of the districts (43%) have API within a range of 5 to 100 while about 7% of the districts has above 100. However, in some of the districts, the API may range up to 427 for *Mirab Armachiho*, 607 for *Sirba Abay*, 641 for *Sherkole*, and for 816 for *Yaso*. The prevention and control strategies are also determined based on which strata do the district has fall (20).

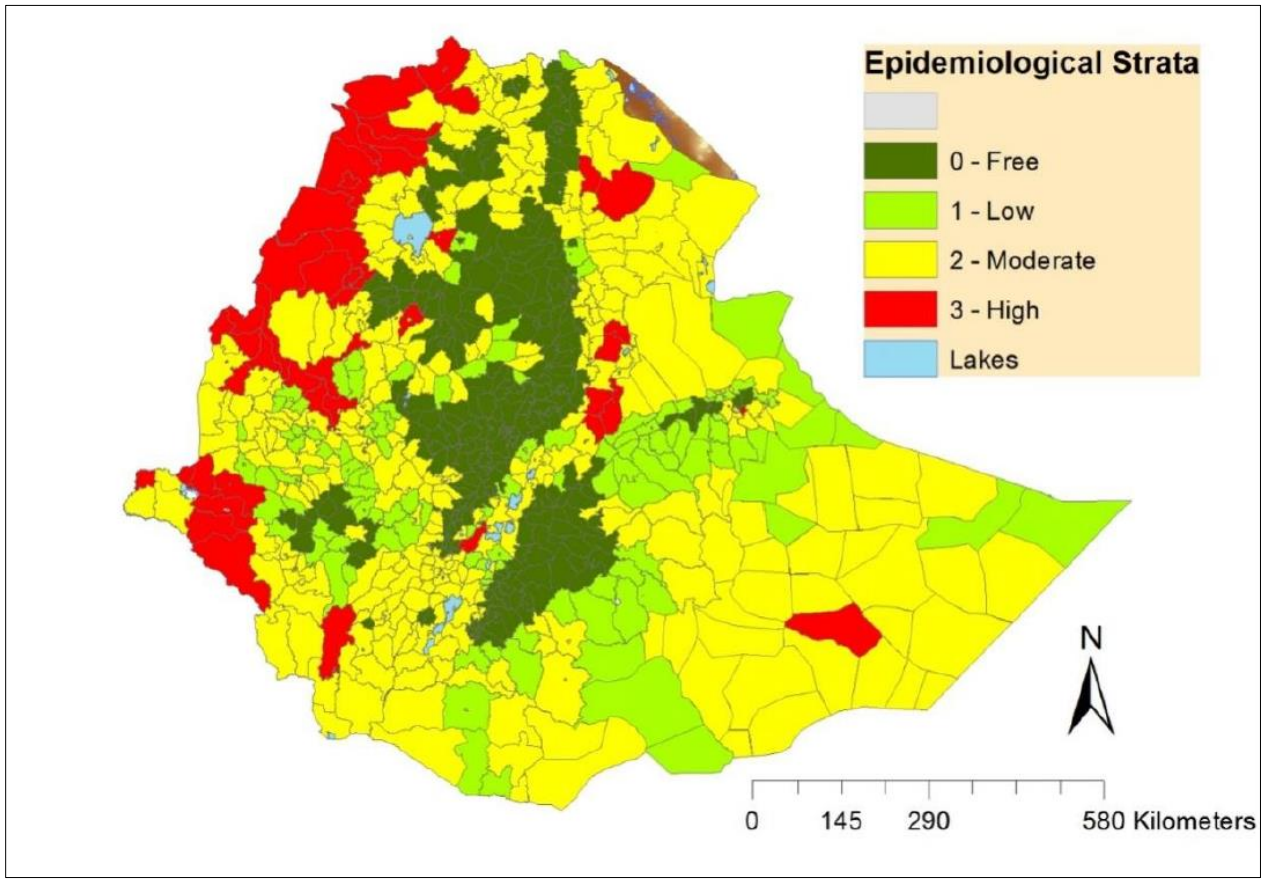


Figure 2: Malaria stratification map (Source: FMoH Ethiopia 2017 (20))

1.5. Malaria prevention and control: Overview and interventions

Malaria infection can be prevented and controlled with different mechanisms. Three innovations are important landmarks in the history of malaria prevention and control. First, Hans Andersag's — chloroquine — is one of the greatest human inventions (44, 45). Second, the discovery of the link between malaria *Plasmodium* and *Anopheles* mosquito by Donald Rose (46). Third, the discovery of DDT by Paul Müller in 1939 and its use for ant-mosquito spray in 1942 was another huge breakthrough for the malaria prevention and control (3, 45).

In 1955, World Health Organization launched the first Global Malaria Eradication Program relaying on the two novel tools: treatment with chloroquine and mosquito control with DDT (45, 47). Despite enormous success in countries in temperate region and reduction of the frequency of outbreaks in some other Asian and Latin American countries, most of sub-

Saharan Africa was neglected in this program. Later in the 1960s, because of the incident of drug resistance in humans and extensive mosquito resistance to insecticides the malaria eradication program stalled. In addition, massive population movements, lack of community participation, and lack of funding facilitated the failure of the program – and officially abolished in 1977 (47).

Largely, in the 1970s, 80s, and early 90s, malaria prevention and control was integrated with the Primary Health Care systems which advocate community-based approaches, and the focus given to malaria compared with the burden was less during this period (45). After this period of neglect, malaria prevention and control program again started to attract attention globally during the reign of Millennium Development Goals (MDGs) (45). In the MDGs malaria received separate attention (Goal number 6) (48). World Health Organization, Roll Back Malaria, The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund), and United Nations Development Programme jointly launched an initiative which was directed towards creating a universal access to malaria prevention and treatment in developing countries. In addition, it was targeted to reduce the world malaria incidence by half by 2015 (48, 49).

Currently, as adopted by the World Health Assembly in May 2015, major worldwide implemented malaria prevention and control intervention strategies are early diagnoses and prompt treatment of cases with artemisinin-based combination therapy (ACT), intermittent preventive treatment in pregnancy (IPT), larval source reduction, use of long-lasting insecticidal nets (LLINs), and indoor residual spraying with insecticide (IRS) (50). In line with the globally recognised strategies —in Ethiopia— malaria prevention interventions broadly consists of all of them except IPT; but two of the latter (i.e. Use of LLINs and IRS) has been the dominant tools (25, 43, 51-54), and were particular area of interest for this thesis.

Long Lasting Insecticidal Nets (LLINs)

Sleeping under bed-nets, which are impregnated with long-lasting insecticides, has been considered as one of the effective tools to prevent malaria (51, 55-58). A high coverage of LLINs results in the reduction of overall malaria transmission because of both its physical barrier and insecticidal property. A comprehensive systematic review of several studies by Kesteman et al. recently reported a median protective-effectiveness of 39.8% (IQR 20.2–50.3%) for LLIN (59). Regular use of treated nets has shown to reduce child mortality by about 25% (57). In Ethiopia, a cohort (60) study have shown reductions in the number of malaria cases in communities using insecticide-treated mosquito nets while a cross-sectional study (61) have shown no significant difference in malaria incidence between bed-net users and non-users.

Although the use of insecticide-treated mosquito nets has become a mainstreamed strategy in malaria prevention and control for several years (45), large-scale expansion was observed recently (62). In 2016, slightly more than half (54%) of the people at risk of malaria in sub-Saharan Africa slept under an insecticide-treated bed-net (ITN or LLIN). This is a remarkable achievement compared to 30% in 2010 (11), yet far from the Sustainable Development Goal (SDG) target of universal access. Similarly, household-level ownership of bed-nets (i.e. at least one functional ITN per household) was high (80%) compared with 50% in 2010, yet only 43% of households had sufficient nets to cover all household members (i.e. one net for every two people). However, the 2017 World Malaria Report show that the rate of increase in LLIN coverage has slowed since 2014 globally (11).

In Ethiopia, likewise, the interventions were largely expanded since 2005 (61). For example, within two years alone (between 2005 and 2007), more than 20 million insecticide-treated bed nets (ITNs) had been distributed to 10 million households. According to the national MIS, in 2011 the bed-net ownership coverage (i.e. at least one bed-net per household) was 55%. In 2015, the LLIN coverage was about 64%, and 32% of them had one LLIN for every two people in the household (25).

Indoor Residual Spraying (IRS)

Indoor Residual Spraying (IRS) is spraying the interior lining of the wall and the roof of the house with insecticide, and it has been one of the cornerstones of malaria prevention for a long time (52, 63, 64). The Cochrane reviews comprehensively summarized that the IRS is effective in reducing malaria incidence (52), and an extensive recent review by Kesteman et al. indicates a median protective effectiveness of 28.5% (IQR 8.8–47.3%) (59). However, regarding the global uptake of the intervention in 2016, compared with a base-case of 2010, the coverage substantially decreased. According to the WHO report, about 30% of IRS-targeted areas were sprayed in 2016 and in 2018 the coverage was expected to increase to 50% (11).

In Ethiopia, IRS has been a key vector control intervention that has contributed greatly to epidemic control and reduction of malaria burden since the 1950s (27). Based on the FMoH data, almost all malarious areas including low-incidence areas has been targeted for IRS every year (20). However, IRS is an intensive operation that demands the mobilization of large number of personnel and other resources. It could be conducted once or twice a year based on the efficacy-duration of the insecticide applied and the malaria transmission seasons in the area (65). The implementation of IRS used to be 'centralized' and operated by a district or zonal health offices while recently it has been integrated to the Health Extension Program (Community-Based-IRS) and operated by the health posts led by Health Extension Workers. In Community-Based IRS, the role of the District Health Office would be mainly planning the activities and allocation and distribution of the spraying resources to health post (65, 66).

Combined intervention (LLIN+IRS)

Despite few and mixed evidences about the effect, and very limited evidence regarding cost-effectiveness (67), there are several situations where LLINs and IRS have been implemented within the same households in Ethiopia or malaria endemic areas elsewhere in Africa (54, 59, 68-72). Regarding the effect of combining LLIN and IRS, findings from mathematical models by Yakob et al. (73), Okumu et al. (74), and Chitnis et al. (75) show

some additional protective value compared with either of them alone. Cross-sectional data show that households concomitantly using LLIN and IRS were 36% (95% CI 7% to 53%) more protected compared to households which only use one of the interventions (71). Furthermore, studies from Kenya (76) and Equatorial Guinea (77) has also show that combining LLINs and IRS prevents more malaria compared with singleton interventions.

Yet, reports from randomized controlled trials has shown conflicting findings regarding the added protective-effect of combined implementation. The studies from Benin (78), Gambia (79), and Sudan (80) has shown no substantial effect while a study from Tanzania has shown significant added protection-effect (i.e. mean plasmodium falciparum prevalence rate (P*f*PR) of 13% in the ITN+IRS arm while it was 26% in the ITN only arm) (81).

Achievements and challenges

The unprecedented expansion of the malaria prevention and control services between 2000 and 2015 has paid-back tremendously. Over the past 15 years, malaria deaths were reduced almost by half (55). Globally, number of deaths reduced from 839,000 to 438,000 and in Africa from 764,000 to 395,000 (62). Between 2010 and 2016, the global rate of new malaria cases declined by 37% and the malaria incidence by 18% (i.e. from 76 to 63 cases per 1000 population at risk) (11). About 70% of the achievement can be directly attributed to the whole ant-malaria interventions, and about 68% of averting cases could be attributed to the bed-nets interventions alone (82). During the same period, Ethiopia achieved about 90% reduction in malaria mortality (20).

Yet, malaria is still one of the biggest challenges for the health system in low-income countries, in general, and in Ethiopia in particular. For example, more than 2.5 million of malaria cases were estimated in Ethiopia in 2016 (11). Unfortunately, the difference in the amount of funding needed compared with actual amount committed to malaria prevention remain wide. Progress has stalled mainly due to resource and budget constraints. For instance, only about USD 2.7 billion was invested to malaria prevention and control interventions in 2016 while each year about USD 6.5 billion is required to deliver the

necessary malaria interventions. On average, only less than USD 2 per person at risk of malaria was committed in the 41 high-burden countries (11). Therefore, there is an evident demand for evidence to be utilized for prioritization of strategies, interventions, and a combination of interventions that effectively prevent, control, and eliminate malaria.

1.6. Evidence for Prioritization of Malaria Prevention with LLIN and IRS

Prioritization of malaria prevention in the global health agenda can be broadly studied from two layers of arguments (83, 84). The first is about prioritization of malaria prevention compared with other health problems. The growing body of evidence on key molecular and epidemiological parameters of the disease creates a good understanding about malaria. Availability of effective prevention tools, well-performing diagnostic and treatment modalities, and political commitment resulted in widespread consensus about prioritization of malaria prevention in general (84-86). Yet, when it comes to some specific issues, these evidences alone are not adequate (83-85).

The second argument, which lays within prevention and control framework, is about which malaria prevention strategy or combinations of malaria strategies would provide the optimal gain to the society (83, 87). In this regard, evidence regarding the economic burden and pro-poor equity (e.g. choosing between treating the poor patient free or applying use-fee to sustainable finance the health service) can be an important question. Cost-efficiency (e.g. choosing between new interventions that has some additional protection with some additional cost, or following the current routine practice) are important consideration. In addition, an equitable access and ownership of malaria prevention interventions should be considered equally important (83, 87) for optimal prioritization of malaria program. Since the present work applied these diverse but interrelated methods (i.e. economic burden, cost-effectiveness, and equity), we broadly explain the approaches and available evidence in sub-sections below here.

1.6.1. Economic Burden of Malaria

The economic burden of malaria can be estimated at a macro - level or at a micro - level using different research designs. The macroeconomic burden of malaria on a population level to the entire economy at large is well-recognized (88-91). A seminal work by Gallup & Sachs is an important study which clearly show that the macroeconomic causal-link runs in both directions (88). Sachs et al. say that 'malaria and poverty are intimately connected' (90). Where malaria is high poverty prevailed, and the reverse is true. The causes can be explained in different pathways. Malaria reduced individuals and firm productivity within the nation. It would discourage foreign investment. Its impact on trade and tourism is also immense. On average, malaria reduce the growth of some African countries with approximately 1.3% (88-91).

According to the recent World Malaria Report, about USD 6.5 billion is annually required to meet the 2030 targets of WHO global malaria strategy (11). This estimate shows that the resources needed for handling and prevention of malaria takes a heavy toll on the economy at large or to the health system in particular.

Malaria affects the household's economy through increased spending on health care – out of pocket expenditure, reduced income due to day losses related to the illness, and premature deaths of productive members of a household. In the long run, it also decreases productivity and affects the household economy through its chronic neurological complication and cognitive deterioration. What is less clear so far is the direction of the causal-link between malaria and poverty at the individual level (91, 92). Several studies indicate that the risk of malaria is similar between poor and rich within the same community or the same area. For example, Worrall et al. (93), based on a review of several kinds of literature, and Filmer (94), using Demographic and Health Surveys data from several countries establishes no link between malaria incidence and wealth status at a micro-level. No difference is found, at household level, in the incidence of fever between

the poor and less-poor (94). Similarly, empirical data from the same area with the current studies also found no association between wealth status and incidence of malaria (30).

The main malaria transmission seasons coincides with the harvesting season (26), and malaria therefore has serious consequences for Ethiopia's subsistence agriculture-based economy and for the nation in general since about three-fourth of employment is generated in the agriculture sector (14). However, we have only few studies that consider the economic burden of malaria to household in Ethiopia (95, 96).

1.6.2. Cost-effectiveness of LLIN and IRS

Resources are always finite and limited, while health care needs are huge and endless. Resource allocation is, therefore, a central part of the decision-making process in any health care system (97). In a low-income country like Ethiopia, the resource limitations are literality devastating. For optimal decision-making, comparison of the additional resources (i.e. costs) of alternatives with the additional benefits (effectiveness) is one of the most important considerations. Cost-effectiveness analysis (CEA) is a form of economic analysis that compares the relative costs and outcomes (effects) of different courses of action. The cost-effectiveness of an intervention is commonly expressed as the Incremental Cost-effectiveness Ratio (ICER)—the ratio of the difference in intervention cost to the difference in health effects from the interventions (97, 98).

Drawing on a seminal work of Goodman et al. (99) published in 1999, a growing number of studies have attempted to quantify the cost-effectiveness of malaria prevention using various approaches (97, 100). There is substantial recent empirical evidence from observational studies and randomized controlled trials, in addition to several modelling exercises (100, 101). Meta-analysis and systematic review, including Cochrane collaboration, of those studies positively conclude that both LLIN and IRS are effective tools of malaria prevention (52, 56, 101, 102). The evidence confirms that both ITN/LLIN and IRS are cost-effective in preventing malaria over the base-case scenario of early diagnosis and prompt treatment (100, 101). What was lacking most from the current

evidence pool in this regard is what would be the effect if we implement the two (LLIN and IRS) simultaneously, in terms of malaria cases prevented and the number of DALY averted? Will it remain a cost-effective option?

1.6.3. Cost-effectiveness of combination of LLIN and IRS

According to a position statement by WHO regarding the insecticidal-treated mosquito net (103); "Neither LLINs nor indoor residual spraying (IRS) alone will be sufficiently effective to reach and maintain the interruption of transmission in holo-endemic regions of Africa or in hyper-endemic countries in other regions". In addition, during malaria elimination and eradication phase, it could be reasonable to assume strategies with a combination of LLIN and IRS would perform optimally in both high and low-incidence setting (87). However, the amount of empirical evidence regarding the effectiveness of the combined implementation is minimal, and not yet clear (87).

In this regard, World Health Organization (WHO) recommends further research in order to determine not only the effectiveness but also the cost-effectiveness of combining LLIN and IRS (87, 103). Following this, few studies attempted to estimate the effectiveness of a combined intervention that came with none-conclusive results (71, 73-81). However, none of those studies has empirically attempt to estimate the cost-effectiveness of the combined intervention while an ongoing study from Mozambique aims to estimate the cost-effectiveness alongside a cluster randomized trial (104).

1.6.4. Equity in Malaria Prevention: LLIN and IRS

The distributional (equity) perspective of access and ownership of malaria prevention interventions (LLIN and IRS) can be examined as who actually own more or less of the prevention interventions. Yet, the equity aspect of malaria prevention intervention is less explored topic (87). However, beyond mere emphasis on general coverage, LLIN ownership and IRS status should be fair regardless of socioeconomic status. The issue of fairness is very critical, especially where the malaria preventions interventions are publicly funded interventions. For example, both LLIN and IRS are mainly financed through the

Ministry of Health either from external donation or direct government budgeting. Therefore, unarguably, the benefits from these publicly financed interventions should be equitably distributed across different socioeconomic gradient.

A test regarding this normative position is that the odds of malaria infection would be similar for all socioeconomic classes or between the poor and the rich (92-94). Consequently, at the individual or household level, the probability of malarial infection is quite similar if either of them were not using the preventive measures in the same neighbourhood. In addition, one could not argue that the better-off are in a better position to access the other non-publicly financed means of malaria prevention (e.g. mosquito repellent, window meshes etc.) given that, availability of those items in the rural setting is limited. Thus, the argument that malaria prevention interventions (LLINs and IRS) should be owned equitably is strong and valid. However, the Ethiopian government has committed to following a pro-poor universal health service delivery strategy, which goes beyond policy statements of creating equal access to health services for all groups of a population (19).

1.7. Rationales of the study

Encouraged by the success achieved during 2000 and 2015, the World Health Assembly approved a new ambitious global technical strategy to accelerate a further reduction in both malaria incidence and mortality. The strategy would be implemented from 2016 to 2030 and comprise three major pillars: reducing the incidence by 90%, bringing down the mortality by 90%, and eliminating malaria in at least 35 countries (50). Ethiopia is one of the countries that embark on the elimination of malaria in this target year (19, 20, 50). In order to achieve these ambitious targets, the country-level malaria prevention and control program should improve the strategies based on accurate and holistic evidence. Malaria prevention and control effort, thus, requires a wide range of pieces of evidence, beyond morbidity and mortality estimates, in order to meticulously design the prevention and control strategies. The topics in this Ph.D. work would address the evidence gap and further provide new evidence in the following three distinct but interlinked areas.

The first study (Paper I) would fill the evidence gap regarding the economic burden of malaria to the rural households. Evidence on the economic burden of malaria is important for prioritization of malaria prevention and treatment at the national and sub-national levels and facilitates better resource allocation in the health care system (88, 90, 105-107). An influential report by Jeffrey Sachs (89) argued that evidence about the economics of malaria should be at a disposal for decision-makers at all stages in order to gain a rational option in policy preparation. Yet, only few evidences are available along the economic burden of malaria to the rural families in Ethiopia. In the last decade, no study of such kind had been conducted in Ethiopia. Moreover, health care payment and financing mechanism in Ethiopia has been through a series of reforms and funding of malaria treatment still remains unclear in general and irregular across regions (108, 109).

Economic evaluations, and in particular cost-effectiveness analysis (CEA), can provide important information for identifying the interventions that represent the best value for money. There is a substantial body of literature on the cost-effectiveness of malaria prevention interventions, and the heavy chunks of empirical evidence has shown that both LLINs and IRS alone are very cost-effective interventions in the faces of huge and devastating health and economic consequence born by malarial illness (67, 99, 101, 110). However, only few empirical studies attempted to quantify the added protective-effectiveness (71, 76-80) of the combined implementation of LLIN and IRS, and none-of those studies have attempted to calculate the cost-effectiveness. Thus, in the second study (Paper II) of this thesis, we proposed to fill this evidence gap through reliably determining the cost and cost-effectiveness of the combined use of LLIN and IRS compared with using IRS alone, LLIN alone, and routine practice. The National Malaria Control Programs (NMCP) in Ethiopia can utilize the evidence generated to inform the choice of optimal packages of interventions.

Beyond the mere emphasis on overall coverage of malaria prevention services in general or LLIN and IRS in particular, there should be equivalent focus on how it should fairly benefit all, regardless of socioeconomic position. Likewise, the Ethiopian government has

committed to following pro-poor universal health service delivery strategy, which should go beyond policy statements about creating equal opportunity to access the health services for all groups of the population (19). In Ethiopia and most likely in most other African countries, both LLIN and IRS programs are mainly financed publicly, either through donation or direct government budgeting (111-113). The distributional implications of benefits from publicly financed interventions is not just a health matter but also an issue of justice. In contrast, little is currently known about who benefits from prevention efforts. Where are those freely distributed bed nets? Who owns them? Whose houses are sprayed or not? These questions reflect concerns about social justice and fairness and have so far not systematically been investigated. In the third paper (Paper II) of this thesis, we use household survey data to evaluate the socioeconomic related dimension of inequalities in malaria prevention interventions (LLIN and IRS) which can inform decision in priority setting and resource allocation.

Chapter II: Objectives

2.1. General objective

The overall aim of this study was to estimate the economic burden of malaria; and to evaluate the cost-effectiveness and the distributional implications of malaria prevention interventions (LLINs and IRS) in Adami Tullu District, south-central Ethiopia.

2.2. Specific objectives

1. To estimates direct and indirect cost of malaria; and identify predictors of cost variability to rural households (Paper I).

2. To evaluate the cost-effectiveness of combined implementation of long-lasting insecticidal nets (LLIN) and indoor residual spray (IRS) compared to LLIN alone, IRS alone, and to routine practice (Paper III).

3. To evaluate the socioeconomic related inequalities in ownership of Long Lasting Insecticidal Nets and Indoor residual spray status (Paper II).

Chapter III: Methods

3.1 Overview

This thesis comprises three sub-studies — each corresponds to the three specific objectives described in Section 2.2. In this chapter, first, we provide a general overview of the study area, setting, and time-line of the studies. Then we briefly explained separately the methods (design, data, measurement, and analysis strategies) used in each of the three sub-studies specifically. Finally, we describe the measures undertaken to ensure ethical standards. At the end of this chapter, we provide a summary of the methodology in Table 6.

3.2. Study area, settings, and time-line of the studies

The trial was conducted in *Adami Tullu* (Full name: *Adami Tullu Judo Kombolcha*) district. The district is located in South-central part of Ethiopia, in East *Showa* Zone of *Oromia* Region. The district has 48 *Kebele* and a population of about 170 thousand. *Adami Tullu* is located in the heart of the Great Rift Valley. The elevation of the district ranges from about 1500 to 2300 meters above sea level, with most of the inhabited villages located in the lower parts. The annual mean temperature ranges from a minimum of 14^0C to maximum of 27^0C. Like most places in Ethiopia, the district has two rainy seasons, the longer (June to September) and the shorter (February to April). However, the rainfall patterns are sometimes irregular and this contributes to the variability of malaria incidence in the area. The map of the study area is presented in Figure 3.

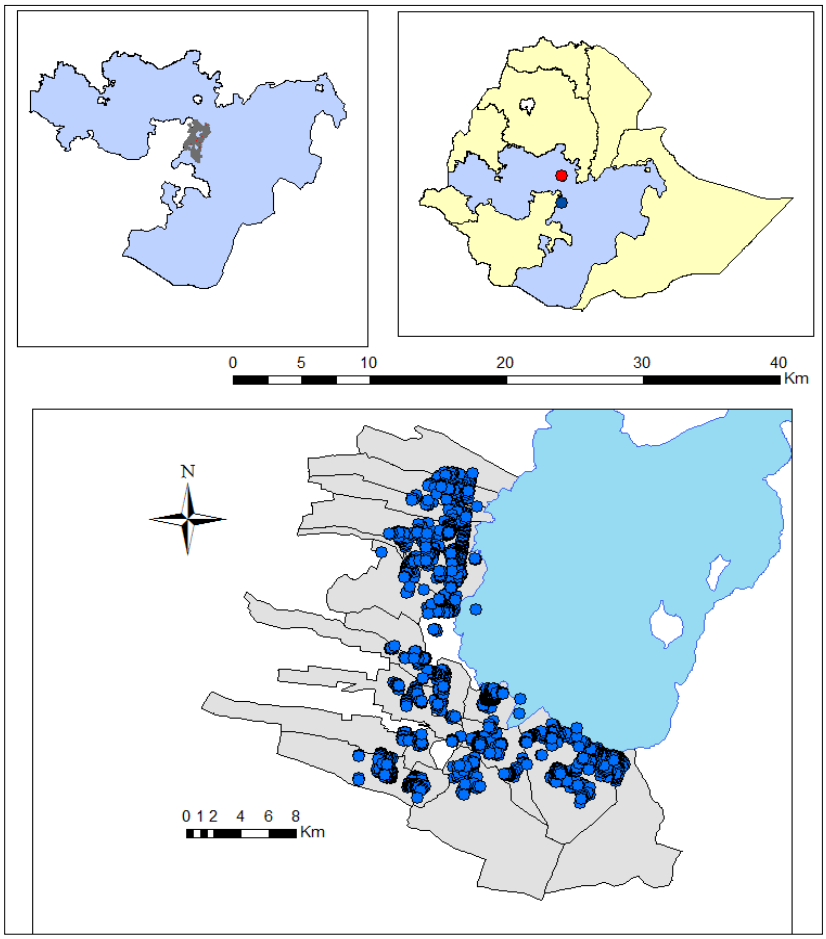


Figure 3: Map of Ethiopia, Oromia region, Adami Tullu district, and the study area.

The peculiar experience happened during the study period in the year 2015/16, like many areas in East Africa: our study area was seriously affected by the drought triggered by *El Nino* (114). This was substantiated by primary meteorological data from the area. On one hand, the rainfall decreased substantially. For instance, the mean annual rainfall in previous four years (2011 – 2014) ranged from the lowest 673 mm in 2011 to the highest 909 mm in 2013, but in the year 2015, it was substantially reduced to 471 mm. On the other hand, the mean high temperature in 2015 (29^0C) was raised by 2 degrees compared with 2014 (27^0C). Another peculiarity to this area is —Zeway Lake: a potential breeding site for malaria vectors, especially for nearby households (Figure 3). Most people base their livelihood on subsistence farming for own consumption (14).

Time-line of the studies

The overall timeline of the project is presented in Figure 4. The census and the pilot project were conducted in 2013. The main trial was conducted from 2014 – 2016. The main trial was launched in September 2014 immediately after randomization was done based on the baseline data that was collected in July 2014.

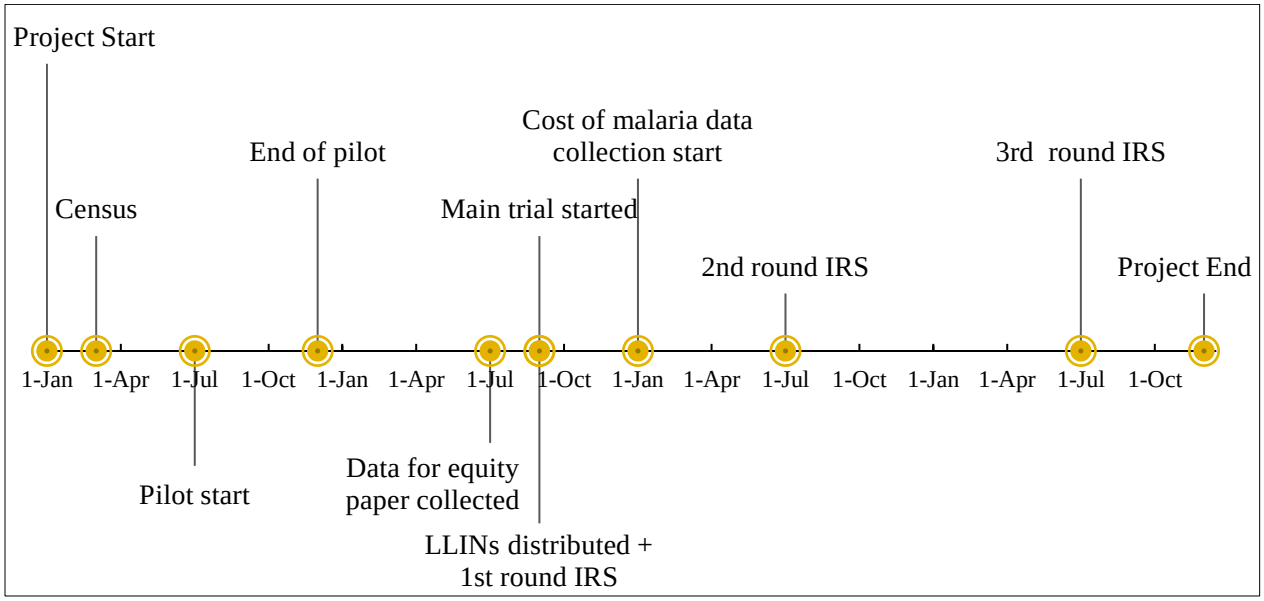


Figure 4: Timeline for the *MalTrials* project and for the specific studies.

3.3. Summary of Methods for Paper I: Economic burden studies

Design and Data

In the first paper, we estimated the economic burden of malaria to the patients and their household using cost of illness design. The cost data were collected from January - December 2015 from 190 malaria cases in Adami Tullu district alongside the RCT. Only villages which were not part of *MalTrials* were included in order to avoid alteration of the true economic burden due to interventions related to the research undertaking (97). For example, in *MalTrials*, designated malaria clinics were established and supported in each villages, which is not necessarily realistic in a larger picture. Three rural health centres and nine health posts were included. To estimate direct and indirect opportunity cost forgone due to malaria illness, we identified, measured, and valued using an ingredient based

bottom-up approach from the household's perspective. We employed an incidence-based prospective approach by measuring the cost per episode of malaria. We estimated costs amongst new cases arising in a predefined period.

Empirical strategy and analysis

We measured the direct costs as out-of-pocket expenditures on the course of seeking and obtaining malaria treatment by patients. The direct costs were evaluated in two groups: (1) direct medical costs (diagnosis, medical supplies, malaria drugs, other drugs, and consultation), and (2) direct non-medical costs (food on the way to the treatment facility, transportation, other non-medical supplies, and services). We estimated indirect costs in terms of numbers of forgone working days of the patients due to the malarial illness (97, 115, 116).

To compute the direct cost, we add the direct medical costs and the direct non-medical costs. The direct cost was initially collected in monetary terms and not further valuation was therefore required. The indirect cost was valued using a human capital approach (97) which first estimate the number of working days lost. We valued the working days lost due to malaria and converted them to monetary-terms using the average wage rate for agricultural workers in Ethiopia. (117). According to the National Labour Force Survey data by International Labour Organization, for average Ethiopian adults older than 18 years, the average daily wage rate for agricultural workers was about ETB 35 in 2013. Proportionally, we assumed that a teenager's (aged 13 to 17 years) wage rate was about half of an adult's, and that the wage rate of children (aged 7 to 12 years-old) was a quarter of an adult's. For kids less than 7 years-old, we considered the wage rate as negligible and we did not estimate the indirect cost. We adopt this framework from a similar study conducted by Cropper et al. in Ethiopia (118). Since the cost information was collected in Ethiopian Birr (ETB), we changed to USD using the 2015 official average exchange rate of ETB 20.5 per USD. To adjust for inflation, we applied a consumer price index. The reference year for all costs reported in this study is 2015 (21).

During data analysis we initially generated the descriptive report with mean costs and their standard deviations (SD), standard error of the mean, and median with interquartile range (IQR) stratified by level of the facility (health centre and health post). Then, we analysed the data for the standard statistical assumptions (normality, multi-collinearity, and heteroscedasticity). Since we had zero-inflated and skewed data, we decided to apply none-parametric models. To compare the median costs across different socioeconomic quantiles and different malaria species, we used Kruskall-Wallis and Mann-Whitney tests. We fitted quantile regression models to identify factors that are associated to the median direct and indirect costs. In order to estimate the 95% confidence intervals for the medians and to estimate robust standard errors for the regression coefficients, we performed bootstrapping technique with 1000 repetitions.

To estimate the inequality in the economic burden of malaria (direct and indirect costs), initially, we generated a wealth index for each patient — based on their households ownership of different assets — using principal components analysis. The wealth index was used to rank case from the poorest to the richest (119). Then, we calculated the concentration index to explore the inequality in the mean and median costs of malaria across different socioeconomic status. We used concentration curves to visually present the degree of inequality (120). All data analyses in this paper was performed using STATA version 14 statistical software (121).

3.4 Summary of Methods for Paper II: Cost Effectiveness Analysis

Brief description of the trial: *MalTrials*

We provide detailed descriptions of the project and the methodology for *MalTrials* in the published protocol (122). Although the primary aim of the *MalTrial* project was to determine whether the combined use of LLINs and IRS would provide additional protection against malaria compared with LLINs each intervention alone or the routine intervention, it also included an extensive entomological study and economic evaluation. In short, *MalTrials* was a cluster randomized controlled trial with a 2 x 2 factorial design

–four arms. Table 2 summarises the description of the interventions in each of the four arms of the trial.

Table 2: Description of the interventions, combinations of intervention and routine arms.

Study arms	Description of the interventions
LLIN alone	Universal coverage of households with LLINs: each household received free LLINs (*PermaNet 2.0*) — proportional allocation to the household size —99% coverage immediately after distribution (October 2014)
IRS alone arm	Universal coverage of households with IRS: using *Propoxur* (isopropoxy-phenyl methylcarbamate) each house sprayed once every year —about 95% coverage for each of the three rounds of spraying (September 2014, July 2015, and July 2016)
Combination (LLIN+IRS)	Each household received LLINs and IRS in parallel with households in the individual arms, and therefore had IRS coverage of 95% and LLIN coverages of 99%.
Routine	Neither LLIN, nor IRS was implemented by either the study project or by the district health office within the study period; Based on the baseline data, the background coverage of LLINs and IRS was about 11% and 75%, respectively

Design: Cost-effectiveness Markov model

Full economic evaluation — using cost-effectiveness analysis — was conducted to compare the cost-effectiveness of combined implementation of LLIN and IRS against each intervention alone and the routine intervention. This cost-effectiveness study has two components: (1) a trial-based CEA, and (2) a literature-based CEA. The justification for the need to conduct a literature-based CEA was to improve external validity of the trial-based CEA in the faces of a 'no-difference' result from the trial. The trial-based CEA inevitably could show that the current routine practice dominates all the prevention alternatives since they are all more costly with similar effectiveness. In addition, the literature-based analysis considers the cost-effectiveness under a scenario of varying

malaria incidence and different levels of protective effectiveness of the interventions based on a literature survey.

In both the trial-based CEA and the literature-based CEA, we followed the same Markov model and analysis procedures while we used effectiveness estimates from a trial for the former; we used effectiveness estimates from literature survey for the latter. We developed a simple Markov malaria transmission model, and we populated it with effectiveness and cost data. We used TreeAge Pro Suit 2017 (© 2017 TreeAge Software, Inc.) software for building the model and for data analysis. In order to facilitate comparability with other similar studies, as much as possible we tried to follow most of the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine (123) during specification of the model. Our cost-effectiveness Markov model is characterised as follows:

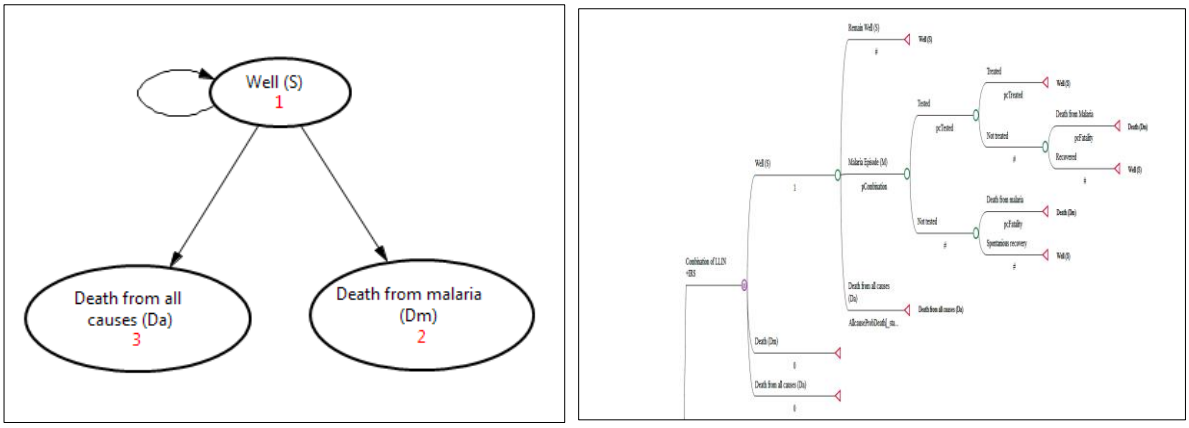
- **Comparators groups:** We compared the four interventions, namely: combination (LLINs+IRS), LLINs alone, IRS alone, and routine intervention. For each intervention, a separate Markov tree was attached.

- **Cycle length:** We define the cycle length in this model as one year. A half-cycle correction was done in order to assume that events occur halfway through a cycle (rather than at the beginning or at the end.

- **Time horizon:** We followed a hypothetical Ethiopian birth-cohort over their lifetime. The time horizon of this evaluation was 80 years and we run the model for 80 cycles.

- **States and disease progression:** To simplify the disease progression, we defined three mutually exclusive health states that represent the dynamics of malaria: well (S), death from malaria (Dm), and death from all other causes (Da) (Figure 5A). Initially, all individuals would be in ‘well’ (S) state susceptible to malaria. A person from a ‘well’ state (S) would be infected and experience an episode of malaria with

certain probability (Figure 5B). The large proportion (about 90%) of individuals with malaria episode are assumed to be diagnosed, treated, and cured; while some might not be diagnosed and remain untreated. Death from malaria when properly treated would be very rare; therefore, we assume zero mortality. Although it would be rare, untreated cases could progress to severe form. Therefore we assume a mortality of 1 per 100 untreated cases (124). To account for the short duration of malaria illness, in addition to the recurrent nature, we consider malaria episode as 'temporary states' in the Markov model (125).



A B

Figure 5: Markov state-transitions diagram (A), and Markov tree diagram (B) for the model.

- **Transition probabilities:** To capture the probabilities of moving from one state to another state – within a specific time called cycle length.

- **Transition rewards:** Transition rewards are costs or outcomes which is associated with an 'event' of changing between health states (98). We had two cost transition rewards in this model, health systems cost of malaria diagnosis (USD 0.51) and treatment (USD 1.17) (Table 4). Since we consider malaria as a temporary state in our model, dis-utility from malaria is also incorporated as transition reward, which is equal to 0.191 (95% CI 0.172 – 0.211) (126, 127). Then combining the incidence data with health-utility (to be exact health dis-utility), we estimated years of life lived

with disability (YLDs). Life year lost due to premature death (YLL) was estimated based on an assumption which basis on the WHO data that about 1 of every 1000 untreated case would die (124). Then, the Disability Adjusted Life Years (DALYs) was calculated by adding YLL and YLD —to estimate the total benefit gained from the intervention (126).

$$DALY = YLL + YLD$$

- **State rewards:** Each state was associated with annual state rewards, related to spending a year in the particular health state. These include the annual cost of prevention in each arm (for LLIN+IRS = USD 4.04, for LLIN alone = USD 1.06, for IRS alone = 3.07, and zero for routine arm) (Table 4) and the annual effectiveness value (DALY averted).

- **Discounting:** Both the cost and health effect were non-differentially discounted with 3% discount rate (123).

Data

Cost

We could obtained input data for the Markov model either from best available literatures or primary sources (Table 4). For both the trial-based CEA and the literature based CEA, we applied primary cost data collected by *Maltrials* research project alongside the main trial. In the measurement of both cost of prevention intervention and cost of diagnosis and treatment of malaria, we applied straightforward costing analysis from the health service providers' perspective as summaries in Table 3. We used Microsoft Excel spreadsheet to extract data and for computation of the costs.

Table 3: Summary of costing method for malaria prevention, diagnosis, and treatment, Adami Tullu 2015.

Type of cost	Identification	Measurement	Valuation
Personnel	Health extension workers, malaria focal persons (supervisors), village/kebele managers, village/kebele chair persons, health centre heads, district health office head and deputy head, zonal malaria coordinator, pharmacist/druggist, store keeper, finance person, casher, spray men, porter, and washer	Number of full working days invested for IRS and LLIN distribution. Percentage of time spent on implementation of IRS LLINs.	Monthly salary, Per-dim
Bed nets and insecticide	LLINs and insecticide (Propoxur)	Number of LLINs handed out to the households, and quantity of insecticides used in the IRS	Price of LLINs and Insecticide from receipts of purchases
Supplies and materials	Complete spray pump, pump spare parts and repair, tip of a nosel, lubricant, filter, personal protective equipment (boots, face shield, helmet, coveralls, gloves, mask, protecting clothing, etc.), stationery, buckets, measuring mug, plastic sheet, refreshment on the training days, attery cell, Soap (Detergent)	Quantity consumed (in appropriate units) from receipts, and payment bills, logbooks.	Purchasing price of the item directly from the invoice, or the current market price of the items where the invoice was not available
Transport costs	Vehicles (car and motorbike), shipping cost (shipment from port of Djibouti), inland freight, unloading/ loading labour from the truck to the main store and from the main store to each village, drivers payment, and fuel	Vehicle logbook, Interviews with drivers and accounts staff from both project and district health office	Price of fuel, and actual expenditure on maintenance of the vehicles, transport by other means (labour).
Storage (warehouse), and space (training hall)	Storage room, Training and meeting hall	Size of the room, number of days rented, From contract documents and payment documentation	Direct monetary term from actual receipts, and payment bills

In Table 4, we present the unit costs of malaria prevention interventions per annum per person year protected, and the unit cost of malaria diagnosis and treatment per episode of malaria from the providers' perspective.

Table 4: Costs of prevention interventions, and diagnosis and treatment of malaria (2014 USD) Adami Tullu.

Costs	**Mean**	**Mean +/- 20% of the mean**		**SD**
Intervention cost of LLIN+IRS	4.04	3.00	4.500	0.2020
Intervention cost of LLIN	1.06	0.848	1.272	0.0530
Intervention cost of IRS	3.07	2.456	3.684	0.1535
Intervention cost of routine	0	Na	Na	Na
Cost of malaria diagnosis at PHCU	0.51	0.408	0.612	0.0255
Cost of malaria treatment at PHCU	1.17	0.936	1.404	0.0585

Effectiveness

The input data for the effectiveness of the intervention for the trial-based analysis were mainly drawn from results of *Maltrials*. The trial provides incidence data in 1,000 person-years of observation (PYO) (Table 5) which were 15.548 for combination (LLINs+IRS), 15.184 for LLINs alone, 15.652 for IRS alone, and 15.144 for routine arms. We then, convert[5]the incidence information into transition probabilities to estimate the 'most likely' values. The minimum (Min.) and the maximum (Max.) values are +/- 5% of the most likely value.

[5] To convert the incidence rate into probability, we applied the following formula where P is probability, t is time period, and r is incidence rate: $P = 1-\exp^{(-r*t)}$

Table 5: Probabilities used in cost-effectiveness analysis

Study arms	Incidence (per 1,000 PYO*)	Transition probabilities of malaria			
		Most likely	Min.	Max.	SD
LLIN+IRS arm	15.548	0.0154	0.0146	0.0162	0.0004
LLIN arm	15.184	0.0151	0.0143	0.0159	0.0004
IRS arm	15.652	0.0155	0.0147	0.0163	0.0004
Routine arm	14.144	0.0140	0.0133	0.0147	0.0004

*PYO = person-years of observation

We applied input data from best available literature for the effectiveness of the interventions for the literature-based CEA model. Therefore, based on a recent comprehensive systematic review, protective-effectiveness of LLIN alone was 40% (35 – 45%) while it was 28.5% (23.5 – 33.5%) for IRS alone (59). Based on this, we assumed that the protective-effectiveness of the combined intervention would take a multiplicative combination of the singleton interventions (128), which is equal to 57% . Then we applied the following equation to compute the transition probability from the protective-effectiveness:

$$\text{Probability } (TPmi) = 1 - PEi * IR$$

Where *TPmi* is transition probability of malaria in the intervention arm *i* (LLIN+IRS, LLIN alone, IRS alone, or routine), *PEi* is protective-effectiveness of intervention *i*, and *IR* is transmission probability without the interventions. Based on the WHO estimate of annual malaria incidence, we assume a base-case (i.e. initial transition probability before or without the presence of the interventions) annual probability of 5.8% (15), while latter we explored this from 1 to 20% in the one-way sensitivity analysis.

Empirical strategy: Cost-effectiveness Analysis

Broadly, we applied three analysis techniques. First, we used Incremental Cost-Effectiveness Ratio (ICER) to compare the interventions. Interventions were ranked in increasing order according to their DALYs averted, and we calculated the incremental cost

and incremental effectiveness by comparing consecutive interventions with the next more effective intervention. We eliminated the interventions that were more costly but less effective than an alternative intervention (absolute dominance). Then, we calculated the incremental cost-effectiveness (ICER) by dividing the incremental cost by the respective incremental effectiveness.

Second, using one-way sensitivity analysis, we test the robustness of model to the two assumptions: protective-effectiveness of the combined intervention and malaria incidence in the area. We performed one-way sensitivity analyses only on the literature-based cost-effectiveness model to examine the effect of changes on the protective-effectiveness of combination and malaria incidence on the overall ICER. We did this for different level of protective-effectiveness of the combined interventions (45.9 – 68.5%) and at different level of annual malaria incidence (1 to 20%) (15, 129) and the results are presented in a tornado diagram, where also the variables time horizon, cost, proportion of cases diagnosed, proportions of cases treated, probability of mortality from sever malaria were included.

Third, using Probabilistic Sensitivity Analysis (PSA), we evaluated the overall-model uncertainty on both trial-based and literature-based model. In PSA, we replaced the variables in the models with distributions. Probabilistic distributions for costs, dis-utilities, and transition probabilities were assigned with most likely (mean), minimum, and maximum values. We applied a gamma distribution for the cost parameters, and beta distribution for the health outcome and transition probabilities parameters. We assumed the minimum and maximum transition probabilities to vary by +/- 5% from the most likely values, and costs to vary +/- 20% from the most likely values. PSA was done using Monte Carlo simulation and the results are presented as cost-effectiveness acceptability curves, cost-effectiveness acceptability frontiers, and scatterplots.

In the interpretation of ICER result, the optimal decision is to choose the strategy which has the highest ICER per DALY averted that falls below the willingness to pay (WTP) threshold (123). In this study (Paper II), we applied the willingness to pay (WTP) threshold,

which is suggested by WHO – one times/three times GDP per capita. According to Choosing Interventions that are Cost-Effective (CHOICE) program, interventions which have an ICER per DALY averted of less than or equal to one times the GDP per capita of the country are considered as 'very cost-effective'. Similarly, interventions with and ICER of one to three-times the GDP per capita (39) as 'cost-effective', and an interventions which have an ICER greater than three-times the GDP per capita as 'not cost-effective (130). The GDP in Ethiopia for the year 2017 was USD 861 (131).

3.5. Summary of Methods for Paper III: Equity analysis

Design and Data

For Paper III, we applied an inequality analysis design using household-level survey data (120). In September 2014, we collected baseline data, which contains detailed household level information about ownership and utilization of LLIN and IRS, as well as socio-demographic and socioeconomic characteristics, and ownership of different household items. We collected this data as part of a baseline assessment of the main trial (*MalTrials*).

Measurement of outcome variables – household level LLIN ownership and IRS status – was the most important task in this study. LLIN ownership was defined as "the household owns at least one functional LLIN" and IRS status was defined as "the house is sprayed within the last twelve months". LLIN ownership was measured by direct observation by the data collectors while IRS status was assessed based on what the household head reported.

Empirical strategy and data analysis

In this inequality analysis, the first task we did was to define the socioeconomic status of the households—wealth index. To construct the wealth index, we could choose one of the two recommended ways of measurement of wealth in the field of welfare economics: either to use data from household consumption expenditure or to use household assets data. In this paper, we applied the latter method because of three reasons. One, consumption expenditure data in our situation would have been likely to be unreliable since most people

base their livelihood on subsistence farming for own consumption. Thus, a market value of much of the produced is never realised (132). Two, consumption expenditure data are very seasonal and fluctuates. Three, to collect consumption and expenditure data from households would be very demanding, strenuous for the respondents, and costly for the project.

So, to construct wealth index from household's asset data as first recommended by Filmer & Pritchett (119), we applied a principal components analysis technique. The asset variables include the availability of various household items (utensils,), car, and cart, housing conditions (number of room, availability of kitchen, material for the wall, roof, floor, water source, and type of latrine facility). The first principal component was used since it explains the larger variance in the data which had an Eigenvalue of 3.2 and overall Kaiser-Meyer-Olkin measure of sample adequacy of 0.68.

We applied two analysis approaches to demonstrate the inequality. First, we visually present the inequality using concentration curve (133). The concentration curve plots the cumulative percentage of the outcome variable (LLIN ownership and IRS status) on the y-axis, against the cumulative percentage of the household on the x-axis ranked by the wealth index from the most poor (poorest) to the least poor (richest). The concentration curve would be a straight diagonal line, from the bottom left corner to the top right corner, if everyone irrespective of the wealth status had exactly the same value of the prevention intervention. In addition to visual inspection of the concentration curves, we did a quantitative test of dominance using the multiple comparison approach which compares the concentration curve with the diagonal line (perfect line of equality) by taking 19 equally spaced points on the diagonal and the curve to examine for statistical significance of the difference between the two (120).

The second approach was to use the concentration index: a relative measure of inequality measures of inequality, which may range from - 1 to 1. A value of 0 indicate perfect equity, negative values indicate that the variable of interest is concentrated among the poorest

groups, while positive values indicate that the variable of interest is concentrated among the richest (120, 133). The standard concentration index, CI(y), mathematically represented in the following equation, is a covariance between outcome variable (LLIN ownership/ IRS treatment) (y_i) and the socioeconomic rank (R_i) of household *i*, multiplied by 2, and then the whole expression divided by the mean (μ) of the outcome variable:

$$CI(y) = \frac{2*cov(y_i,R_i)}{\mu}$$

A good measure of inequality should take into account the scale of measurement (nominal, ordinal, cardinal, ratio, and fixed) and the range (bounded and unbounded) of the outcome variable; yet, the 'standard concentration index' has not considered these properties. Since both of the health outcome variables in this study (LLIN ownership and IRS status) were binary (Yes/No), a 'normalized concentration index' is appropriate method over the conventional one. Thus, we employed "Erreygers normalized concentration index" which was first provided by Erreygers and Van Ourti (134) as follows;

$$CCI = 4 * \mu * CI(y)$$

Where $CI(y)$ is the standard concentration index and μ is the mean (i.e. Proportion of LLIN ownership or IRS coverage).

As first proofed by Wagstaff et al. (135), a concentration index is decomposable to its contributing factors. We performed a decomposition analysis to further research on how much does socioeconomic and demographic factors do contribute to the measured inequality. We explored and compared the contribution of education, religion, ethnicity, household size, place of residence (village), housing conditions, access to infrastructure (electricity and piped water), ownership and access to mass media and telecommunication service (radio, television, mobile telephone). All analyses in Paper III was done using STATA version 14 using the *conindex* ad-in (136, 137).

3.6. Ethical considerations

This study is compliant with recommended basic international and national research ethical standards (138), and all the research team followed the standards strictly. The study was approved by the Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University, the Ministry of Science and Technology in Ethiopia (ref: 3.10/446/06) and the Regional Committee for Medical and Health Research Ethics, Western Norway (ref: 2013/986/REK Vest).

Participation in the study was voluntary and we obtained an informed consent from each household heads. We read the consent form to the participants and they were asked for informed consent before data collection began. The consent includes consent for publication of results from the data (Annex 2). We obtained an official letter of permission from all levels of the administrative hierarchy starting from the Federal Ministry of Health to the District Health Office. We strictly kept confidentiality and anonymity of the household and individual identifier in the data.

There was no harm anticipated related to those malaria prevention interventions applied in the trial. Rather, both LLIN and IRS were well-known interventions recognized for preventing malaria. Thus, to avoid ethical dilemma with respect to an equitable distribution of benefits from the research — principle of equipoise — the villages were assigned to different arms randomly.

Table 6: Summary of the methods in this thesis.

Papers	Study design	Data source	Statistical approach	Sample size
Paper I	Cost of illness study from household's perspective	Primary data collected	Cost of illness estimation; Principal components analysis; Test of normality, multi-collinearity, & heteroscedasticity; Kruskall-Wallis and Mann-Whitney tests; Quantile regression and bootstrapping; Concentration index & concentration curve	190
Paper II	Cost-effectiveness analysis with Markov modelling	Primary data & Literature survey	Cost of illness analysis Markov modelling One way sensitivity analysis Probabilistic sensitivity analysis DALY	n/a
Paper III	Inequality analysis	Primary data from the baseline survey	Principal components analysis; Binary logit regression; concentration curve & concentration index; Decomposition analysis	6,069

Chapter IV: Summary of Results

In this chapter, I present only brief summary of results from the three papers since we reported the results in detail in each manuscript separately. We present below here, key results from Paper I, Paper II, and Paper III.

4.1 Economic cost of malaria and predictors of cost variability (Paper I)

In Paper I, we estimated the economic burden of malaria to the rural households in addition to highlighting the socioeconomic related inequality in economic burden and identifying the predictors of direct and indirect costs of malaria.

Overall, the median cost of the households per episode of malaria was nearly USD 5 (IQR: USD 2.98 – 8.10), and the indirect cost accounted for about 60% of the total. From the total direct cost, the direct medical cost part was 62% higher than what the non-medical counterpart was. Nearly one-fifth (17%) of the malaria patients at the Health Centres or Health Posts did not get the anti-malaria drug from the facility where they were first tested, instead they were sent home with a prescription only.

In the regression model, we identified that the socioeconomic status, duration of the illness, self-reported history of malaria episode in the last six months, and level of the facility where the patients visited (Health Centre vs Health Post) as significant predictors of variation in the direct cost of malaria. For instance, for every additional kilometre of distance between the patients' residence and the health facility, the direct cost increased by 27 US cents. For every additional day of illness the patient suffered, the direct cost increased by 41 US-cents. While direct costs per malaria episode are substantial, we also found that indirect costs are important sources of economic burden. Likewise, the age of the patient, availability of antimalarial drug, malaria history in the last 6 months, and the level of the facility visited were significant predictors of indirect cost, while surprisingly the severity variables were insignificant.

When we compare the costs between different groups, on average, patients from poor households incur significantly higher direct cost compared with relatively richer households (Concentration index = -0.155 & SE = 0.029). However, the indirect cost distributed uniformly regardless of socioeconomic status (Concentration index = 0.078 & SE = 0.059).

Patients diagnosed with *Plasmodium falciparum* malaria incurred significantly higher total cost — mainly due to the indirect cost — than patients with *Plasmodium vivax* malaria. Among those cases treated at health centres compared with those treated at health posts, the direct cost was significantly higher while the indirect cost was lower.

4.2 Cost-effectiveness of malaria preventions: combination of LLIN & IRS (Paper II)

In the trial-based cost-effectiveness analysis, we found that the routine practice strongly dominates all the other three alternatives (i.e. the routine intervention was less costly, but with similar effectiveness). The expected costs were 0.45, 22.16, 63.28, and 83.12 for routine practice, LLIN alone, IRS alone, and combined interventions respectively. The combination was about 25% more costly than IRS alone and nearly four times higher than LLIN alone. In addition, the PSA (Monte Carlo Simulation with 100,000 replications) — indicates that the expected cost of LLIN alone had exhibited less variability compared with the IRS alone. The expected health benefits in terms of DALYs averted were within a range of 0.005 to 0.007.

In the literature-based cost-effectiveness (Table 7), we found an ICER of USD 1403 per DALY averted for combination (LLIN+ IRS) compared with LLIN alone, and an ICER of 207 per DALY averted for LLIN alone compared with the routine practice. The expected costs of the prevention interventions were 1.9, 22.8, 64.1, and 83.4 for routine practice, LLIN alone, IRS alone, and the combination (LLIN+IRS) respectively. The health benefit (DALYs averted) from the combined intervention was the highest and followed by LLINs,

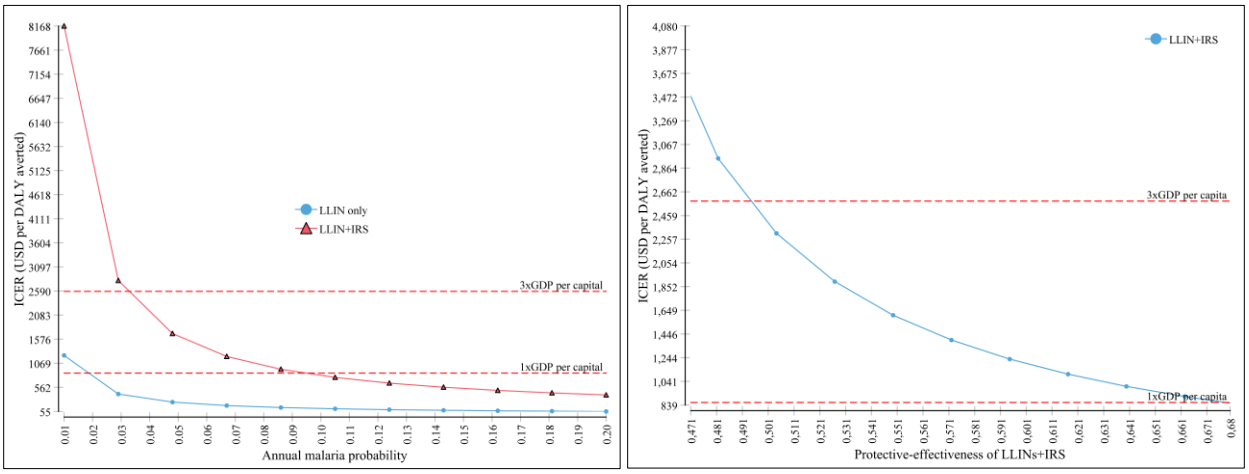
IRS, and routine practice respectively. Since LLIN dominate IRS alone (i.e. LLIN alone was less costly but more effective), we eliminate IRS alone from further consideration.

Table 7: Literature-based cost-effectiveness analysis ICER results, Adami Tullu, Ethiopia 2015

Strategy	Cost (USD)	Incr Cost	Eff (DALYs)	Incr Eff	ICER
Excluding dominated					
Routine practice	1.9		10.451		
LLIN alone	22.8	20.9	10.350	0.101	207
LLIN+IRS	83.4	60.6	10.307	0.043	1403
All					
Routine practice	1.9		10.451		
LLIN alone	22.8	20.4	10.350	0.101	207
IRS alone	64.1	41.4	10.379	-0.029	-1422
LLIN+IRS	83.4	60.4	10.301	0.043	1403

The Sensitivity analysis findings

The sensitivity analysis show that the ICERs were mainly sensitive to change in the annual malaria probability and the protective-effectiveness of combined intervention. The one-way sensitivity analysis at 1 times GDP per capita WTP for annual incidence lower than 2%, none of the interventions are "very cost-effective" while between 2 - 9% LLINs are 'very cost-effective' option, and only when it exceeds 9% does the combined intervention become 'very cost-effective'. At a WTP threshold of 3 times GDP per capita, the combined intervention would be cost-effective even at annual malaria incidence of 3.5% or more (Figure 6A). With the 3 times GDP per capita WTP and at base-case annual malaria probability (5.8%), the combined intervention would be cost-effective if it has a protective-effect of about 50% (Figure 6B).



A B

Figure 6: Sensitivity of ICER to variation in annual malaria probability (A), and protective-effectiveness of combined intervention (B)

The probabilistic sensitivity analysis — the Cost-effectiveness Acceptability Curve (CEAC) — shows that at 1 times GDP per capita WTP threshold, the probability of a combined intervention being a 'very cost-effective' option was below 10%. However, at a WTP threshold of 3 times GDP per capita the combined intervention has about 90% probability of being a 'cost-effective' option (Figure 7).

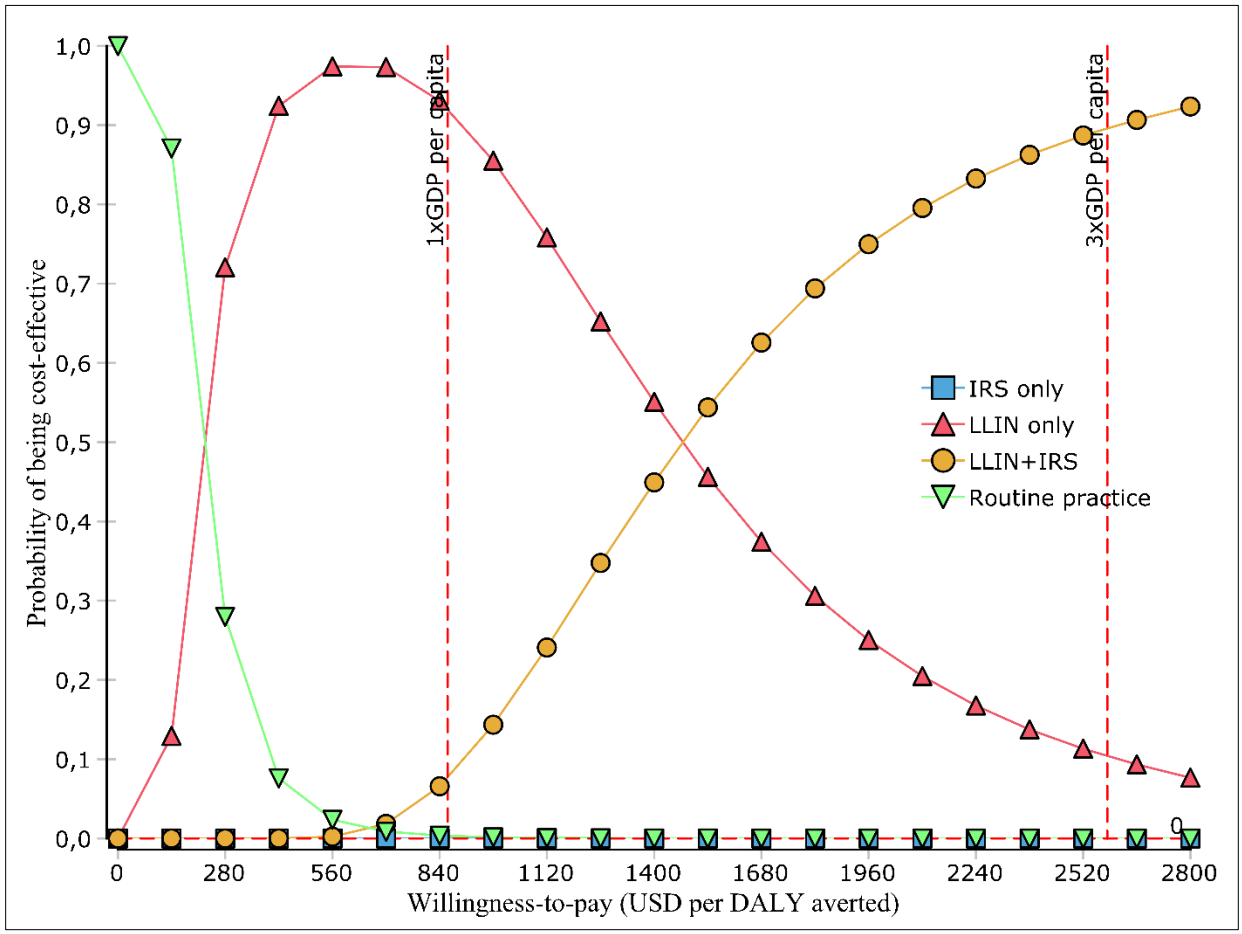


Figure 7: Cost-effectiveness acceptability frontier.

4.3 Equity in malaria prevention intervention (Paper III)

Involving more than six-thousand rural households from Adami Tullu, in the third paper, we aimed to shed light on the equity aspect of the malaria prevention interventions in Ethiopia. The overall LLIN ownership was 11.6%. Almost three quarters (72.48%) of the houses were sprayed at least at one time in the last twelve months. Nearly a quarter of households had neither owned any LLIN nor does their house was sprayed, whereas about one-tenth (9.2%) of the households owned LLIN and their housed were sprayed. The regression model shows that LLIN ownership was significantly higher among those households with better wealth-status, larger household size, who had a latrine, and who had radio. Household head's educational status was a significant positive predictor of IRS status.

When it comes to the socioeconomic related equity of LLINs and IRS, the results are mixed. Along one side, the rich disproportionately owned LLIN. The coverage of LLIN (i.e. ownership of at least one functional LLIN per household) was 8% in the poorest quintile while it was nearly two times (14.7%) higher in the richest quintile. The concentration curve for LLIN is clearly below the diagonal (line of equality), indicating a pro-rich distribution. The test of dominance, using multiple comparison approach, indicates that the concentration curve is significantly below the diagonal line. Moreover, the Erreygers normalised concentration index (0.0627) was significantly different from zero. On the other side, IRS status (i.e. sprayed in the last 12 months) was equitable across the socioeconomic group. The coverage of the IRS was similar across socioeconomic quintiles, ranging from nearly 73% among the poorest and 69% among the richest. The concentration curve is also closely aligned with the diagonal, indicating that there was no noticeable inequality in houses sprayed according to different socioeconomic status.

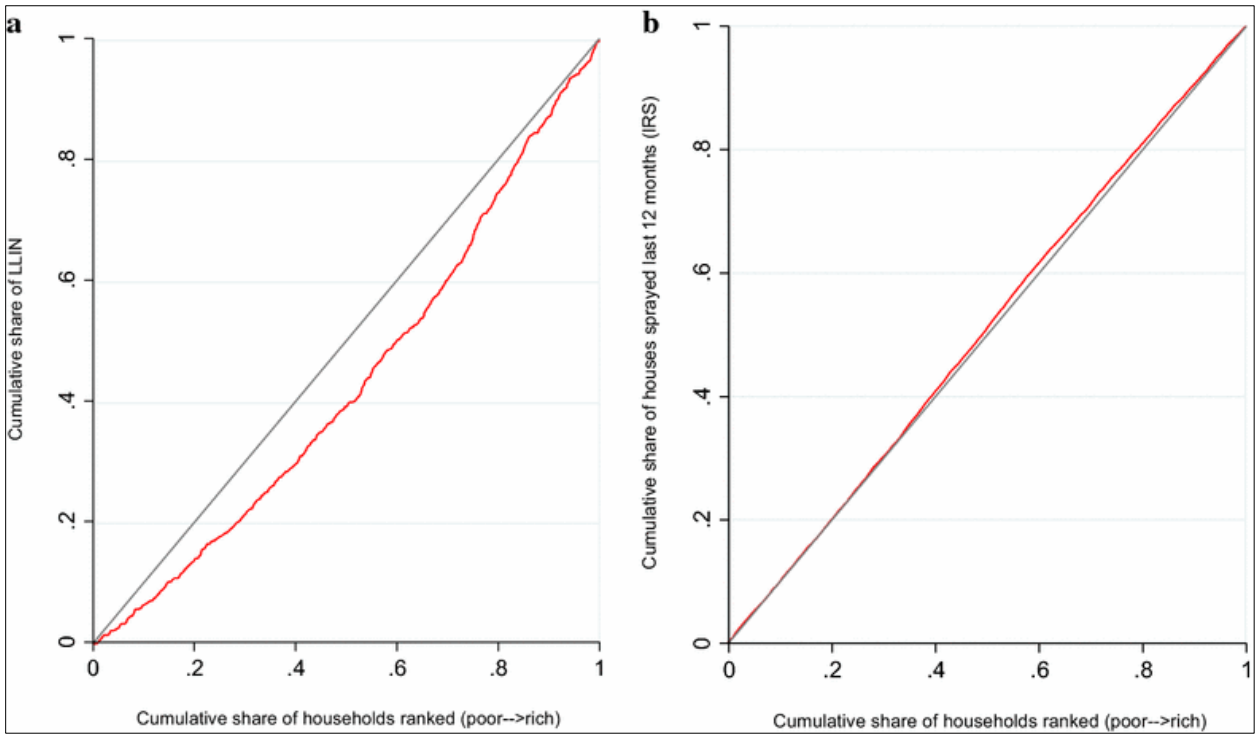


Figure 8: Concentrations curves for LLIN ownership (a), IRS status in the last 12 months (b)

According to the decomposition analysis, the contribution of the wealth status itself, adjusting for other relevant factors, was very high (90.77%). Difference in a housing situation (- 42.2%), access to mass media and telecommunication (24.9%), and size of the household (14.9%), were also predominantly contribute to the observed inequality. Other variables, which had contributed less to the inequality, were ethnicity (4.2%), religion (2.63%), and educational status (3.4%). The sign presented here as positive or negative shows that the factor was concentrated among the rich or among the poor household respectively (120).

Chapter V: Discussion

5.1 Discussion of main findings

Decisions, whether priority setting of a disease control program or selection of the most cost-effective interventions, demand a wide range of evidence beyond morbidity and mortality data (105). The same is true for specific policy decisions about malaria prevention and control (87). In this respect, the present work has offered responses to some of the key questions described as objects in chapter 2, while some issues still remain unclear and several new important questions has emanated.

Is economic burden of malaria catastrophic to rural households in Ethiopia?

One of the questions, which also motivated the first study, was the extent of the economic burden of malaria to the patient and to the household. We found in this study that the economic burden of malaria was huge to poorer households. The follow-up question would be — would this be catastrophic? To provide an appropriate answer to this question, understanding the economic status of the rural household in Ethiopia is equally important as quantifying the economic burden of malaria. In Ethiopia, more than a quarter of the total population is living in absolute poverty (18, 139): even those households in the middle or second richest quintile could be below the poverty-line by standardized living status measurement (18). However, we were not able to determine the exact incidences of catastrophic cases since we did not look at the total household income/expenditure.

In addition, while not causal, the negative relationship between socioeconomic status and economic burden of malaria demonstrated in our study suggests the strong and classical relationships between malarial disease and poverty (89). Despite that, the causal link is less clear at an individual level, unarguably malaria is a disease of poverty (90, 93, 113, 140). The direct cost of malaria is disproportionately high among the poor group against their limited capacity to pay. Therefore, malaria treatment, prevention, and control plans should not be merely considered as disease prevention efforts, but rather they should be taken as part of the national poverty reduction and development plan.

What are the factors for the variability of the economic burden of malaria?

This study is the first in Ethiopia if not in Africa (Paper I) which attempted to compare the cost of *Plasmodium falciparum* and *Plasmodium vivax*. We found that in general, the cost of *P.falciparum* is significantly higher than that of *P.vivax*, and the indirect cost was particularly high. In this regard, the larger share of the literature on economic of malaria is predominantly focus on falciparum malaria while understanding the cases of vivax is equally important (67, 99, 101, 141). Most of the previous economic evaluation studies were either not disaggregated by specious or only consider *Plasmodium falciparum (141).* As Ethiopia is one of high *P.vivax* affected country, future evaluations of malaria should incorporate detailed evaluation of *P.vivax* component.

In this study, we also compared the direct cost of malaria between health posts and health centres. The direct cost at a health post is low compared with the direct cost at a health centre. However, finding from the present work suggested that what was happening at the facility level did not comply with what was promised in the national use-fee exemption system. What the guidelines have promised was that there should be no charge for any service at a health post level and no-user-fee charge for malaria diagnosis and treatment at all levels in primary health care units (109). Still, some facilities charge patients for diagnosis and treatment — against what the national and regional guidelines dictate. For instant, 12% of those examined at health post level and 30 % of those examined at health centres had paid for antimalarial drugs. Furthermore, this study identified that lack of drugs at the public facilities was one of the cause for the higher economic burden to the household. Therefore, health systems research using a mixed-approach (qualitative and quantitative) with large sample size would be important to understand the source behind this kind of disparity.

Is combined implementation of IRS and LLIN cost-effective?

None of the few previous works on the evaluation of combining LLIN and IRS compared with singleton interventions attempted to calculate the cost-effectiveness. There has been recently an ongoing work in Mozambique which aims to estimate full economic evaluation

(104). Our attempt to conduct CEA of a combined intervention alongside RCT was to some extent challenged with 'no-difference' in effect amongst intervention arms of the study compared with the routine arm; therefore, the trial-based cost-effectiveness analysis automatically indicates no preference of any of the interventions over the other. This might be mainly because of the low power of the study (142), because of low malaria incidence in the area, or because of reasons that are not clear to us. The incidence of malaria during the trial period was 37% lower than what we anticipated based on data from the pilot study (30).

The literature-based cost-effectiveness result of the present work indicates that the combined intervention of the IRS and LLIN is 'cost-effective' alternative with an ICER of USD 1403 per DALY averted compared with WTP of 3 times GDP per DALY for Ethiopia. This cost-effectiveness evidence can be taken as important evidence to inform a policy decision to adopt or not to adopt large-scale implementation of malaria prevention program with combined implementation of LLINs and IRS. Nevertheless, since some of the inputs parameter and assumptions employed in this literature-based CEA might vary across different epidemiological, entomological, environmental, economic, and social contexts, this cost-effectiveness finding should be interpreted carefully based on specific conditions.

How much does annual malaria incidence and protective-effectiveness influence the cost-effectiveness?

It is plausible to assume that the cost-effectiveness of malaria prevention interventions, whether in a combined form or as singletons, are a direct function of the cost and effectiveness of the intervention. Subsequently, the effectiveness of an intervention is mainly contingent on the prevalence/incidence of the disease in the area and the efficacy of the intervention. This implies that a highly efficacious intervention could be not very important in areas where the disease burden is relatively low, while a moderately efficacious intervention might be very important in high disease burden areas (97).

The present work confirmed that malaria endemicity in the area and the protective-effectiveness of the combined intervention determine the cost-effectiveness of the combined intervention. The combined intervention to be accepted as 'very cost-effective' option in the context of Ethiopia or with another country of comparable epidemiological and economic profile, it should have at least 50% protective-effectiveness at a background malaria incidence of 5.8 per cent —at the WTP threshold of 3 times GDP per capita per DALY averted. Similarly, the interventions to be cost-effective option in low-malaria incidence areas, the expected protective-effectiveness should be high.

These finding have two key policy implications about prioritization of the malaria control strategy during low incidence setting, especially at the phases of elimination and eradication. First, benefits from an intensified malaria control initiative should not be underestimated and the programs should not be a victim of its own success (143). Practically, when the uptake and effective coverage of malaria control program increases, malaria incidence will certainly reduce. In this instance, such a versatile malaria prevention interventions like the IRS and LLIN will not remain to be sufficiently competitive in terms of cost-effectiveness parameter. Therefore, the ICER for LLINs and IRS will rise exceedingly (143). Therefore, the malaria prevention programs may compensate this by expanding the willingness thresholds from the conventional level (i.e. one times or three times GDP per capita per DALY averted) (144).

Second, targeted coverage of interventions based on micro-level planning might be an important part of the malaria control program. Disaggregate malaria data at a district level is essential for better targeting of interventions and for local planning (micro-preparation). In this respect, the National Malaria Control Program in Ethiopia has also recently stratified all districts based on annual malaria incidence (API) into four groups (i.e. Free, low, moderate, and high) and started conducting interventions based on such information (20).

The ICERs we found in this study for LLIN alone and combination (LLIN+IRS) is higher compared to findings from other relatively older studies, or with other malaria prevention

interventions, or recent studies in other places in Africa. An early study by Goodman, Coleman and Mills's (99) which compare the cost-effectiveness of a wide range of malaria control interventions, and a recent review by White et al. (101) can be good examples to demonstrate this difference. Based on their finding, in a low-income country, the cost-effectiveness per DALY averted for most of the malaria prevention and control intervention was within a range of USD 19 to USD 85. For example, it costs about 1 to 8 for improved case-management and 3 for chemoprophylaxis for children if the intervention was embedded into the existed health delivery system (in 1995 USD per DALY averted) (101). The reasons for higher ICER in our study, as explained in detail in Paper II, could be due to a combination of a difference in the malaria burden (15), an increase in the costs of interventions (101, 145), and a variability in malaria transmission dynamics (26, 146), between our study setting and elsewhere.

Is there any inequality in LLIN ownership or IRS status?

The LLIN coverage reported in the present work was very low (11%) compared with the national report and estimate from other studies in Ethiopia and elsewhere. This result was initially somewhat surprising. However, the follow-up study (unpublished) indicates that only 4% of LLINs were able to survive at the end of the second year after the distribution. Our results from all the equity analysis (descriptive, concentration curve, and concentration index) consistently show pro-rich inequality of LLIN ownership. The few available LLINs were concentrated among the richest group. Findings from the present work can provide an important and new insight into both policy and operational decisions in malaria prevention program. What about fairness in the implementation of malaria prevention? Our data did not explore how the implementation was conducted.

We found no link between households IRS status (sprayed versus not sprayed in the last 12 months) and socioeconomic position. The equitable and relatively good coverage of IRS status in this study is a notable achievement and might be partly driven by the nature of the intervention since IRS intervention requires only minimal compliance from the household side. The spray is conducted using community-based approaches once a year, administered

from the District Health Office (147). However, the cost of the program, the quality of the spray, and plastering of the wall of the houses with mud or other material might be some of the challenges for IRS program effectiveness (148, 149).

5.2 Discussion of methodology

As all studies, economic evaluations and inequality analysis are also liable for factors that could affect the internal validity and external validity (generalizability) of the findings (97, 120). Despite all steps we took to secure the quality of the studies and to ensure the rigour and reliability of the findings in this dissertation, there are still some caveat that deserves due consideration in the interpretation of our outcomes. In this part of the discussion section, I critically examine the designs of the studies, the sampling procedures, the data collection process, the specification of the models, and the selection of the analyse techniques; and evaluate the potential impact of the limitations on validity, reliability, and/or generalizability of our findings. Random error because of chance should be always in mind in understanding our findings, and I will discussed this at the end of this section (150, 151).

5.2.1 Designs of the studies

Papers included in this thesis employed combinations of study designs, which ranges from costing design (Paper I) to equity analysis using a cross-sectional survey design (Paper III), from Randomized Controlled Trials to full-economic evaluation (Paper II). The selection of a design depends on the type of the research questions under investigation, the cost of the research and budget availability, ethical issues, and time (e.g. the urgency of the evidence needed) (97, 150, 152).

In Paper I, we applied a cost of illness design, which estimates direct and indirect cost born due to a specific illness (malaria). This design is developed to calculate the economic burden of health problems in a population in a certain geographical area (97, 153). These studies attract much interest from researchers, health advocates, and policymakers recently (154). However, inconsistencies in the way they were conducted limit the comparability of

findings. Furthermore, lack of transparency in the way the costs are reported made interpretation difficult. The transparency about how the costing study was done is very important in a cost of illness studies. In our report, we provide a detailed report about which items were included, which items were not included, and how the calculations was done. However, we were not able to measure the economic burden to the entire society because of practical limitation while large body of literatures on economic evaluation encourages the costing from a societal perspective.

The other alternative approach, instead of a cost of illness design, to estimate the economic burden of a disease would be to use Willingness to Pay (WTP) approach. A WTP approach applies a stated preference method to estimate individual welfare change associated with morbidity or mortality from the particular disease (155). Usually, estimates from a cost of illness methods provide a lower estimate compared with estimates resulting from WTP methods because of the fact that cost of illness estimates do not capture the pain and suffering, preventive expenditures associated with illness, or the value of reduced mortality risk perception (156).

In Paper II, we employed full economic evaluation using cost-effectiveness analysis. Our cost-effectiveness analysis has two parts: trial-based and literature-based. There is a growing interest to use RCT for cost-effectiveness evaluation (157, 158). Despite high internal validity achieved with such kind of trial-based CEA, the main challenge associated with such kind of design is low generalizability (159, 160). However, our study has an extensive literature-based scenario analysis, which will increase the external validity of the estimates; and would additionally provide decision-makers flexibility to interpret results based on different contexts (157, 161).

We applied inequality analysis design using cross-sectional data in Paper III. Health equity has become a popular topic during the last two decades following an increasing demand from policymakers and the availability of large household data, in addition to an increased

computing capacity. This design would be more important in a large data that covers relatively large geographic areas (regional and national data).

5.2.2 Sample size and selection of study participants (sampling)

In undertaking robust economic evaluations and equity analysis, both determining the size of the sample and designing how the samples should be drawn from the source population—sampling—are important steps (142, 150, 152). An inadequate sample could have made the power of our studies weak—which cannot detect the true effect-size from an extraneous effect of confounding or just a random error (chance); while inappropriate sampling procedure could introduce selection bias. Selection bias occurs when the samples are not representative of the target population about which conclusions are to be drawn (162).

For Paper I, 190 malaria cases from nine health posts and three health centres were enrolled. Although the sample was adequate to estimate the overall average cost of malaria to the household, it might not be adequate to conduct sub-group analysis on some of the variables. For example, post-hoc power analysis indicates that our sample was adequate to compare the cost between different malaria specious (i.e. *Plasmodium falciparum* Vs *Plasmodium vivax*) while it was not sufficient to compare the cost among those presented at the Health Center with the cost at Health Post level.

Regarding the sampling procedure for Paper I, our focus was to capture the maximum variability and to represent all segment of cases as much as possible. So, we attempted to enrol all malaria cases presented to the selected facilities in the whole year (2015) to capture the variability that might arise from seasonal variation. For instance, the proportion of *P.vivax* to *P. falciparum* malaria would be different during high transmission season compared to low transmission seasons. In addition, we deliberately did this study in villages different from the main trial, but the same district, in order to avoid alteration of the real costs because of the research undertaking while keeping all other resemblance.

However, the some of the socioeconomic background of the patients in this study might be different from that of the trial finding.

Furthermore, since our samples were patients selected at health facilities (i.e. malaria cases seeking treatment at public primary health care units), the cost estimates if the patients were drawn from house-to-house survey might be somehow different from our findings. Those cases presented at health facilities might have different patterns of expenditure and disease features from those cases who did not. Thus, this could introduce a selection bias, which to some extent affect the external validity—generalizability—of our findings to the entire malaria cases (162).

We also excluded cases with mixed infection (i.e. those malaria cases positive for both *P.vivax* and *P.falciparum*) since we had an initial plan to compare the costs between the two forms of malaria. Therefore, to some extent, this might underestimate both the direct and the indirect costs since cases with a mixed infection are relatively severe. The treatment regimen for a mixed infection is also slightly different and which is relatively costly compared with a single infection.

Both our trial-based cost-effectiveness estimates (Paper II) and the inequality analysis (Paper III) rely on the sample size estimate from of the main trial. In preparation for the main trial, we performed a six-month pilot-study. We utilised the results (intra-cluster correlation coefficient) from the pilot-study for the sample size computation. Therefore, we calculated the sample size with adequate power (80%) and with a precision to detect expected variation in malaria incidence between different arms of the study. Thus, more than 30 thousand individuals from about 6 thousand households were enrolled. Therefore, the second and the third articles use relatively large sample size.

However, this large sample size might be compromised to some extent by the confined geographical distribution of the samples. The sample villages were located within about five-kilometre radius from the Lake *Ziway* (Figure 3). This could create not only a homogeneous of malarial risk (Paper II) but also less variability in socioeconomic status

and access to the prevention intervention (Paper III) — unlike the true situation in the target population. To some extent, these would limit the generalizability of our results to a wider population. In addition, since the villages are located close, the issue of intervention contamination can be raised; despite the nature of the intervention (LLIN and IRS) and how it was carried out are less prone to contamination (122).

Despite the fact that the ways of living in the study area are similar to other typical rural places in Ethiopia in most aspects, the study area has some unique features, such as the lack, wide irrigation area, which potentially influence the comparability of malaria and malaria prevention dynamic in our study area with broader countrywide picture.

5.2.3 Data collection and measurement error

How the data is collected — how the key outcome and the explanatory variables are measured — is practically important. The costs in these studies were measured in three steps. First, we collect the cost of malaria prevention interventions from the providers' perspective, alongside the implementation of the intervention. Second, we collect the cost of malaria diagnosis and treatment from the provider's perspective. Both of the above cost data were collected by the Ph.D. candidate using a modified and pre-tested, costing Excel workbook, which was initially prepared by WHO. The unit costs resulting from these data were eventually used in the CEA model.

For estimation of provider's side cost of prevention, diagnosis, and treatment of malaria; since the research team was deeply involved in the administration of the intervention, we have highly reliable cost estimates compared with other previous studies. However, for some of the cost ingredients (e.g. price of spray pump and personal protective equipment), we mainly depended on records from district health office administration and finance office. In addition, some of the cost items might be changed within a short period (e.g. salary), and few cost items incurred at national and regional level (e.g. mass media and communication costs) were omitted. This might slightly underestimate the actual unit cost

of the interventions although this may not have substantial implication on the cost-effectiveness estimates.

Third, cost data on malaria episode to the patients and their households (Paper I) was collected using three trained nurses as data collectors, and a pre-tested questionnaire adopted from a costing tool that was first used by Hansen and Yeung. We asked questions about out-of-pocket expenditures, for medical and non-medical expenses related to malarial illness in order to measure the direct cost of malaria. The indirect cost was in this study initially measured using questions about the number of days absent from work, or/and by how much does the working capacity decreased from the normal, for days in which the patient went to work while sick. To minimize the recall bias that might be introduced because of a longer duration of time between the incident of the illness and the time of data collection, we carried out the patient interview on the 10^{th} days after they were identified in the health facilities. Yet their response might be potentially influenced by social desirability bias since these kinds of information are sensitive in a rural setting in Ethiopia.

In the measurement of malaria incidence, one of the most extraordinary achievements in this trial was that we collected at weekly data for about 2.5 years from more than 6 thousand households. We visited each household, every week to ask if there was any febrile member within the last 48 hours. If there was a febrile case in the household, they were referred to the health post or testing (and treatment) centers, which is located very close to the villages, to be tested with RDT. However, measurement errors—information bias—could be introduced into our study because of different reasons. For example, some of the households might not report the fever while some of the febrile cases referred to be tested might not come to the health post or to the centers (162).

Sensitivity and specificity of the applied testing technique might significantly influence the cost-effectiveness estimate through changing the annual malaria probability in the area and the expected cost of diagnosis and treatment. In this work, we applied RDT that has

relatively good sensitivity and specificity compared with blood film microscopy. The results would have been different if we used molecular testing (e.g. detection of parasite nucleic acids using polymerase chain reaction (PCR)). The PCR technique is more sensitive than both smear microscopy and RDT. However, the economic evaluation results would have limited importance if we had used PCR as a confirmatory method since the use of PCR in routine patient care in rural health facilities in a low-income setting is unlikely in the near future.

In paper III, measurement of LLIN ownership was confirmed by observing at least one functional LLIN in the household by the data collector. Self-report LLIN ownership and utilization data rather overestimate and therefore our result would have been less reliable (163). However, IRS status (i.e. sprayed in the last 12 months or not) was only based on self-report of the household head. The reported IRS status (about 75%) in this study might be somehow inflated because of recall bias (162, 163).

5.2.4 Perspective, model specification, and analysis approach

Our decisions is mainly governed by the research questions and the nature of the variables — mainly the outcome variable — during model specification and choosing one analysis techniques over the other alternative approaches. In addition, we should also take into account data availability, feasibility, and relevance of the result while specifying the model or making the final choice of analytical approaches.

Regarding which cost to include and which to exclude, perspective matters! Different perspectives can be chosen in costing and economic evaluation studies (i.e. household, patient, provider, employer, societal etc.). Perspective defines which resources consumed or costs incurred should be accounted, and which should not be. The purpose and the targeted audience of the research (i.e. usually the payer) are the basis for the selection of the most appropriate perspective. For example, in Paper I, a household's perspective was taken. This perspective enable us to estimate the costs in detail. However, the societal perspective, as widely accepted, would have provide us the full economic burden to the

society. This can partly explain why cost estimates from our study were lower than estimates from other studies. The difference in the settings, malaria treatment regime, diagnosis tests employed, the patient groups, and epidemiological profiles may also have contributed to low cost estimates. Furthermore, indirect costs because of giving care for malaria ill child or for an adult patient, for that matter, from family members were not included in this survey. This could as well lead to the relatively low indirect cost in this study.

We did the cost-effectiveness analysis (Paper II) from the provider's perspective (164). Since the 'main payer' for preventive interventions of malaria in Ethiopia (most probably the same in other low-income countries) is the Ministry of Health (i.e. health service provider). In Ethiopia, the National Malaria Prevention and Control Department of the FMoH not only has the mandate to coordinate all malaria prevention activities in the country, but also it is the ultimate payer. However, most of the funds (78.6%) for malaria is generated from external sources, mainly from United Nations Children's Fund, The Global Fund, President's Malaria Initiative, and WHO. Most of the funds are also specifically designated for malaria prevention (165). Therefore, our cost-effectiveness findings would be relevant for decisions-making not only by the FMoH of Ethiopia, but also potentially important for some of multilateral and bilateral donor organizations (84).

Multiple-sourced, unclear, and donor-dependent financing of malaria prevention was another methodological challenge to our study regarding how to define the WTP threshold. Practically it is complex to precisely delineate the WTP threshold anywhere, but in Ethiopia due to the fact that the financing of health care in general and malaria programs, in particular, it is particularly challenging (100). In this study, we used 1 times and 3 times GDP per capita per DALY averted thresholds (166). However, it is important to note that this kind of cost-effectiveness evidence would be most relevant in a country where there is functional and established disease control priority-setting system that utilizes economic evaluation in decision-making (151, 158, 167). Thus, for the literature-based CEA we

provide flexible and transparent result in our scenario analysis so that it may be applied in decisions in different contexts.

When it comes to model specification in the first paper, we employed straightforward approaches in the valuation of direct cost into monetary term (168). However, the valuation of indirect cost is complex (97), and there are several alternative approaches, including the human capital and friction cost techniques (169-171). In the friction cost approach, we assumes that society only incurs productivity-losses during the period it takes to replace a worker (the so-called 'friction period') due to illness. Estimates from a friction cost approach better reflect the economic impact of the illness since it accounts for short-term absences and reduced productivity while at work, and usually provides a considerably lower estimate compared with the human capital approach. However, from practical perspective, the friction cost approach requires detail data on the friction period, which is unstable and often not known in the informal sector. In this study, therefore, we employed a human capital approach estimates only time-absent from work (172).

Human capital approach employs certain assumptions in the valuation of the indirect cost that have its own limitation on both the internal validity and generalizability of our findings that demand careful consideration in the interpretation. For example, a daily wage rate we assumed to convert the working days lost to monitory value—average daily wage rate for the agricultural worker—was the same for all adults, teenager, or children, while in reality, it would be different for each individual. The human capital approach does not consider labour-substitution while, in fact, it is common in self-employed agricultural based household economy in our study area. In addition, costs that might result from long-term complication and sequels were not accounted.

Regarding data analysis, we applied a variety of statistical techniques based on the designs and the natures of the outcome variable. In Paper I, we applied non-parametric statistical techniques (Quantile regression, Kruskall-Wallis, and Mann-Whitney test) because of the skewness of the cost variables. We also applied bootstrapping (with 1000 repetitions) to

predict 95% confidence intervals for the median costs and robust regression coefficients. In paper II, we applied Markov modelling and probabilistic sensitivity analysis these are robust techniques, and bases their theoretical roots in Bayesian technique (97, 98). However, because of lack of accurate estimates about the magnitude of the events, our cost-effectiveness model did not capture health-loses from a complication of severe malaria (anaemia, convulsions, and long-term neurological sequel). This would have underestimate the actual benefit of the prevention intervention (100) although the effect on the ICER estimates was minimal since the probability of severe cases are rare in the cases of treated malaria (124). Furthermore, the sensitivity analyses provide us a great deal of flexibility to explore the cost-effectiveness of the combined intervention (LLIN+IRS) in the faces of different malaria endemicity and different potential levels of effectiveness of the combined intervention. Therefore, our result have wide range of relevance since we are able to capture most of the possible scenarios.

There had been a debate on the choice of different variations of concentration index, taking into account the 'unusual properties' of binary variables compared with variables in a ratio scale (i.e. bound range, mirror-property, and invariant to positive linear transformation), given that most of the health-outcomes are measured in a binary form usually (134, 173-176). It has been argued that the Erreyger-normalized concentration index is more suitable for binary outcome variables, like what we had in Paper III (176, 177). We, therefore, applied Erreyger-normalized concentration index in this study to show the inequality in LLINs and IRS status. Yet, this is an area of methodological research to advance the measures of the inequality to be simpler, but inclusive of other policy-relevant characteristics like 'sensitivity to poverty' and 'sensitivity to extremity' (176, 177).

5.2.5 Random error (chance)

Random error or chance is the extent to which sampling variability explains the observed association in the data between an exposure and an outcome (152). The basic procedure in most studies with a human subject is that we draw a sample, we study the sample, and we

attempt to draw an inference about the population based on what we found in the sample. However, different samples from the same population would give different results because of chance only (142). The effect of random error may either underestimate or overestimate the true effect (152). The role of chance can be assessed using tests of statistical significance with confidence intervals around the point estimate (142). This type of error can be reduced by increasing the sample size (142, 152). The papers in this thesis addressed the role of chance by performing statistical tests appropriate for the measured effect sizes. We also include in the reports the point-estimates together with a 95% confidence interval and appropriate test statistics; and P-values (cutoff point of ≤ 0.05). Furthermore, a bootstrapping technique (Paper I), a probabilistic sensitivity analysis with Monte Carlo Simulation (Paper II), using robust regression coefficients and standard errors (Paper I & III) would also reduce the role of chance in our studies to some extent.

Chapter VI: Conclusion and Recommendations

6.1. Conclusions

Based on the findings of the studies in this thesis, we conclude the following;

- The economic costs of malaria to households in rural Ethiopia represent a potentially high economic burden, mainly to the poor; and both provider and demand-side factors influence the amount of direct and indirect cost. Reducing the malaria burden could contribute to poverty reduction as well.

- Based on the current trial-based analysis, the combination of LLINs and IRS is not likely to be a cost-effective option compared with singleton intervention. However, based on the literature-based analysis, the combined intervention has potential to be a cost-effective alternative at 3 times GDP per capita per DALY averted. The annual probability of malaria (incidence) and protective-effectiveness of the combined intervention were the key determinants of the cost-effectiveness of the combined intervention.

- The ownership of LLIN was very low and significantly pro-rich, while IRS status was equitable across socioeconomic strata.

6.2. Recommendations and future perspectives

Concerted, coordinated, and focused actions are needed to tackle malaria in Ethiopia. The availability of effective and affordable prevention and treatment strategies is an opportunity. However, the National Malaria Control Program needs to recognize the economic burden and clearly identify mechanisms for ensuring universal access of LLINs and IRS for households based on up-to-date and local malaria incidence data all the years. Therefore, maintaining a good system for continuous monitoring of malaria incidence in all geographical regions of Ethiopia is important for local targeting of the cost-effectiveness prevention interventions. The diagnostic and treatment service should be also available in all health facilities in malaria-endemic areas uninterrupted and free of charge to benefit the poor.

Both LLIN and IRS are mainly publicly financed interventions by the FMoH. Thus, the benefits of these interventions should be equitable—regardless of socioeconomic position. However, to move towards equity in ownership of LLIN throughout the years, a mechanism that would give special priority for the poor should be designed at the point of distribution or periodic refill. In addition, unless it is accompanied by teaching how to properly handle and effectively use the LLINs, the sole emphasis on the distribution of LLINs is not likely to be sufficient to ensure the equitable and effective universal coverage. Furthermore, periodic refill of LLINs based on local monitoring data may improve the implementation and equity of LLIN. Therefore, local data on 'useful life' of LLIN and tracking mechanism should be in place for the timely implementation of LLIN.

Pragmatic operational research may have paramount importance in the creation of well-refined understanding about malaria prevention strategies from local and national perspectives since the evidence regarding the added protective-effect and cost-effectiveness of combined intervention is not yet strong. Studies that explore poverty reduction and financial risk protective-impact of different malaria prevention strategies—in a combined or as a singleton—should be undertaken. For this purpose, different approaches can be applied (effectiveness—equity trade-offs, extended cost-effectiveness

analysis, and benefit incidence analysis). Finally, public health policymakers and program managers in Ethiopia, or elsewhere, should consider pieces of evidence on both cost-effectiveness and the equity in making malaria prevention and control policy choices.

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Appendices

Paper I

PLOS ONE

RESEARCH ARTICLE

Economic burden of malaria and predictors of cost variability to rural households in south-central Ethiopia

Alemayehu Hailu[1,2]*, Bernt Lindtjørn[1], Wakgari Deressa[3], Taye Gari[4], Eskindir Loha[4], Bjarne Robberstad[1,5]

1 Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, **2** Department of Reproductive Health and Health Service Management, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia, **3** Department of Preventive Medicine, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia, **4** School of Public and Environmental Health, Hawassa University, Hawassa, Ethiopia, **5** Center for Intervention Science in Maternal and Child Health (CISMAC), University of Bergen, Bergen, Norway

* alemayehu4all@gmail.com

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Abstract

Background

While recognizing the recent remarkable achievement in the global malaria reduction, the disease remains a challenge to the malaria endemic countries in Africa. Beyond the huge health consequence of malaria, policymakers need to be informed about the economic burden of the disease to the households. However, evidence on the economic burden of malaria in Ethiopia is scanty. The aims of this study were to estimate the economic burden of malaria episode and to identify predictors of cost variability to the rural households.

Methods

A prospective costing approach from a household perspective was employed. A total of 190 malaria patients were enrolled to the study from three health centers and nine health posts in Adami Tullu district in south-central Ethiopia, in 2015. Primary data were collected on expenditures due to malaria, forgone working days because of illness, socioeconomic and demographic situation, and households' assets. Quantile regression was applied to predict factors associated with the cost variation. Socioeconomic related inequality was measured using concentration index and concentration curve.

Results

The median cost of malaria per episode to the household was USD 5.06 (IQR: 2.98–8.10). The direct cost accounted for 39%, while the indirect counterpart accounted for 61%. The history of malaria in the last six months and the level of the facility visited in the health system predominantly influenced the direct cost. The indirect cost was mainly influenced by the availability of antimalarial drugs in the health facility. The concentration curve and the concentration index for direct cost indicate significant pro-rich inequality. *Plasmodium falciparum* is significantly more costly for households compared to *Plasmodium vivax*.

Conclusion

The economic burden of malaria to the rural households in Ethiopia was substantial—mainly to the poor—indicating that reducing malaria burden could contribute to the poverty reduction as well.

Introduction

An intensified and increased commitment and financial allocation for malaria prevention and control measures have reduced the burden of malaria mortality rate among under five children by 29% globally within five years, since 2010 [1]. Despite being a largely preventable and treatable disease, malaria accounts for about 212 million of cases and 429,000 deaths globally in 2015 alone [1]. Sub-Saharan Africa continues to bear a disproportionate share of the global burden with more than 90% of malaria cases and deaths [2] with Ethiopia as one of the hardest-hit countries. According to the 2016 World Malaria Report, more than 1.8 million of microscopically confirmed cases were reported in the country [1].

Beyond the huge health consequence, malaria imposes a heavy economic burden on individuals, households and the entire economy [3]. Malaria alone reduces the potential economic growth rate by 1.3% per year in some African countries as a single disease [4]. Gallup and Sachs claimed that, at macro-level, malaria and poverty are intimately connected, in which the malaria is the main contributor to poverty [4], while at micro or household level, the causal link yet remains unclear.

Unlike most of the other African malaria endemic countries, malaria follows a unique epidemiological pattern in Ethiopia. For example, the parasite transmission is seasonal at low to moderate intensity, the national prevalence is estimated to be less than 0.5% [5], and the contribution of *Plasmodium vivax* is substantially high: about 40% of the cases. These factors contribute to a uniquely unstable nature of the transmission pattern in the country, and all age groups of the population are therefore susceptible to severe malaria. These consequently not only make the malaria prevention and control program in Ethiopia more challenging, but it also makes the economic impact to the household potentially overwhelming [3, 6–8]. The recurrent and severe form of *Plasmodium falciparum*, and relapsing and pernicious form of *Plasmodium vivax*, expose poor households to further economic impoverishment in the course of getting treatment and repressed productivity [9].

Evidence on the economic burden of malaria is important for prioritization of prevention and treatment service at the national and sub-national levels and facilitates better resource allocation in the health care system [10–12]. However, only a few of these estimates are available and little research has been conducted on the economic burden of malaria on the rural households in Ethiopia. One of the few, a community-based cross-sectional study done by Deressa et al. in Adami Tullu [13], estimated that the mean direct cost of malaria per patient was 1.6 and the indirect counterpart was 4.1 in 2003 United States Dollar (USD). Another study from Tigray, Tembien, by Cropper et al. indicates a total cost ranging from 7 to 24 for adult patients, 7 to 23 for teenage patients, and 4 to12 for children in 1997 USD [6]. This study also indicates that households in such malarious areas are willing to spend about 15% of their annual household income to prevent malaria [6]. Thus, according to these studies, malaria is clearly one of a major cause of economic burden to rural households in Ethiopia.

The Sustainable Development Goals (SDG) propose to reduce malaria cases and death rate by at least 90% and to eliminate malaria in 35 countries by the year 2030 [14]. Ethiopia is one

of the countries targeted for the elimination plan. The strategy encompasses three major pillars. One of the pillars is to ensure universal access to malaria prevention, diagnosis, and treatment [14]. However, in order to achieve these targets, the country-level malaria prevention and control program need to be precisely designed towards alleviating the demand side barriers, mainly cost to the household, by way of providing financial risk protection to households during the time of illness [15–17].

From a practical point of view, the inherent trade-offs between health service cost, health service utilization, productivity loss, and socioeconomic status invites debates on user-fees and out-of-pocket expenditures at the point of treatment [18]. On one hand, there has been a tendency to increase user-fees for basic health services as a means to ensure the sustainability of government supported health systems in low-income countries [19]. On the other hand, increasing costs of basic health services may result in deferral or shift from formal health care, mainly amongst the poor [20, 21].

In the last decade, health care payment and financing mechanism in Ethiopia has been through series of reforms, and in particular, for malaria diagnosis and treatment; but, financing still remains irregular across regions [22, 23]. Moreover, evidence regarding the overall economic burden of malaria to the households is scant. The present study estimates the extent of the direct and indirect cost of malaria; and identifies predictors of cost variability to rural households among cases presented in primary health care units in south-central Ethiopia.

Methodology

Study setting and participant selection

This costing study was conducted alongside a large cluster randomized controlled trial, which aims to evaluate the effectiveness, cost and cost-effectiveness of the combined use of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) against each intervention alone in preventing malarial infection [24]. The study was conducted in Adami Tullu district in Oromia region of south-central Ethiopia. This area is predominantly agricultural, where households mainly depended on subsistent farming and livestock production for subsistence.

For the costing study, we collected data from villages which were not included in the main trial in order to avoid alteration of the 'real' economic burden due to interventions related with the research undertaking [25]. Three rural health centers and nine health posts (i.e three health posts attached to each health centers) were included. From January—December 2015, 190 malaria cases identified in the selected health facilities were included into the study (about 36 cases from each health center and 10 cases from each health post). The health posts are the lowest level in the Ethiopian health care delivery system, and each serve populations of about 5,000, whereas health centers are the next higher level and intended to serve for about 25,000 populations.

Data collection

A structured closed-ended and partially open-ended pre-tested questionnaire was used. We adopted a household costing tool first prepared by Hansen and Yeung [26]. The questionnaire was prepared in English and then translated to *Afan Oromo* and then back translated to English to check for consistency. The questionnaire had three main sections: general socio-demographic characteristics, direct and indirect cost information, and socioeconomic characteristics.

Data were collected by trained nurses who administered face-to-face interviews to either the head of household or directly to the household member who had the malaria attack. In order to give adequate time for incidents of expenditures related with the malaria episode, the

interview was conducted on the 10th day after the patient was examined and treated at the health facility. All cases were confirmed malaria positive (*P. falciparum or P. vivax*) by either Rapid Diagnostic Test (RDT) or microscopic blood film examination. Mixed cases were excluded from this study.

Cost of illness estimation

The cost of illness was estimated by identifying, measuring, and valuing the opportunity cost of the forgone resources caused by the malaria. We employed an incidence-based prospective approach by measuring the cost per episode of malaria to the patient and to the household. The cost estimation was done amongst new cases arising in a predefined period. This provides an estimate of the saving that potentially could accrue if the preventive measure is implemented. [25, 27, 28].

Measurement. We followed an ingredient based bottom-up approach to identify and measure all costs at patient level. Direct costs measured in this study were all out-of-pocket expenditures on the course of seeking and obtaining malaria treatment by patients. The direct costs were identified and measured in two groups: (1) direct medical costs (diagnosis, medical supplies, malaria drugs, other drugs, and consultation), and (2) direct non-medical costs (food on the way to the treatment facility, transportation, other non-medical supplies and services). All direct cost information was collected in Ethiopian Birr (ETB). Indirect costs were measured in terms of number of forgone working days of the patients due to the malarial illness. Indirect costs due to caregiving for an ill child or any other patients from family members were not included in this study.

Valuation. Direct cost was the sum of direct medical costs and direct non-medical costs, and at the outset estimated in monetary values. Indirect cost was valued using a *human capital approach* [25]. Thus, the value of a labor day (the wage rate) was used to convert the workdays lost into monetary value. For adults older than 18 years, the average daily wage rate for agricultural workers was used [29]. According to the 2013 National Labor Force Survey (NLFS) report, the average monthly wage rate for agricultural worker in Ethiopia was ETB 697, which we divided by 20 in order to obtain the daily wage rate of ETB 35. Proportionally, we assume that a teenager's (aged 13 to17 years-old) daily agricultural productivity is half of an adult's and for children's (aged 7 to 12 years-old) daily productivity is a quarter of an adult's. For children less than 7 years-old, we considered the wage rate as negligible and the indirect cost was not estimated. We adopt this framework from a similar labor valuation study in Ethiopia [30].

All costs were converted to USD using the official National Bank of Ethiopia average exchange rate for 2015 (US$1 = ETB 20.5). We used a consumer price index in order to account for annual inflation. The reference year for all cost estimates in this study is 2015 USD [31].

Statistical analysis

Patient level data analysis were performed using STATA statistical software, version 14 [32]. Average costs information were stratified and presented by the level of health facility (health post and health center). For all cost information, we report the mean with standard deviation (SD), standard error of the mean (SEM), and median with interquartile range (IQR). The data had been examined for the following statistical assumptions: normality, multicollinearity, and heteroscedasticity. To deal with skewed cost data, Kruskall-Wallis and Mann-Whitney test (non-parametric tests) were used to compare the median costs across different socioeconomic quantiles and malaria species (*P. vivax* and *P. falciparum*). Then, separate quantile regression models were fitted to identify factors associated with variability of median direct and indirect

cost of malaria. We performed bootstrapping with 1000 repetitions to estimate 95% confidence intervals for the median cost and robust standard error of the regression coefficients.

Principal components analysis (PCA) was used to construct a wealth index based on household characteristics, such as availability of various household assets, housing conditions, water source, and type of latrine facility [33]. We used the first principal component with an Eigen value of 3.2 in order to rank the household by wealth status. The overall Kaiser-Meyer-Olkin (KMO) measure of sample adequacy was 0.68.

The concentration index was estimated to explore the inequality in mean and median costs of malaria across different socioeconomic status and concentration curves was illustrated to visually present the distribution [34].

Ethical consideration

All study participants were informed about the objectives of the study and written informed consent was obtained from each participant before interview. Participation in the study was voluntary. The study was approved by the Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University, the Ministry of Science and Technology in Ethiopia (ref: 3.10/446/06) and the Regional Committee for Medical and Health Research Ethics, Western Norway (ref: 2013/986/REK Vest). A permit to conduct this study was obtained from Oromia Regional State Health Bureau.

Results

Characteristics of the study participants

Table 1 shows a summary of the study household's characteristics and description of the malaria episodes. Out of the 190 participants responded, 108 (56.8%) of the participants were identifies at the health centers and 82 (43.2%) were identified at the health posts. The mean household size was 5.1 (range from 1 to 14). The majority of the study participants were Oromo (187, 98%), Muslim (169, 89%), farmers (171, 90%), and from male-headed households (187, 98.4%). More than half (110, 57.9%) of the households' heads had no formal education but they were able to "read and write", but only 28 (14.7%) had "attended formal education". The mean age of the malaria patients was 16 year. The mean duration of fever before seeking health care was 1.3 days, and the duration of the malaria episodes was 3.2 days on average.

Economic burden of malaria: Direct, indirect and total cost

Table 2 shows the summary of the direct, indirect and total cost of malaria amongst those treated at the health center (a), health post (b), and overall for both levels of care (c). The overall total median cost of malaria per episode to the household was USD 5.06 (Bootstrap 95% CI: 4.42–5.69) and mean total cost of USD 6.1 (Bootstrap 95% CI: 5.34–6.86). The direct cost of USD 2.39 (95% CI: 2.58–2.95) accounted for 39% and the indirect cost of USD 3.76 (Bootstrap 95% CI: 1.51–2.99) accounted for 61% of the total cost. Direct medical cost (median = USD 1.56) was 62% higher than the non-medical (median = USD 0.59) counterpart.

Cost of diagnosis. The overall median diagnostic testing cost was USD 0.15. However, at health post level, the large majority of the patients were tested with RDT and no user-fee was incurred for the diagnosis testing. For example, 73 out of 82 cases had not paid anything for testing. On the other side, at the health center level, 82% of the cases were diagnosed with blood film microscopic examination while the remaining 18% were diagnosed with RDT. The

Table 1. Socio-demographic characteristics and the situation of the malaria illness, Adami Tullu district south-central Ethiopia, 2015.

Characteristics	Mean (SD)	Median (IQR)
Age of household head (year)	35.0 (9.2)	35 (28, 40)
Age of the malaria sick member (year)	16.0 (11.8)	14 (6, 22)
Duration of illness (days)	3.2 (0.9)	3 (3, 4)
Duration of fever before seeking health care (days)	1.3 (1.1)	1 (1, 2)
		n (%)
Days between onset of fever and treatment initiation		
Same day		43 (22.6)
Next day		97 (51.0)
After two days and more		50 (26.3)
Severity of the fever (as reported by the patient)		
Mild		31 (16.3)
Moderate		141 (74.2)
Severe		18 (9.5)
Sex of head of the household		
Male		187 (98.4)
Female		3 (1.6)
Educational status of head of the household		
Illiterate (Can't read and write)		52 (27.4)
Only can read and write		110 (57.9)
Formal education attended		28 (14.7)
Occupation of head of the household		
Farmer		171 (90)
Other economic activity		19 (10)
Ethnicity of head of the household		
Oromo		187 (98.4)
Amhara		3 (1.6)
Religion of head of the household		
Muslim		169 (88.9)
Orthodox Christian		15 (7.9)
Protestant Christian		5 (2.6)
Wakefeta		1 (0.5)

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median diagnostic cost at health center level was USD 0.24 (Table 2), and ranged from USD 0.15 to USD 0.49.

Cost of antimalarial drug. One hundred fifty-eight (83%) of the patients received the anti-malaria drug directly from the public facility where they were examined and tested, while the others only received the prescription and went back without the antimalarial drug at the public primary health care facility. Out of those examined at the health post level, 11 (12%) cases report that they paid for the antimalarial drug with payment ranging from USD 0.09 to USD 0.58 USD. Of those seen at the health centers, 32 (30%) reported that they paid from USD 0.1 to USD 0.78 for the antimalarial drug. which ranges from USD 0.1 to USD 0.78 (Table 2).

Predictors of malaria cost variability

Table 3 presents the multiple quantile regression coefficients with 95% confidence interval for different factors associated with variability in costs of malaria. The household's socioeconomic

Table 2. Direct, indirect and total malaria costs to the household (2015 USD) at health centers, health posts, and overall for both level of care, Adami Tullu district south-central Ethiopia.

Cost categories	Median	[IQR: p25	p75]	Mean	SD	SEM
a. Cost at Health Center						
Direct Medical cost	0.83	0.59	1.10	0.93	0.44	0.0426
Malaria testing cost	0.24	0.20	0.24	0.25	0.21	0.0200
Malarial drug cost	0.00	0.00	0.10	0.10	0.20	0.0194
Other drug cost	0.37	0.00	0.51	0.40	0.42	0.0403
Consultation fees	0.15	0.15	0.24	0.18	0.06	0.0060
Direct non-medical cost	1.88	1.15	2.80	1.97	1.22	0.1171
Transportation cost	0.59	0.00	1.24	0.74	0.68	0.0658
Food	0.98	0.39	1.56	1.03	0.75	0.0722
Other Items	0.00	0.00	0.29	0.20	0.29	0.0283
Direct Cost	2.98	2.10	3.80	2.90	1.29	0.1239
Indirect Cost	2.05	0.00	5.25	3.77	5.27	0.5887
Total Cost	4.76	3.20	9.69	6.67	5.12	0.5726
b. Cost at Health Post						
Direct Medical cost	0.00	0.00	0.39	0.30	0.48	0.0525
Malaria testing cost	0.00	0.00	0.00	0.03	0.11	0.0118
Malarial drug cost	0.00	0.00	0.00	0.05	0.14	0.0160
Other drug cost	0.00	0.00	0.39	0.19	0.29	0.0322
Consultation fees	0.00	0.00	0.00	0.03	0.07	0.0079
Direct non-medical cost	1.10	0.00	2.68	1.39	1.34	0.1478
Transportation cost	0.00	0.00	1.46	0.68	0.83	0.0921
Food	0.49	0.00	1.22	0.63	0.66	0.0732
Other Items	0.00	0.00	0.00	0.08	0.25	0.0273
Direct Cost	1.22	0.00	3.22	1.69	1.67	0.1841
Indirect Cost	3.30	1.05	6.28	3.74	3.52	0.4471
Total Cost	5.08	2.66	7.50	5.43	3.77	0.4791
c. Overall cost						
Direct Medical cost	0.59	0.24	0.88	0.67	0.55	0.0401
Malaria testing cost	0.15	0.00	0.24	0.16	0.20	0.0147
Malarial drug cost	0.00	0.00	0.00	0.08	0.18	0.0131
Other drug cost	0.10	0.00	0.39	0.31	0.38	0.0277
Consultation fees	0.15	0.00	0.24	0.12	0.10	0.0073
Direct no-medical cost	1.56	0.49	2.78	1.72	1.30	0.0943
Transportation cost	0.49	0.00	1.46	0.71	0.75	0.0545
Food	0.88	0.00	1.46	0.86	0.74	0.0536
Other Items	0.00	0.00	0.24	0.15	0.28	0.0204
Direct Cost	2.59	0.88	3.51	2.39	1.58	0.1145
Indirect Cost	2.25	0.00	5.80	3.76	4.57	0.3836
Total Cost	5.06	2.98	8.10	6.15	4.61	0.3869

Mean and median cost includes households reporting no expenditure (0)

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status (wealth score), duration of illness, previous history of malaria episode in the last six months (self-reported), and the level of the facility where the patients visited significantly influenced the direct cost. For example, on average, for every additional kilometer of distance between the patients' residence and the health facility, the direct cost increased by USD 0.27;

Table 3. Quantile (median) regression of factors associated with variability of direct, indirect and total cost of malaria, Adami Tullu district south-central Ethiopia, 2015.

Cost of Malaria	Coef.	SE*	P-value*	[95% CI] *	
Direct Cost (n = 189, Pseudo R^2 = 0.29)					
Wealth score	-0.222	0.063	< 0.001	-0.345	-0.098
Duration of illness (days)	0.413	0.171	0.010	0.077	0.748
Distance from home to the facility in km	0.271	0.064	< 0.001	0.146	0.396
Age of the patients	0.005	0.013	0.710	-0.020	0.030
Dummy for severe fever (ref = Mild)	-0.580	0.445	0.192	-1.452	0.291
Dummy for moderate fever (ref = Mild)	-0.884	0.653	0.176	-2.164	0.396
Treatment on the next day (ref = same day)	-0.235	0.376	0.533	-0.972	0.503
Treatment after two days and more (ref = same day)	0.378	0.341	0.268	-0.291	1.047
Received only prescription at PHCUs[¥]	-0.259	0.297	0.512	-0.842	0.324
Self-reported malaria episode last 6 month	-0.774	0.403	0.055	-1.563	0.015
Treated at health center (ref = treated at health post)	1.251	0.325	< 0.001	0.615	1.888
_cons	-0.048	0.781	0.951	-1.578	1.483
Indirect Cost (n = 141[£], Pseudo R^2 = 0.15)					
Wealth Score	-0.043	0.192	0.822	-0.419	0.333
Duration of illness	-0.653	0.513	0.203	-1.658	0.352
Distance from home to the facility in km	-0.096	0.116	0.408	-0.322	0.131
Age of the patients	0.092	0.065	0.157	-0.035	0.219
Dummy for severe fever (ref = Mild)	0.569	0.914	0.534	-1.222	2.360
Dummy for moderate fever (ref = Mild)	-0.860	1.822	0.637	-4.430	2.711
Treatment on the next day (ref = same day)	-0.200	1.392	0.886	-2.929	2.528
Treatment after two days and more (ref = same day)	-0.764	1.118	0.494	-2.954	1.426
Received only prescription at PHCUs	2.905	1.316	0.027	0.325	5.484
Had self-reported malaria episode last 6 month	-2.386	1.175	0.042	-4.689	-0.083
Treated at health center (ref = treated at health post)	-1.920	0.821	0.019	-3.529	-0.310
_cons	4.531	2.296	0.048	0.032	9.031

*Bootstrap standard error (SE), p-value and 95% confidence interval (CI) for the coefficient with 1000 replications.

[£] We only estimate the indirect cost for age greater than 7;

[¥] Primary health care units. ref = Reference category for dummy variables.

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and, for every additional day of illness the patient suffered, the direct cost increased by USD 0.41, but interestingly the severity variables were insignificant (Table 3).

Likewise, the age of the patient, whether the patient received the drug directly from primary health care unit or sent out with only prescription (i.e availability of the antimalarial drug), history of malaria in the last six months, and the level of the facility visited significantly influenced the indirect cost. Among those treated at health centers, the direct cost was significantly higher, while the indirect cost was lower compared with those treated at health posts.

The mean and median cost distribution across wealth status is presented in Table 4. For the direct cost, the concentration curve (Fig 1A) and the concentration index of -0.155 (SE = 0.029, $P < 0.001$) indicates an inequity that patients from the poor households incur significantly higher cost (pro-rich distribution). However, the concentration index of 0.078 (SE = 0.059) and the concentration curve which was closely aligned with the diagonal line (Fig 1B) for the indirect cost distribution indicates that there was no noticeable difference in accordance with different socioeconomic status.

Table 4. Mean malaria costs and concentration indices across different socio economic status, Adami Tullu district in south-central Ethiopia, 2015.

Socioeconomic status	Direct cost		Indirect cost	
	Mean	Median	Mean	Median
Poorest	3.06	3.22	3.24	2.25
2nd Poorest	3.01	3.22	3.67	3.63
Middle	2.37	2.37	3.10	1.88
2nd Richest	1.82	1.66	4.67	4.00
Richest	1.67	1.05	3.99	1.45
Concentration Index (CI)	-0.155		0.078	
Standard error	0.029		0.059	
P-Value	< 0.001		0.185	
Kruskal Wallis test (P-value)	< 0.001		0.327	

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Fifty-seven (30%) of the cases were diagnosed with *P. vivax*, while 133 (70%) were diagnosed with *P.* falciparum. Of those *P. vivax* cases, the history of malaria (self-reported) in the last six month were 25%, while it was only 18% among those *P. falciparum* cases. Table 5 illustrates the mean and median cost of malaria by species. *P. falciparum* is significantly costly for households, especially in terms of the indirect costs (Mann-Whitney test P <0.001).

Discussion

Transparent and data-driven evidence regarding the economic burden of malaria is more important than ever in this era of elimination and eradication [14] to inform prioritization of essential health service packages and policy decisions at national and regional levels. This study is the only one to provide empirical estimates regarding the economic burden of malaria to Ethiopian household in the last decade. In this study, we first estimated the economic burden of malaria in terms of direct and indirect cost to the rural household. Then, we identified predictors for variability in the cost.

We found that the median cost of malaria per episode to the household was USD 5.06. The direct cost accounted for nearly 40% and we found a significantly pro-rich inequality. In

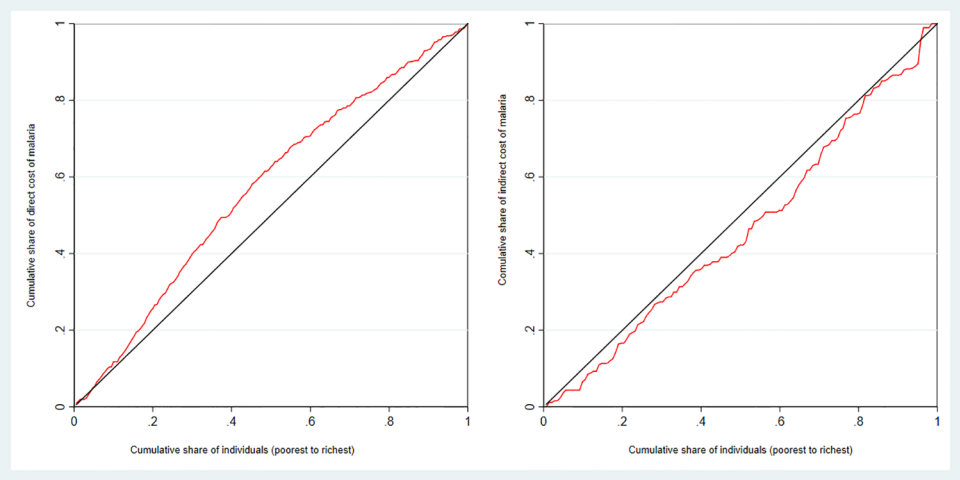

Fig 1. Concentrations curves for direct (A), and indirect (B) cost of malaria.

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Table 5. Analysis of the difference in median and mean cost of P. falciparum and P. vivax malaria, Adami Tullu district in south-central Ethiopia, 2015.

Cost of malaria Malaria species	Mean	Median	Mean	Median	Significance of the difference in median (Mann-Whitney test)	
	P. falciparum		*P. vivax*		Z	P-value
Direct Cost	2.16	2.20	2.92	3.07	-3.072	0.002
Indirect Cost	4.55	3.72	0.92	0.00	5.150	< 0.001
Total Cost	6.74	5.80	3.80	3.76	3.388	< 0.001

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addition, socioeconomic status, distance between the patient's residence and the health facility visited, incident of malaria in the last six months, level of the facility visited (health center versus health post) in the health system, and availability of the antimalarial drug in the health facility significantly influence either direct cost, indirect cost, or both.

The cost related to malaria episodes could be considered substantial to households in Ethiopia; where, according to World Bank report [35], more than a quarter of the total population is living in absolute poverty. The poverty situation is worse in the rural households [36]. The recurrent nature of malaria and a coincidence of malaria peak season with harvesting season accentuated the burden for the rural poor who are already dependent on subsistence farming and with limited coping options [8, 37]. The burden of malaria[38]

Comparing evidence of economic burden of malaria from different settings, time periods, patient groups, and epidemiological profiles is challenging [25]., Yet, several studies from various settings from African and Asian countries using different costing methods and patient-groups consistently found that the cost of malaria is substantial as we did [39–46]. To mention few, a population-based cost estimate from Sudan (Khartoum) among all age groups reports direct treatment expenditure of USD 6.3 and indirect cost per fully cured case of USD 3.2 [43]. A hospital-based estimate among children less than 3 year-old treated at outpatients from Asia, Papua New Guinea, reports ranging from USD 7.54 in one state (Madang) to USD 9.20 in another state (Maprik) [44].

Our cost estimates were slightly lower compared to most previous studies from Ethiopia [6, 21] or elsewhere [39, 40, 43, 44]. This might be due to several reasons. On one side, a recent policy change in introduction of Artemisinin-based Combination Therapy (ACT) and Rapid Diagnostic Testing (RDT) kits improved the malaria management in the country [47, 48]. This effective drug (ACT) and swift diagnostic method (RDT) likely have shortened the duration of the illness, and decreased both the direct and indirect costs [49]. On the other side, despite these drugs and the kit are quite expensive to the health system (provider), large-scale subsidization of these medicines in the public and private health facilities have decreased the patient's costs compared with the previous sulfadoxine-pyrimethamine (*Fansidar*®) based regimen [50, 51]. Furthermore, malaria diagnosis and treatment have been directed more towards health post level by the health extension workers [7], which also reduce the total cost to some extent. According to a recent systematic review which includes several studies from sub-Saharan Africa, cost of malaria diagnosis and treatment is irregular and context dependent [40]. Changes in policy or technology (e.g. new malaria treatment guideline, new malaria diagnostic tool, new user-fee payment system, new malaria drug logistic system, etc.) is likely to change the cost of malaria at both patients and health systems level.

After all, we believe, a proper implementation of a day-to- day malaria management at all level of the health system and every health facility is more crucial to provide affordable and swift service to the suffering patients. For instance, the current study show indirect cost was mainly influenced by availability of the antimalarial drug in the health facilities. On average,

those patients examined and diagnosed with malaria but sent back home with only prescription paper—without a drug—had incurred about USD 2.9 higher indirect cost compared with patient received the drug directly from the public primary health care facilities. Most likely, either these patients had spent long time searching for anti-malaria drug from a private drug store/pharmacy or they stayed at home without any access to treatment. In both cases, these patients were prone to delayed treatment, longer duration of illness, and expensive and counterfactual drugs [52]. In fact, Federal Ministry of Health of Ethiopia commissioned evaluation indicates that stock-out of essential drugs (i.e. including malaria drugs) from public health care facilities is very common and the average stock-out duration is about 100 days [53]. Although this study is somehow older, there is less evidence which proves the improvement of pharmaceutical supply system in Ethiopia within this period [52].

Cost information disaggregated by level of hierarchy in the health system is quite important and provides an opportunity for in-depth analysis of the policy options. In the Wilcoxon rank-sum test, we found that the difference in total cost between health post and health center was not significantly different from zero (P = 0.291). Similarly, the median indirect cost at health center was not significantly different from its counterpart at health post (P = 0.29). However, the direct cost at health post was significantly lower compared with direct cost at health center ($P < 0.001$) health post In line with the national health sector transformation plan, malaria diagnosis and treatment services at health post shall be free of user-fee charges [51]. However, it is not necessarily meant that the direct costs at health post were negligible; given that the non-medical cost attached to transportation, food, and other items were palpable (Table 2).

Those who had previous malarial illness in the last six month (i.e self-reported malaria) incurred significantly lower cost, mainly in the indirect cost. On average, those who had malaria in the last six month incurred USD 2.4 less indirect cost compared with those had not. This could be due to different reasons: self-medication with 'leftover' drugs [21, 54]; improved resilience, better coping mechanisms, and better informed from the experience of the recent illness [55]. To some extent, it was due to most of the recurrent cases of malaria being *P. vivax*, which is less severe and less costly as we found in this study (Table 5). This needs again further research to look the interaction between disease recurrences, health care seeking behavior, resilience, and productivity.

The bivariate analysis, the multiple quantile regression, the concentration index, and the concentration curve consistently indicate that the household's socioeconomic status significantly influenced the direct cost, while the influence was consistently not statistically significant for the indirect cost. Poor shouldering the highest financial burden against their limited ability to pay is a striking finding. Out-of-pocket payments for malaria treatment can impoverish some households who are already on 'border-line' when it becomes recurrent and catastrophic in size, especially in a health system running without any mechanism for financial risk protection [9, 17, 38, 56]. When the share of out-of-pocket payments is greater than 10% of the total expenditure/income, the risk of the health expenditure to be catastrophic in size is very high [38].

On the other side, in the quantile regression, severity of the illness was not a significant predictor of neither direct costs nor the indirect cost. This might be mainly because of two methodological challenges: First, the severity classification method applied was reliant on self-reported fever, which is more prone to misclassification, and recall bias, might underestimate the true association between costs and severity to some extent. Second, in this study, we only include uncomplicated malaria cases and large majority (90%) of them had only mild to moderate level of fever. The area is also one of malaria endemic area; and, sever and complicated cases are less likely to occur because of resilience of the community to malaria developed along period. Hence, it is more challenging to capture adequate variability in terms of severity in the

first instance. Otherwise, the cost of sever and complicated malaria is hugely larger than mild and uncomplicated cases. Hence, we suggests an in-depth estimation of the cost of sever and complicated malaria; such studies would have a paramount importance.

Similarly, the indirect cost was not consistent and not significantly different across wealth quantiles. Indirect cost, in this study, was entirely an estimate of working day lost which is homogenous across wealth quantile and could be affected by several interconnected of factors. Working day lost by the patents should be influence by the extent of the illness in terms of severity and duration in addition to the response/ reaction of the patients and the family to the illness, for example, some patients might stay at home while some other patients stay at work irrespective of the severity of the illness. To some extent, treatment and diagnostic service provided, for instance, some patients might got the service in the nearby facility while some might need to travel far and spend additional days off work seeking the service, might influence the indirect cost.

This study provides empirical evidence based on patient level data. However, selection of participants was done at health facilities with careful considerations to included households from divert socioeconomic and demographic background to make results representative for rural households in the most part of Oromia region, if not Ethiopia. Despite all efforts, indisputably, cases identified from health facilities are usually different from what could have been if we used a community-based household survey. To some extent, this could affect our cost estimates although it is difficult to speculate the direction of the influence. Furthermore, to avoid over/underestimation because of the seasonality nature of malaria, we collected data for one full year. We also applied a multiple quantile regression method to produce standard errors that are more robust to outliers than ordinary least squares regression.

This study has some limitations that require results to be interpreted with care. Initially we assumed to include 260 participants, but the sample size was revised based on the preliminary analysis of the first 100 samples. Given that, we include adequate number of participant to estimate the cost with reasonable margins of error and standard deviation. However, our sample size might not be sufficient to testing hypotheses or to identifying some of the associated factors (e.g severity and immediate treatment seeking behavior). For instance, although this study did not find significant association between direct costs and malaria history in the last six months at 95% CI, some of the regression coefficients are non-negligible in size and could have become significant with large sample size (Table 3).

The other limitation of our study is that the assumption in wage rate estimation we employed in this study for teenagers (half of adults' wage) and for children (quarter of adults' wage) should have been cross-validated using local data from the study area or from other comparable districts. The involvement of teens and children in household chores and the responsibilities they take might be somehow different from place to place. In addition, the assumption we employed to convert the workdays lost into monetary value did not account for individual-level variations in actual or potential earning within the same age-group. The same value of labor (i.e the average wage rate for agricultural worker) was considered for patients within the same age group. The accuracy of our estimates may therefore depend on local variability of factors such as primary school coverage. Measuring indirect cost is a challenging exercise, especially in situations where labor markets are poorly defined, self-employed farming is the primary occupation of most households (90%), and seasonal variability of wage rate is high.

Finally, in this study we only considered costs associated with the current episode of malaria to the household, and we did not take into account long-term cost implications from complications, such as anemia, neurological sequel, cognitive loss, loss in school performance and

future employability. A compressive study from the societal perspective could give a more complete result [25].

Conclusion

In conclusion, the economic costs of malaria to households in rural Ethiopia represent a potentially high economic burden, mainly to the poor. An implication is that reducing malaria burden could contribute also to poverty reduction as well. Both provider and demand side factors influence the amount of direct and indirect cost. The national malaria program needs to recognize this economic burden and identify mechanisms for ensuring that the poor have uninterrupted easy access to malaria treatment services largely either subsidized or free of charge. The results of this costing study can be used as input to a full economic evaluation of the prevention of malaria in Ethiopia.

Supporting information

S1 File. Cost of malaria.
(XLS)

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Author Contributions

Conceptualization: Alemayehu Hailu, Bernt Lindtjørn, Wakgari Deressa, Bjarne Robberstad.

Data curation: Alemayehu Hailu.

Formal analysis: Alemayehu Hailu, Bjarne Robberstad.

Funding acquisition: Alemayehu Hailu, Bernt Lindtjørn, Wakgari Deressa, Eskindir Loha, Bjarne Robberstad.

Investigation: Alemayehu Hailu.

Methodology: Alemayehu Hailu, Bernt Lindtjørn, Wakgari Deressa, Bjarne Robberstad.

Project administration: Alemayehu Hailu, Wakgari Deressa, Taye Gari, Eskindir Loha, Bjarne Robberstad.

Resources: Alemayehu Hailu, Bernt Lindtjørn, Wakgari Deressa, Bjarne Robberstad.

Software: Alemayehu Hailu.

Supervision: Alemayehu Hailu, Bernt Lindtjørn, Wakgari Deressa, Taye Gari, Eskindir Loha.

Validation: Alemayehu Hailu, Bernt Lindtjørn, Wakgari Deressa, Taye Gari, Bjarne Robberstad.

Visualization: Wakgari Deressa, Bjarne Robberstad.

Writing – original draft: Alemayehu Hailu.

Writing – review & editing: Alemayehu Hailu, Bernt Lindtjørn, Wakgari Deressa, Taye Gari, Eskindir Loha, Bjarne Robberstad.

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Paper II

Cost-effectiveness of combined intervention of Long Lasting Insecticidal Nets and Indoor Residual Spraying compared with each intervention alone for malaria prevention in Ethiopia.

Alemayehu Hailu [1, 2, *], Bernt Lindtjørn [1], Wakgari Deressa [3], Taye Gari [4], Eskindir Loha [4], Bjarne Robberstad [1,5]

[1] Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway;

[2] Department of Reproductive Health and Health Service Management, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia;

[3] Department of Preventive Medicine, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia;

[4] School of Public and Environmental Health, Hawassa University, Hawassa, Ethiopia;

[5] Center for Intervention Science in Maternal and Child Health (CISMAC), University of Bergen, Bergen, Norway.

[*]Corresponding author

E-mail: alemayehu4all@gmail.com

Abstract

Background

The effectiveness of Long Lasting Insecticidal Nets (LLINs) and Indoor Residual Spraying (IRS), for malaria prevention, have been established in several studies. However, the available evidence about the additional resources required for a combined implementation (LLIN+IRS) with respect to the added protection afforded is limited. Therefore, the aim of this study was to compare the cost-effectiveness of combined implementation of LLINs and IRS, compared with LLINs alone, IRS alone, and routine practice in Ethiopia.

Methods

The study was performed alongside a Randomized Controlled Trial conducted in Adami Tullu district, in Ethiopia, from 2014 - 2016. In addition, literature-based cost-effectiveness analysis — using effectiveness information from a systematic review of published articles was conducted. Costing of the interventions were done from the providers' perspective. The health-effect was measured using Disability Adjusted Life Years (DALYs) averted, and combined with cost information using a Markov life-cycle model. In the base-case analysis, health-effects were based on the current trial, and in addition, a scenario analysis was performed based on a literature survey.

Results

The current trial-based analysis had shown that routine practice is not less effective and therefore dominates both the combined intervention and singleton intervention due to lower costs. The literature-based analysis had shown that combined intervention had an Incremental Cost-Effectiveness Ratio of USD 1403 per DALY averted, and USD 207 per DALY averted was estimated for LLIN alone. In order for the ICER for the combined intervention to be within a range of 1 GDP per capita per DALY averted, the annual malaria incidence in the area should be at least 9%, and the protective-effectiveness of combined implementation should be at least 50%.

Conclusions

Based on the current trial-based analysis, LLINs and IRS are not cost-effective compared to routine practice. However, based on the literature-based analysis, LLIN alone is likely to be cost-effective compared to 1 GDP per capita per DALY averted. The annual malaria probability and

protective-effectiveness of combined intervention are key determinants of the cost-effectiveness of the interventions.

Trial registration: PACTR201411000882128 (8 September 2014).
Key-words: Malaria; Malaria prevention; Economic Evaluation; LLIN; IRS; Cost-effectiveness; Ethiopia

Background

Scale up of malaria prevention – mainly with the mass distribution of bed nets and indoor residual spraying of the interior lining of the wall of the houses – have brought a remarkable reduction in the global burden of malaria in the last decade [1, 2]. Empirically, the effectiveness and the cost-effectiveness of both Long Lasting Insecticidal Nets (LLINs) and Indoor Residual Spraying (IRS), for malaria prevention, are well-established [3-7]. However, evidence also indicates that neither LLIN nor IRS – alone – will be sufficient to reach and maintain the interruption of transmission in highly malarious regions of Africa [8-10].

In Ethiopia, LLINs and IRS are usually implemented separately in different districts or different villages [11, 12]. While LLINs and IRS in some villages have been implemented simultaneously within the same households [12-16], little is known about the effect and cost-effectiveness of the combined use of LLINs and IRS [12, 17]. Moreover, are the additional costs of the combined interventions reasonable from a provider's perspective given the combined benefits? [7].

Mathematical models by Yakob et al. [18], Okumu et al. [19], and Chitnis et al. [20] shows that there might be some additional protective value by a combined implementation of LLINs and IRS compared to either of them alone. A review of cross-sectional data from 17 different countries in sub-Saharan Africa also shows that people in households which use both bed-nets and IRS are about 36% (95% CI 7% to 53%) better protected compared to households which only use one of the interventions in medium malaria transmission areas [16]. Similarly, studies from Kenya [21] and Tanzania [22] also report positive results of combining LLINs and IRS. Kleinschmidt and colleagues, based on literature search and a cross-sectional survey from Bioko island of Equatorial Guinea, conclude that the increased resource use of the combined intervention is justifiable because of additional effectiveness compared with each intervention alone [23]. On the other hand, randomized trials from Benin [24], Gambia [25], and Sudan [26] report that there is no added effect in the combined implementation, compared with each intervention implemented separately.

However, none of those studies estimated the effect at a general population level, nor did they attempt to evaluate the cost and cost-effectiveness of the interventions. In the battle against malaria the need for transparent evidence based on randomized controlled trials, which integrates robust decision modelling, is critical to allocate scarce resources appropriately [27]. Such

evidence will be useful to guide the selection of the packages of interventions for malaria elimination programs. Specifically, the pressing questions in this line of inquiry are; first, what are the additional effects of combining both LLIN and IRS compared with singleton interventions or the routine practice? Second, is the value of added protection substantial enough to justify the additional resources (i.e. cost) required for a combined implementation? Therefore, the aim of this study is to compare the cost-effectiveness of combined implementation of IRS and LLIN, compared with LLIN alone, IRS alone and routine practice in Ethiopia.

Methods

Study design and settings

This cost-effectiveness study was conducted alongside a cluster randomized controlled trial (*MalTrials*), which compare both the effectiveness, cost, and cost-effectiveness of combined implementation of universal coverage of Long Lasting Insecticidal Nets and Indoor Residual Spraying (LLIN+IRS) against universal coverage of LLIN alone, IRS alone, and the routine practice [28]. *MalTrials* also has substantial entomological components that compare vector outcomes. Furthermore, to improve external validity, this study considers the cost-effectiveness under a scenario of varying annual malaria incidence and different levels of protective-effectiveness of the interventions based on a literature survey.

The trial was conducted in 2014 - 2016 in Adami Tullu (*Adami Tullu Judo Kombolcha*) district, which has a population of about 170 thousand [29]. Adami Tullu is located in the heart of the Great Rift Valley. The elevation of the district ranges from about 1500 to 2300 meters above sea level, with most of the inhabited villages located in the lower parts. The annual mean temperature ranges from a minimum of 14^0C to a maximum of 27^0C. Like most places in Ethiopia, the district has two rainy seasons, the longer (June to September) and the shorter (February to April). However, the rainfall patterns are irregular and this contributes to the variability of malaria incidence in the area.

Description of the interventions compared

The detail descriptions of the interventions are provided in the published protocol [28]. In brief, the universal coverage of households with Long Lasting Insecticidal Nets entailed each household receiving free LLINs (*PermaNet 2.0*) in October 2014. The distribution of the LLIN was conducted based on the national malaria prevention guideline, which recommends

proportional allocation of bed nets to the size of the household. The Health Extension Workers distributed the bed net from Health Posts. A day before the distribution date, all households in these groups had been mobilized to come to the health posts for collecting the bed nets, after which the LLIN coverage was 99%. The second intervention was universal coverage of households with indoor residual spraying using the insecticide. The type of the insecticide used for the spray was *Propoxur (*isopropoxy-phenyl methylcarbamate) which is one of very effective insecticide currently. The spray was conducted once every year in September 2014, July 2015, and July 2016. On average, the IRS coverage was about 95% for each of the three rounds of spraying.

In the combined implementation arms, households received LLINs and IRS in parallel with households in the individual arms, and therefore had IRS coverage of 95% and LLIN coverages of 99%. Finally, in the routine arm, neither LLIN distribution nor IRS was implemented by either the study project or by the district health office within the study period, and the background coverage of LLINs and IRS based on the baseline survey was on average 11% and 75%, respectively.

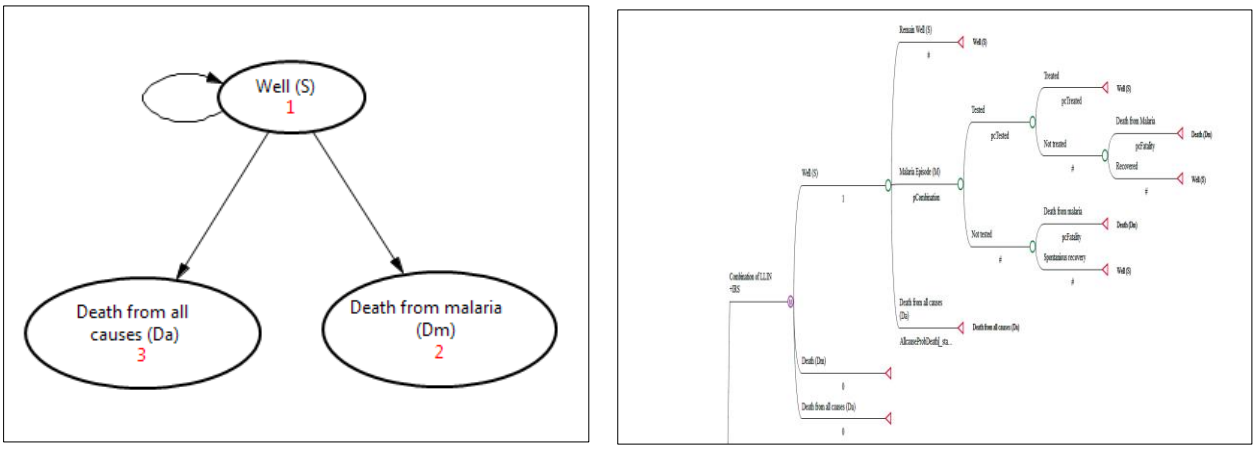
Cost-effectiveness modelling

We developed a simple malaria transmission model (Figure 1) and populated it with effectiveness and cost data from the trial. We used TreeAge Pro Suit 2017 (© 2017 TreeAge Software, Inc.) software for building the model and for data analysis. Three mutually exclusive health states that represent the dynamics of malaria were defined: well (S), death from malaria (Dm), and death from all other causes (Da). According to this model, initially, all individuals are in 'well' (S) state, and they all are susceptible to malaria. Then, a person from a 'well' state (S) could be infected and experience a malaria episode (M) with a certain probability. Once inflicted with malaria (M), some could be diagnosed, treated, and cured; while some might not be diagnosed and therefore remain untreated (Figure 2). In order to account for ongoing risk, recurrent nature, and short duration of malaria illness, we consider malaria episode as 'temporary states' [30].

In this model, we followed a hypothetical Ethiopian birth cohort over their lifetime (i.e. the time horizon in this evaluation was 80 years). A similar Markov life-cycle cohort model was employed for each intervention group (LLIN alone, IRS alone, LLIN+IRS) and control group (Routine). Each state was associated with annual state rewards, related to spending a year in the particular

health state. These include the annual cost of prevention and the annual effectiveness value: DALY averted. Health systems cost of malaria diagnosis and treatment, and *dis-utility* from malaria episode were accounted as a transition rewards per event. Both the cost and health effect were non-differentially discounted with 3% discount rate.

Transition probabilities were used to capture the probabilities of moving from one state to another state – within a specific time period called cycle length. The cycle length in this model is defined as one year. A half-cycle correction was done in order to assume that events occur half-way through a cycle (rather than at the beginning or at the end). We base the transition probabilities on primary data (i.e. based on the incidence data from the trial) and a few estimates from WHO (Table 1). The most likely annual probabilities for malaria were computed from the trial result of malaria incidence per 1,000 Persons Year of Observation (PYO) which were 15.548 for combination, 15.184 for LLINs alone, 15.652 for IRS alone, and 15.144 for routine arms. Then, we applied a formula, $P = 1 - e^{-rt}$, in order to convert the incidences into transition probabilities using, where P is probability, e base of natural logarithm, r is incidence rate, and t is time period [31]. The model includes age-specific all-cause mortality rates (Da) from WHO population life-table [32], and malaria-specific death rate (Dm) (i.e. 1 per 100 untreated cases) from WHO estimate [33].



A **B**

Figure 1: Markov state-transitions (A) and Markov tree diagrams (B) for the model.

Measurement of health effect

The health effect for the trial-based cost-effectiveness analysis was entirely based on the randomized controlled trial results (*Maltrials*). We later relaxed this presumption to perform a

scenario analysis (literature-based cost-effectiveness analysis) on expected values of incidence and effectiveness from literature survey. Using the malaria incidence information, Disability Adjusted Life Years (DALYs) averted was used as a health outcome measure in this analysis. The DALYs estimate combines the Years of Life Lost (YLL) due to premature death and Years of Life lived with Disability (YLD) [34]. The YLDs for malaria infection was calculated using standard disability weights (Table 1) [35]. Death due to treated uncomplicated malaria is very rare and assume zero mortality. Uncomplicated malaria might progress to severe malaria if untreated, and we, therefore, assume a mortality of 1 per 100 for untreated cases [33].

In order to estimate malaria incidence, both active and passive malaria case detection methods were implemented intensively in four study arms. Every household was visited every week and asked if there was any household member who had a fever in the last 48 hours. All febrile cases were then tested with a rapid diagnostic test (RDT) and blood slides were collected for confirmatory diagnosis.

Measurement of intervention costs

Identification, measurement, and valuation of the cost of the intervention and cost of malaria diagnosis and treatment was conducted from providers' perspective [27]. The costing of prevention interventions was conducted along-side the implementation of indoor residual spraying and the distribution of LLINs using ingredient costing approach.

Identification: All costs related to the undertaking or facilitation of the research activities were excluded. For LLINs, the purchasing cost of the bed nets (LLINs), shipment, customs clearance, and transportation fee to the project implementation district were included in the analysis. Moreover, at the project site, cost of transportation including payments for loading and unloading of the nets, rent fee for storage space, stationary materials for orientation training and data registration cost were included. On the dates of distribution, personnel cost and transportation cost of the bed nets to each of the villages were included. For the IRS, cost of the insecticide (*Propoxur*), spraying materials, equipment, storage, personnel, and other operating expenditures used for the indoor residual spraying were accounted.

Measurement: Cost data were collected prospectively, immediately starting from the beginning of the trial using financial expenditure records (invoices) from the project accountant services of the implementation of the interventions and from the district health office. We used a spreadsheet

to record cost information. The types and quantity of each resource used in the intervention were registered.

We captured the economic costs of the interventions, whether they incurred a financial expenditure or not. For example, the time spent by health personnel involved in prevention or treating malaria was accounted, despite that their salaries were already covered by health services. While they did not receive additional salaries for the specific malaria intervention being evaluated in the trial, they could have spent their time on other activities representing opportunity costs.

Valuation: In order to identify the economic value of the resources used, we used the purchasing price for most of the materials and equipment, including for the bed nets and the insecticides. For items where the price was not known from the invoice or the available records, we use estimated values for the items from market inventory data. Cost items were divided into recurrent and capital costs. Recurrent costs were defined as costs which are incurred regularly and with duration of less than a year. Capital costs were defined as items, expected to last longer than one year [27]. Capital costs were annuitized based on the useful life-year, initial unit price, and interest rate of 6% [36]. For example, LLIN costs were assumed to be effective for two years, and hence the purchase cost was annualized over this period. Unit cost was calculated by dividing the total cost of the intervention for the total population covered with the specific interventions. All costs were converted to USD using the official National Bank of Ethiopia average exchange rate for 2014 (USD 1= ETB 20.1). We used a consumer price index in order to account for annual inflation. The reference year for all cost estimates in this study is 2014 USD.

For costs in the routine arms, we only accounted the cost of case diagnosis and treatment of malaria in the health facilities (health posts and health centre). We used Microsoft Excel (2016) for compilation and analysis of the cost data.

Measurement of diagnosis and treatment cost of malaria

A combination of top-down and activity-based costing techniques was applied in order to track all cost items. Using Excel spreadsheet, we systematically extract data on expenses for testing and treating a case of malaria from the providers' perspective. Primary cost data on diagnosis and treatment of malaria were collected from the same district where the trial was conducted, but from Primary Health Care Units (PHCU) which were not included in the study area. The data was

collected from 9 Health Posts, 3 Health Centres, the District Health Office (Adami Tullu), Oromia Regional Health Bureau, and Federal Ministry of Health Pharmaceuticals Funds and Supply Agency (PFSA).

Personal cost includes the cost of health professionals' time involved in treating malaria. The average time spent on diagnosis and treatment of a case of malaria was combined with the apportioned net monetary value of the personnel time to estimate the personnel cost. At Health Centres, Health Officers, Nurses, Laboratory Technicians, and other administrative staffs were involved in the diagnosis and treatment of malaria cases, while only the Health Extension Workers were involved at Health Posts. We divided the entire treatment process into a set of activities along the clinical pathway and allocated monetary values for the drug and other supplies consumed for each activity. Finally, all cost were converted to 2014 USD.

Cost-effectiveness analysis (CEA)

Incremental cost-effectiveness ratio (ICER), cost-effectiveness scatterplot, and cost-effectiveness acceptability curve were used to summarize and present the cost-effectiveness result [27]. The expected costs and health outcomes (DALY averted) were calculated for each of the four alternative options. We ranked interventions according to DALYs averted, and each intervention was therefore compared with the next more effective intervention, before calculating incremental costs, incremental effectiveness, and incremental cost-effectiveness (ICER). We eliminate from comparison the interventions that cost more but provide fewer benefits than an alternative intervention (dominance).

Based on the economic theory of maximization of expected health benefits from the interventions, the optimal decision is to choose the strategy with the highest ICER per DALY that just falls at or below the willingness to pay (WTP) threshold [37]. In this study we cautiously apply the WTP threshold suggested by World Health Organization's (WHO's) Choosing Interventions that are Cost-Effective (CHOICE) program that interventions for which the ICER per DALY averted is less than one GDP per capita as 'very cost-effective', between one and three-times GDP per capita as 'cost-effective', and greater than three-times GDP per capita as 'not cost-effective [38]. The GDP in Ethiopia for the year 2017 is USD 861 [39].

Probabilistic sensitivity analysis

Overall-model uncertainty was analysed with probabilistic sensitivity analyses (PSA) using Monte Carlo simulation, and the results are presented as cost-effectiveness acceptability curves, cost-effectiveness acceptability frontiers, and scatterplots. In PSA, the variables in the model were replaced with distributions. Probabilistic distributions for costs, dis-utilities, and transition probabilities were assigned with most likely (mean), minimum, and maximum values. We assumed those cost parameters to hold a gamma distribution, and health outcome and transition probabilities to follow a beta distribution. We considered the minimum and maximum transition probabilities to vary +/- 5% from the most likely values. We consider the minimum and maximum intervention costs to vary +/- 20% from the most likely values (Table 1).

Table 1: Probabilities and costs (2014 USD) used in cost-effectiveness analysis of combined intervention of LLIN and IRS

Parameters*	**Most likely**	**Min.**	**Max.**	**SD**	**Source**
Probability of malaria in combined arm	0.0154	0.0146	0.0162	0.0004	Primary
Probability of malaria in LLIN arm	0.0151	0.0143	0.0159	0.0004	Primary
Probability of malaria in IRS arm	0.0155	0.0147	0.0163	0.0004	Primary
Probability of malaria in routine arm	0.0140	0.0133	0.0147	0.0004	Primary
Proportions of malaria cases tested (%)	90	80	100	0.0500	Primary
Proportions of malaria cases treated (%)	90	80	100	0.0500	Primary
Probability of death from untreated malaria	0.01	0.005	0.02	0.0004	[33]
Intervention cost of LLIN+IRS	4.04	3.00	4.500	0.2020	Primary
Intervention cost of LLIN	1.06	0.848	1.272	0.0530	Primary
Intervention cost of IRS	3.07	2.456	3.684	0.1535	Primary
Intervention cost of routine	0	0	0	0.0000	Primary
Cost of malaria diagnosis at PHCU	0.51	0.408	0.612	0.0255	Primary
Cost of malaria treatment at PHCU	1.17	0.936	1.404	0.0585	Primary
DALY: disability weight-malaria	0.191	0.172	0.211	0.0098	[35]
DALY: disability weight - death	1	1	1		[35]
DALY: disability weight - well	0	0	0		[35]
Discount rate health utility (%)	3	0	5		[37]
Discount rate cost (%)	3	0	5		[37]
Number of cycles (Year)	80	10	80		[40]

SD = Standard Deviation; Min = Minimum value; Max = Maximum value; GBD = Global Burden of Disease study
** The values for Probabilities and DALYs are presented per cycle while Costs and Proportions are presented per event.*

Scenario analysis with literature-based cost-effectiveness model

The overall incidence of malaria in the study area was low during the study period compared with historical data and national average estimate [41]. Even though the interaction of weather changes and malaria incidence is complicated, a likely explanation for such a low incidence, in addition to the intensive intervention of the research project, could be the atypical weather during the study period. During the years 2015 and 2016, the study area was seriously stricken by drought which was related to an *El Nino* event. Meteorological data from the study area show that rainfall decreased from 673 mm to 909 mm during 2011 to 2014 to 471 mm in 2015. At the same time, the average annual high temperature in 2015 (29^0C) was 2^0C higher compared to 2014 (27^0C).

Furthermore, the trial finding unexpectedly showed that the incremental protective effectiveness of either the combined intervention or the singleton intervention was not significantly different from the routine practice. While this result has been observed also in a few other studies [17], a majority of the empirical literature concludes that LLIN and IRS have substantial protective-effectiveness against malaria [17]. While we believe the internal validity of these results are good for the timing and context of this trial, the generalizability of the effectiveness and cost-effectiveness of combined implementation of LLIN and IRS are more uncertain.

Therefore, the relevance of this scenario analysis with literature-based cost-effectiveness modelling was twofold. First, we wanted to reduce a limitation of the trial-based evaluation — poor external validity. Second, we wanted to give decision-makers more flexibility to interpret results subject to a broader set of contexts.

In the literature-based cost-effectiveness analysis, we change the input values from the trial-based analysis for malaria risk in the area (annual malaria probability) and protective-effectiveness of the interventions. We define annual malaria probability as the probability of acquiring a malaria episode per person within a given year. In this study, we applied Annual Parasitic Incidence (API) which is equivalent to malaria probability per annum per 1,000 population at risk in a specific area. Annual Parasitic Incidence is most common and reliable estimate of malaria probability in a specified geographic area [42]. In Ethiopia, about 17% of the districts on average have API lower than 5; and 43% of the districts have 5 to 100 API while nearly 7% has API greater than 100 [43]. Nearly 33% of the district are malaria-free. Based on the World Health

Observatory data, the average API for Ethiopia is 58 per 1,000 population at risk in 2015. Therefore, we assume a base-case 5.8% annual malaria probability in the area with the routine interventions (i.e. background malaria risk in the area) [41], which corresponds to a probability of malaria per cycle of 0.058. For intervention arms, we multiply the annual malaria probability by the protective-effectiveness of the interventions to estimate the transition probability in the corresponding arms with the presence of the interventions [31].

Regarding effectiveness, we utilised a systematic review to assume that the most likely values for protective effectiveness are 40% (35 – 45%) for LLINs alone and 28.5% (23.5 – 33.5%) for IRS alone [17]. In addition, we calculated that the protective-effectiveness of the combined intervention from the multiplicative combination [44] of the individual risk of malaria of the singleton interventions (LLIN and IRS). This resulted in a protective-effectiveness of 57% for the combined intervention.

One-Way Sensitivity Analysis

To test the robustness of model conclusion to these assumptions, we performed one-way sensitivity analyses on the literature-based cost-effectiveness model, in addition to PSA. We did this for different level of protective-effectiveness of the combined interventions (47.1 – 67.1%) and at different level of annual malaria incidence (1 to 20%), and present results in a tornado diagram, where also the variables time horizon, cost, proportion of cases diagnosed, proportions of cases treated, probability of mortality from severe malaria were included. We evaluated the incremental cost-effectiveness values against the willingness to pay thresholds of less than or equal to 1 times GDP per capita.

Results

The results of this paper are organized and presented in three parts. First, we describe the cost of the interventions and cost of malaria diagnosis and treatment from the providers' perspective. Second, we present the cost-effectiveness analysis results based on trial based effectiveness and incidence estimates and cost data from the adjunct costing study, and together with probabilistic sensitivity analysis findings. Third, we present results from the literature-based cost-effectiveness analyses with probabilistic sensitivity- and one-way sensitivity analyses.

Cost of interventions

The economic costs of malaria prevention interventions from the providers' perspective are presented in Table 2. About 7,740 LLINs were distributed with 99% coverage within LLIN arm and combination arm for about 3,000 households. The annualized total cost for LLIN arm per 10,000 population was USD 10,641. About 88% of the cost is due to the bed net (LLIN) itself, while only 12% was expenditure for the delivery of the intervention (6% for personnel and 5% for transportation costs). Therefore, the unit cost of LLIN per person year-protected was USD 1.06. Similarly, with 95% of households covered with IRS costs a total of USD 30,660 per 10,000 population. From the total cost, about 58% (17,799) was spent for the purchase of the insecticide, and 26% (7,883) was for personnel. The unit cost of malaria prevention with IRS alone per person-year protected was USD 3.07.

In the combined implementation of the interventions (LLIN+IRS), USD 40,408 was incurred in order to universally cover about 10,000 population with both LLIN and IRS. In the combined implementation, about 48%, 22%, and 17% of the cost was attributed to the cost of the insecticide (*Propoxur*), the personnel, and the bed nets (LLINs) respectively. The unit cost of combined intervention (LLIN+IRS) per person-year protected was USD 4.04 (Table 2).

Table 2: Itemised cost of malaria prevention intervention per 10,000 population and unit costs in Adami Tullu, Ethiopia, 2014 USD

Costs	LLIN	IRS	LLIN+IRS
Costs of interventions per 10,000 population			
Personnel cost	675	7883	8216
The bed net cost	9321	NA	9058
The insecticide cost	NA	17799	17799
Materials & Supplies	74	2232	2248
Transport costs	527	1561	1876
Training hall	44	1186	1211
Annualised total cost	10,641	30,660	40,408
*Unit costs**			
Cost per person year protected	1.06	3.07	4.04
Cost per under-five child year protected	6.98	20.12	26.51
Cost per pregnant woman year protected	78.67	227.67	298.74
Cost per household covered	5.49	15.56	20.51
Total number of household in the study arms	1387 (23%)	1526 (25%)	1615 (26%)

*The unit costs were computed by dividing the 'annualized total cost'—incurred to implement the interventions—with corresponding denominator population. The denominators were drawn from the baseline survey.

Unlike the above three intervention arms, in the routine arm of the study, prevention intervention was implemented neither by the research project nor by the district health office. Therefore, the only cost incurred in this arm, from the health service provided perspective, was the cost of diagnosis (testing) and treatment of malaria cases. The health systems provider's perspective cost of diagnosis and treatment of malaria is presented in Table 3.

Table 3: Unit cost of diagnosis and treatment, and total cost per 10,000 malaria cases at primary health care units in Adami Tullu, Ethiopia, 2014 USD

Cost of diagnosis and treatment of malaria	Unit costs			Cost/10,000 cases
	Health centre	Health post	Overall	
Diagnosis				
Personnel	0.12	0.41	0.26	2,600
Materials and supplies	0.33	0.16	0.25	2,500
Total cost of diagnosis	0.45	0.57	0.51	5,100
Treatment				
Personnel	0.09	0.14	0.12	1,200
Drug	1.06	1.06	1.06	10,600
Total cost of treatment	1.15	1.19	1.18	11,700
Total cost of diagnosis and treatment	1.60	1.76	1.69	16,800

Trial-based cost-effectiveness results

The trial-based cost-effectiveness results (Table 4) indicate that the routine practice was not less effective than the other three alternatives, and therefore strongly dominates them because of lower costs. The expected costs from the model were 0.45, 22.16, 63.28, and 83.12 for routine practice, LLIN alone, IRS alone, and combined interventions respectively. Combination (LLIN+IRS) was about 25% more costly than IRS alone and about four times higher than LLIN alone. In terms of expected health effectiveness, all the four alternative interventions averted almost similar amount of DALYs in a range of 10.26 to 10.27 DALYs (Table 4).

Table 4: Trial-Based cost-effectiveness analysis ICER results, Adami Tullu, Ethiopia

Strategy	Cost (USD)	Incr Cost	Eff (DALYs)	Incr Eff	ICER
Excluding dominated					
Routine practice	0.5		10.26		
All					
Routine practice	0.5	0	10.259		0
LLIN alone	22.2	21.7	10.264	-0.005	-4528
IRS alone	63.3	62.8	10.266	-0.007	-9610
LLIN+IRS	83.1	82.7	10.265	-0.006	-13546

The probabilistic sensitivity analysis — the cost-effectiveness scatterplot for the four alternative malaria prevention strategy (Figure 2) — indicates that the expected cost of LLIN alone had less variation and clearly lower than the cost of IRS alone.

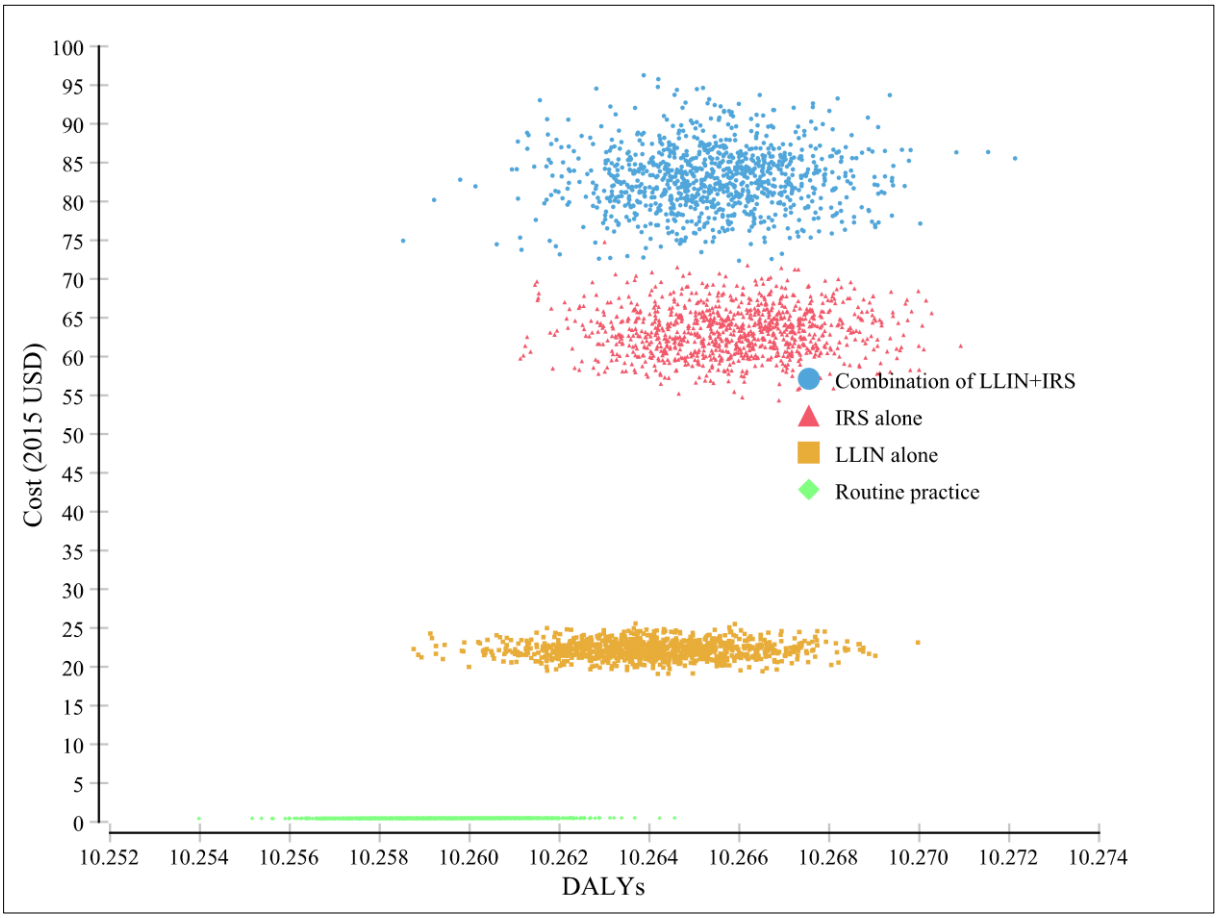


Figure 2: Scatterplot of the costs and health-effects of the four malaria prevention alternatives from the Monte Carlo Simulation (100,000 replication)

Literature-based cost-effectiveness results

The literature-based cost-effectiveness analysis results are presented in Table 5. With the modified assumptions of intervention effectiveness and malaria incidence, the expected costs from the model were 1.87, 22.79, 64.09, and 83.41 for routine practice, LLIN alone, IRS alone, and the combined interventions respectively. The combination intervention was almost one third more costly than the expected cost of IRS alone (64.09), and about 3.5 times higher than LLIN alone. In terms of health-effect, the routine practice has the highest expected DALYs, while the combination of LLIN+IRS averted most DALYs and was the most effective of the three active alternatives. LLIN averted slightly more DALYs than IRS.

IRS alone was 'absolutely dominated' by LLIN alone (i.e. IRS alone being more costly but less effective compared to LLIN alone). IRS alone was therefore eliminated from further consideration. The model predicts that the ICER for combination (LLIN+IRS) was USD 1,403 per DALY averted compared to LLIN alone, and the ICER for LLIN alone was USD 207 per DALY averted compared to the routine practice.

Table 5: Literature-based cost-effectiveness analysis ICER results, Adami Tullu, Ethiopia

Strategy	Cost (USD)	Incr Cost	Eff (DALYs)	Incr Eff	ICER
Excluding dominated					
Routine practice	1.9		10.451		
LLIN alone	22.8	20.9	10.350	0.101	207
LLIN+IRS	83.4	60.6	10.307	0.043	1403
All					
Routine practice	1.9		10.451		
LLIN alone	22.8	20.4	10.350	0.101	207
IRS alone	64.1	41.4	10.379	-0.029	-1422
LLIN+IRS	83.4	60.4	10.301	0.043	1403

Figure 3 shows the cost-effectiveness acceptability curves (CEAC) for literature-based CEA of the four malaria prevention alternatives at different levels of willingness to pay per DALY averted. For example, the probability of combined intervention (LLIN+IRS) being cost-effective option was less than 10% at a willingness to pay threshold of USD 861 per DALY averted while at a willingness to pay threshold of USD 2583 per DALY averted (3 times GDP per capita) the probability of the combined intervention being cost-effective is nearly 90%.

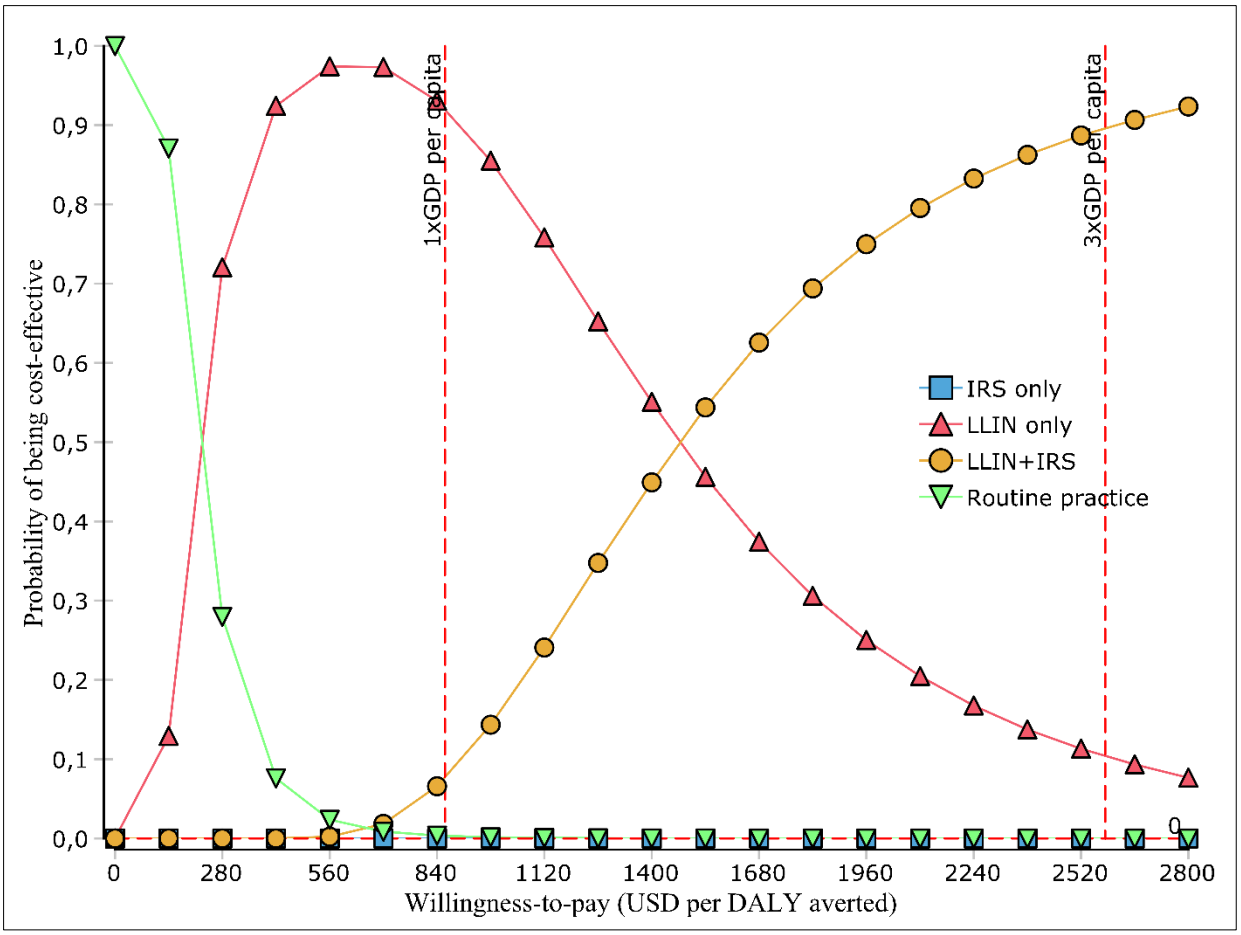


Figure 3: Cost-effectiveness acceptability frontier.

Scenario analysis results of the literature-based model

Annual malaria probability:

In a one-way sensitivity analysis, we tested the effect of the background malaria risk on the cost-effectiveness of the interventions by varying the annual malaria probability from 1 to 20% while keeping all other variables at their base-case values. The results show that the combined intervention (LLIN+IRS) becomes cost-effective compared to LLIN alone when the annual malaria probability is higher than about 9% if the WTP threshold is defined at 1 times GDP per capita per DALY averted. LLIN alone becomes cost-effective when the probability is higher than about 2% (Figure 4). If we defined the willingness to pay threshold at 3 times GDP per capita, the combined intervention becomes cost-effective in areas where the annual malaria probability is higher than 3.5%.

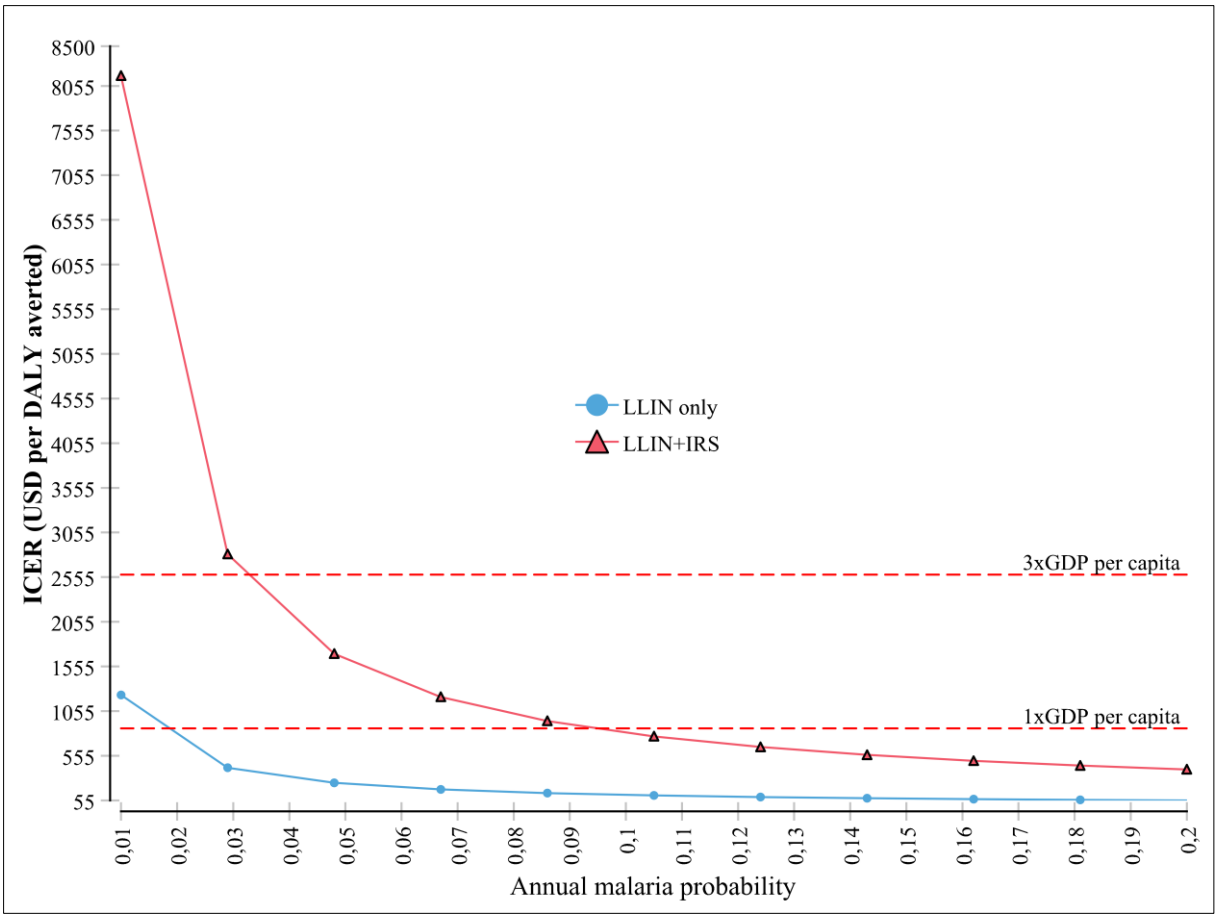


Figure 4: Sensitivity of ICER to variations in the annual malaria incidence in the area.

Protective-effectiveness of the combined intervention

At 5.8% annual malaria probability, the one-way sensitivity analysis results in Figure 5 presents the sensitivity of the ICER against the 57.1% protective effectiveness of the combined intervention +/- 10% (47.1 – 67.1%) given that the IRS alone reduced the malaria probability by 28.5% (23.5 – 33.5 %) and LLIN alone by 40% (33 – 45%). The protective-effectiveness of combined implementation (LLIN+IRS) should be nearly 50% and above, in order for the ICER to be in a range of 3 times GDP per capita per DALY averted (Figure 5).

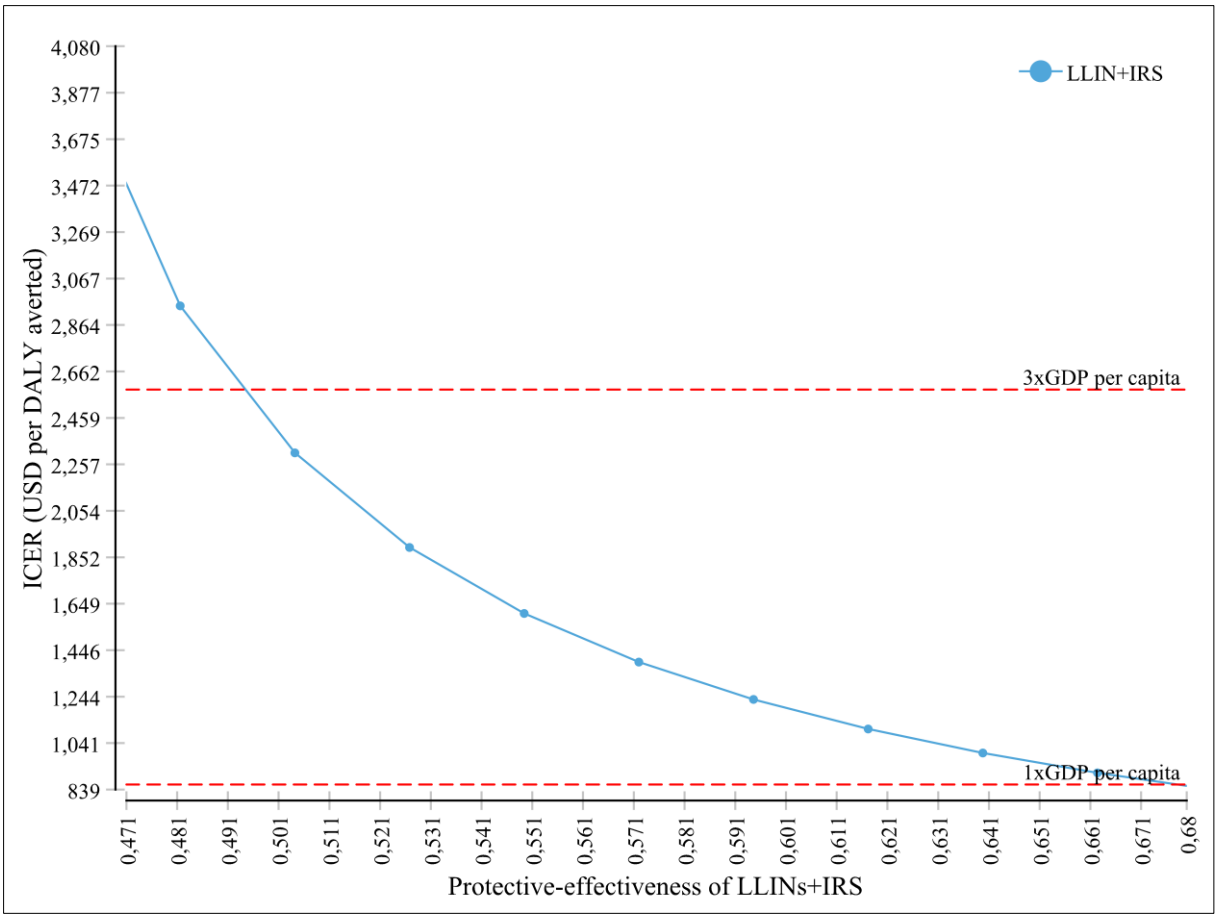


Figure 5: Sensitivity of ICER to variations in the protective-effectiveness of combined intervention.

Similarly, one-way sensitivity analysis with the Tornado diagrams shows that ICERs in the literature-based analysis was mainly sensitive to change in annual malaria incidence in the area and the level of protective-effectiveness of combined intervention. In addition, variability in the discount rate of costs and health-effect, and protective-effectiveness of LLIN alone modestly influenced the ICER.

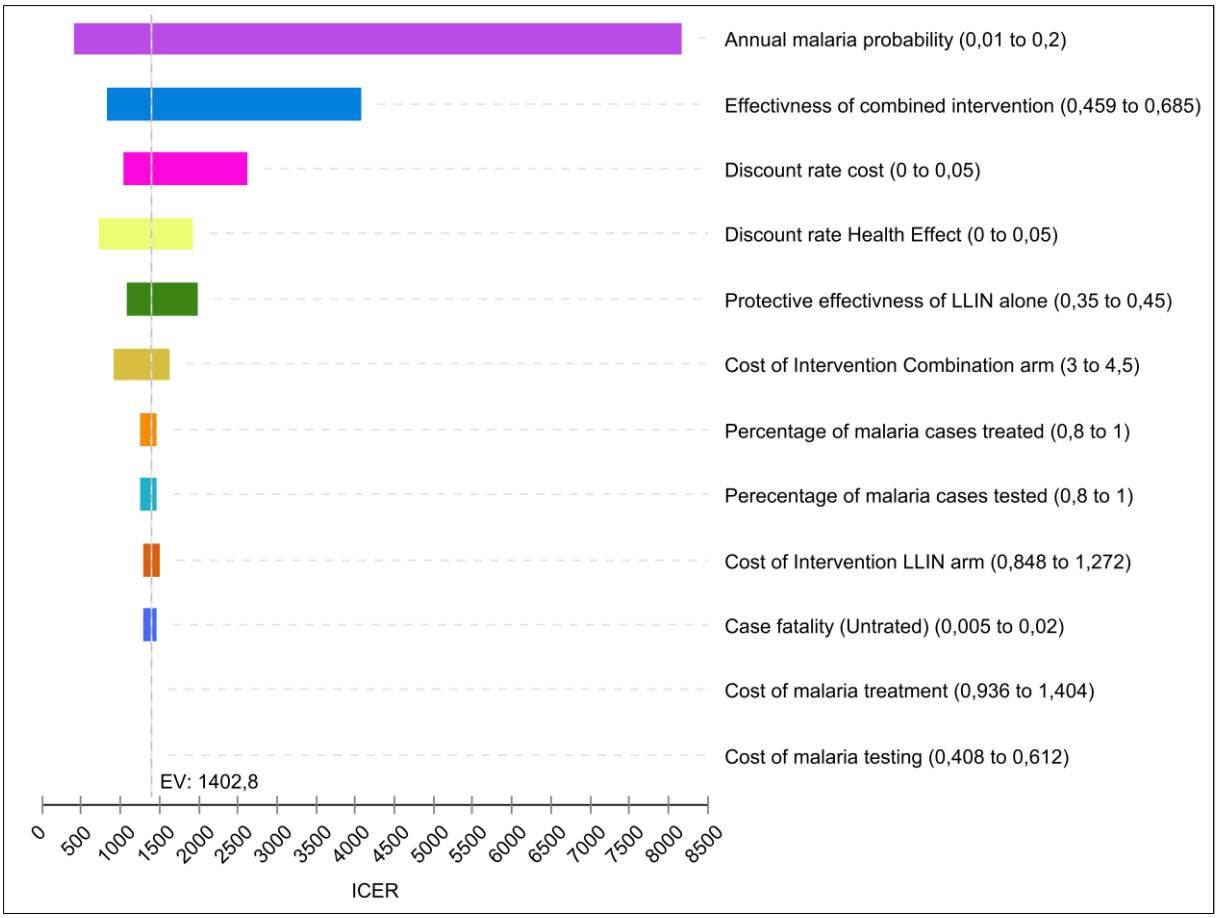


Figure 6: Tornado diagram - ICER LLIN+IRS vs. LLIN only

Discussion

This cluster randomised controlled trial found no significant difference in the effects of malaria prevention. The effectiveness of all the three intervention arms was the same as the routine arm, and the economic evaluation inevitably shows that the current routine practice dominates all the prevention alternatives since they are all more costly. When generalising key inputs from the trial and replacing them with literature-based assumptions, the economic evaluation shows that both — LLINs alone with ICER of USD 207 and the combined intervention with ICER of USD 1403 — are likely to be 'cost-effective' compared to a willingness to pay threshold of 3 times GDP per capita per DALY averted. At a willingness to pay threshold of 1 GDP, only LLIN alone is cost-effective. However, IRS is dominated by LLIN (more costly but less effective).

This study is the first in Ethiopia which compared the cost-effectiveness of malaria prevention interventions. What we found from our literature-based analysis is that the ICER for both combined intervention and LLIN alone are relatively high compared with most of the previous studies on malaria prevention. For example, Goodman et al., analysing the cost-effectiveness of malaria in sub-Saharan Africa, found an ICER (in 1995 USD per DALY averted) ranging only from 32 to 58 for ITN and from 16 to 29 for IRS [45]. Another study by Morel et al. [46] examined the cost-effectiveness of mixes of curative and preventive interventions; and they reported an ICER (in 2005 international dollar per DALY averted) ranging from 10 for Case management with artemisinin-based combination therapy to 96 for combination of the four interventions together (i.e. IRS, ITN, Case management with artemisinin-based combination therapy (ACT), and intermittent presumptive treatment in pregnancy). Using a systematic review of studies published between 2000 and 2010 White et al. [6] reported a median ICER (in 2010 USD) 27 (range 8.15 - 110) for LLIN/ITN and 143 (range 135 - 150) for IRS. Similarly, a recent systematic review also shows that the ICERs reported in our study are higher compared with other studies in Africa and elsewhere [7].

The relatively higher ICER in this study compared with other studies in Africa can be partly explained by the differences in malaria burden, the increment of costs of interventions, and unique malaria dynamics in Ethiopia. In the last 15 years, the incidence of malaria in sub-Saharan Africa decreased significantly [2, 41, 47], while the cost of the interventions increased [48]. The cost of the intervention increased mainly because of the replacement of DDT with Proxure, use of LLINs instead of ITNs, and the introduction of the ACT — all the three recent changes were not only associated with improving malaria prevention and control, but also with increased cost to the health system. Particularly IRS was costly in our study and this was mainly caused by the price of insecticide. In addition, the difference in malaria epidemiology in Ethiopia compared with other places in African or elsewhere could also largely contribute to this disparity [49]. The epidemiologic profile of malaria in Ethiopia is in a number of ways different compare to other African countries. For example, malaria transmission in Ethiopia is low to moderate, unstable, and seasonal while it is high, stable, and perineal elsewhere [49, 50].

Practically, economic evaluation of malaria prevention interventions is complex [7, 51]. Unlike typical cost-effectiveness evaluations, in some cases, the effects of combined interventions might be the same with the effect of individual interventions alone; and subsequently, the incremental

effect could be negligible. In other cases, any of the intervention might not be effective at all — even compared with 'doing-nothing' [17]. In our study also we found that the effectiveness of the combined intervention was the same with both singleton and routine interventions. This might be partly explained by the 'counter-balanced effect' between incremental health effect and cost saved resulting from adding IRS over high LLIN coverage or vice versa. On the other hand, the strong protective effect from active case finding and treatment by itself might dilute the 'modest' protective-effects from other preventive measures (i.e. LLIN and IRS). It is also important to note that in this trial — across all the four study arms — a weekly visit to each household was conducted in order to identify any febrile member of the household, and almost all febrile cases were tested with RDT, and if found positive, treated with the appropriate ant-malaria drug [28]. Therefore, we strongly recommend further pragmatic trials from different setting from our study to estimate protective-effectiveness of the intervention.

In general, the cost-effectiveness of malaria prevention intervention is a function of the health benefit gained and the resources required to implement the intervention [27]. In the one-way sensitivity analysis, first, we tested the effect of the background malaria incidence in the area on the cost-effectiveness of the interventions by varying the annual probability of malaria infection for an individual from 1 to 20%. On account of this, the ICER for combined intervention varied from about USD 8,000 to USD 200 per DALY averted. Moreover, the annual malaria incidence should be at least about 9% in order for the combined intervention to be cost-effective compared with a willingness to pay threshold of 1 times GDP per capita per DALY averted for Ethiopia (USD 861). However, what the recent data from Ethiopian Ministry of Health indicates is that only a few areas in Ethiopia have malaria risk levels of such magnitude. Only about 6 to 7% of the districts in Ethiopia, mostly in Western lowlands and few in the Rift Valley, have annual incidence rates exceeding 9% [43], and based on the results of this analysis should be the focus of attention for future prevention campaigns.

These findings should be interpreted in the light of at least two important issues about the dynamics of malaria control program at low incidence setting (i.e. at stages of elimination and eradication) should look like. First, malaria control program should not be a victim of its own success [52]. When the malaria control program succeeds, malaria incidence will certainly reduce. In this case, such a versatile malaria prevention interventions like IRS and LLIN will not

continue to be sufficiently competitive in terms of cost-effectiveness parameter, and LLINs and IRS will both appear to be not cost-effective [52]. Therefore, it has been argued that for malaria prevention programs the willingness to pay thresholds should be expanded from the conventional level [53]. Second, the need for disaggregate malaria data at a district level is crucial for better targeting of interventions and for local planning (micro-planning). In this regard, the National Malaria Control Program in Ethiopia has also recently stratified all districts based on annual malaria incidence into four groups (i.e. free, low, moderate, and high) and started conducting interventions based on the strata [43].

The second parameter that we examined in the one-way sensitivity analysis was the protective-effectiveness of combined intervention. We found that the combined intervention (LLIN+IRS) should have a minimum of 50% protective-effectiveness in order to be 'cost-effective' alternative and should have a minimum of 68% protective-effectiveness to be 'very cost-effective' (Figure 5). It is important to remember that none of the interventions have an inherent degree of effectiveness. Rather, it is the manner how it is implemented, the identification of those areas where it is most suitable, and the proper use by the community which determine the effectiveness most. However, based on a recent systematic review [17], it would be very challenging to achieve a protective-effectiveness of such level (50%) against the current supply side and demand-side barrier which reduces the effectiveness of both individual and combined interventions. The major demand side barriers for LLIN, observed in our visits, includes under-utilization, misuse, and lack of convenient sleeping space to hang-up the bed nets; while refusal, covering the wall of the house with a mud or other material, and rudimentary nature of the wall for some of the houses were challenges for IRS. The financial and human capacity of the district to execute the interventions, the price of the insecticide, and the quality of the LLINs can be considered as major supply-side barriers. IRS demands strong and very close supervision.

The costing analysis shows that the unit cost of IRS per person-year protected was predominantly influenced by the price of the insecticide, which alone accounted for about sixty percent of the cost. Regarding the cost of LLIN, in addition to the price of the bed nets, useful life-year (durability) of the bed nets was important parameters which determined the cost of LLIN per person-year protected. The life-year of the LLINs determines the frequency of the redistribution (refill). In Ethiopia, based on the National Malaria Program, LLINs were intended to serve for about three years and therefore the distribution campaigns are held once every three year [11].

However, what we observed in our study was that the LLINs worn out faster, and had little effect after one to two years. Local production of the bed nets with low cost and better quality could reduce the price of the bed nets. A strong quality control mechanism in the production, procurement, and distribution of the nets can be considered not only to maintain the fabric integrity of the nets but also to maintain the insecticidal property. Above all, well-coordinated IEC and advocacy program promoting proper utilization of the LLIN could improve both effectiveness and longevity of the LLINs.

In this study, most of the cost items of malaria prevention interventions at the district level were identified, measured, and valued prospectively alongside the community trial using robust techniques [27]. Yet, there are some caveats that deserve due consideration with respect to the data, generalizability, and relevance of this study. The first limitation was that the costing was done only from the local providers' perspective and a few cost items incurred at national and regional levels (e.g. mass-media and communication costs etc.) were omitted. Although this might not have substantial implication when we compare the cost and cost-effectiveness of the prevention interventions, this might to some extent underestimate the actual unit cost of the interventions.

The second limitation to our model was that we were not able to account for health-loss from co-morbidities of severe malaria such as anaemia, convulsions, and long-term neurological sequel because of lack of accurate estimates about the magnitude of these events. Despite the effect on the ICER would be minimal since the probability of severe cases is rare in the cases of treated malaria [33], this might underestimate the actual benefit of the prevention intervention slightly [54].

A third limitation of this study is in the decision we made in choosing 1 times or 3 times GDP per capita per DALY averted as a willingness to pay thresholds for interpretation of the ICER results. Despite long-standing debate in economic evaluation literature on this issue [55], it is particularly important for the evaluation of malaria prevention interventions in Ethiopia [54]. It is difficult to precisely define the WTP threshold in Ethiopia due to the fact that the financing of health care in general and malaria programs, in particular, are complex. For example, the larger share of the funding (78.6%) for malaria is generated from different and external sources (UNICEF, PMI, GLOBAL FUND, WHO etc.) and most of which is also ear-marked for malaria (vertical

program) [56]. This kinds of cost-effectiveness evidence would be most relevant in a country where there is functional and established disease control priority-setting system which utilizes economic evaluation in decision making [57].

Conclusions

Based on the current trial-based analysis, LLINs and IRS are not cost-effective compared to routine practice. However, based on the literature-based analysis, LLIN alone appear as likely to be cost-effective if willingness to pay is defined at 1 times GDP per capita per DALY averted, while IRS is dominated by LLIN (i.e. more costly but less effective). The annual malaria risk in the area and protective-effectiveness of combined intervention and LLIN are the key determinants of the cost-effectiveness of the interventions. Malaria program implementation should provide high focus to the improvement of the protective-effectiveness of IRS and LLIN.

List of abbreviations

ACE = Artemisinin-based combination therapy; CEA = Cost-Effectiveness Analysis, CEAC = Cost-Effectiveness Acceptability Curves; DALY = Disability Adjusted Life Year; ETB = Ethiopian Birr; GDP = Gross Domestic Product; ICER = Incremental Cost Effectiveness Ratio; IRS = Indoor Residual Spraying; LLIN = Long Lasting Insecticidal Nets; PMI = Presidential Malaria Initiative; RDT = Rapid Diagnosis Test, USD = United States Dollar; WHO = World Health Organization, WTP = Willingness to Pay;

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University, the Ministry of Science and Technology in Ethiopia (ref: 3.10/446/06) and the Regional Committee for Medical and Health Research Ethics, Western Norway (ref: 2013/986/REK Vest). Participation in the study was voluntary and informed consent was obtained from each participant.

Consent for publication

The data were collected after taking informed consent (including consent for publication) from the participants.

Availability of data and material

The datasets supporting the conclusions of this article will be fully available.

Competing interests

The authors have declared that no competing interests exist.

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Authors' contributions

AH and BR undertook the data analysis and developed the first draft of the methodology section. The first draft manuscript was prepared by AH. All authors substantially participated in the conception of the research idea, design of data collection tools, and interpretation of the result. AH and TG coordinated and supervised the data collection for the trial. All the authors read and approved the final manuscript.

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Paper III

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Equity in long-lasting insecticidal nets and indoor residual spraying for malaria prevention in a rural South Central Ethiopia

Alemayehu Hailu[1,2*], Bernt Lindtjørn[1], Wakgari Deressa[3], Taye Gari[4], Eskindir Loha[4] and Bjarne Robberstad[1,5]

Abstract

Background: While recognizing the recent achievement in the global fight against malaria, the disease remains a challenge to health systems in low-income countries. Beyond widespread consensuses about prioritizing malaria prevention, little is known about the prevailing status of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) across different levels of wealth strata. The aim of this study was to evaluate the socioeconomic related dimension of inequalities in malaria prevention interventions.

Methods: This study was conducted in July–August 2014 in Adami Tullu district in the South-central Ethiopia, among 6069 households. A cross-sectional data were collected on household characteristics, LLIN ownership and IRS coverage. Principal component analysis technique was used for ranking households based on socioeconomic position. The inequality was measured using concentration indices and concentration curve. Decomposition method was employed in order to quantify the percentage contribution of each socioeconomic related variable on the overall inequality.

Results: The proportion of households with at least one LLIN was 11.6 % and IRS coverage was 72.5 %. The Erreygers normalized concentration index was 0.0627 for LLIN and 0.0383 for IRS. Inequality in LLIN ownership was mainly associated with difference in housing situation, household size and access to mass-media and telecommunication service.

Conclusion: Coverage of LLIN was low and significant more likely to be owned by the rich households, whereas houses were sprayed equitably. The current mass free distribution of LLINs should be followed by periodic refill based on continuous monitoring data.

Keywords: Ethiopia, Equity, Malaria prevention, LLIN, IRS, Inequality analysis, Concentration index

Background

In the last decade, the global fight against malaria reaches on promising phase. Between 2000 and 2013, malaria mortality was reduced by 47 % worldwide and by 54 % in Africa. During the same period, deaths from malaria dropped by half in Ethiopia. However, malaria still remains to be one of the major challenges for the health system in low-income countries. The disease is widespread around the globe, putting approximately 3.3 billion people at risk [1].

Malaria is one of the leading health problems in Ethiopia. Records from the Ministry of Health (MoH) reveal that more than 75 % of the total land mass is endemic and about 68 % of the population is living in a malarious area [2]. The World Health Organization (WHO) report more than 3.7 million cases of malaria infection for the year 2012 [3], and more than 2.1 million of cases for 2013 [4], in Ethiopia. Malaria is also one of the leading causes of outpatient visits, inpatient admissions and hospital deaths. In the malaria endemic districts of Oromia region, malaria account for up to 29 % of all outpatient visits [5], while in Adami Tullu district, where this

*Correspondence: alemayehu4all@gmail.com
[2] Department of Reproductive Health and Health Service Management, School of Public Health, Addis Ababa University, P.O. Box 9086, Addis Ababa, Ethiopia
Full list of author information is available at the end of the article

paper emanates, malaria parasitic prevalence peaks up to 10.4 % [6]. A recent study by Gari et al. similarly reported a higher incidence of malaria cases (4.6 cases per 10,000 person-weeks of observation) from the same area [7].

The incidence peaks biannually from September to December and April to May, both coinciding with harvesting seasons [8]. This has a serious consequence for Ethiopian farmers whom constitute the vast majority of the total population. The consequences regard both the farmers, who are dependent on subsistence agriculture for livelihood, but also more broadly the economic development of the country. Studies consistently show also malaria imposes heavy sanctions on economic growth and causes household impoverishment [9, 10].

Malaria causes multifaceted problems which demand priority as well as synergistic intervention. Prevention of malaria using long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) has been demonstrated to be cost-effective interventions in different contexts. A systematic review indicates a median incremental cost effectiveness ratio (ICER) per disability adjusted life year (DALY) averted of $27 for insecticide-treated nets (ITNs), and $143 for IRS [11]. These tools have been scaled up in the last decade aiming towards a universal access and to interrupt malaria transmission in malaria-endemic developing countries [12].

The results of the last two malaria indicator surveys (MIS) showed a remarkable stride in malaria prevention and control services in Ethiopia. For example: ITN ownership in malaria endemic areas improved from 3.4 % in 2005 [13] to 65.6 % in 2007 [14]. Overall, 68 % of households in malaria endemic areas were protected by at least one LLIN or indoor residual spraying of households with insecticide [15]. Thirty percent of IRS targeted areas were sprayed in 2007 and in 2008 the coverage increased to 50 % [16]. So far, (since 2005 till 2014), a total of 64.2 million ITNs have been distributed [17]. Currently, Ethiopia aims to achieve universal coverage by distributing one LLIN per 1.8 persons through mass and free distribution campaigns at the community level through the health extension workers and health facilities. Usually, LLINs are distributed by periodic mass campaigns that occur about every 3 years in a rotation basis [2].

Beyond mere emphasis on overall coverage, malaria prevention services in general and LLIN ownership and IRS status in particular, should be fair regardless of socioeconomic status over time. Both LLIN and IRS are mainly financed through the MoH either from donation or direct government budgeting. Therefore, unarguably, the benefits from these publicly financed interventions shall be distributed equitably. A test regarding this normative position is that the odds of malaria infection should be the same for all socioeconomic classes [18]. Worrall et al. [19], based on review of several literatures, and Filmer [20], using 29 Demographic and Heath Surveys (DHS) data from 22 countries, establish a very weak link between malaria incidence and wealth status at micro-level. No differences were found at the household level in the incidence of fever between the poor and less poor [20]. Similarly, a recent study by Gari et al. from the same area also found no significant association between wealth status and incidence of malaria [7].

The underlying assumption is that at individual or household level, the odds of malarial infection is quite similar if either of them are not using the preventive measures. Therefore the argument that the socioeconomically better-off are in a better position to access the other non-publicly financed means of malaria prevention including mosquito repellent or window meshes could not be justified given that the availability in rural setting is limited. For this reason, this paper emphasizes that malaria prevention interventions (LLINs and IRS) should be owned equitably at any given time. However, the Ethiopian government has committed to follow pro-poor universal health service delivery strategy, which goes beyond policy statements of creating equal access to health services for all groups of population [21].

In a nutshell, in this malaria elimination and eradication era, information on the equity dimension is more important than ever for priority setting and resource allocation [22–24]. In contrast, little is currently known about who benefits from prevention efforts. Where are those freely distributed bed nets? Who owns them? Whose houses are sprayed or not? These questions reflect concerns about social justice and fairness, and have so far not systematically been investigated. In this paper, household survey data were used to evaluate the socioeconomic related dimension of inequalities in malaria prevention interventions (LLIN and IRS) in a district in south-central Ethiopia. Therefore, the hypothesis is that the poor families are equally likely to own the LLINs and to live in a house treated with IRS compared with better-offs.

Methods

Study area and participants

This study is part of a large cluster randomized controlled trial, which aim to evaluate the combined use of LLINs and IRS against each intervention alone in preventing malarial infection [25]. This study uses data from a baseline household survey conducted in July–August 2014 in Adami Tullu district of Oromia region in south-central Ethiopia. The survey was conducted in 13 villages, located within 5 km from the shore of Lake Ziway. Overall, 31,284 individuals from 6069 households were included.

The district is situated in the heart of the Great Rift Valley. Most of the villages are located in the lowland portion, while the elevation ranges from low altitude of 1500 m to higher altitude of 2300 m above sea level. The area is partly dry and arid, where malaria is largely seasonal, and partly swampy and marshy, where malaria is largely perennial.

Data collection

The data were obtained from the head of the household by trained nurses who performed face-to-face interviews using a pre-tested structured questionnaire. The questionnaire contains information about socioeconomic position, including questions about demographic situation, ownership of different household assets, ownership and utilization of malaria prevention services, and general health service utilization.

Data analysis and model specifications

Measuring socioeconomic status

The two recommended ways to consider for measuring socioeconomic status is to use consumption expenditure levels of the households and to use asset based wealth index. Nonetheless, consumption expenditure measurement in the present situation would have been likely to be unreliable, since most people base their livelihood on subsistence farming for own consumption, so that the market value of much of the produced is never realized [26]. For this reason, principal components analysis (PCA) was used to construct a wealth index based on household characteristics: such as, availability of various household assets, housing conditions, water source, and type of latrine facility. An equation provided by Filmer and Pritchett [27] was used to calculate the wealth index (A), for individual i, defined as follows:

$$A_i = \sum_k \left[f_k \frac{(a_{ik} - \bar{a}_k)}{s_k} \right]$$

where, a_{ik} is the value of household characteristics or k for household i (i.e. 0 = if the household didn't own that specific characteristics; 1 = if the household own that characteristics), $\bar{a}_k$ is the sample mean, s_k is the sample standard deviation, and fk are the weights (eigenvectors) extracted from the first principal component which are correlation matrix of the data [26, 27].

Measuring LLIN ownership and IRS status

The primary health outcome variables are household level LLIN ownership and IRS status. LLIN ownership and IRS with insecticide were defined as "the household owns at least one functional LLIN" and "the house is sprayed within the last 12 months", respectively. LLIN ownership was measured by direct observation by the data collectors while IRS status was assessed based on what the household head reported. A binary logit regression model was employed in order to predict the probability of LLIN ownership and IRS status of the households. The unit of analysis in this study is at household level.

Measuring inequality

The main measures of inequality is the concentration curve and concentration index (CI) [28]. The concentration curve plots the cumulative percentage of the health variable (LLIN and IRS ownership) on the y-axis against the cumulative percentage of the population on x-axis, ranked by wealth index beginning with the poorest, and ending with the least poor (richest). If everyone irrespective of the wealth status has exactly the same value of the prevention measures, then the concentration curve will be a straight diagonal line, from the bottom left corner to the top right corner. Besides visual inspection of the concentration curve, a dominance test using the multiple comparison approach was applied to examine for statistical significance of the difference between the concentration curve and the line of equality (diagonal).

A concentration index is a relative measure of inequality. A CI ranges from −1 to 1, with a value of 0 indicating perfect equity. The index takes a negative value when the variable of interest is concentrated among the poorest groups and a positive value when it is concentrated among the richest group [28, 29]. The conventional concentration index (CI) is a covariance between LLIN ownership/IRS treatment (y_i) and the socioeconomic rank (R_i) of that household, multiplied by two, and then the whole expression divided by the mean of the outcome variable (μ).

$$CI(\mathrm{y}) = \frac{2 * \mathrm{cov}(y_i, R_i)}{\mu}$$

However, the health outcome variables (LLIN ownership and IRS) were binary in which case a normalized concentration index is preferred over the conventional CI. "Erreygers normalized concentration index" was employed, which is provided by Erreygers and Van Ourti [30] as follows;

$$CCI = 4 * \mu * CI(y)$$

where, $CI(y)$ is the generalized concentration index and μ is the mean (in this case proportion of LLIN ownership or IRS coverage).

Decomposition analysis

Wagstaff et al. proved that concentration index are decomposable into its contributing factors [31]. They showed that, for each factor, its contribution is the

product of the sensitivity of the outcome variable with respect to that factor and the degree of socioeconomic status inequality in that factor. They provide a linear additive regression model for outcome variable y, against to a set of k determinants, x_k, as follows:

$$y = \alpha + \sum_k B_k x_k + \varepsilon$$

Then concentration index for y (i.e. Concentration index of LLIN) (CIy) can be written as:

$$CIy = \sum_k \left(\frac{B_k \bar{x}_k}{\mu}\right) C_k + \left(\frac{GC_\varepsilon}{\mu}\right)$$

where $\bar{x}_k$ is the mean value of the determinant x_k, μ is the mean of the outcome variables (LLIN), C_k is the concentration index of the determinant x_k; $GC\varepsilon$ is the residual component that captures wealth-related inequality in LLIN that is not accounted for by systematic variation in determinants across wealth groups, and $\left(\frac{B_k \bar{x}_k}{\mu}\right)$ is the impact of each determinant on the probability of LLIN ownership and represents the elasticity (η_k) of the outcome variable with respect to the determinant x_k evaluated at the mean *y*. In this paper, this decomposition technique was used to estimate, and compare the contribution of socioeconomic effects to that of education, religion, ethnicity, household size, place of residence (village), housing conditions, access to infrastructure (electricity and piped water), ownership and access to mass-media and telecommunication service (radio, television, mobile telephone). All analyses were conducted using STATA version 14 [32].

Results

Characteristics of the study population

Table 1 shows a summary of the study participants and distribution of LLINs and IRS among households classified into different socioeconomic and demographic groups. A total of 6069 households were enrolled into the study. The mean household size was 5.1 (range from 1 to 14). The majority of the study participants were Oromo (5512, 91 %), muslim (5199, 86 %) and illiterate (3335, 55 %).

LLIN ownership and IRS coverage

The overall LLIN ownership was 704 (11.6 %), ranging from 98 (8.0 %) in the poorest quintile to 178 (14.7 %) in the richest quintile. Regarding IRS, about three quarters of the houses were sprayed in the last 12 months. A quarter of households had neither own any LLIN nor their house was sprayed, whereas 557 (9.2 %) of the households owned LLIN meanwhile their house is sprayed in the last 12 months.

The binary logit model for LLIN ownership show that households wealth status, larger household size, having a latrine, and having a radio were significantly positively associated with LLIN ownership, where as having a separate cooking space from the main room and having a larger number of sleeping spaces, were significantly and negatively associate with household LLIN ownership (Table 2). Similarly, the logit model for the IRS shows that educational status of head of the household was significantly associated with the probability of having IRS (Table 3).

Equity in LLIN and IRS ownership

The concentration curve for LLIN is clearly below the diagonal line (Fig. 1a), indicating a pro-rich distribution. The dominance test based on the multiple comparison approach indicates that the concentration curve is significantly below the line of equality at 19 evenly spaced points. Similarly, the Erreygers normalized concentration index of 0.06270 (SE = 0.03898) was significantly different from zero (P < 0.0001) (Table 4).

On the other hand, the concentration curve for IRS is closely aligned with the diagonal line (Fig. 1b), indicating that there was no noticeable difference in houses sprayed according to different socioeconomic status. The Erreygers normalized concentration index of −0.03834 (SE = 0.01139) for the IRS was not significantly different from zero.

The decomposition analysis shows that inequality in ownership of LLIN is largely driven by the wealth itself (90.77 %), whereas ethnicity (4.25 %), religion (2.63 %) and educational status (3.4 %) of the head of the household had little influence on inequality. Difference in housing situation, access to mass media and telecommunication, and household size, were also found to be predominantly contributing for the inequality. The positive or negative sign of the CI or the percentage contribution in Table 5 demonstrates that the factor was concentrated among rich or poor household respectively. For example, higher educational attainment, larger household size, those who have bed and latrine, as reported in Table 5, are concentrated among the richest households. The percentage contribution of wealth is an estimate of the pure effect of wealth on the total inequality, adjusting for other relevant factors.

Discussion

This study is the first to provide empirical evidence about socioeconomic inequalities in malaria prevention interventions from a district in Ethiopia. This study tries to evaluate the household level coverage and equity dimension of LLIN ownership and IRS status. The main finding from this study indicates very low ownership of LLIN and

Table 1 Description of malaria prevention by different household characteristics

Household characteristics	N (%)	LLIN n (%)	IRS n (%)	Both LLIN and IRS n (%)	Nothing at all n (%)
Ethnicity					
Oromo	5512 (90.82)	640 (11.61)	4034 (73.19)	497 (9.02)	1335 (24.22)
Amhara	46 (0.76)	5(10.87)	28 (60.87)	5 (10.87)	18 (39.13)
Gurage	58 (0.96)	8 (13.79)	47 (81.03)	7 (12.07)	10 (17.24)
Other ethnicity	453 (7.48)	51 (11.23)	290 (64.02)	48 (10.60)	160 (35.32)
Religion					
Muslim	5199 (85.66)	562 (10.81)	3739 (71.92)	436 (8.39)	1334 (25.66)
Orthodox christian	709 (11.68)	128 (18.05)	557 (78.56)	112 (15.80)	136 (19.18)
Protestant christian	149 (2.46)	12 (8.05)	96 (64.43)	8 (5.37)	49 (32.89)
Other religion[a]	12 (0.20)	2 (16.67)	7 (58.33)	1 (8.33)	4 (33.33)
Educational status					
Illiterate	3336 (54.95)	334 (10.01)	2584 (77.48)	278 (8.34)	695 (20.84)
Can read and write only	562 (9.26)	67 (11.92)	421 (74.91)	49 (8.72)	123 (21.89)
Elementary (1–4)	519 (8.55)	102 (19.65)	342 (65.90)	78 (15.03)	153 (29.48)
Junior Elementary (5–8)	972 (16.02)	120 (12.33)	636 (65.36)	90 (9.25)	307 (31.55)
High school (9–12)	513 (8.45)	71 (13.84)	344 (67.06)	52 (10.14)	150 (29.24)
Above high school	77 (1.30)	9 (11.69)	52 (67.53)	9 (11.69)	25 (32.47)
NR[b]	90 (1.47)	1 (1.11)	20 (22.22)	1 (1.11)	70 (77.78)
Wealth quintiles					
Poorest	1214 (20.00)	98 (8.07)	882 (72.65)	77 (6.34)	311 (25.62)
2nd poorest	1214 (20.00)	112 (9.23)	912 (75.12)	80 (6.59)	270 (22.24)
Middle	1214 (20.00)	144 (11.86)	916 (75.45)	124 (10.21)	278 (22.90)
2nd richest	1213 (20.00)	172 (14.18)	851 (70.16)	138 (11.38)	328 (27.04)
Richest	1214 (20.00)	178 (14.66)	838 (69.03)	138 (11.37)	336 (27.68)
Overall total	6069 (100.00)	704 (11.60)	4399 (72.48)	557 (9.18)	1523 (25.09)

[a] Other religion practiced in that area was *Wakefeta*

[b] No response (missing) for educational status question

low coverage of IRS in general, while the findings on the coverage across wealth status were mixed. On one side, LLINs were distributed significantly in favor of the rich, while IRS on the other side was distributed equitably regardless of household wealth status.

The very low ownership of LLIN (11.6 %) found in this study is totally unparalleled with finding from most of other studies [33, 34] including the malaria indicator survey [16]. The reason for this big difference might be due to the gap in the time period between this survey and the last LLIN distribution conducted in the area. A report from the district indicates that the last LLINs distribution, for most of the villages, was conducted 2 years ago by the Districts' Health Office. Nonetheless, the national malaria prevention guidelines dictates that all sleeping spaces in malaria endemic areas should be covered at least with one LLIN at any time [2].

The observed significant difference in both LLINs ownership and IRS status across villages might be mainly due to the districts' malaria prevention schedule which is conducted on a rotating basis. Those villages which receive the interventions recently reported higher ownership while others received a couple of years back report low.

In the bivariate analysis, the associations between LLIN ownership and having separate cooking space or having more number of sleeping space were non-significant. However, in the multiple logit model (i.e. adjusted for wealth status, cluster, ethnicity, religion, education, and household size), both "having a separate cooking space" and "more number of sleeping space" are significantly negatively associated with LLIN ownership, which is contrary to prior expectations. The first speculation is that households with limited number of sleeping space for hanging the nets might apply them less frequently and subsequently the nets might have survived longer, while nets in household which had adequate space for hanging-up worn-out quicker. Loha et al. also reports that lack of convenient space was a barrier for hang-up the bed nets from quite similar sociodemographic area [35]. These finding have important implications that the national LLINs distribution programme should critically consider

Table 2 Logit model predicting the probability of LLIN ownership

Variable	Coef.	Robust SE	P value	[95 % Conf. interval]	
Wealth status (ref. = reachest Q)					
Poorest Q	−0.8390	0.2541	0.001	−1.3370	−0.3410
Second poorest Q	−0.6149	0.2152	0.004	−1.0367	−0.1931
Middle Q	−0.3240	0.1748	0.064	−0.6666	0.0187
Second richest	−0.1249	0.1501	0.405	−0.4190	0.1693
Ethnicity (ref. = other ethnicity)					
Oromo	−0.4490	0.2419	0.063	−0.9232	0.0251
Amhara	−0.3835	0.5992	0.522	−1.5580	0.7909
Gurage	0.6176	0.4832	0.201	−0.3294	1.5646
Religion (ref. = other religion)					
Orthodox	0.3698	0.7026	0.599	−1.0072	1.7468
Muslim	0.1984	0.7006	0.777	−1.1747	1.5715
Protestant	−0.1818	0.7495	0.808	−1.6508	1.2873
Education (ref. = above high school)					
Illiterate	0.3061	0.3550	0.388	−0.3896	1.0019
Can read and write only	0.4762	0.3534	0.178	−0.2163	1.1688
Elementary (1 − 4)	0.7490	0.3633	0.039	0.0369	1.4612
Junior Elementary (5 − 8)	0.3550	0.3786	0.348	−0.3871	1.0971
High School (9 − 12)	0.5916	0.3955	0.135	−0.1835	1.3667
Household size	0.0556	0.0261	0.033	0.0044	0.1068
Villages (ref. = Kebele #13)					
Kebele1	2.3848	0.4098	0.000	1.5815	3.1881
Kebele2	4.7088	0.4908	0.000	3.7468	5.6707
Kebele3	1.5564	0.3727	0.000	0.8260	2.2868
Kebele4	1.9868	0.3083	0.000	1.3826	2.5910
Kebele5	0.5895	0.4206	0.161	−0.2348	1.4137
Kebele6	−0.5098	0.8708	0.558	−2.2165	1.1968
Kebele7	0.7979	0.5923	0.178	−0.3629	1.9587
Kebele8	−1.6184	1.0035	0.107	−3.5852	0.3484
Kebele9	−0.5220	0.4334	0.228	−1.3714	0.3275
Kebele10	1.6388	0.3679	0.000	0.9176	2.3600
Kebele11	0.9948	0.4361	0.023	0.1402	1.8495
Kebele12	1.7502	0.3978	0.000	0.9705	2.5299
Housing					
Has a bed	0.0791	0.1433	0.581	−0.2018	0.3599
Has a separate cooking space	−0.3018	0.1148	0.009	−0.5269	−0.0768
Number of living rooms	0.0579	0.1010	0.566	−0.1400	0.2558
Number of sleeping space	−0.2148	0.0769	0.005	−0.3656	−0.0641
Has a latrine	0.3659	0.1145	0.001	0.1414	0.5904
Roof (1 corrugated iron, 0 thatch/leaf)	−0.2038	0.1322	0.123	−0.4629	0.0553
Wall(1 mud &wood and better, 0 rudimentary)	0.2154	0.3255	0.508	−0.4226	0.8535
Communication access					
Has television	0.2903	0.1897	0.126	−0.0814	0.6620
Has radio	0.2446	0.0995	0.014	0.0495	0.4397
Has mobile telephone	0.0059	0.1294	0.964	−0.2478	0.2595
Infrastructure and utility					
Has electricity	0.0295	0.1829	0.872	−0.3290	0.3880
Use piped water for drinking	0.0191	0.1695	0.910	−0.3132	0.3514
_Constant	−3.6198	0.9835	0.000	−5.5475	−1.6921

Table 3 Logit model predicting the probability of IRS status of the household

Variable	Coef.	Robust SE	P value	[95 % Conf. interval]	
Wealth status (ref. = reachest Q)					
Poorest Q	−0.7766	0.3046	0.0110	−1.3737	−0.1795
Second poorest Q	−0.6166	0.2203	0.0050	−1.0483	−0.1849
Middle Q	−0.4146	0.1786	0.0200	−0.7647	−0.0645
Second richest	−0.4790	0.1380	0.0010	−0.7495	−0.2085
Ethnicity (ref. = other ethnicity)					
Oromo	−0.5795	0.1772	0.0010	−0.9269	−0.2322
Amhara	−0.5909	0.3829	0.1230	−1.3414	0.1596
Gurage	0.8654	0.3414	0.0110	0.1963	1.5345
Religion (ref. = other religion)					
Orthodox	0.2692	0.5776	0.6410	−0.8629	1.4013
Muslim	0.0498	0.5325	0.9250	−0.9938	1.0935
Protestant	−0.0749	0.5819	0.8980	−1.2154	1.0656
Education (ref. = above high school)					
Illiterate	1.2899	0.3798	0.0010	0.5454	2.0344
Can read and write only	1.1435	0.3658	0.0020	0.4265	1.8605
Elementary (1−4)	1.1823	0.4136	0.0040	0.3717	1.9929
Junior elementary (5−8)	1.1041	0.3995	0.0060	0.3210	1.8872
High school (9−12)	1.0489	0.4004	0.0090	0.2641	1.8336
Household size	0.0331	0.0195	0.0890	−0.0050	0.0712
Villages (ref. = Kebele #13)					
Kebele1	−0.1902	0.4541	0.6750	−1.0802	0.6998
Kebele2	−1.8311	0.5471	0.0010	−2.9035	−0.7588
Kebele3	0.8239	0.4677	0.0780	−0.0927	1.7405
Kebele4	2.9881	0.6129	0.0000	1.7869	4.1894
Kebele5	−0.9067	0.3628	0.0120	−1.6178	−0.1956
Kebele6	−0.6001	0.8312	0.4700	−2.2291	1.0289
Kebele7	2.3747	0.4985	0.0000	1.3977	3.3516
Kebele8	−6.1193	0.8757	0.0000	−7.8357	−4.4030
Kebele9	−2.1782	0.4496	0.0000	−3.0595	−1.2970
Kebele10	−0.3213	0.4660	0.4910	−1.2347	0.5921
Kebele11	1.0652	0.4392	0.0150	0.2044	1.9260
Kebele12	−0.0950	0.4770	0.8420	−1.0300	0.8400
Housing					
Has a bed	0.2100	0.1189	0.0770	−0.0231	0.4431
Has a separate cooking space	−0.0274	0.1247	0.8260	−0.2718	0.2169
Number of living rooms	−0.0380	0.1217	0.7550	−0.2764	0.2005
Number of sleeping space	−0.0574	0.0949	0.5450	−0.2434	0.1287
Has a latrine	−0.3592	0.1077	0.0010	−0.5703	−0.1481
Roof (1 corrugated iron, 0 thatch/leaf)	−0.3412	0.1275	0.0070	−0.5912	−0.0913
Wall (1 mud and wood and better, 0 rudimentary)	−0.2931	0.2303	0.2030	−0.7445	0.1583
Communication access					
Has television	0.0543	0.2082	0.7940	−0.3538	0.4624
Has radio	0.1525	0.1001	0.1270	−0.0436	0.3487
Has mobile telephone	0.0499	0.0990	0.6140	−0.1441	0.2440
Infrastructure and utility					
Has electricity	−0.5746	0.1847	0.0020	−0.9366	−0.2126
Use piped water for drinking	−0.6268	0.2007	0.0020	−1.0201	−0.2335
_Constant	2.0583	0.8134	0.0110	0.4642	3.6525

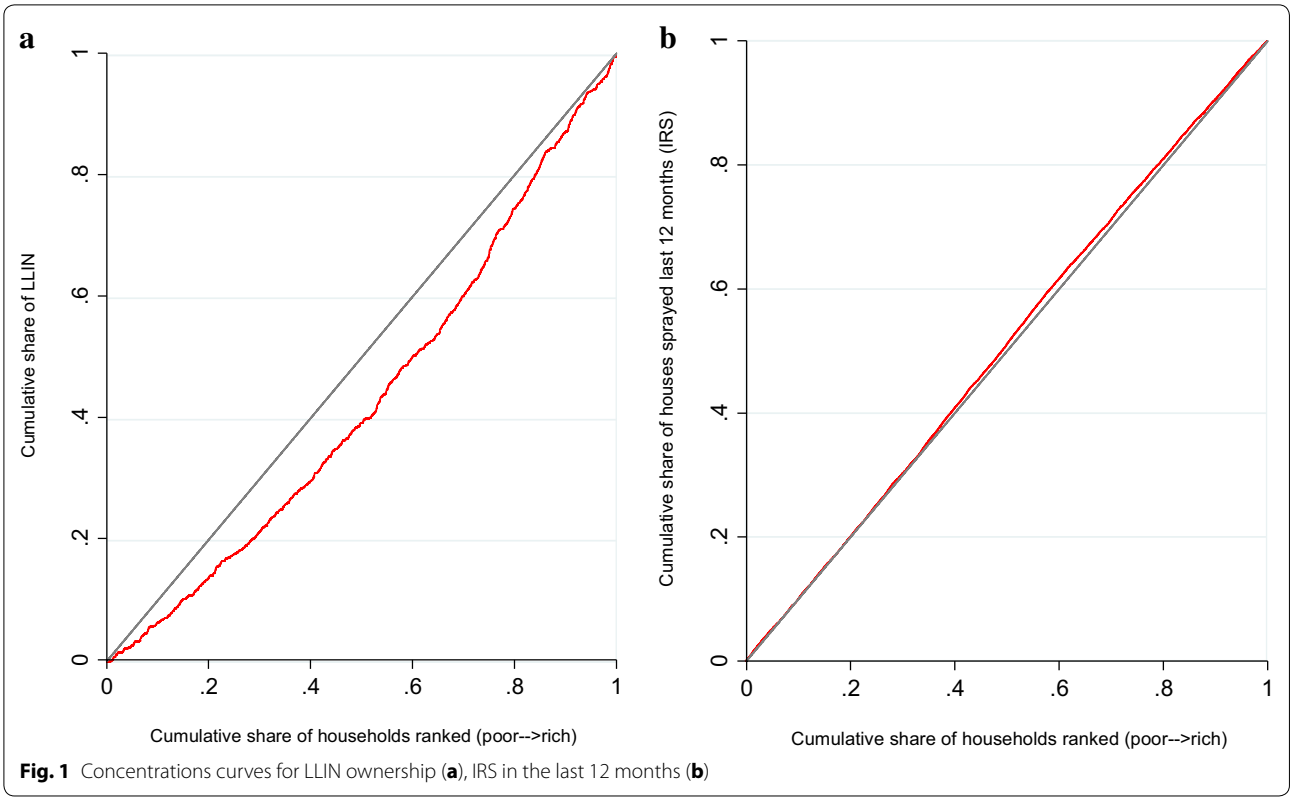

Fig. 1 Concentrations curves for LLIN ownership (**a**), IRS in the last 12 months (**b**)

Table 4 Erreygers normalised and generalized concentration indices for LLIN and IRS distribution

Concentration Index (CI)	Malaria prevention programs	
	LLIN	IRS
Erreygers normalised CI	0.06270**	−0.03834
Generalized CI	0.13495**	−0.01323
95 % confidence interval	(0.09526, 0.17465)**	(−0.02232, −0.00413)*
Standard error (delta method)	0.03898	0.01139

Significant at 0.001**, 0.01* level of significance

number of sleeping space in addition to household size based allotment of the nets for optimizing the efficiency of available LLINs. Moreover, the relationship between LLIN ownership, number of sleeping spaces and useful life time of the LLIN is not sufficiently well understood, which warrants more research.

LLINs are significantly more likely to be owned by the rich, even when analyses are adjusted for village. In a situation where the coverage is low and the inequality in ownership is high, an empirical study [36] and a mathematical model [37] highlight that community wide protection of the LLINs could be diminished. The uses of LLINs decrease probability of bites of mosquitoes for the ultimate users without significantly decreasing the population of mosquito. Consequently, the potential advantage of the 'positive externality' to those who could not own by themselves might be nullified.

Various studies from sub-Saharan Africa consistently report the cost as a main barrier to ownership of LLIN among the poorest households [38]. In this study area, LLINs were distributed free of charge, and the cost argument is, therefore, less apparent. Several questions need consideration to better understand the causalities. From the demand side—one may ask whether the poor are reluctant to collect their share from the health posts? Are the poor unable to avail themselves on the dates and place of distribution? Did the LLINs in the poorest households wear out faster and got lost because of improper handling? Do the poor sell the LLINs received? The current study didn't investigate these matters. However, in the field site stay, the authors frequently observed that several of LLINs were used for other purposes, such as collecting crops and vegetables in the farm, for fencing or as a fishing net). As a consequence, it could be that the "useful life" of the LLINs differs between the socio-economic strata.

In contrast, the equitable distribution of the IRS between socio-economic strata is surely a notable achievement and might be partly driven by the nature

Table 5 Decomposition of Erreygers normalised concentration index for LLIN ownership in Adami Tullu, Ethiopia, 2014

Variable	Concentration index (CI)	Contribution to CI	Percentage contribution (%)
Wealth status		0.0569	90.77
Ethnicity (1 other ethnicity, 0 otherwise)		−0.0027	−4.26
Religion (1 other religion, 0 otherwise)		0.0016	2.63
Educational status of the head of household		0.0021	3.40
Household size	0.1047	0.0094	14.94
Village (1 village 13, 0 otherwise)		0.0015	2.37
Housing situation		*−0.0264*	*−42.19*
Has a bed	0.1996	0.0022	3.54
Has a separate cooking space	0.3253	−0.0157	−24.98
Number of living rooms	0.0804	−0.0001	−0.20
Number of sleeping space	0.1090	−0.0128	−20.40
Has a latrine	0.1758	0.0103	16.45
Roof (1 corrugated iron, 0 thatch/leaf)	0.2808	−0.0103	−16.35
Wall (1 mud and wood and better, 0 rudimentary)	−0.0028	−0.0002	−0.25
Access to mass media and communication		*0.0156*	*24.93*
Has television	0.7805	0.0053	8.48
Has radio	0.3656	0.0106	16.88
Has mobile telephone	0.2422	−0.0003	−0.43
Infrastructure and utility		0.0011	*1.74*
Has electricity	0.2367	0.0009	1.36
Use piped water for drinking	0.1081	0.0002	0.38
Residual		*0.00356*	0.00
Total	*0.0627*		

Subtotal are highlighted in italics

of the intervention, which requires minimal compliance from the household side. The spray is conducted using community-based approaches, including annual campaigns, administered from the District Health Office. The IRS programme has been well accepted and implemented for more than half a century throughout the country [39]. Thus, this coverage mainly reflects the performance of the health system and the IRS is a dependable vector control option.

Based on the decomposition analysis, the wealth status was the single most dominant factor for the overall socioeconomic related inequality in LLIN ownership. This finding suggests that any effort in improving the welfare of the household should be considered as a fight against malaria and vice versa [10]. Housing condition and access to mass media and telecommunication also contributed to the observed inequality. This finding has an implication that inequality in LLINs ownership is partly driven by differential access to sources of information. The government needs to consider the LLIN promotion strategies targeting the poor. These findings have important policy implications that sole emphasis on the distribution of LLINs is not sufficient to ensure neither the coverage nor the equity; it should be accompanied by teaching how to properly handle and effectively use the LLINs. In order to achieve equity in ownership of LLIN throughout the year, a priority, in both scale-up and replacement distribution should be given to the poor.

There is an ongoing debate on which specific concentration index is the most appropriate based on the properties of the indices and the nature of the variable under investigation. However, there seems to be increasing support that the concentration index needs to be adjusted for the binary nature of health outcome variables. This study apply Errygers normalized concentration index and its decomposition—appropriate measures of inequality for binary outcome [30].

These findings should be interpreted carefully, especially the wealth measurement and the classification method employed was applicable for relative ranking only. In a rural situation where more than a quarter of the total population is living in absolute poverty [40], even those households in the middle or second richest quintile could be below poverty line by standardized living status measurement. The other concern could be raised about the generalizability of the findings. The proportion of the population who owned a LLIN was much lower than comparable studies, and this study was conducted in a

single district. This study may not be a full representative of the malaria situation of a rural Ethiopia.

A third limitation to this study is that it only focuses on horizontal equity. Socioeconomic related inequalities in health services are only considered unfair, when they do not correspond to differences in need for health care across socioeconomic groups. In other way, horizontal equity means that households in equal need for the service should receive equal service irrespective of other characteristics such as wealth status, ethnicity, religion or geographical location. On the other side, vertical equity describes the extent to which households with greater needs received more service [29]. For example:, households which are located more close to the mosquito breeding site might have higher LLIN need while this study did not consider standardization based on difference in need.

Conclusion

The ownership of LLIN is significantly pro-rich, while IRS status is equitable across socio-economic strata. The distribution campaign should be followed by periodic refill based on continuous monitoring data. Local data on 'useful life' of LLIN and tracking information should be ready for timely planning of LLIN distribution.

Abbreviations

CI: concentration index; DALY: disability adjusted life year; DHS: demographic and heath survey; ICER: incremental cost effectiveness ratio; IRB: institutional review board; IRB: institutional review board; IRS: indoor residual spraying; ITN: insecticide treated net; ITN: insecticide treated net; LLIN: long-lasting insecticidal net; MIS: malaria indicator survey; MoH: Ministry of Health; PCA: principal components analysis; SE: standard error; WHO: World Health Organization.

Authors' contributions

All authors (AH, BR, WD, TG, EL and BL) substantially participated in the conception of the research idea and design of data collection tools. AH, BR, WD, EL and BL have done interpretation of the result and write-up of this manuscript. AH and TG coordinated and supervised the data collection. Analysis of the data was done by AH and BR. The initial draft manuscript was prepared by AH. All authors read and approved the final manuscript.

Author details

[1] Center for International Health, University of Bergen, Bergen, Norway. [2] Department of Reproductive Health and Health Service Management, School of Public Health, Addis Ababa University, P.O. Box 9086, Addis Ababa, Ethiopia. [3] Department of Preventive Medicine, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia. [4] School of Public and Environmental Health, Hawassa University, Hawassa, Ethiopia. [5] Center for Intervention Science in Maternal and Child Health (CISMAC), University of Bergen, Bergen, Norway.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and material

This study is part of an ongoing randomized controlled cluster trial (MalTrials). The full data will be publicly availed when the trial is complete.

Consent to publication

The data were collected after taking informed consent (including consent for publication) from the participants.

Ethical approval

The study was approved by the Institutional Review Board (IRB) of the College of Health Sciences at Addis Ababa University, the Ministry of Science and Technology in Ethiopia (ref: 3.10/446/06) and the Regional Committee for Medical and Health Research Ethics, Western Norway (ref: 2013/986/REK Vest). Participation in the study was voluntary and informed consent was obtained from each participant.

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Data Collection Instruments & Ethical Approvals

QUESTIONNAIRE TO CONDUCT CENSUS ON SELECTED SOCIO-DEMOGRAPHIC VARIABLES AND TO GATHER DATA ON MALARIA PREVENTION AND TREATMENT PRACTICES

General Information

GI1	Household number	_____	
GI2	GPS reading of the household	N_____ _0_____'	E_____ 0_____' Elevation_____
GI3	Site in which the interview is being conducted	a) Kebele _____b)Zone_____ c)Gare _____	
GI4	Personnel (name and signature)	a) Interviewer_____ b) Supervisor_____	
GI5	Date of visit	[_____|_____| _____| dd | mm| yyyy	

Introduction and Consent

My name is_____ and I'm working for Hawassa University and Addis Ababa University. We are conducting a survey about malaria in collaboration with the Woreda Health Office. We would very much appreciate your participation in this survey. This information will help the Oromia Regional Health Bureau to plan health services. This interview could take less than 15 minutes to complete. Whatever information you provide will be kept strictly confidential and will not be shown to other persons. Participation in this survey is voluntary and you can choose not to answer any individual questions or all of the questions. However, we hope that you will participate fully in this survey since your views are important. There will be weekly visit for the next 2 years.

Do you have any questions about the survey? May I begin the interview now?

Verbal consent given to interview, check box ☐

Section 1: Household members' listing and socio-demographic and economic characteristics											
Q101	Total number of household members	Number _____									
Start listing from the respondent him/herself											
Q102a		**102b**	**102 c**	**102d**	**102e**	**102f**	**102g**	**102h**	**102i**	**102j**	**102k**
Individual ID	**Household Members**	**Age**	**Sex**	**Relationship to head of household**	**Educational status**	**Marital Status**	**Current pregnancy status**	**Duration of pregnancy in months**	**Occupation**	**Ethnicity**	**Religion**
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											

Sex
1. Male
2. Female

Relationship
1. head
2.Wife or husband
3. Child;
4. Relative
5. Maid;
6. Other

Educational Status
(6 years and above)
- **I=** Illiterate
- **RW=** Read and Write only
- If formal education**,** write the highest grade **C**ompleted

Marital Status
1.Maried
2.Living together
3.Divorced or separated
4.Widowed
5. Naver married/naver lived together;

Occupation
(18 years and above)
1. Employed
2. House wife
3. Farmer
4. Day laborer
5. Trader
6. Fishery
7. Student
8. No job/dependent
9. Housemaid
10. Others

Ethnicity
1.Oromo
2. Amhara
3. Gurage
4. Other (Specify__)

Religion
1.Orthodox
2.Muslim
3.Protestant
4.Other (Specify__)

Q103	Does your household have: Electricity? A watch? A radio? A television? A mobile telephone? A non-mobile telephone? A refrigerator? A table? A chair? A bed? An electric mitad? A kerosene lamp/pressure lamp?	Yes No Electricity……1 2 Watch……1 2 Radio……1 2 Television……1 2 Mobile Telephone……1 2 Non-Mobile Telephone……1 2 Refrigerator……1 2 Table……1 2 Chair……1 2 Bed……1 2 Electric Mitad……1 2 Kerosene/Pressure Lamp……1 2	
Q104	Do you have a separate room which is used as a kitchen?	Yes……1 No……2	
Q105	Main material of the floor. ***(Record observation)***	Earth/Dung ……1 Ceramic Tiles……2 Cement……3 Other……96 Specify_____	
Q106	Main material of the roof ***(Record observation)***	Thatch/Leaf……1 Corrugated Iron……2 Cement/Concrete……3 Other……96 (Specify)_____	
Q107	Main material of the exterior wall. ***(Record observation)***	No wall……1 Wood……2 Wood with mud……3 Wood with mud and cement……4 Cement blocks……5 Other……96 (Specify)_____	
Q108	How many rooms in this household are used for sleeping?	Number of rooms[__|__]	
Q109	How many sleeping spaces such as mats, rugs, mattresses or beds are used in this household?		
Q110	Does any member of this household own: A bicycle? A motorcycle? An animal-drawn cart? A car or truck?	Yes No Bicycle……1 2 Motorcycle……1 2 Animal-drawn cart……1 2 Car/truck……1 2	
Q111	Does any member of this household own any land that can be used for agriculture?	Yes……1 No……2	→ **Skip to Q113**
Q112	How many (LOCAL UNITS) of agricultural land do members of this household own? ***(If unknown enter 98)***	Local units [___|___] Specify the local unit_____	
Q113	Does this household own any livestock, herds, or farm animals?	Yes……1 No……2	
Q114	How many of the following animals does this household own? Milk cows, oxen, or bulls? Horses, donkeys, or mules? Goats? Sheep? Chickens? ***(If unknown, enter 98)***	Milk cows, oxen, or bulls------ [ ][ ][ ] Horses, donkeys, or mules----- [ ][ ][ ] Goats---------- [ ][ ][ ] Sheep---------- [ ][ ][ ] Chickens---------- [ ][ ][ ]	
Q115	Does any member of this household have an account with a bank/credit association/micro finance?	Yes……1 No……2	

Q116	What is the main source of drinking water for members of your household? ***(Do not read out Responses)***		**Piped (Tap)** Piped into dwelling……..…1 Piped into compound……...2 Piped outside compound….3 Covered Well……...…4 Protected Spring…….…..5 **Open Well/Spring** Open Well……6 Open Spring……..…7 **Surface Water** River…….……..8 Pond/Lake/Dam…..……9 Rainwater…….10 Other…..……..11 Specify_____	
Q117	What kind of toilet facility do most members of your household use? ***(observe latrine)***		Flush toilet…….…...……..1 Pit latrine/traditional pit toilet..……2 Ventilated improved pit latrine (VIP) …3 No facility/Bush/Field… ……..….4 Other…….……..…5 Other(Specify)_____		→ **Skip to Q201**
Q118	Do you share this facility with other households?		Yes…….1 No..……...2		
Section 2: Malaria prevention and treatment					
Q201	Does your household have any mosquito net that can be used while sleeping?		Yes…….1 No..……→ 2		**Skip to Q211**
Q202	How many mosquito nets do your household have?		Number of Nets _____		
Q203	Ask respondent to show you the net(s) in the household.	NET #1 _____ Observed ..... 1 Not observed..... 2	NET #2 _____ Observed.....1 Not observed 2	NET #3 _____ Observed.....1 Not observed.. 2	
Q204	How long ago did your household obtain the mosquito net?	____ ____ Months ago	____ ___ Months ago	____ ____ Months ago	
Q205	Where did you obtain the net?	Government Clinic/hospital Health extension worker…….1 Retail shop Pharmacy…….2 Workplace……3 Other (specify)_____.....4 Don‘t know.....98	Government Clinic/hospital Health extension worker…….1 Retail shop Pharmacy…….2 Workplace……3 Other (specify)_____....4 Don‘t know…….98	Government Clinic/hospital Health extension worker……1 Retail shop Pharmacy…….2 Workplace……...3 Other (specify.....4 Don‘t know…….98	
Q206	Did you purchase the net?	YES.....1 NO.....2 Not sure..... 8	YES.....1 NO.....2 Not sure..... 8	YES.....1 NO.....2 Not sure..... 8 →	skip to 208

Q207	How much did you pay for the net when it was purchased?	_____ birr	_____ birr	_____ birr	
Q208	Did anyone sleep under the mosquito net last night?	Yes…….1 No..……...2 Not sure……8	Yes…….1 No..……...2 Not sure……8	Yes…….1 No..……...2 Not sure……8	**Skip to Q211**
Q209	Who slept under this mosquito net last night?	Individual ID 1. _____ 2. _____ 3. _____ 4. _____	Individual ID 1. _____ 2. _____ 3. _____ 4. _____	Individual ID 1_____ 2_____ 3_____ 4_____	
Q210	Why did no-one sleep under this mosquito net last night?	No malaria…….. 1 No nuisance/insects… 2 No space for net …….3 Irritation ……4 Suffocation / too hot ….5 Difficult hanging net ….6 Shape ……..7 Absence from home …..8 Other..... 9 Don‘t know…….....98	No malaria……. 1 No nuisance/insects.. 2 No space for net ….3 Irritation ……4 Suffocation / too hot ..5 Difficult hanging net ..6 Shape ……..7 Absence from home ..8 Other..... 9 Don‘t know…….98	No malaria….. 1 No nuisance/insects.. 2 No space for net …3 Irritation ……4 Suffocation / too hot ...5 Difficult hanging net ..6 Shape ……..7 Absence from home…..8 Other..... 9 Don‘t know…….98	
Q211	Has your house ever been sprayed with insecticide for malaria prevention by spraymen from the District Health Office?			Yes…….1 No..……...2 Not sure..……8	**Skip to Q215**
Q212	How many months ago was your house sprayed? ***(If less than one month, record 0)***			Months ago [___/___] Not sure…..8	
Q213	At any time in the past 12 months, have the walls in your dwelling been plastered or painted?			Yes..... ...1 No..... 2	
Q214	How many months ago were the walls plastered or painted? *If less than one month, record 0*.			MONTHS AGO , _____ _____	
Q215	Was there death of family member in the last one year?	Yes…….1 No..……...2	→ When did it occur? _____months ago	Sex Male……1 Female…2	Age _____ **Year/Month**

Health service seeking and utilization									
ID	**Q215**	**Q216**	**Q217**	**Q218**	**Q219**	**Q220**	**Q221**	**Q222**	**Q223**
	Have any of your family members faced any health problem during the **last 2** months? **Yes……1** **No…….2 ► Q221**	What was the sickness/ injury faced? Malaria…….1 Diarrhea……..2 Injury……..3 Dental……..4 Opthalmic……5 Skin disease……6 Ear/nose/throt (ENT)….7 Tuberclosis…….8 Other (specify)_____	For how many days were he/she absent from usual activity due to the health problem during the **last 2** months?	Has he/she received medical assistance or consulted from health institutions or traditional healers during the **last 2** months? **Yes……1** **No…….2 ► Q220**	Where did he/she receive or consult medical assistance primarily? Hospital.....1 Health center.....2 Health post.....3 Private Clinics.....4 Private Pharmacy.....5 Traditional healer.....6 Religious/spiritual.....7 Other (specify)……..8	What was the main reason for he/she not to consult health institutions/ traditional healer during the **last 2** months? Lack of money.....1 Expensive.....2 Too far .....3 Do not believe in medicine.....4 Lack of health professional.....5 Poor quality/ service.....6 Did not require medical assistance. 7 Other (specify).....8	Have any of your family member consulted any medical assistance during the **last 12** months? (Regardless of whether sick or not)? **Yes……1** **No…….2**	How many times have he/she consulted any medical assistance during the **last 12** months?	Has member of your family been ill with a fever at any time in the last 7days? **Yes……1** **No…….2**
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									

Addis Ababa University, College Health Sciences, School of Public Health
Questionnaire for household costs of malaria
MalTrials

Introduction

Good Morning/Good Afternoon. My name is _____. I am working for a research team from Addis Ababa University School of Public Health. This team is conducting a study on "Cost of malaria to the patient and their family". This study is very helpful to estimate the economic cost of malaria. The ultimate aim is to design appropriate strategies in local and national level by different stakeholders.

You are selected for this study based on a voluntary basis. You have full right not to participate in this study, however we encourage you to participate since your responses are very crucial to look at the cost of malaria.

During our stay we will ask you some questions. These questions include socio-demographic variables and cost information. In this interview, there are no procedures and questions that may harm or give you a feeling of discomfort. We would like to assure you that your personal identifications will not be written on the questionnaire. Your response will be kept confidential. All records of this study will be kept in a locked cabinet. If the findings of this study are ever presented in a workshop or seminar your name or other personal identification will not be mentioned.

Our interview may take around 30-40 minutes. If you feel discomfort or want to withdraw in the middle of our interview, it is your right to discontinue. It is also your right not to give a response to some of our questions if you don't want to respond. Do you have any questions?

If you want to ask questions for clarification about the study later on; you can contact Mr. Alemayehu Desalegne, by phone numbers 09-13-57-95-07

May I have your permission to proceed to the interview?

Yes …… (Continue)

No …… (Stop)

Household Identification	**Interviewer Identification**	**Supervisor identification**
Questionnaire ID:	Name:	Name:
Region:	Date: / /	Date: / /
Woreda:	Signature	Signature:
Kebele:		

Section I: Questionnaire for household costs

Household roster

1	2	3	4	5	6	7	8	9	10	11
	Name	**Relation to household head** 1. head 2.Wife or husband 3. Child; 4. Relative 5. Maid; 6. Other	**Age**	**Sex** Male------1 Female---2	**Educational status** ***(6 years and above)*** **I=** Illiterate **RW=** Read and Write only If formal education, write the highest grade Completed	**Marital Status** 1.Maried 2.Living together 3.Divorced or separated 4.Widowed 5. Naver married/naver lived together;	**Occupation** ***(18 years and above)*** 1. Employed 2. House wife 3. Farmer 4. Day laborer 5. Trader 6. Fishery 7. Student 8. No job/dependent 9. Housemaid 10. Others	**Ethnicity** **Ethnicity** **1.Oromo** **2. Amhara** **3. Gurage** **4. Siltte** **5. Hadiya** **6. Other (Specify__)**	**Religion** **Religion** **1.Orthodox** **2.Muslim** **3.Protestant** **4.Other (Specify__)**	**Confirmed malaria by a health professional in the last two weeks** Yes---1 No----2
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										

Direct and Indirect cost

12	13	14	15	16	17
Which individual(s) have been ill with **malaria** in the last two weeks?	How many days ago did the fever start?	How severe was the fever?	Did they get better?	How long did the illness last?	What is the main activity of this individual (during this season)?
Use a separate line for each individual	*Write number of days.*	*Mild fever……..1 (loss of appetite, headache)* *Moderate fever.....2 (sitting down, tired)* *Severe fever……3 (fitting, convulsions)* *Other (specify…….4* *Don't know……..99*	*Yes……1* *Still ill....2* *Died…..3* *Don't know...99*	*Write number of days.* *Don't know..99*	*Farmer……..1* *Laborer……2* *Shopkeeper/Retail.....3* *Business……4* *Childcare……..5* *Student……..6* *Civil Servant……..7* *Child (Not studying)….8* *No Occupation…… 9* *Other (Specify)……10*
Name	*Days*	*Severity*	*Outcome*	*Duration of illness*	*Main activity*
1.					
2.					

18.1	18.2	18.3	18.4	18.5	18.6
For how many days were you/they **totally** unable to carry on your/their usual activities because of this illness over the last 2 weeks?	For how many days did you/ they go for usual activity while you feel sick but unable to work as usual because of this illness over the last 2 weeks?	By how much did your/their ability to work did decrease from the usual because of this illness over the last 2 weeks?	Is there anyone who worked on behalf of you/they for your/their usual duties while you/they were sick over the last 2 weeks?	Who is he/she?	What is the main activity of this individual (during this season)?
Write number of days. *If none, write… 0* *Don't know…99*	*Write number of days.* *If none, write… 0* *Don't know…99*	By more than two-third……1 By two-third……..2 By half……3 By one-fourth……4 Not that much……..5	*Yes…….1* *No……..2* *Don't know…99*	Family member, Individual code: _____ Your son……1 Wife/husband……2 Your brother/sister……..3 Your neighbour/friend……4 Colleague ……5 *Other (Specify)……6*	*Farmer……..1* *Laborer……2* *Shopkeeper/Retail.....3* *Business……4* *Childcare……..5* *Student……..6* *Civil Servant……..7* *Child (Not studying)….8* *No Occupation…… 9* *Other (Specify)……10*
Duration off work	*Days*				*Main activity*
1.					
2.					

19	20	21	22	23	24	25
Did you/they get treatment from someone (eg drug shop, clinic)	Why did you/they not get treatment from someone for this illness?	Where did they get treatment? I will read you a list, please say yes or no after each one. Did you get treatment from a:	Which is the **first** one where you sought care for the illness?	How many days after the beginning of the fever did you/they start taking treatment from this provider?	What was/were the most important reason/s for choosing this provider?	How far is this provider from here?
Yes ……1 *(Go to question 21)* *No ……. 2*	*Not severe enough….1* *Got better……2* *Not enough money…3* *Too far away……..4* *No transport…….5* *Family would not let me……6* *Other (Specify……..7*	*Public Hospital……1* *Private Hospital……..2* *Health center……..3* *Health post……..4* *Private Clinics……..5* *Private Pharmacy……..6* *Traditional healer……..7* *Religious/spiritual……8* *Other (specify)……..9*	*Use same code as in question 10.*	*Same day…0* *Next day…..1* *Day after next…2* *More than 2 days later, write the number of days later*	*Proximity……..1* *Good reputation…….2* *Inexpensive……..3* *Good personal experience……..4* *Qualification of staff……5* *Availability of drugs……6* *Relative/Friend works here……..7* *Can get treatment on credit……8* *Just to see ……..9* *Other (specify)…….10*	*Write answer in kilometers* *If less than 1km, write "<1km* *Don't know...99*
Treatment	*Reason no*	*Providers*	*First provider*	*Time to treat*	*Reasons for Provider Choice*	*Distance*
1.						
2.						

26	27	28		29	30	31
How did you travel to this provider?	How many people made the journey	How long did the journey take to go from your home to this provider?		How much in total did you pay for transport for the journey to and back from this provider	Who did you see at this facility?	Did you/person with the fever have to stay overnight at this facility? If, yes, how many nights
Walk……..1 *Cart……..2* *Bicycle……..3* *Motorcycle…….4* *Private car…….5* *Public taxi/bus…6* *Boat……..7* *Donkey/Horse….8* *Other (Specify)...9*		*Journey time*			*Doctor……..1* *Health Officer…….2* *Nurse……..3* *Nursing assistant…….4* *Pharmacist……5* *Health Extension Worker…6* *Shopkeeper……..7* *TBA……8* *Traditional Healer ……..9* *Other (Specify)……..10*	*Write number of nights If no overnight stay, write 0* *(Cost information is collected later)*
Transport	*Journey people*	*Journey time*		*Transport cost*	*Provider person*	*Overnight*
		Hours	*Minutes*			
1.						
2.						

32	33	34	35	36		37
Were you/the person with fever advised to have diagnostic test?	Which test?	How much did the test cost	What was the test result?	How much time did you spend waiting at this provider		Did you receive medicines at this facility or a prescription to obtain medicines from a pharmacy?
No advice, no test…….1 *No advice, but had test….2* *Advised but decline……3* *Advised and had test……4* *If no test, go to question 36*	*RDT……1* *Microscopy……2* *Both RDT and microscopy…3* *Don't know...99*	*If free or write "0"* *Don't' know……99*	*Positive……1* *Negative……..2* *Don't know…..3*			*Received medicine ……..1* *Received prescription……..2* *No, did not receive medicine or prescription……..3* *Don't know……..99* *If **no** medicine or prescription Go to question 43*
Diagnosis	*Test*	*Test cost*	*Test result*	*Wait*		
				Hours	*Minutes*	
1.						
2.						

38	39	40	41	42	43
I would like to ask you about the medicines. Please tell me what you received, how many and how much it costs. If you still have the medicines, please let me see them.					Did the provider recommend any drug? (Whether or not you took his/her advice)
Drug codes (for question 38-42) *Chloroquine ……1* *Amodiaquine ……..2* *SP ……3* *Quinine ……..4* *Artesunate alone……..5* *Artemether alone……6* *Dihyrodartemisinin alone……7*	*Co-artem……8* *Duocotexcin……9* *Artesunate-Amodiaquine……..10* *Artesunate-SP……11*			*Amoxicillin……..12* *Penicillin……13* *Cotrimoxazole……14* *Paracetemol……15* *Other (specify) ……..16* *Don't know……99*	*Use drug codes* *If no recommendation write 0*
Use drug code above	*Tablet ……..1* *Syrup……..2* *Injection……3* *Infusion……4*	*Quantity bought* *If tablets came in a box write the number of tablets in the box* *Don't know…….99*	*Duration* *Write number of days drug was taken*	*Cost* *If only total cost of drugs is known then write "Total" and the cost* *Don't know……99*	
Drug code	*Formulation code*	*Drug quantity*	*Drug duration*	*Drug cost*	*Recommendation*
1. a.					
b					
c					
d					
2. a					
b					
c					
d					

44	**45**	**46**		**47**	**48**
In addition to the cost of drugs and any tests that you have already told me about, did you have to pay for the consultation?	Did you pay for special food before or during the visit to this provider? If so how much?	Are there any other costs related to this provider, that you have not already mentioned		Were you asked by the health care provider to return for more treatment / check-up?	How many more visits did you make to this health care provider?
Ask in cash or in kind (convert later, if necessary) If free, write 0	*Ask in cash or in kind (convert later, if necessary) If none, write 0*	*Write what was paid for and the cost* *Medical supplies……1* ***Inpatient stay……..2*** *Other investigations…..3* *Other (specify)…….4* *None……5*		*Yes ……..1 No…….2*	*Write number of additional visits If none, write 0*
Consultation cost	Food costs	*Other cost*		*Follow up Advised*	*Return Visits*
		Item code	*Cost*		
1.					
2.					

Who pays?

51	52	53	54	55
Did your household pay for everything or were some of the costs covered by insurance or outside assistance	What was the source of support from outside the household	How much did you receive from outside the household?	Did you have enough cash or did you have to borrow money or sell something to get the necessary cash	How much did you have to borrow?
Household paid for everything ……..1 *(Go to question 54)* *Some additional support ……. 2* *(Go to question 52)*	*Insurance….1* *Employer…..2* *Charity……..3* *Equib……..4* *Other _____5* *Specify*	*Write amount*	*Sufficient cash……..1* *Borrowed from friend/relative……..2* *Borrowed from the health care provider…3* *Sold livestock……..4* *Sold property……..5* *Sold labour……6*	*Write amount borrowed*
Outside	Outside source	Outside Amount		
1				
2.				

Section II: Socioeconomic status

Q201	Does your household have: Electricity? A watch? A radio? A television? A mobile telephone? A non-mobile telephone? A refrigerator? A table? A chair? A bed? An electric mitad? A kerosene lamp/pressure lamp?	Yes No Electricity……1 2 Watch……1 2 Radio……1 2 Television……1 2 Mobile Telephone……1 2 Non-Mobile Telephone……1 2 Refrigerator……1 2 Table……1 2 Chair……1 2 Bed……1 2 Electric Mitad……1 2 Kerosene/Pressure Lamp……1 2	
Q202	Do you have a separate room which is used as a kitchen?	Yes……1 No……2	
Q203	Main material of the floor. ***(Record observation)***	Earth/Dung ……1 Ceramic Tiles……2 Cement…… . . . . ……3 Other……96 Specify_____	
Q204	Main material of the roof ***(Record observation)***	Thatch/Leaf……1 Corrugated Iron . . . . . ……2 Cement/Concrete . . . . . …… . . . . 3 Other……96 (Specify)_____	
Q205	Main material of the exterior wall. ***(Record observation)***	No wall……1 Wood……2 Wood with mud……3 Wood with mud and cement……4 Cement blocks……5 Other……96 (Specify)_____	
Q206	How many rooms in this household are used for sleeping?	Number of rooms[__|__]	
Q207	How many sleeping spaces such as mats, rugs, mattresses or beds are used in this household?		
Q208	Does any member of this household own: A bicycle? A motorcycle? An animal-drawn cart? A car or truck?	Yes No Bicycle……1 2 Motorcycle……1 2 Animal-drawn cart……1 2 Car/truck……1 2	
Q209	Does any member of this household own any land that can be used for agriculture?	Yes……1 No……2	**Skip to Q211**
Q210	How many (LOCAL UNITS) of agricultural land do members of this household own? ***(If unknown, enter 98)***	Local units [___|___] Specify the local unit_____	

Q211	Does this household own any livestock, herds, or farm animals?	Yes……1 No……2	**Skip to Q213**
Q212	How many of the following animals does this household own? Milk cows, oxen, or bulls? Horses, donkeys, or mules? Goats? Sheep? Chickens? ***(If unknown, enter 98)***	Milk cows, oxen, or bulls------ | | | Horses, donkeys, or mules----- | | | Goats---------- | | | Sheep---------- | | | Chickens---------- | | |	
Q213	Does any member of this household have an account with a bank/credit association/micro finance?	Yes……1 No……2	
Q214	What is the main source of drinking water for members of your household? ***(Do not read out Responses)***	**Piped (Tap)** Piped into dwelling……1 Piped into compound……2 Piped outside compound….3 Covered Well……4 Protected Spring……5 **Open Well/Spring** Open Well……6 Open Spring……7 **Surface Water** River……8 Pond/Lake/Dam……9 Rainwater……10 Other……11 Specify_____	
Q215	What kind of toilet facility do most members of your household use? ***(observe latrine)***	Flush toilet……1 Pit latrine/traditional pit toilet……2 Ventilated improved pit latrine (VIP) …3 No facility/Bush/Field… ……4 Other……5 Other(Specify)_____	
Q216	Do you share this facility with other households?	Yes……1 No……2	

Thank you so much!!!

ANNEX 3
Form AAUMF 03-008

IRB's Decision

Meeting No: 052/2013 Date (D/M/Y): July 03/2013
Protocol number: 024/13/ SPH Assigned No.....

Protocol Title: Combining indoor residual spraying & long-lasting insecticidal nets for malaria prevention: a cluster randomized controlled trial in Ethiopia	
Principal Investigators:	Dr. Wakgari Deressa
Institute:	AAU-CHS School of Public Health
Elements Reviewed (AAUMF 01-008)	☑ Attached ☐ Not attached
Review of Revised Application ☐ Yes ☐ No	Date of Previous review:
Decision of the meeting:	☑ **Approved** ☐ Approved with Recommendation ☐ Resubmission ☐ Disapproved

I. Elements approved- 1. Protocol Version No. .....
2. Protocol Version Date.....
3. Informed consent Version No. .....
4. Informed Consent Version Date .....

II. Obligations of the PI-
1. Should comply with the standard international & national scientific and ethical guidelines
2. All amendments and changes made in protocol and consent form needs IRB approval
3. The PI should report SAE within 10 days of the event
4. End of the study, including manuscripts and thesis works should be reported to the IRB

III. **TO ESTM** ☑

Institution Review Board (IRB) Approval: Period from **July 15, 2013** to **July 15, 2015**

Follow up report expected in
3 Months ___ 6 months ___ 9 months ✓ one year ___

Chairperson, IRB
Dr. Yimtubezenash W/Amanuel
Signature
Date: 15/07/13

Institutional Review Board Office (IRB) Faculty of Medicine ADDIS ABABA UNIVERSITY

Associate Director of Research and Technology Transfer
Signature
Date 28/07/13

College of Health Science Addis Ababa University

በኢትዮጵያ ፌዴራላዊ ዴሞክራሲያዊ ሪፐብሊክ
የሳይንስና ቴክኖሎጂ ሚኒስቴር
The Federal Democratic Republic of Ethiopia
Ministry of Science and Technology

ቁጥር Ref. No. 3,10/446/06

ቀን Date 03/03/06

To: Addis Ababa University, ~~Aklilu Lemma Institute~~ School of Public Health
Addis Ababa

Re: combining indoor residual spraying and long lasting insecticidal net for malaria prevention: a cluster randomized controlled trials in Ethiopia

Dear sir/Mr./s/Dr.

The National Research Ethics Review committee (NRERC) has reviewed the aforementioned project protocol in an expedited manner. We are writing to advise you that NRERC has granted

Full Approval

To the above named project, for a period of **one year (October 30, 2013- October 29, 2014).** All your most recently submitted documents have been approved for use in this study. The study should comply with the standard international and national scientific and ethical guidelines. Any change to the approved protocol or consent material must be reviewed and approved through the amendment process prior to its implementation. In addition, any adverse or unanticipated events should be reported within 24-48 hours to the NRERC. Please ensure that you submit progress report once in a four month and annual renewal application 30 days prior to the expiry date.

We, therefore, request your esteemed organization to ensure the commencement and conduct of the study accordingly and wish for the successful completion of the project.

With regards,

Yohannes Sitotaw

Secretary of NRERC

Cc _ Dr. Wakgari Deressa (PI)

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You may Contact

ፖ.ሳ.ቁ. P.O.Box 2490
አዲስ አበባ ኢትዮጵያ Addis Ababa, Ethiopia
E-mail most@ethionet.et
ስልክ Tel. 251-011-4-674353
Web site:-http://www.most.gov.et
ፋክስ Fax +251-011-4-66 02 41

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Officer:	Telephone:	Our date:	Our reference
REK vest	Øyvind Straume	55978497	01.07.2013	2013/986/REK vest
			Your date:	Deres referanse:
			28.05.2013	

Bernt Lindtjørn
Postboks 7804

2013/986 Vil en kombinasjon av myggnett og innendørs sprøyting med insektmidler bedre forebyggelsen av malaria i Etiopia?
Combining indoor residual spraying and long-lasting insecticidal nets for malaria prevention: a cluster randomized controlled trial in Ethiopia.

Body responsible for the research: University in Bergen
Project Manager: Bernt Lindtjørn

With reference to your application about abovementioned project. The Regional Committee for Medical and Health Research Ethics, Western Norway (REK Vest) reviewed the application in the meeting, 20.06.2013 , pursuant to The Health Research Act § 10.

Description of the project
This study aims to assess whether the combined use of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) increases protection against malaria. The proposal is to conduct a cluster randomised controlled trial in Ethiopia to measure malaria incidence and transmission, insecticide resistance, and to assess whether mosquito nets result in an age shift in malaria morbidity before and after trials. The intervention will consist of four "arms": (IRS+LLINs, LLINs alone, IRS alone and control (routine practice)). The study will include up to 10 000 participants.

The Committee`s considerations

Application/Study Protocol
The Committee finds the project to be of great scientific and social importance and relevance for a major health burden in large regions of the world.

Is randomisation justifiable?
The Committee discussed at some length whether or not it was acceptable to include a control group which receives no intervention, other than routine practice, in the project. According to the Health Research Act, research must be based on respect for the research participants' human rights and dignity. The participants' welfare and integrity shall have priority over scientific and social interests. From that perspective; a randomisation where 1/4 of the participants receive a considerable poorer treatment (routine practice) is highly problematic.

Furthermore the Committee debated the scientific value of the inclusion of the control group. The applicant points to Pinder and colleagues which estimates 50% incidence reduction from LLINs and a 75% incidence reduction from IRS+LLINs. Quite clearly IRS and LLIN will have effect, compared to nothing, so how is it justified to include the control group?

In the end the Committee decided to allow the study with all four arms and emphasises that every participant will have access to weekly visits, early diagnosis, transportation and state of the art treatment for malaria. The paradox the Committee pointed out is that if 1/4 of the participants were forced not to attend the study they would actually be put in a worse situation ("routine practice", with no particular follow-up) than as participants in the control group. The Committee also emphasised that from a scientific point of view, inclusion of the control group allows for a more reliable comparison between groups. The protocol also includes environmental risk factors such as availability of and distance to mosquito breeding sites, temperature and rainfall, which is relevant for comparison between groups, the control group included. The Committee accepts the applicant`s argument that a wide study design would make the results more applicable in countries with resource limitations.

Furthermore the Committee emphasises that a single project were one would follow-up the control group only, in itself probably would have been approved.

Finally the Committee stresses that no participants in the control group in any way can be impeded of getting hold of mosquito protection from other sources.

Consent
The Committee notes that consent might be problematic if one member of the family household does not wish to attend. Any reluctance to attend by any family member must be respected.

Assessment by local ethics Committee
REC Western Norway notes that the project will be submitted to the Institutional Review Board of the College og Health Sciences at Addis Ababa University, Ethiopia. REC Western Norway asks the Review Board to carefully consider and assess the problematic aspects discussed in the chapter above.

Information
The Committee recommends using the Norwegian REC`s template in English. It can be found at helseforskning.etikkom.no under "deadlines and forms" and "Templates for Participation Information and Consent."

Timeframe
The project will end 31.12.2016 and all data will then be anonymised.

Decision
REC Western Norway approves the project in accordance with the submitted application.

Final Report and Amendments
The Project Manager shall submit a final report to the REC Western Norway no later than 01.07.2017., according to Health Research Act § 12. The Project Manager shall submit an application of approval to REC Western Norway if there is significant changes in the project protocol, according to Health Research Act § 11.

Appeal
The Project Manager may appeal the committee's decision, see the Administration Act § 28. The appeal must be sent to the REC Western Norway within three weeks of receiving this letter. If the decision is upheld by REC Western Norway, the appeal will be forwarded to the National Research Ethics Committee for Medical and Health Research for a final assessment.

Med vennlig hilsen

Jon Lekven
Committee chairman

Øyvind Straume
Senior Executive Officer

Kopi til: postmottak@uib.no

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የሳይንስና ቴክኖሎጂ ሚኒስቴር
The Federal Democratic Republic of Ethiopia
Ministry of Science and Technology

ቁጥር 3:10/837/07
Ref. No.
ቀን 21/5/07
Date

To: Addis Ababa University, College of Health Sciences, and Ethics Committee

Addis Ababa

Re: Combining indoor residual spraying and long lasting insecticidal net for malaria prevention: a cluster randomized controlled trials in Ethiopia.

Dear Sir/Madam /Mr./Mrs./Dr.

We are writing this letter in reference to your renewal request letter dated January 20, 2015.

After having in depth review of your request, the National Research Ethics Review Committee has accepted your renewal request for one year from January 27, 2015 to January 26, 2016. This is, therefore, to notify that the ethical approval is renewed and your group can proceed in accordance to the latest approved document. Please ensure that you submit a biannual report and an annual renewal application 30 days prior to expire date. We are confident that you as PI of the project and your esteemed organization will monitor the ethical implication of the project as it is stipulated in the latest approved document.

With regards,

Yohannes Sitotaw
Secretary of NRERC

CC: _ Chairperson, NRERC

_ **Dr. Wakgari Deressa** (PI)

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ፖ.ሳ.ቁ.
P.O.Box 2490

አዲስ አበባ ኢትዮጵያ
Addis Ababa, Ethiopia
E-mail most@ethionet.et

ስልክ
Tel. 251-011-4-674353
Web site:-http://www.most.gov.et

ፋክስ
Fax +251-011-4-66 02 41

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የሳይንስና ቴክኖሎጂ ሚኒስቴር
The Federal Democratic Republic of Ethiopia
Ministry of Science and Technology

ቁጥር Ref. No. 3.10/085/2016

ቀን Date Jan 5, 2016

To: Addis Ababa University, Collage of Health Science Ethics Committee

Addis Ababa

Re: Combining indoor residual spraying & long-lasting insecticidal nets for malaria prevention: a cluster randomized controlled trail in Ethiopia

Dear Sir/Madam /Mr./Mrs./Dr.

We are writing this letter in reference to your Amendment request letter dated Dec 8, 2015.

After having in depth review of your request, the National Research Ethics Review Committee has accepted your renewal request for one year from **(January 5, 2016- January 4, 2017).**This is, therefore, to notify that the ethical approval is renewed and your group can proceed in accordance to the latest approved document. Please ensure that you submit a biannual report and an annual renewal application 30 days prior to expire date. We are confident that you as PI of the project and your esteemed organization will monitor the ethical implication of the project as it is stipulated in the latest approved document.

With regards,

Yohannes Sitotaw
Secretary of NRERC

CC: _ Chairperson, NRERC

_Dr. Wakgari Deressa (PI)

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ስልክ Tel. 251-011-4-674353
Web site:-http://www.most.gov.et
ፋክስ Fax +251-011-4-66 02 41