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Malaria Control and Elimination in Africa: Why are Some Countries Doing Better than Others?

THESIS

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MASTER OF SCIENCE

in Biomedical and Translational Science

by

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2018

DEDICATION

To

Youth

My Families and Friends

Faith and Hope in Science

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ABSTRACT OF THE THESIS

Malaria Control and Elimination in Africa:

Why are Some Countries Doing Better than Others?

By

Xiaoming Wang

Master of Science in Biomedical and Translational Science

University of California, Irvine, 2018

Professor Sheldon Greenfield, Chair

Objectives: To determine social, economic, biological and environmental factors critical to malaria control effectiveness in African countries that are with contrasting responses to the malaria control and elimination efforts, and use this information to inform the development of improved malaria control strategies in Africa.

Methods: A systematic analysis was conducted using longitudinally collected data from publically available data sources for the period of 2000 and 2016, for 8 African countries with contrasting malaria incidence dynamics. Single- and multivariable linear regression analyses were performed to determine the impact of various risk factors on malaria incidence. The risk factors included autocorrelation with a one year time lag, study

country, and economic status, internal and external malaria control budgets, bednet coverage, indoor residual spray coverage, and insecticide resistance status.

Results: Malaria incidence exhibited highly significant autocorrelation. *Per capita* government funding for malaria control and insecticide resistance were the two significant factors correlating with malaria incidence.

Conclusions: This study indicates the significance of malaria control investment from African countries themselves and insecticide resistance management in malaria control and elimination in Africa.

Key Words: Malaria incidence, National government funding, Malaria control effectiveness, Insecticide resistance

INTRODUCTION

1. Malaria Burden

Malaria has been a devastating public health problem worldwide over centuries[2, 3]. It is serious and life-threatening, but a preventable and treatable disease caused by *Plasmodium* parasites and transmitted by female *Anopheles* mosquitoes via blood feeding[4]. A total of 216 million malaria cases and 445, 000 malaria deaths were reported from 91 countries globally in 2016, an increase of 5 million cases over 2015 according to World Health Organization[5]. Malaria remains one of the deadliest diseases, and nearly 50% population in the world are at risk for malaria infection despite of intensive control efforts[6].

African region carries the heaviest malaria burden with an estimate of 194 million clinical cases and 407, 000 deaths (91.5%) in 2016, about 90% of all malaria-induced morbidities and 92% of malaria mortalities in the world. Children, infants and pregnant women are particularly vulnerable populations. Malaria has been a major or leading cause of mortality among pre-school (<5 years) and school children, although there was a near 50% decline of malaria deaths in these age groups during the past 5 years[6-8]. Malaria in pregnancy is a main risk factor for fetus mortality and poor birth outcome due to lower immunity and medicine contraindications of pregnant women[9]. HIV/AIDS patients, migrants, mobile populations and travelers also are high-risk populations[10]. Malaria also induces a major economic burden as a consequence of increasing healthcare costs, decreasing workforce and associated poverty in addition to life losses[11].

There are many possible reasons why Africa is in a malaria disaster. For example, the tropical and subtropical environments and warm and humid weather conditions of the sub-Saharan African countries are particularly suitable for the survival and development of malaria mosquito vectors and parasites[12]. In some countries malaria transmission occurs seasonally but in most countries transmission can occur all year around[13]. Insufficient protection and prevention also contribute to the high malaria morbidity[14]. Furthermore, lack of resources and political instability negatively affect the malaria control activities[15].

2. Malaria Control and Elimination

There have been unprecedented investments in malaria control and elimination efforts globally since 2000. Governments of the malaria endemic countries and developed countries (e.g., United States and WHO) and non-governmental organizations (e.g., The World Bank, Global Fund and Bill & Melinda Gates Foundation) have devoted billions of dollars to fund malaria control and elimination. Various control efforts, initiatives and research agendas have been developed to facilitate the malaria elimination and eradication efforts[16, 17]. Related researches are being conducted to develop new effective tools[6, 18]. Important malaria control techniques, testing methods, prevention and treatment therapies have been developed, adopted or delivered. Insecticide treated nets (ITNs) and indoor residual spraying (IRS) are the most common and efficient method for malaria control[5]. ITNs and treatment (Artemisinin-based combination therapy, ACT) are distributed free of charge, malaria diagnosis (Rapid Diagnostic Test, RDTs) and prevention (Intermittent preventive treatment in pregnancy, IPTp) are widely used in most African malaria endemic countries[5, 19, 20], but malaria burden remains high in the sub-Saharan African countries.

Scale-up of malaria control and elimination interventions has led a significant reduction in the number of malaria cases and deaths in the past 15 years. Between 2000 and 2015, the global malaria mobility and morbidity declined by 37% and 60%, respectively[1]. The success of malaria control has inspired the goal of malaria elimination and eradication. Steps and phases for malaria control, elimination and eradication are shown in Figure 1. Countries with zero indigenous cases for more than 3 consecutive years are eligible to request malaria free certification from WHO. Since 2000, 17 countries and territories had no indigenous malaria cases or endemic malaria, 2 were certified as malaria free, and 21 with the potential to eliminate malaria by year 2020 (pre-elimination)[1, 6]. In spite of the fact that malaria incidence and mortality rates are declining globally these years, the decline rates are lowering and some regions are even experiencing increasing or re-emergent malaria[5].

3. Malaria Inequality in Africa

Although the overall malaria burden is decreasing worldwide, the magnitude of reduction and current malaria burden vary greatly among countries and regions. For example, of the 91 countries with indigenous malaria cases in 2016, the African region (176 million, 90%) harbored the most malaria cases, followed by South-east Asia (10.9 million, 7%) and Eastern Mediterranean Regions (3.6 million, 2%)[6]. Many countries exhibited an increased trend of malaria burden: 16 countries showing a >20% increase in total malaria cases in 2016 over 2015[5].

In sub-Saharan Africa, there were 4 countries with > 20% decrease in malaria case and 8 with increased number of cases from 2015 to 2016 (Figure 2). The malaria incidence differences among countries and regions represent different stages on the malaria

elimination path. Morocco was certified malaria free in 2010 after maintaining zero case of malaria for more than 3 years since 2008[21]. Algeria and Egypt are at malaria pre-elimination stage. According to World Malaria Report 2017[5], 6 countries (Algeria, Botswana, Cape Verde, Comoros, South Africa and Swaziland) in Africa have been identified as "eliminating countries by 2020 (E-2020)". Furthermore, malaria incidence in Africa shows endemicity differences across the regions. West, Central and East African countries showed higher malaria incidence than the Northern Africa. Several countries in Southern Africa show low malaria endemicity (e.g., Swaziland and Botswana) whereas most countries exhibit high disease endemicity. The malaria incidence varies across African countries, and it's important to explore the malaria transmission pattern and why some countries are doing better than others in malaria control and elimination.

4. Mechanisms of Differential Responses to Malaria Interventions

4.1 Social and Economic Factors

The global malaria distribution shows an apparent correlation between malaria and poverty[22]. Gross domestic product (GDP) and related productivity, costs of malaria control, knowledge, attitude and practice of malaria prevention and treatment, culture, human behavior, human migration and policy adoption may all affect malaria transmission[23-26]. "Social vulnerability" has been found to be an important risk factor to malaria and other vector-borne diseases (VBD) by leading to a larger high risk population with poor access to malaria prevention and control tools[27, 28]. Multiple social and economic factors, such as GDP, malaria funds, education and culture etc., are always taken into consideration in malaria intervention.

4.2 Entomological and Ecological Factors

The ability of *Anopheles* mosquito to develop and reproduce is another key determinant for malaria transmission. ITNs and IRS are the first-line malaria prevention and control tools[29]. During the past decade, malaria vector behavioral changes [30-32] (e.g., blood feeding sources and resting time change, etc.) due to selection pressure have resulted in increased outdoor transmission[33]. In addition, mosquito population becomes increasingly resistant to insecticides[34].

Because mosquito development and reproduction are contingent on suitable temperature and availability of breeding habitats, mosquito distribution is strongly limited by climate conditions and subsequently, malaria endemicity also is affected by climate change[35]. Environmental modifications such as land use and land coverage change[36, 37], dam constructions[38] , urbanization[39] and other environmental factors were reported significantly related to changes in malaria transmission.

4.3 Epidemiological Factors

Access to antimalarial drugs and therapy effectiveness are important to the wellbeing of malaria patients, but also to malaria transmission as lack of access to antimalarial drugs and treatment failure may increase the size of malaria reservoirs who can then contribute to new transmission. Children and pregnant women are the most vulnerable populations[40-42], so delivery of treatment to these most vulnerable populations is critical[43]. Obviously, anti-malarial drug resistance represents a major obstacle to malaria control as currently observed in Southeast Asia, and a challenging threat to Africa, although no drug resistance has been reported yet.

5. Gaps in Knowledge

Intensive efforts have been in place for malaria control and elimination in African countries in the past 15 years. These include internal and external fund investments, introduction and scale-up of new malaria control tools such as long-lasting nets and artemisinin-combination therapy, rapid diagnosis kits and other focal interventions such as mass drug administration and mosquito larval control (Appendix 1). As discussed above, there is a large variability among African countries in the response to these intervention efforts. There are many potential reasons for this, but a comprehensive and systematic analysis is lacking. Analysis of the mechanisms for treatment success or failure would provide valuable information to guide future malaria control and elimination effort in Africa.

6. Objectives and Significance

In this thesis I want to address one key question: **why are some countries doing better than others in malaria control and elimination in Africa**? To answer this question, I examined the relation between malaria morbidity and various risk factors (social, economic, entomological and intervention measures) based on publically available data sources. I examined eight sub-Saharan African countries, representing the East, West, Central and Southern African regions. These eight countries also represent three clusters in terms of the malaria incidence trend in the past 16 years: increasing trend, sustained transmission and downward trend. The result of this study may shed light on the key steps that the society can take to enhance malaria control effectiveness.

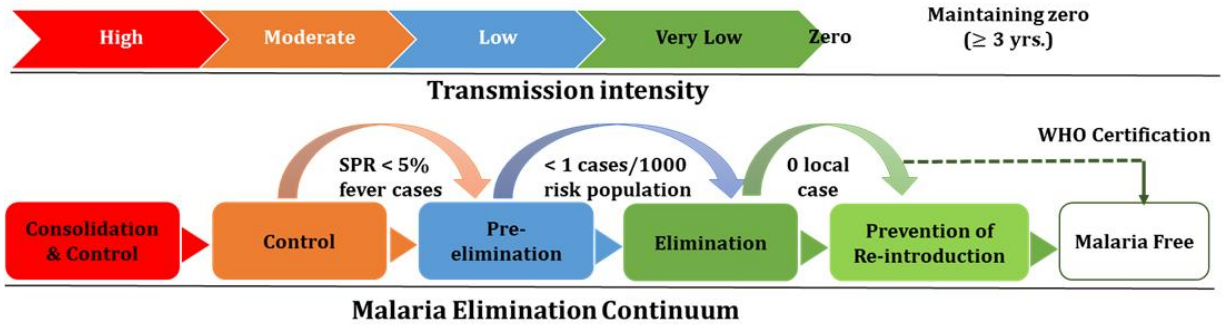

Figure 1. Malaria control to elimination continuum. SPR refers to slide positivity rate.

Adopted from: *A framework for malaria elimination 2017*[1].

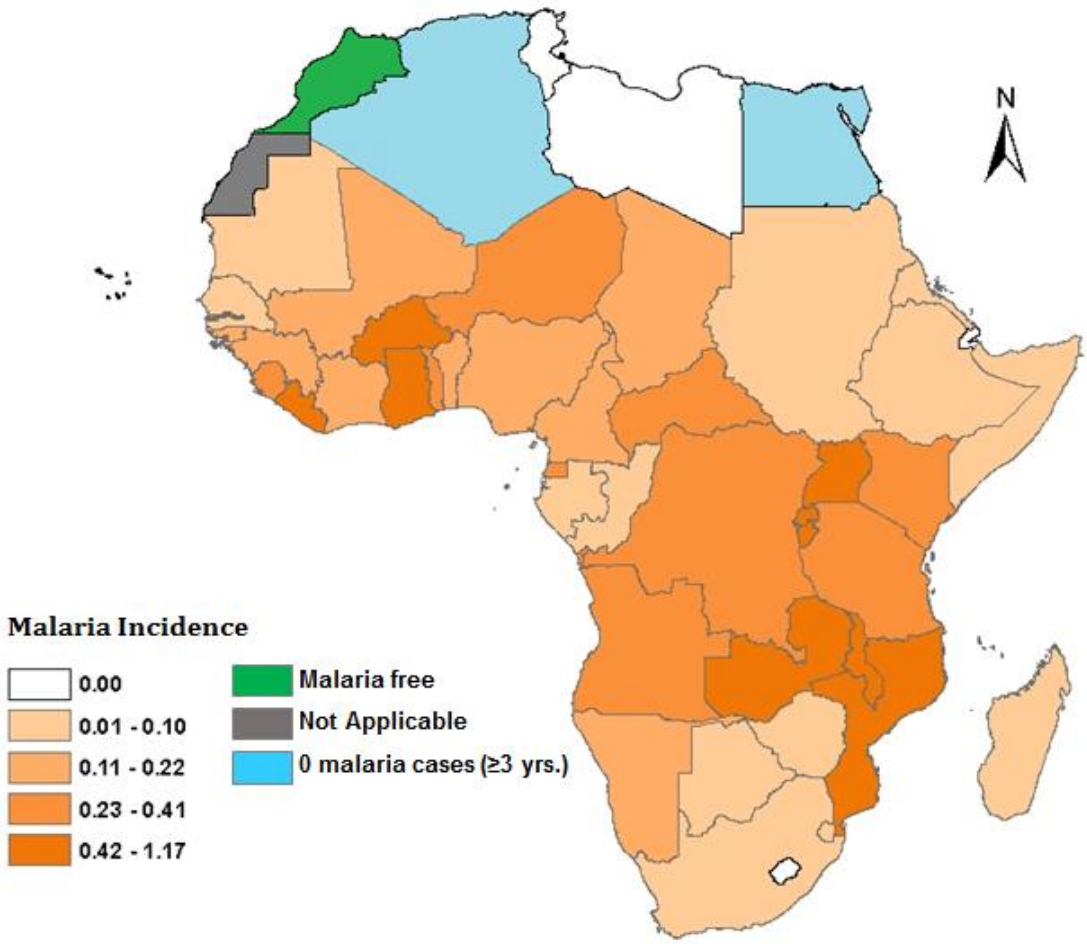

Figure 2. Malaria status in African countries in 2016. Countries with zero indigenous cases for more than 3 consecutive years are eligible to request malaria free certification from WHO. *Data Source: World Malaria Report 2017.*

CHAPTER 1. BACKGROUND

1. Malaria Epidemiology and Transmission

Malaria is a life-threatening mosquito-borne infectious disease, caused by *Plasmodium* parasites that are transmitted by infected female *Anopheles* mosquitoes through bites and blood feeding. There are four human malaria parasite species, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae,* and one zoonotic malaria parasite species, *Plasmodium knowlesi*[44]. *P. falciparum* is the most prevalent and also the deadliest species in Africa[45]. *P. vivax* is not common in most African countries, but it is often a dominant malaria species outside of Africa[46]. Malaria can cause febrile flu-like symptoms such as fever, headache and chills 1-2 weeks after infection, and may lead to severe illness or even death if not treated in time[4].

1.1 Transmission

There are two main hosts for malaria parasites: human and *Anopheles* mosquitoes. Malaria parasites develop from the gametocyte stage to the sporozoite stage in the mosquito midgut and salivary glands under appropriate temperature and humidity (*Sporogonic cycle*). Malaria parasites are transmitted and spread by female *Anopheles* mosquitoes via blood feeding. Sporozoites infect human liver cells, mature into schizonts, and then release merozoites to blood cells. Among the 5 malaria parasites, mature *P. vivax* and *P. ovale* parasites (hypnozoites) can persist in the liver for weeks to years and cause relapses (*Exo-erythrocytic cycle*). In the blood cells, parasites will develop from ring stage trophozoites to

schizonts, and release merozoites (*Erythrocytic cycle*). Blood stage parasites can cause clinical malaria manifestations[47].

1.2 Malaria Vectors

The main method of malaria prevention is vector control. The geographical distributions of dominant mosquito vector species vary greatly across countries. For example, in West African countries such as Ghana and Guinea, *An. gambiae* and *An. funestus* are dominant vector, whereas in East Africa such as Ethiopia, the dominant vector is *An. arabiensis*, but in Tanzania and Democratic Republic of the Congo the most important vector is *An. gambiae s.s..*[48]

1.3 Risk Populations

Malaria is a leading cause of illness and morbidity in Africa[49]. In malaria endemic regions, infants, children, pregnant women and patients with HIV/AIDs are most vulnerable to malaria disease [10]. Malaria infection can cause adverse maternal effects and is a risk to the fetus and newborn children[50]. Migrant workers tend to have high malaria risk as they often lack appropriate protection from mosquito biting [51].

1.4 Malaria Prevention, Diagnosis and Treatment[4]

ITNs and IRS are the first-line vector control tools for malaria. Antimalarial prophylaxis can be used for malaria prevention, especially for travelers. Microscopy or RDT is recommended for diagnostic testing of suspected malaria cases. ACT is regarded as the best available therapy for *P. falciparum* malaria, and chloroquine (CQ) is widely used for treating *P. vivax*[52].

2. Malaria Burden, Control and Elimination

The overall trend of malaria case incidence has declined since 2000, and malaria deaths have exhibited even larger reductions due to the scale up of RDT and ACT treatment, and improved knowledge from the residents (Figure 3). Despite significant reduction in malaria burden in the past 15 years, malaria in Africa is still high. According to the World Health Organization, nearly half of the population is at risk of malaria and 90% malaria cases occurred in sub-Saharan Africa. However, there are several African countries showing successful malaria control (Table 1): six countries aim to reach zero indigenous cases of malaria by 2020, and seven countries are projected to reduce case incidence by 20-40% and 2 by more than 40% by 2020. Why are some Africa countries more successful than others in malaria control?

3. Challenges in Malaria Control and Elimination in Africa

3.1 Malaria Vector Insecticide Resistance

Insecticide-based vector control through the use of LLINs and IRS represents the largest investment in malaria control in Africa and worldwide. Among the four classes of synthetic insecticides (pyrethroid, organochlorine, organophosphate and carbamate), pyrethroids are the only class approved by WHO for bednet impregnation[5, 53]. Scale-up of ITNs has resulted in the rapid increase and spread of pyrethroid resistance, which has hampered the effectiveness of the current malaria vector control tools[54]. Resistance to organochlorine (mainly DDT), carbamate (e.g., Propoxur) and organophosphate (e.g., Malathion) is also widespread in African malaria vectors[55]. More than 60 countries reported resistance to at least one insecticide by 2016, and resistance to two or more insecticide classes in 50

countries globally[6]. Most malaria epidemic countries and regions in Africa reported resistance to at least one class of insecticide by 2016.

Understanding the mechanisms and impact of insecticide resistance on malaria is important to the monitoring and management of insecticide resistance[34, 56, 57]. WHO has recently released guideline for insecticide resistance and management in *Global Plan for Insecticide Resistance Management (GPIRM)*[58] and *Framework for Monitoring and Management of Insecticide Resistance in malaria vectors (IRMMPS)*[53]. New procedures for malaria vector insecticide resistance testing were released [59]. Important knowledge gaps include 1) how effective the LLINs and IRS deployed in the field in reducing malaria incidence, and 2) what are the alternative tools and approaches for malaria vector control in the face multiple-insecticide resistance?

3.2 Malaria Vector Behavioral Change and Malaria Residual Transmission

LLINs reduce human-mosquito contact rate and protect people sleeping under the nets. A number of recent studies show that vectors have evolved with behavioral changes from biting early and biting outdoors[60]. Anopheles mosquitoes may shift their resting site from indoor to outdoor, avoiding the contact with the insecticides sprayed inside the house wall [61]. There are reports that mosquitoes increase feeding on animals such as dogs, cows, poultry and livestock[62, 63].

LLINs and IRS target indoor mosquito vectors and malaria transmission. “Residual transmission”, defined as transmission that occurs despite high coverage of ITNs/LLINs and IRS[64], is increasingly common. Malaria residual transmission may result from mosquito

behavioral changes and ineffective nets or IRS due to insecticide resistance or degradation of net quality [65]. Residual transmission will render malaria control and elimination more difficult. There is an urgent need for new tools, approaches and strategies to control residual transmission[66].

3.3 Malaria Parasite Drug Resistance

Resistance to antimalarial drugs is another major threat to malaria control and elimination. Antimalarial drug resistance was first reported in 1950s with the widely used treatment, chloroquine (CQ). Resistance to sulfadoxine-pyrimethamine (SP) was reported a few years after its introduction, and now resistance is prevalent across Africa[67]. ACTs have been recommended as the first-line treatment for uncomplicated *P. falciparum* in nearly all malaria endemic countries since 2005[52]. Artemisinin resistance has been detected in the Great Mekong sub region in Asia in recent years[68, 69], but only several isolated cases of artemisinin resistance were reported in Africa[70, 71]. Resistance to the drugs used in the combination therapy is widespread in Africa[72, 73]. To date, *P. vivax* was found resistant to CQ in low prevalence in several Africa countries with endemic vivax malaria, but no resistance to ACTs was found[74, 75]. Despite apparently low artemisinin resistance in African malaria parasites, containing the emergence and spread of ACT resistance in Africa is of paramount importance [76].

4. Comparative Effectiveness Research in Malaria

Comparative effectiveness research (CER) is the generation, conduct and synthesis of evidence that compares interventions and strategies to prevent, diagnose, treat and monitor health conditions[77]. The main purpose is to translate research finding into valuable and

informed decision-making in health care[78]. Malaria risks and vector ecology vary across African countries, and the effectiveness of prevention, diagnosis and treatment methods may vary accordingly. Comparative effectiveness research for malaria is lacking.

5. Study Aims

The central aim of the study is to determine why some countries are doing better than others in malaria control and elimination in Africa. Eight sub-Saharan countries with four different classical malaria transmission patterns were selected in the study. **The specific aims are:**

1) To determine key social & economic factors that are related to malaria control effectiveness in Africa. The hypothesis is that malaria incidence is correlated with malaria control investment (external fund donation and internal government support), GDP *per capita* (economy level), policy adoption (LLINs/ITNs & IRS coverage, larviciding status) and case management (ACT coverage).

2) To determine key entomological factors related to the effectiveness of malaria control in Africa. The major hypothesis is that malaria incidence is correlated with malaria transmission stability and vector insecticide resistance.

3) To determine the overall malaria control effectiveness and the underlying reasons for contrasting response to malaria control and elimination efforts among African countries.

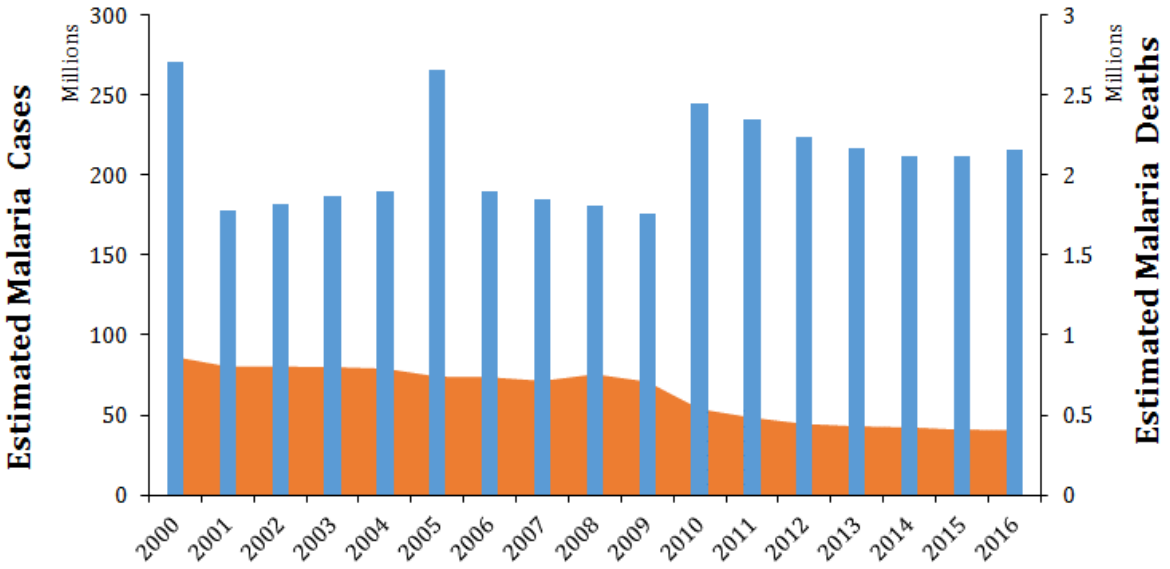

Figure 3. Dynamics of the estimated malaria cases and deaths in sub-Saharan region during the past 15 years. *Data Source: World Malaria Report 2013-2017*.

Table 1. Regional malaria trends and status in Africa by 2016. *Data Source: World Malaria Report 2017.*

Region	Control: Malaria incidence increase, 2010-2016	E-2020*	Projected to reduce incidence by ≥40% by 2020	Projected to reduce incidence by <40% by 2020
West Africa Malaria cases: 6.9 million in 2010 40.6 million in 2016	Mauritania; Guinea-Bissau; Gambia; Guinea; Togo; Liberia; Benin; Sierra Leone; Mali; Côte d'lvoire; Niger; Ghana; Burkina Faso; Nigeria	Algeria; Cabo Verde	Algeria	Cabo Verde; Senegal
Central Africa Malaria cases: 6.3 million in 2010 31.7 million in 2016	Gabon; Equatorial Guinea; Congo; Central African Republic; Chad; Cameroon; Angola; Burundi; Democratic Republic of the Congo			Sao Tome and Principe
East and Southern Africa Malaria cases: 13.5 million in 2010 41.5 million in 2016	United Republic of Tanzania (Zanzibar); South Sudan; Madagascar; Ethiopia; Kenya; Rwanda; Malawi; Zambia; United Republic of Tanzania (mainland); Mozambique; Uganda			Zimbabwe
East and Southern Africa (Low Transmission)** Malaria cases: 82, 000 in 2010 56, 000 in 2016		Botswana; Comoros; South Africa; Swaziland	Comoros	Botswana; South Africa; Eritrea

*E-2020: Countries that have the potential to reach zero indigenous cases of malaria by 2020.

** Countries with elimination programmes: Botswana, Comoros, Namibia, South Africa and Swaziland.

CHAPTER 2. METHODS

1. Data Sources and Cohort

This is a systematic review and analysis based on longitudinally collected data from public available data sources, including the World Health Organization (WHO) and the World Bank by individual African countries. The analysis covered the period of 2000-2016 when more complete malaria data are available. Specially, data on malaria incidence and mortality, risk population size, entomological factors (ITN coverage, IRS coverage, and insecticide resistance status), total malaria drug courses being delivered and funding on malaria control were obtained from the World Malaria Report 2017[5]. The World Malaria Report is a document published by the WHO and provides a comprehensive overview of progress in malaria control and elimination. It is published yearly and includes up-to-date assessment of malaria burden, progress towards global targets and elimination, related policies, financial investment, gaps and recommendations[5].

Social economic data such as Gross Domestic Product (GDP) and per-capital GDP, country human population size were obtained from the World Bank. The World Bank is a component of the World Bank Group, which is one of the world's largest sources of funding and knowledge for developing countries[79]. The World Bank provides free and open access to their comprehensive social economic data. GDP data were originally from World Bank national accounts data and OECD (Organisation for Economic Co-operation and

Development) National Accounts data files. GDP data are converted from domestic currencies.

For this analysis, I selected 8 African countries from East, West, Central and Southern Africa, representing three distinct pattern of malaria transmission dynamics: increasing (increasing malaria incidence in the past 5 years; Kenya, Ghana and Mozambique), sustained (no significant improvement in malaria incidence; Ethiopia, Zimbabwe and Guinea) and downward to pre-elimination (Botswana and Swaziland).

2. Data Collection

I used malaria incidence & mortality as dependent variables. Malaria deaths were reported malaria-induced deaths, including deaths due to malaria alone or due to co-infections with other diseases such as TB and HIV. Malaria cases were total suspected and confirmed indigenous cases. Because malaria diagnosis was often lacking in many health facilities in Africa, diagnosis based on malaria-like clinical symptoms was considered as "suspected" malaria, and this methods of measuring malaria morbidity is an acceptable method[5]. Malaria incidence and mortality were calculated using population size under risk, not the country's total population size. UN population and risk population (low risk population + high risk population) in 2009-2016 were extracted from World Malaria Report in corresponding years. Populations of each African country in years were obtained from The World Bank (http://www.worldbank.org/). Total malaria cases and deaths from 2000 to 2016 were extracted from World Malaria Report. Because the annual malaria report released by the WHO only covers a certain period, I extracted data from multiple reports.

Malaria case and death data were extracted from World Malaria Reports 2013, 2015, 2016 and 2017 (reference).

Malaria control budgets contributed by external donors and local governments in 2000-2016 were collected from the World Malaria Report. All the fund data were contributions targeted to malaria control and reported by donors in US dollars. The government funds were from national malaria control programs (NMCP). The main external donors included Global Fund (Data Source: The Global Fund), United States President's Malaria Initiative (PMI), United States Agency for International Development (USAID) (Source: www.foreignassistance.gov), United Kingdom of Great Britain and Northern Ireland government (UK) (Source: OECD Database), The World Bank (Source: OECD Database), United Nations Children's Fund (UNICEF), Non-Government Organizations (NGOs) (e.g. Wellcome Trust) and foundations (e.g. Bill & Melinda Gates Foundation). GDP amounts for each African country from 2000 to 2016 were sourced from The World Bank. GDP per capita were calculated based on the total populations of each country in current years. Antimalarial drug course distribution data, policy adoption (coverage of LLINs + ITNS and IRS) in 2000-2016 were also extracted from the World Malaria Report.

All the *shapefiles* (.dbf, .prj, .shp and .shx files) with administrative areas and boundaries used for generating malaria risk maps were downloaded from maplibrary.org for geographical analysis.

3. Measures

3.1 Study Sites

Eight sub-Saharan countries in four African regions were selected in this study (Figure 4):

1) West Africa: Ghana and Guinea. Both countries exhibit high transmission regions with an increasing malaria incidence over years.
2) East Africa: Ethiopia and Kenya. Both countries exhibit high transmission regions with an increasing malaria incidence.
3) South Africa: Botswana and Swaziland. Both countries have low transmission regions with a decreasing malaria incidence, approaching pre-elimination stage.
4) Central/South Africa: Mozambique and Zimbabwe, Both countries show low transmission regions with an increasing malaria incidence.

We selected these 8 countries because they represent three contrasting pattern of malaria incidence dynamics in Africa. In West Africa, 14 countries have been showing significant increases in malaria incidence from 2010 to 2016[5]. Ghana, Guinea and 10 countries experienced more than 50% increases. In East Africa, 10 countries like Ethiopia, Uganda and Kenya, had increasing malaria case incidence. The circumstances in South African countries can be complex. Several Southern African countries show a decreasing malaria incidence in 2010-2016, including Swaziland, Botswana, South Africa, Comoros and Eritrea. Only Namibia had increasing malaria incidence. However, several countries like

Zimbabwe, Namibia, showed sustained trend of malaria incidence, without significant increase or decrease in malaria incidence.

3.2 Variables

The dependent variables in the study are malaria incidence and mortality. Annual total suspected malaria cases and malaria deaths in the 8 countries were collected from World Malaria Reports. The total risk population in each country was estimated in each year. The malaria incidence and mortality rates were calculated as the ratio of the total malaria cases/deaths and risk population.

The main independent variables in the study were malaria control budgets (external donations, government funds, and total budgets), GDP *per capita* in current US dollars, LLINs/ITNs coverage (%), IRS coverage (%), the first year with reported mosquito insecticide resistance, resistance status (confirmed resistance, possible resistance, or suspected resistance) (Table 2).

For the linear model and comparative effectiveness analysis, all variables described above were included. The independent variables were divided into entomological and ecological, social-economic and epidemiological risk factors.

4. Missing Data

Missing values for risk population in 2000-2008 were calculated using the average risk ratio in years 2009-2016, which were available in World Malaria Reports.

5. Statistical Analysis

JMP® Pro 12 (SAS Institute Inc., Cary, NC, 1989-2007) was used for all statistical analyses. All data were first entered in *.xlsx* format and transferred to *.jmp* format for use in JMP. The dependent variable is malaria incidence rate and mortality rate.

5.1 Dependent variables: Malaria Incidences and Mortality Rates

The ratio of population under malaria risk was calculated by dividing the total risk population by the total human population for the country. Malaria incidence rate is calculated following World Malaria Reports, WHO, as:

$$Malaria\ Incidence\ (per\ 1000\ person\ year) = 1000 \times \frac{Malaria\ cases\ in\ current\ year}{Total\ Risk\ Population}$$

Malaria mortality rate is calculated as:

$$Malaria\ Mortality\ Rate\ (\%) = 100 \times \frac{Malaria\ deaths\ in\ current\ year}{Total\ Risk\ Population}$$

5.2 Independent Variables

5.2.1 Malaria Control Budgets

The malaria control budget contributed by external donors in current U.S. dollars is the sum of the amounts donated by Global Fund, PMI, USAID, and United Kingdom of Great Britain and Northern Ireland government, The World Bank, UNICEF and other NGOs for malaria control. The total malaria control budget per capita was calculated:

$$Total\ Malaria\ Control\ Budget\ (\$)\ per\ capita = \frac{External\ Donations + NMCP\ Funds}{Total\ UN\ Population}$$

5.2.2 Economic Status

The economic status is measured as GDP per capita in current US dollars in current years, and calculated as the total GDP divided by the country's population size in that year.

5.2.3 Case Management

The case management status was presented as percentage of malaria patients receiving first-line treatment courses delivered (including ACT), and is calculated as:

$$Case\ Management\ (\%) = 100 \times \frac{Malaria\ Treatment\ Delivered\ Courses}{Total\ Risk\ Population}$$

I conducted clustering analysis using Hierarchical cluster complete linkage method to classify the 8 countries into 3 different transmission patterns. I then used univariate analysis and multivariate analysis to determine the association among malaria incidence rate and social economic, entomological and other risk factors.

Table 2. Characteristics of the variables in the study

Variables	Data Source	Type	Description
Malaria Case	World Malaria Report	Continuous	Total suspected indigenous cases (total number of *P. f., P. v.* and other cases)
Malaria Deaths	World Malaria Report	Continuous	Presumed and confirmed or only confirmed malaria deaths.
Total Population	The World Bank	Continuous	All the residents, data source includes UN, national census reports, Eurostat, U.S. Census Bureau and Secretariat of the Pacific Community.
Risk Population	World Malaria Report for 2009-2016; Estimation for 1990-2008	Continuous	Population living in malaria endemic regions and at risk of malaria infection.
Malaria Incidence	-	Continuous	The number of new malaria cases per 1000 population at risk within the current year.
Malaria Mortality Rate	-	Continuous	The number of malaria deaths per population at risk within the current year.
Malaria Control Budget (External Donors)	World Malaria Report	Continuous	Budgets of donations for malaria control from Global Fund, PMI, USAID, and United Kingdom of Great Britain and Northern Ireland government, The World Bank, UNICEF and NGOs.
Malaria Control Budget (Government Funds)	World Malaria Report	Continuous	Budgets of national malaria control program (NMCP).

Gross Domestic Product (GDP)	The World Bank	Continuous	The sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products
GDP *per Capita*	-	Continuous	Average GDP per population in the country in the year.
IRS Coverage	World Malaria Report	Continuous	The population proportion with access to IRS (%)
ITNs/LLINs Coverage	World Malaria Report	Continuous	The modelled population proportion with access to a LLIN/ITN (%)
IRS Adoption	World Malaria Report	Dichotomous	Whether IRS is adopted in the country in current year.
ITNs/LLINs Adoption	World Malaria Report	Dichotomous	Whether LLINs/ITNs are adopted in the country in current year.
Larviciding Adoption	World Malaria Report	Dichotomous	Whether larviciding is adopted in the country in current year.
ACT Delivery	World Malaria Report	Dichotomous	Whether ACT is adopted and delivered in the country in current year.
ACT Coverage	World Malaria Report	Continuous	The risk population proportion with access to ACT (%).
Malaria Control Budget *per capita*	-	Continuous	Average malaria control budget (internal/external) per risk population

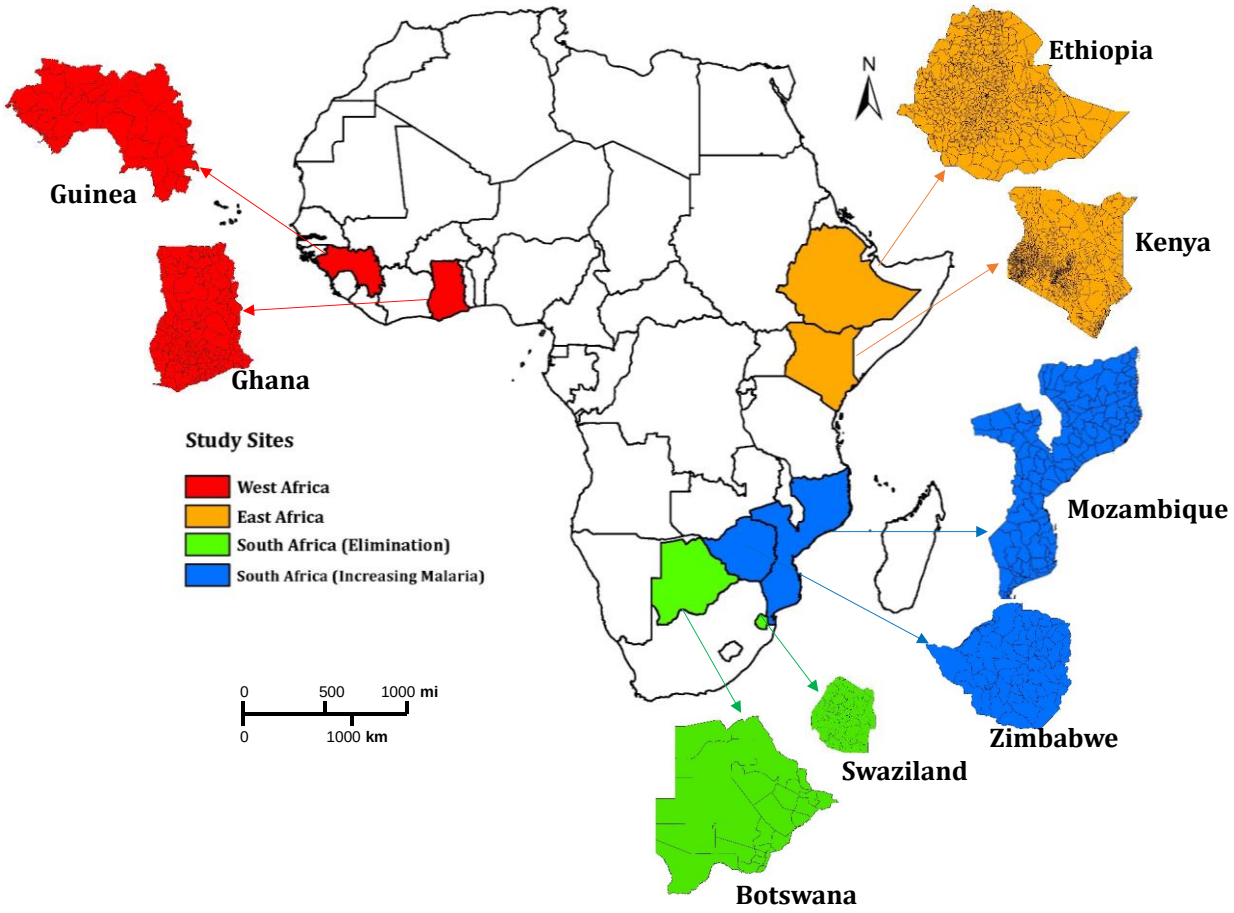

Figure 4. Distribution of Study Countries.

CHAPTER 3. RESULTS

1. Malaria Incidence and Mortality Rate in Study Countries

1.1 Malaria Cases

The total malaria cases in the 8 countries changed dynamically during the past 17 years (Figure 5). During this period, Kenya had an average of 7.7 million malaria cases (95% CI: 5.5 - 10.0 million), and Ethiopia 3.5 million cases (95% CI: 2.4 - 4.7 million). Malaria cases have been stably high over these years, and exhibit an increasing trend during the past 6 years. The large decline in reported malaria case number in 2008 in Kenya was due to a doctor and nurse strike (reference). Similar to Kenya, Ghana and Mozambique also showed a continuously increasing trend in malaria case numbers. Malaria case numbers in Zimbabwe and Guinea were relatively lower and did not show an increasing trend. There have been fewer than 1500 suspected malaria case in Botswana and Swaziland since 2011. Low malaria case number in these two countries made them eligible to be categorized as pre-elimination countries.

1.2 Malaria Incidence

Malaria incidence shows a similar trend as total malaria cases (Figure 6). Botswana (26.9 per thousand / person year ± standard error 5.0) and Swaziland (42.3 ± 9.7) had the lowest malaria incidences. Please note that all incidence measures reported in this thesis use the unit of the number of cases per 1000 person year. The average malaria incidences over the study period in other study countries were 62.7 ± 8.6 for Ethiopia, 42.3 ± 9.7 for Guinea,

199.6 ± 24.3 for Ghana, 144.8 ± 12.5 for Zimbabwe, 232.0 ± 26.9 for Kenya, 264.2 ± 46.1 for Mozambique.

1.3 Malaria Mortality Rates

The malaria mortality rates generally exhibited rapid reduction in recent years, but several countries had much higher rates (Figure 7). By 2016, Mozambique (53.6%), Ghana (49.8%) and Kenya (31.6%) harbored higher malaria mortality rates than other countries. Botswana and Swaziland showed < 1% malaria-induced mortality rates. Ethiopia, Guinea and Zimbabwe made good progress in reducing malaria deaths despite of sustained malaria transmission.

1.4 Classification of the Study Countries

The malaria incidence pattern of the 8 countries from 4 geographic regions was classified into 3 clusters using Hierarchical cluster complete linkage method (Figure 8):

Cluster 1: countries with increasing malaria incidence: Kenya, Ghana and Mozambique;

Cluster 2: countries with sustained malaria incidence: Ethiopia, Guinea and Zimbabwe;

Cluster 3: countries with malaria elimination: Botswana and Swaziland.

2. Social Economic Status and Malaria Control Efforts in the Study Countries

2.1 Economic Development Status

Economic status was calculated in *per capita* GDP in US dollars. The overall GDP per capita in most countries showed an increasing trend. There was no significant difference for

cluster 1 and 2 with increasing and sustained malaria incidences. And the countries in cluster 3 with malaria elimination had the highest GDP *per capita* at US $ 5164 averagely during the past 5 years. There were significant difference in *per-capita* GDP levels among the three clusters (One-way ANOVA, $F_{2, 37}$=64.7, *P*<0.0001) (Fig. 11; Table 3). In 2016, the *per-capita* GDP values were US $6,924 in Botswana, US $2,770 in Swaziland, US $1,455 in Kenya, US $1,513 in Ghana, US $1,029 in Zimbabwe, US $707 in Ethiopia, US $662 in Guinea and US $382 in Mozambique.

2.2 Malaria Control Budget

Over the past decade there has been steady increase in the overall investment for malaria control (Figure 12). Malaria control investment came from two sources: domestic investment from malaria-endemic government countries and international donation. The absolute size of investment varied among countries due to risk population size differences, the country's economic status and other factors (Figure 9). For example, the total budget for malaria control in 2016 was US $58.4 million in Kenya, and $65.2 million in Ethiopia (East Africa), $70.6 million and $43.0 million in Ghana and Guinea (West Africa), $87.8 million and $31.3 million in Mozambique and Zimbabwe (South Africa with increasing malaria transmission), $0.86 million in Swaziland and nearly zero in Botswana (South Africa with low malaria transmission at malaria elimination stage) (Figure 10). Most malaria control budget (>90%) came from external donations from the Global Fund, PMI, USAID, and other donors, particularly those countries in Cluster 1 with increasing malaria incidence (Table 3).

We used *per-capita* budget for malaria control in the analysis to correct for the human population size effect. The external funding for malaria control in countries in Cluster 1 (increasing trend of malaria incidence) was the highest, followed by the countries in clusters 2 and 3 (Figure 10B). In East Africa (Kenya and Ethiopia), the investment per population was stable at around US $1-2/person in malaria control since 2006. Malaria control funding was increased to US $3-4 per person per year for the past 5 years in the two West Africa countries (Ghana and Guinea). The average funding for malaria control in Mozambique was US $3 per person in 2016. The overall trends show a steady and stable increase in malaria control funding for countries in Cluster1 and Cluster 2 (Figure 12A, 12B). Botswana and Swaziland are at pre-elimination stage, the malaria control investment was only US $1-2 per person per year in both countries (Figure 12C).

2.3 LLINs and IRS Coverage

LLINs and IRS are the major methods for malaria control and prevention in Africa. Between 2014 and 2016, ~505 million LLINs were delivered to sub-Saharan countries, among them, 33 million nets delivered in Ethiopia, 19.6 million in Ghana, 17.6 million in Mozambique and 16.9 million in Kenya.

The LLIN free distribution policy was adopted in 2006 in Kenya, 2004 in Ethiopia and Ghana, 2009 in Guinea, Botswana and Zimbabwe, 2003 in Mozambique, 2002 in Swaziland. Overall LLIN coverage has been increasing in most countries (Figure 10C). In the two South African countries in the pre-elimination stage, LLIN coverage has been low in Swaziland and Botswana (Figure 13G, 13H). Higher ITN coverage was reported in countries in Cluster 1 and 3 than that of Cluster 2 (Table 3).

IRS was implemented in 2003 in Kenya and Mozambique, 1960 in Ethiopia, 2005 in Ghana, 2013 in Guinea, 1947 in Zimbabwe, 1946 in Swaziland and 1950 in Botswana. The number of countries implementing IRS and malaria incidence declined in the past 5 years due to insecticide resistance. In the 8 study countries, the IRS coverage decreased since 2012. In Mozambique, Kenya, Guinea and Botswana, the IRS coverages were 0 in 2016. IRS coverage was higher in countries in Cluster 2 (Table 3).

2.4 Larval Control

Larval source management (LSM) is one of the WHO recommended core vector management tools that target the mosquito breeding sites and mosquito immatures (larvae and pupae), but implementation varied among countries. Larval source management was not widely implemented in Kenya, Guinea and Mozambique, but there are different larval control tools being used. Swaziland and Ethiopia adopted larval control since 1960, Ghana in 1999, Zimbabwe, and Botswana in 2012.

2.5 Malaria Transmission Seasons

Malaria endemicity may vary among countries due to the climate conditions (Table 4). Countries in West and East Africa can have a transmission season that lasts for 6-7 months or all year around transmission. In contrast, Botswana and Swaziland, have malaria transmission typically last for 3-4 months, November to March.

2.6 Insecticide Resistance

Resistance to pyrethroids, the insecticide used in all ITNs and IRS spraying, is widespread. 81% of the malaria endemic countries report insecticide resistance. The starting year that pyrethroids were used for vector control and mosquito resistance status

are presented in Table 5. Mozambique was the earliest country to report pyrethroids resistance in 1999, followed by Zimbabwe in 2000 and Guinea in 2001. Kenya detected insecticide resistance in 2009 and by now, more than 75% reports showed confirmed resistance. There were 94 tests conducted in Zimbabwe since 2010, and only 18 tests (19%) got confirmed resistance results, representing the lowest reported resistance. By 2016 Ghana reported 177 tests, 154 (87%) of which showed confirmed resistance, representing the highest resistance.

2.7 Case Management

The case management coverages changed over years in different countries (Figure 14). In 2016, Mozambique had the highest coverage with 49.0% risk population access to first-treatment courses, followed by Guinea (27.1%) and Kenya (23.4%). Botswana and Swaziland had the lowest case management ratios (< 0.5%) due to very few malaria cases in the country.

At the cluster level, countries in Cluster 1 with increasing malaria incidences received highest treatment coverage. Cluster 3 in the malaria pre-elimination stage had the lowest first line malaria treatment delivery and coverage (Table 3).

3. Multivariable Regression for Variables and Malaria Incidence in Study Countries

Using the data from the 8 countries, multivariable linear regression models with standard least-squares method were done to determine the impact of risk factors on malaria incidence differences. The model included autocorrelation with a one year time lag, clusters,

countries nested within clusters, and economic status (GDP *per capita*), internal and external malaria control budgets, ITN and IRS coverage, and insecticide resistance status (Table 4).

As expected, malaria incidence exhibited highly significant autocorrelation. Clusters showed a significant effect, similar to the country classification results discussed above. Economic status (per-capita GDP), ITN coverage and IRS coverage did not affect malaria incidence significantly. The analysis detected two significant factors: per-capita government funding for malaria control and insecticide resistance (Table 6). The more government funding for malaria control, the lower malaria incidence. Similarly, the higher insecticide resistance, the higher malaria incidence.

We then performed the same analysis separately for countries in each cluster, and found:

Countries in Cluster 1 with increasing malaria incidence. Using the data from the three countries showing increasing malaria incidence trend (Ghana, Kenya and Mozambique), the only significant factor detected was the per-capita government funding for malaria control. This indicates the importance of national malaria control program (Table 7).

Countries in Cluster 2 with sustained malaria incidence. Using data from Ethiopia, Guinea and Zimbabwe that show sustained malaria control, funding was the only factor associated with malaria incidence changes (Table 8).

Countries in Cluster 3 with malaria pre-elimination. Data from Botswana and Swaziland, the two countries in malaria pre-elimination stage, I found ITN coverage was the only significant factor for malaria incidence (Table 9), indicating the importance of malaria intervention.

Table 3. Summary of characteristics of all candidate variables (Mean ±SE).

	Cluster 1 Increasing malaria incidence			Cluster 2 Sustained malaria transmission			Cluster 3 Malaria pre-elimination	
	Kenya	**Ghana**	**Mozambique**	**Ethiopia**	**Guinea**	**Zimbabwe**	**Botswana**	**Swaziland**
Malaria incidence (per 1000 pop)	365.4 ±21.6[a]	440.9 ±34.3[a]	411.4 ± 56.2[a]	108.1 ±10.5[b]	104.7 ±11.0[b]	121.3 ±12.1[b]	2.2 ±1.6[d]	2.2 ±0.4[d]
GDP per capita ($)	1304.9 ±51.9[a]	1550.2 ±79.8[b]	541.1 ±43.0[c]	578.8 ±44.1[c]	702.4 ±18.4[c]	1017.6 ±12.4[d]	6998.2 ±153.9[c]	3330.0 ±193.3[c]
External fund (million, US $)	69.7 ±10.3[a]	73.1 ±8.5[a]	62.7±7.0[a]	85.6 ±19.0[a]	27.3 ±4.4[b]	24.6 ±6.6[b]	0.3 ±0.3[c]	1.0 ±0.3[c]
Government fund (million, US $)	1.7 ±0.3[a]	9.0 ±0.4[a]	28.8 ±15.1[b]	19.7[b]	2.6 ±0.9[a]	0.8 ±0.1[a]	1.7 ±0.2[a]	2.9 ±2.2[a]
Total fund (million, US $)	71.0 ±10.2[a]	82.2 ±8.7[a]	91.5 ±6.7[a]	89.4 ±22.8[a]	29.9 ±4.7[b]	25.4 ±6.6[b]	2.0 ±0.3[c]	3.9 ±1.9[c]
Total fund per capita (US $)	1.6 ±0.2[a]	3.1 ±0.3[b]	3.4 ±0.6[b]	0.9 ±0.2[a]	2.5 ±0.4[a]	1.7 ±0.4[a]	0.9 ±0.1[c]	3.1 ±1.5[a]
Insecticide resistance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
ITN coverage (%)	74.2 ±2.4[a]	74.9 ±3.9[a]	68.0 ±4.4[a]	53.6 ±2.5[b]	55.0 ±8.8[b]	41.6 ±4.7[b]	0	71.2 ±2.2[a]
IRS coverage (%)	1.5 ±1.5[a]	7.5 ±1.2[b]	26.0 ±5.5[b]	23.4 ±4.4[b]	-	28.1 ±0.6[b]	11.3 ± 1.2[c]	1.9 ±1.6[a]
Treatment coverage (%)	26.5 ±2.5[a]	24.2 ±8.4[a]	45.8 ±6.6[b]	13.2 ±2.0[c]	12.4 ±4.0[c]	10.8 ±2.3[c]	0.3 ±0.1[d]	0.1 ±0.02[d]
Total Treatment Courses Delivered (thousand)	10703.9 ±632.0[a]	6413.4 ±2224.7[a]	12470.0 ±1893.5[a]	8537.8 ±1143.2[a]	1518.9 ±507.7[b]	965.3 ±71.6[b]	3.5 ±8.7[c]	0.4 ±0.08[d]

Note:

[1] All the candidate variables were significantly different among different groups (One-way ANOVA, $P<0.05$).

[2] All the candidate variables were significantly different among different clusters (One-way ANOVA, $P<0.05$) except for Total fund per capita (One-way ANOVA, $F_{2, 37}=1.60$, $P=0.216$) and Government fund (One-way ANOVA, $F_{2, 32}=2.44$, $P=0.103$).

[3] Countries in one row with different letters (a, b, c, d) indicate the significant difference at $P < 0.05$.

Table 4. Malaria Transmission Seasons in the Study Countries.

Country	Malaria Start Month	Malaria End Month	Transmission Length	Malaria Endemic Regions
Guinea	North: June; South: May	Northeast: November; Others: December	North: 6 month; South: 7 months	Whole country
Ghana	North: May; Middle: April; South: March	North: November; South: December; Southwest: January	North: 6 month; South: 7 months	Whole country
Ethiopia	North: June-July; West: May; South: April	North: November; South: April-May	North: 6 month; South: 7-12 months	West, North and East
Kenya	April-May	April-May	7-12 months	West and South
Mozambique	December	April-May	5-6 months	Whole country
Zimbabwe	January	March-April	3-4 months	East
Botswana	North: Jan	March to April	North: 3-4 months	North
Swaziland	November-December	March	4 months	Country Border

Table 5. Pyrethroid Insecticide Resistance Status of the Study Countries.

Country	First Year Detected*	Number of tests*	Confirmed resistance	Possible resistance	Susceptible
Guinea	2001	25	19	1	5
Ghana	2004	177	154	20	3
Ethiopia	2003	341	290	31	20
Kenya	2009	550	434	78	38
Mozambique	1999	273	87	59	127
Zimbabwe	2000	94	18	10	66
Botswana	2002**	20	10	2	8

Data source: IR mapper

* Data collected from Malaria Threat Map with tests from 2010-2016

** 2002 possible resistance, mortality: 97.6%

Table 6. Linear regression model of malaria incidence and related impact factors for the 8 study countries*.

Variables	Estimated Beta	Standard Error	*P* value
Autocorrelation	0.3838211	0.141548	**0.0095**
Clusters			**0.0011**
Cluster 1	168.70888	77.73368	**0.0354**
Cluster 2	5.637838	77.74418	0.9425
Countries (nested Clusters)			0.3286
Cluster 1: Country [Ghana]	-78.54552	34.09611	**0.0260**
Cluster 1: Country [Kenya]	4.4276043	29.00013	0.8794
Cluster 2: Country [Ethiopia]	2.0004448	28.23065	0.9438
Cluster 2: Country [Guinea]	-8.929042	36.62872	0.8085
Cluster 3: Country [Botswana]	-35.50489	71.49961	0.6220
Economic Status			
GDP per capita	0.0137636	0.050921	0.7882
Malaria Budgets			
External Fund per capita	1.0390393	16.1905	0.9491
Government Fund per capita	264.40608	119.9677	**0.0328**
Malaria Prevention			
Insecticide Resistance	-46.23303	22.23858	**0.0435**
ITN Coverage	-0.200166	0.553777	0.7195
IRS Coverage	-0.034599	1.139099	0.9759
Case Management			
Treatment Coverage	-1.047131	0.851155	0.2251

* Linear regression: R^2=0.81, P<0.0001 (ANOVA, $F_{15, 44}$=12.36) for adjusted model

Numbers in bold indicate significant difference (P<0.05). .

Table 7. Linear regression model of malaria incidence and related impact factors for cluster 1 with increasing malaria incidence (Ghana, Kenya and Mozambique).

Variables	Estimated Beta	Standard Error	*P* value
Autocorrelation	0.2640925	0.264198	0.3334
Countries			
Country[Ghana]	-182.3833	81.13401	**0.0400**
Country[Kenya]	36.812134	62.26416	0.5632
Economic Status			
GDP per capita	0.0340287	0.140133	0.8114
Malaria Budgets			
External Fund per capita	-34.7471	33.78723	0.3201
Government Fund per capita	976.00979	330.5374	**0.0099**
Malaria Prevention			
Insecticide Resistance (IR**=0)	-49.03643	44.65973	0.2895
ITN Coverage	0.2237804	1.030207	0.8310
IRS Coverage	-3.973215	4.566568	0.3980
Case Management			
Treatment Coverage	-1.498066	1.222581	0.2393

*Linear regression: R^2=0.70, *P*=0.019 (ANOVA, $F_{10, 15}$=3.26) for adjusted model.

Numbers in bold indicate significant difference (*P*<0.05).

Table 8. Linear regression model of malaria incidence and related impact factors for cluster 2 with sustained malaria incidence (Ethiopia, Guinea and Zimbabwe).

Variables	Estimated Beta	Standard Error	*P* value
Autocorrelation	-0.468152	0.176376	**0.0180**
Countries			
Country[Ethiopia]	-41.13635	17.23065	**0.0306**
Country[Guinea]	-0.705522	15.33008	0.9639
Economic Status			
GDP per capita	-0.066285	0.044159	0.1541
Malaria Budgets			
External Fund per capita	20.07608	9.862897	0.0599
Government Fund per capita	378.32022	133.1696	**0.0124**
Malaria Prevention			
Insecticide Resistance	-8.982735	15.58778	0.5730
ITN Coverage	-0.639435	0.431475	0.1590
IRS Coverage	0.5501426	0.691141	0.4385
Case Management			
Treatment Coverage	0.1395575	0.804212	0.8646

*Linear regression: R^2=0.78, *P*=0.002 (ANOVA, $F_{10, 15}$=5.32) for adjusted model.

Numbers in bold indicate significant difference (*P*<0.05).

Table 9. Linear regression model of malaria incidence and related impact factors for cluster 3 with malaria pre-elimination (Botswana and Swaziland).

Variables	Estimated Beta	Standard Error	*P* value
Autocorrelation	0.1087738	0.125106	0.4244
Countries			
Country[Botswana]	-8.022766	3.324425	0.0606
Economic Status			
GDP per capita	0.0018518	0.001572	0.2917
Malaria Budgets			
External Fund per capita	-	-	-
Government Fund per capita	-	-	-
Malaria Prevention			
Insecticide Resistance	-	-	-
ITN Coverage	-0.32998	0.073421	**0.0064**
IRS Coverage	0.0498812	0.040191	0.2696
Case Management			
Treatment Coverage	5.2929295	1.853678	**0.0356**

*Linear regression: R^2=0.94, *P*=0.007 (ANOVA, $F_{6, 5}$=12.26) for adjusted model.

Numbers in bold indicate significant difference (*P*<0.05).

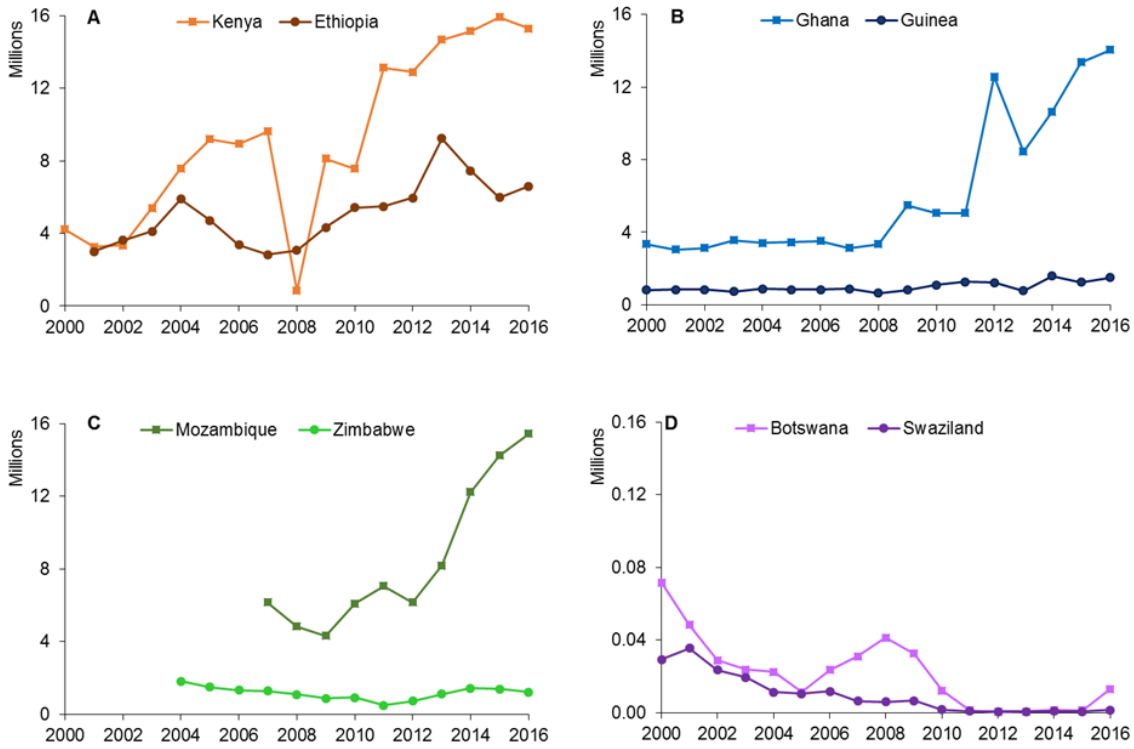

Figure 5. Total Malaria Cases in 8 Study Countries. Total suspected malaria cases in A) East Africa (Kenya and Ethiopia), B) West Africa (Ghana and Guinea), C) Central/Southern Africa (Mozambique and Zimbabwe), and D) Southern Africa (Botswana and Swaziland,) Africa years 2000-2016.

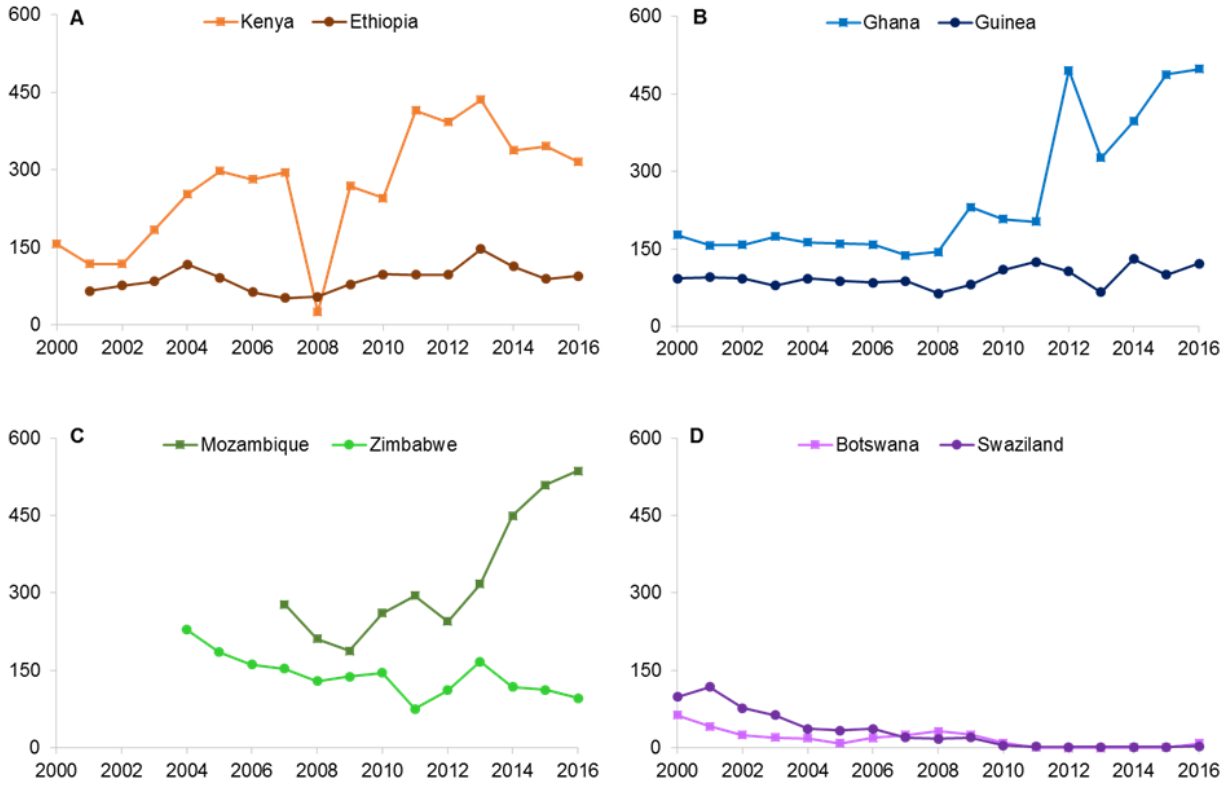

Figure 6. Malaria incidences (per 1000 person year) of study countries in 2000-2016.

Malaria incidences in A) East Africa (Kenya and Ethiopia), B) West Africa (Ghana and Guinea), C) Central/South Africa (Mozambique and Zimbabwe), and D) South Africa (Botswana and Swaziland) in years 2000-2016.

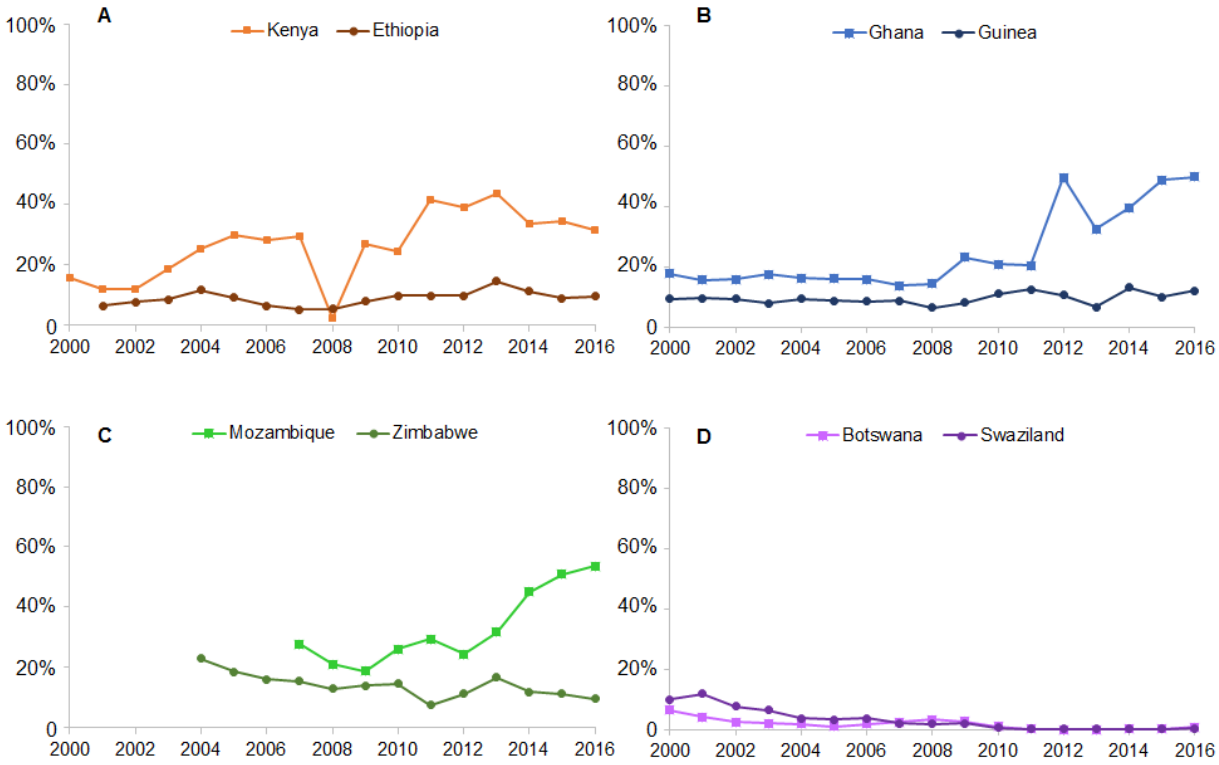

Figure 7. Malaria mortality rates (%) of study countries in 2000-2016. Malaria mortality rates (%) in A) East Africa (Kenya and Ethiopia), B) West Africa (Ghana and Guinea), C) Central/South Africa (Mozambique and Zimbabwe), and D) South Africa (Botswana and Swaziland) Africa in years 2000-2016.

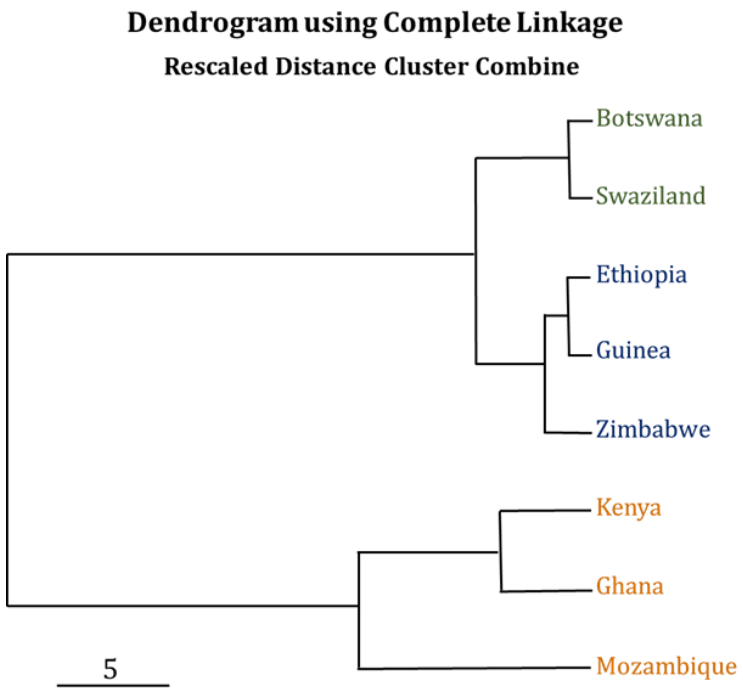

Figure 8. Malaria incidence clustering analysis result. Clustering analysis using Hierarchical cluster complete linkage method. Results were shown in Dendrogram**.** Botswana and Swaziland: malaria pre-elimination countries; Ethiopia, Guinea and Zimbabwe: countries with sustained malaria transmission; Kenya, Ghana and Mozambique: countries showing increasing trend of malaria incidence.

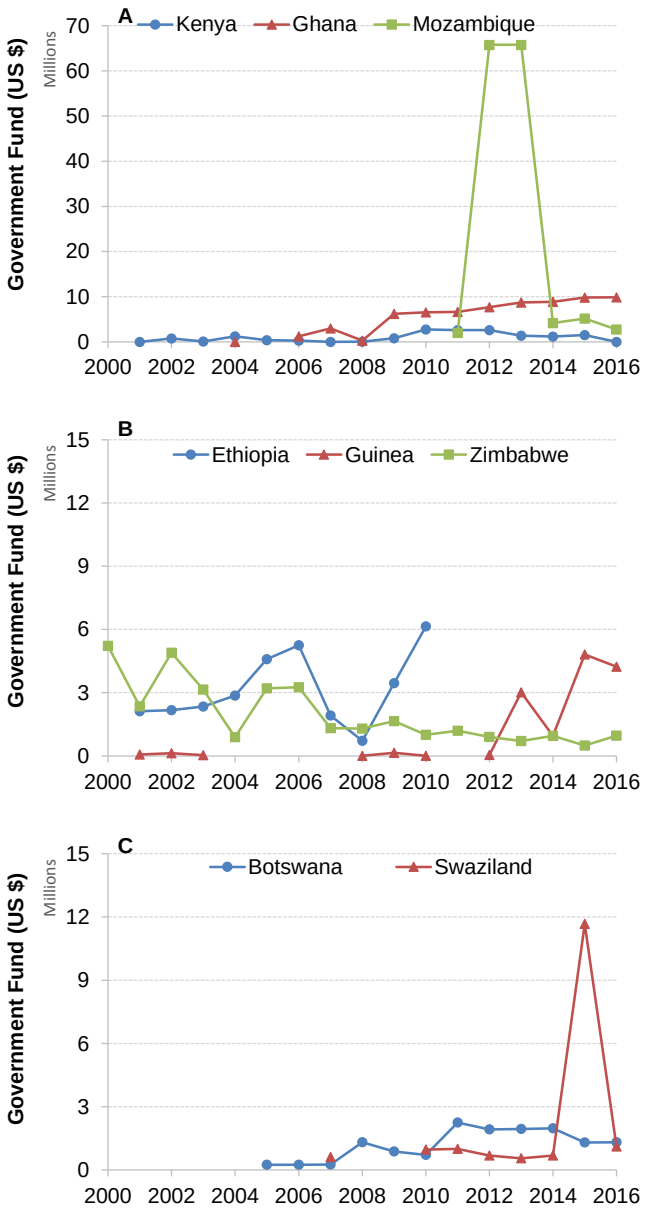

Figure 9. Malaria Control Budget Contributed by Governments (US $). Budgets of national malaria control programs (NMCP) in A) Countries with increasing malaria: Kenya, Ghana and Mozambique; B) countries with sustained malaria: Ethiopia, Guinea and Zimbabwe; C) countries in malaria pre-elimination stage: Botswana and Swaziland in years 2000-2016.

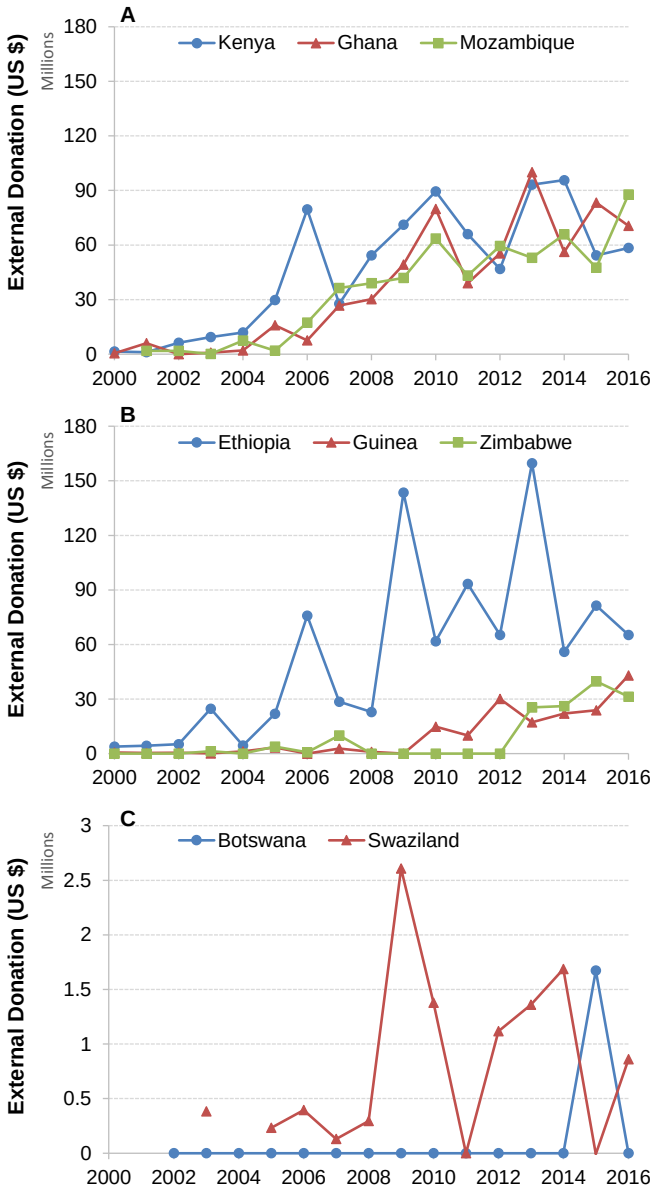

Figure 10. Malaria Control Budget Contributed by External Donors (US $). Budgets of donations for malaria control from Global Fund, PMI, USAID, and United Kingdom of Great Britain and Northern Ireland government, The World Bank, UNICEF and NGOs in A) Countries with increasing malaria: Kenya, Ghana and Mozambique; B) countries with sustained malaria: Ethiopia, Guinea and Zimbabwe; C) countries in malaria pre-elimination stage: Botswana and Swaziland in years 2000-2016.

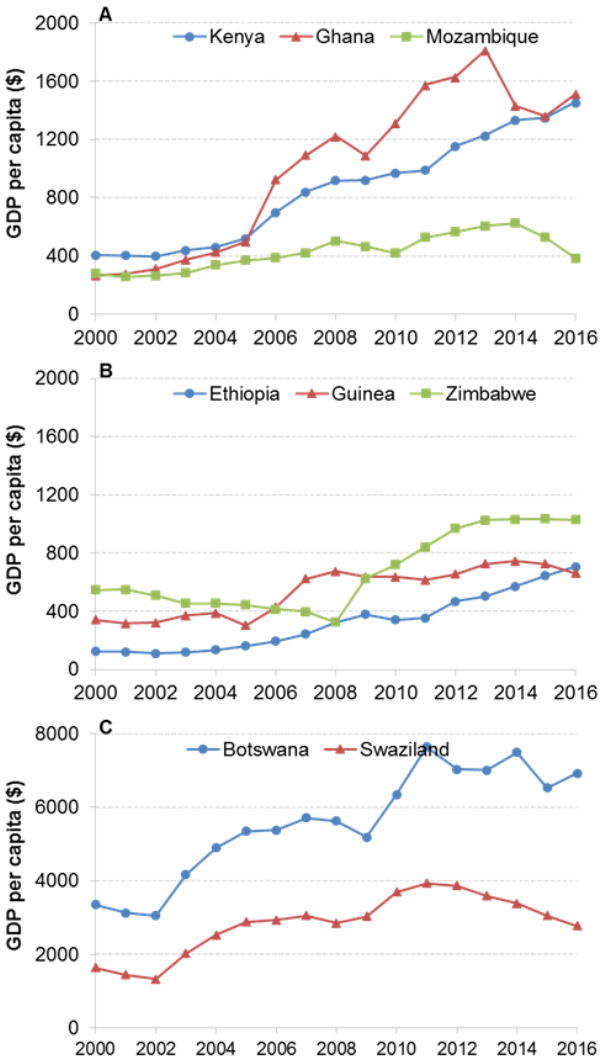

Figure 11. Total *per capita* Gross Domestic Product (GDP) (in US $) of the study countries in years 1990-2016. A) Countries with increasing malaria trend: Kenya, Ghana and Mozambique; B) countries with sustained malaria: Ethiopia, Guinea and Zimbabwe; C) countries in malaria pre-elimination: Botswana and Swaziland.

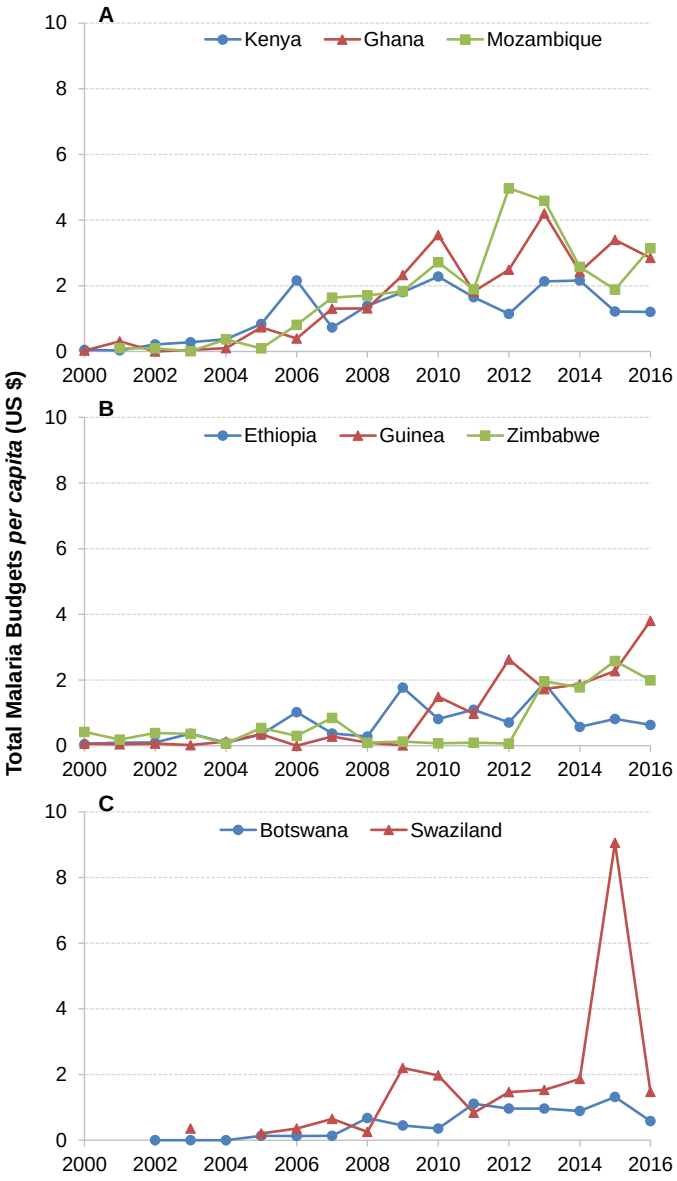

Figure 12. Per capita Malaria Control Budget (US $) in years 1990-2016. A) Countries with an increasing malaria trend: Kenya, Ghana and Mozambique; B) countries with sustained malaria: Ethiopia, Guinea and Zimbabwe; C) countries in malaria pre-elimination stage: Botswana and Swaziland.

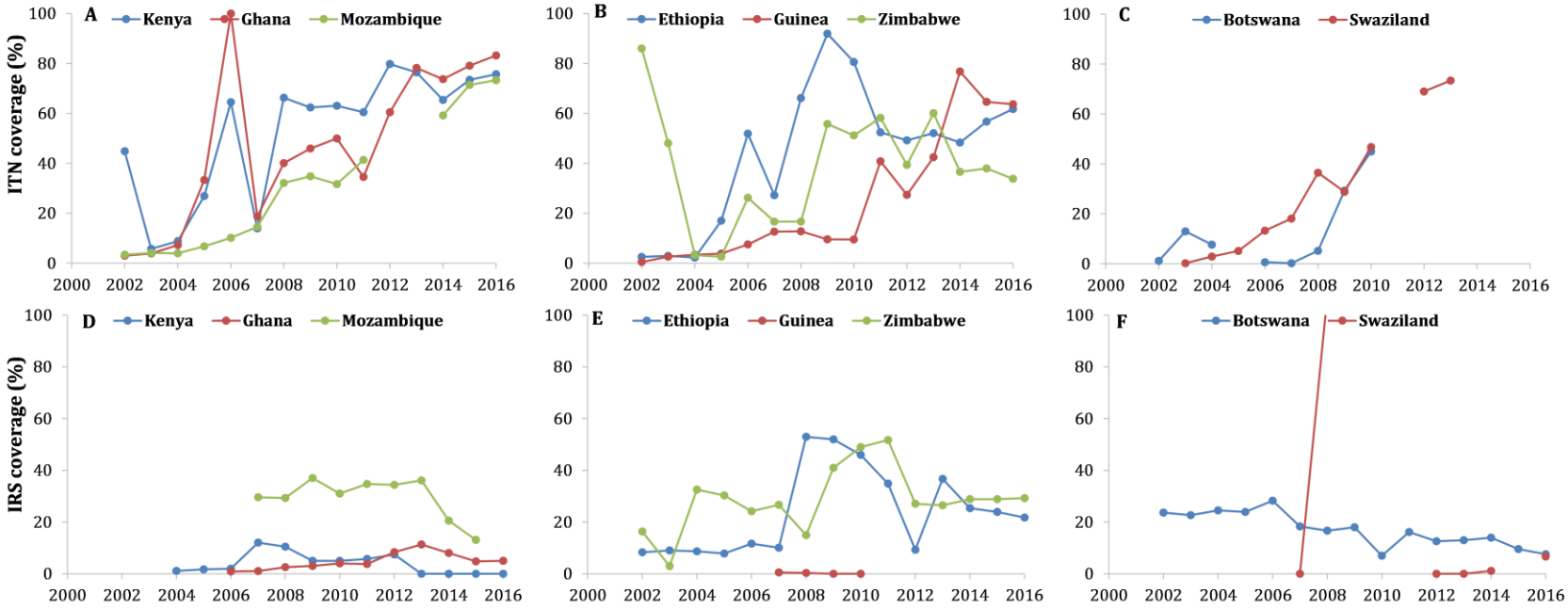

Figure 13. ITN and IRS coverage (%) in study countries in year 2000 to 2016. A, B, C, ITN coverage; D, E, F, IRS coverage

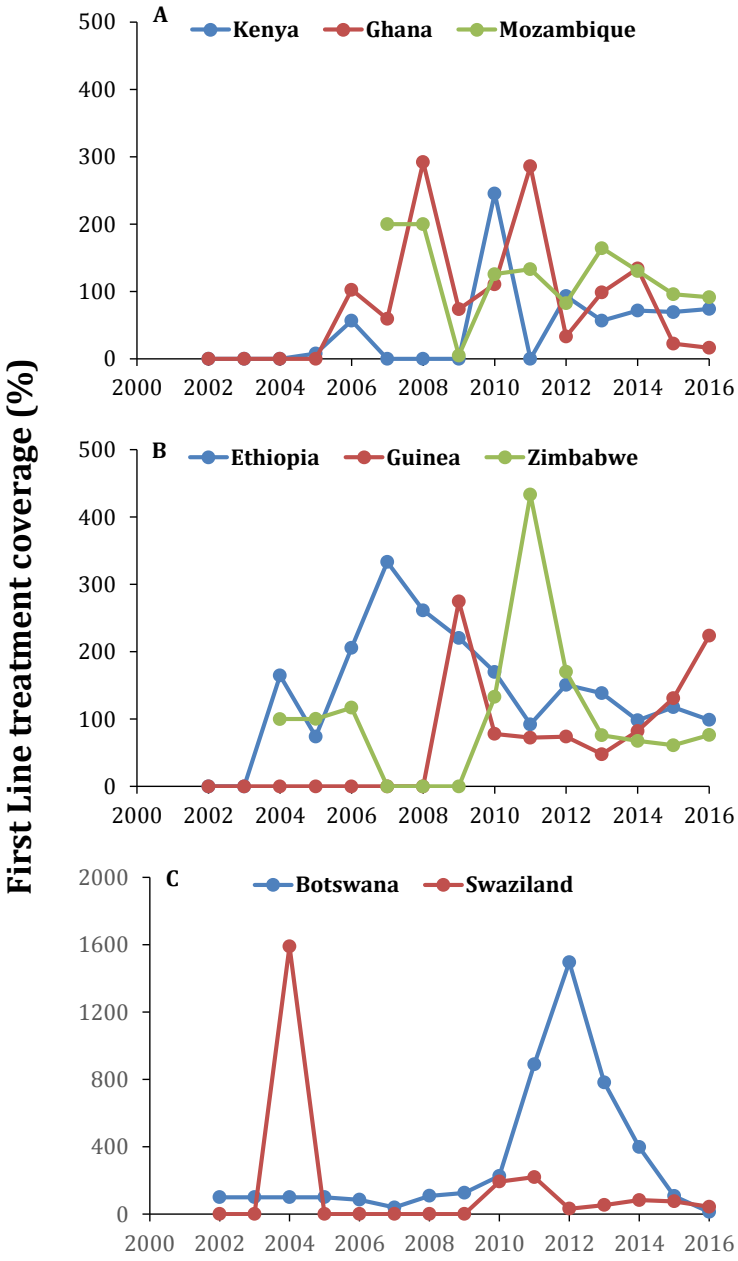

Figure 14. Treatment Coverage (%) of the study countries in years 2000-2016. A) Countries with an increasing malaria trend: Kenya, Ghana and Mozambique; B) countries with sustained malaria: Ethiopia, Guinea and Zimbabwe; C) countries in malaria pre-elimination stage: Botswana and Swaziland.

CHAPTER 4. DISCUSSION

In the present study, we performed a systematic review, Univariate and multivariable regression analysis to determine the impact of social economic, biological and environmental factors on malaria incidence dynamics in Africa. Longitudinal data from publically available data sources across the past 17 years for eight African countries were collected and analyzed, including Ghana and Guinea from West Africa, Ethiopia and Kenya from East Africa, Mozambique and Zimbabwe from Southern/Central Africa, and Botswana and Swaziland from Southern Africa. The overall malaria endemicity was assessed, and three distinct malaria transmission patterns in these countries were found: malaria incidence with an increasing trend, sustained transmission and incidence reduced to pre-elimination level. The countries showing increasing malaria incidence trend were Kenya, Ghana and Mozambique. The countries showing sustained malaria transmission were Ethiopia, Guinea and Zimbabwe. The countries in malaria pre-elimination stage were Botswana and Swaziland. The key factors I analyzed included per-capital GDP, national malaria control budget and malaria budget from international donors. Biological factors include LLIN coverage, IRS coverage and insecticide resistance, and malaria case management.

1. Economic Status: *per-capita* GDP

Malaria has been thought to be difficult to control in African countries due to the its strong association with poverty[80]. Poverty can affect healthcare equality[81], and consequently, people's access to malaria prevention, diagnosis and treatment. A vicious cycle between poverty and malaria indicates that economic development is a major determinant

of malaria incidence. The *per-capita* GDP variation showed that there was a large economic development disparity among our 8 study countries. For example, in 2016 the *per-capita* GDP in Botswana was US $6,924 whereas US $382 in Mozambique, a difference more than US $6000. Botswana is in the pre-elimination stage but Mozambique is showing increasing malaria over years.

2. Malaria Control Budget: National Government and External Funds

The malaria control requires funds to support activities from bednet distribution, drug and diagnosis kit procurement, and case management. The overall malaria control investment has been in a steady increase in Africa, and most malaria control budgets come from international donations from organizations such as Global Fund, PMI, USAID, The World Bank, UNICEF and various NGOs. In the past decade, the international funding for malaria control has been increasing, and the external funding amount in a country was positively associated with its malaria disease incidence: the higher malaria incidence, the more donations a country received. Though external funding represented most of the malaria control budget, my analysis showed that only national government malaria investment was significantly associated with malaria incidence reduction. The reason for this is that national government malaria investment reflects the determination and perhaps overall organization of the malaria control efforts.

3. Malaria Intervention Tools: LLINs/ITNs, IRS and Insecticide Resistance

LLINs and IRS are the core malaria vector control tools used in Africa. Research has demonstrated the efficacy of LLINs and IRS in malaria control,[85] the scale up of LLIN and IRS was made possible by funding from the Global Funds and PMI since 2005.

3.1 LLINs and IRS coverage

The overall LLIN coverage has been increasing over years in our study countries. The LLIN coverage was high in countries with increasing malaria incidence trend and in countries in the pre-elimination stage, at around 70% in 2016. The target ITN coverage by the WHO is 80%. I observed dramatic changes in some years in several countries. For example, the peak coverage in Ghana was in 2005. The reason for this was due to a calculation change in the size of risk population as LLIN coverage was calculated as the number of LLIN distributed divided by the risk population. In Zimbabwe, domestic violence and international sanction in 2004 and 2005 contributed to the sharp decline of LLIN coverage.

Overall IRS coverage was low in all 8 study countries. IRS is an effective tool in malaria control, but is also an expensive method in the insecticide and labor cost in relation to its short duration of protection. IRS coverage fluctuated over time, which reflected the consequence of funding availability. Overall, the countries with increasing malaria trend and countries in malaria pre-elimination stage had lower IRS coverage.

3.2 Insecticide Resistance

Insecticide resistance is an inevitable consequence associated with scale up of insecticide-based malaria control measures. Meta-analysis on the impact of insecticide resistance on the effectiveness of LLINs and IRS found that insecticide resistance increased the survivorship of malaria vectors, but there is insufficient evidence on its impact on clinical malaria incidence.[86, 87] In this study I found a significant negative association between insecticide resistance and malaria incidences with odds ratio of 20, suggesting insecticide resistance is a major obstacle to malaria control.

WHO has urged effective insecticide resistance management. There are several useful approaches for insecticide resistance management: 1) insecticide resistance monitoring by better understanding insecticide resistance mechanisms and developing field applicable sensitive resistance biomarkers; 2) implement new malaria vector control strategies, such as rotation of insecticides to reduce selection pressure on mosquitoes and mosaic use of insecticides to provide refugia for the susceptible mosquitoes; 3) control the spread of insecticide resistance genes by limiting the spread of resistant mosquito populations; and 4) develop alternative vector control methods using products with totally different mosquito killing mechanisms. Methods under development include genetically modified mosquitoes, use of biological insecticides, sterile male release, and house modification to control human-vector contact rate.

4. Case Management

ACTs are the most effective first-line treatment for uncomplicated malaria. Failure for timely treatment can cause severe malaria and mortality. In most African countries, the national malaria control guideline requires treating symptomatic malaria patients. In my

univariate regression analysis for cluster of countries in pre-elimination stage, treatment coverage was negatively associated with malaria incidence. In countered with high transmission, asymptomatic malaria is extremely common which contributes to continuous transmission and leads to clinical illness. This may explain why no significant correlation between treatment coverage and malaria incidence was found.

5. Autocorrelation

In this study, autocorrelation with 1 to 5 year time lag was used to examine the correlation between malaria incidence in the present year and previous years. Regression models found that 1-year lag showed the largest correlation (R^2=0.61 for 1-year lag, and 0.42, 027, 0.17 for 2, 3, 4-year lags). Therefore, in the multivariate model, I used 1-year time lag in the model. The autocorrelation was positive, suggesting that malaria incidence in the present year was highly correlated with incidence in the previous year (Appendix 2).

6. Other Factors

Malaria transmission is modulated by entomological and ecological factors such as seasonality and climate change, etc. Climate change has been found associated with increased epidemic intensity in areas previously with no or little malaria[89, 90]. Transmission duration is an important factor that should be considered in malaria control measures. For example, areas with perennial transmission may require multiple IRS in a year and more intense malaria vector control than areas with a short transmission season. Among the 8 countries I examined, the countries with perennial transmission exhibited higher malaria incidence and also increasing trend of malaria.

7. Significance and Values

This study examined entomological, ecological, social-economical and biological factors that may affect malaria disease incidence, and identified national malaria control investment and insecticide resistance were the significant factors associated with clinical malaria incidence. The implications of these findings include:

1) The study comprehensively examined risk factors for clinical malaria incidence in selected African countries. A comprehensive analysis of risk factors distinguishes from past studies that focused on single or a small number of factors.
2) The study determined that national government funding in malaria control is significantly associated with reduced malaria incidence. This finding suggests the determination of the African countries themselves for malaria control is very important.
3) Insecticide resistance represents a major obstacle to malaria control and elimination. Resistance management and developing alternative malaria control tools are imperative to further reduce malaria in Africa.

8. Limitation of the Study

This study has several limitations. First, data reliability may be questioned. Although I used data from the WHO statistics, malaria incidence data at the country level in Africa where there is limited surveillance and diagnosis may have a large confidence interval. Second, some variables contained missing data. I limited my analysis to the period of 2000-2016 to minimize the missing data. Third, malaria data and the associated risk factor data are aggregated data at the country level, some risk factors such as climate and mosquito

densities which are available only on the site level can't be analyzed. Fourth, insecticide resistance is a quantitative variable. Because the resistance data available were a binary valuable (presence or absence), further analysis on the quantitative measurement of resistance and malaria incidence should be examined.

9. Conclusions

Using a comprehensive multivariate analysis, I found that national government funding from African countries and insecticide resistance were the factors significantly associated with clinical malaria control incidence. This study indicates the significance of malaria control investment from African countries themselves and insecticide resistance management in malaria control and elimination in Africa.

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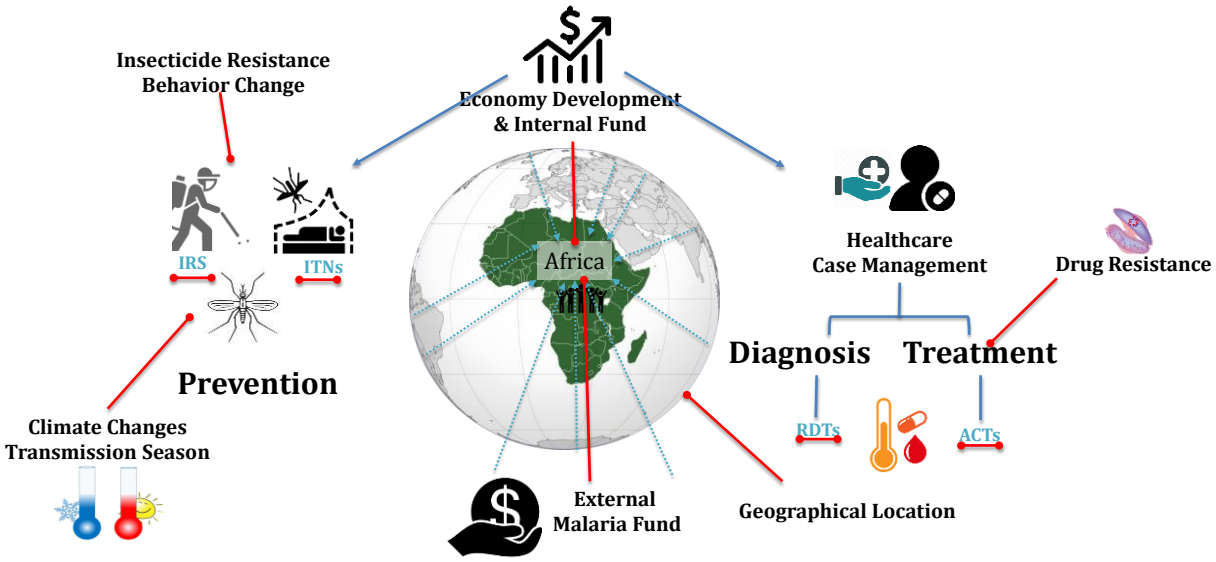
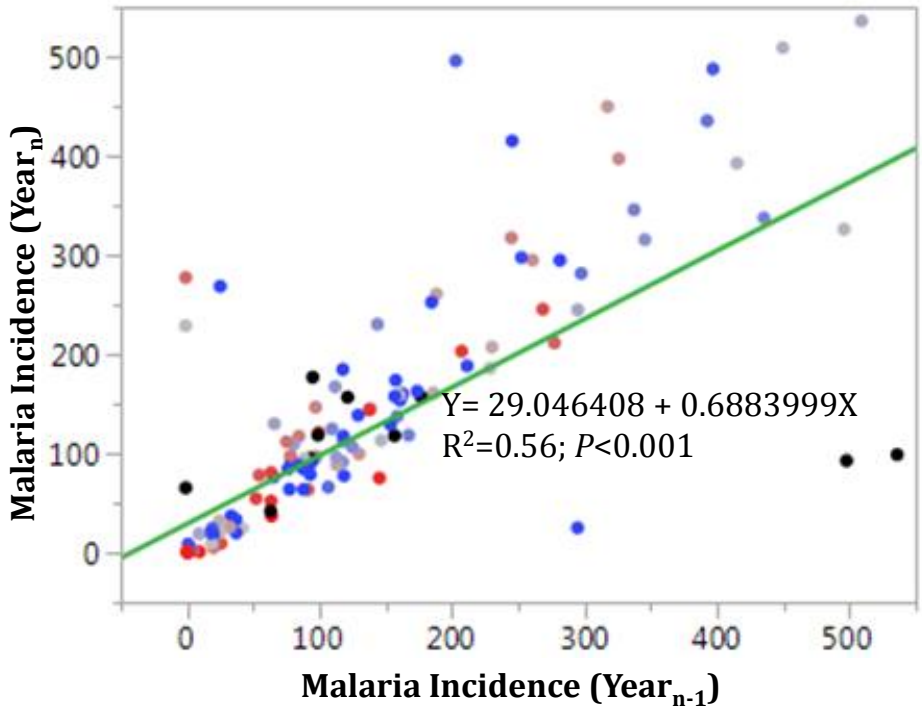
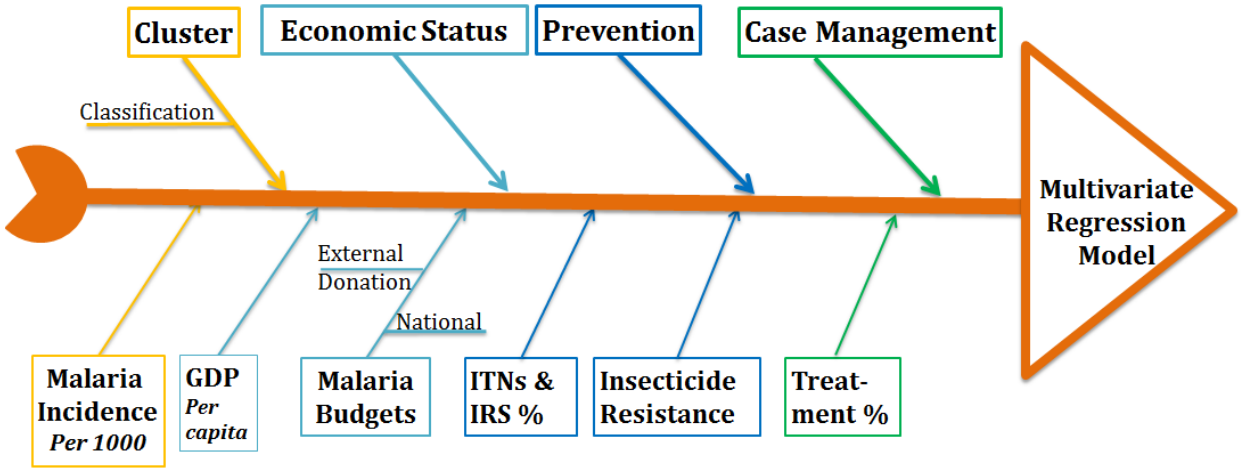


Appendix 1. Potential factors influencing malaria disease in Africa.



Appendix 2 Malaria incidence one year lag autocorrelation. The correlation between malaria incidence in current year and last year.



Appendix 3 Study Methods.