ESTIMATES OF MALARIA ATTRIBUTABLE FRACTION AMONG CHILDREN IN ONA ARA LOCAL GOVERNMENT AREA , OYO STATE

BY

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CERTIFICATION

I certify that this project was done under my supervision by Owolabi Boluwaji Benedicta of the Department of Epidemiology and Medical Statistics, Faculty of Public Health, College of Medicine, University of Ibadan, Ibadan, Nigeria.

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DEDICATION

This project is dedicated to the glory of God and also to my parents Dr. and Mrs. H.O Owolabi.

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ABSTRACT

Malaria remains a major public health problem particularly in the tropics and about 90% of malaria in Africa occur in young children who are more vulnerable than adults. Fever is one of the major symptoms of malaria; however, not all fever cases is a result of malaria. Therefore this study estimated the proportion of fever cases that can be attributed to malaria among children in south west Nigeria.

The study period was from February 2011 to June 2011. Participants who have been residing in the community for six months or more who gave written or verbal informed consent were enrolled into the study. Records of all children (≤ 12yrs) eligible for the study were used for the analysis. Malaria attributable fraction (MAF) was estimated using 3 approaches: Classical method parametric regression method such as logistic regression model and Non parametric regression method such as local linear smoothing.

The mean age of the respondents was 5.6±3.2 years. According to age group, the proportion of children with fever increased during the first 3 years of life and thereafter decreased but was not significant with age. The prevalence of Parasitemia also decreased with increasing age as those with age < 3years of age had the largest Parasitemia of 56.4% and those with age ≥ 10years had the lowest Parasitemia of 39.3%. The proportion of MAF obtained from the classical method was 0.2652(95% CI, 0.1784-0.3520), the logistic estimate for those with parasite density less than 1000µl was 0.0385 (95% CI, 0.0105- 0.0665) and for those with parasite density ≥1000µl was 0.3215 (95% CI, 0.2738- 0.3691). The non parametric estimate of the MAF obtained was 0.2447 (95% CI, 0.1785- 0.3119).

The prevalence of malaria disease and fever during childhood remained high. The study observed that fever rates increases sharply for low exposures and also approaches 1 for high exposures, it also suggests a monotone pattern of the conditional probability of $P(Y = 1|X = x)$. However, other causes of fever should be considered in the case of management of febrile illnesses during childhood. The logistic estimate for parasite density category of ≥1000µl gave the highest malaria attributable fraction and had the smallest Confidence interval followed by the local linear estimate. Therefore the logistic method is a better estimate while classical method behaved the worst.

Keyword: Malaria attributable fraction, Fever, Local linear smoothing.

CHAPTER ONE

1.1 Introduction

Malaria is a disease caused by plasmodium spp parasites that infects about 154 to 289 million people per year resulting in approximately 660,000 deaths worldwide. The anopheles mosquitoes transmit the parasites to humans when they bite. Of the four common species that cause malaria, the most serious type is Plasmodium *falciparum* and it can be life threatening. Another relatively new specie Plasmoium *Knowlesi* is also a dangerous species that is typically found only in a long tailed and pig tailed macaque monkeys. The other three common species of malaria are less serious and are usually not life threatening. It is possible to be infected with more than one species of Plasmodium at the same time. The incubation period for malaria symptoms is about one to three weeks but may be extended to eight to ten months after the initial infected mosquito bites occur. Some people may have dominant parasites that may get reactivated years after the initial reaction.

1.2 Malaria transmission

The intensity of transmission depends on factors related to the parasite, the vector, the human host and the environment. About 20 different Anopheles species are locally important around the world. All of the important vector species bite at night. Anopheles mosquitoes breed in water and each of the species has its own breeding preference e.g some prefer shallow collections of fresh water, such as puddles, rice fields and hoof prints. Transmission is more intense in places where the mosquito life span is longer and where it prefers to bite humans rather than other animals.

Transmission also depends on climatic conditions that may affect the number and survival of mosquitoes, such as rainfall patterns, temperature and humidity. In many places, transmission is seasonal, with the peak during and just after the rainy season. Malaria epidemics can occur when climate and other conditions suddenly favour transmission in areas where people have little or no immunity to malaria. They can also occur when people with low immunity move into the areas with intense malaria transmission e.g to find work or as refugees.

Human immunity is another important factor especially among adults in areas of moderate or intense transmission conditions. Partial immunity is developed over the years of exposure and while it never provides complete perfection it does reduce the risk that malaria infection will cause severe disease. For this reason, most malaria deaths in Africa occur in young children, whereas in areas with less transmission and low immunity, all age groups are at risk.

1.3 Identification/ Symptoms of Malaria

The most prominent clinical feature of malaria is fever, classical descriptions of fever with a regular recurring pattern every two or three days is not usually present when the disease begins. Irregular fever may occur due to mixed infections, ineffective use of prophylactic drugs and partial treatment. Patients commonly feel well on the day when fever is absent. Early diagnosis with prompt appropriate treatment is essential as malaria can be a fatal disease. If the initial blood film is negative for malaria parasites, it should be repeated within 12-24 hours and preferably when temperature is rising. One negative test does not exclude the diagnosis particularly if the patient has taken anti-biotic which may result in partial treatment of the infection. The rapidly rising temperature is commonly associated with shaking chills, muscle pains, back pain, nausea and headache and the episode normally ends with profuse sweating.

1.4 The burden of malaria in Africa

About 90% of all malaria death in the world today occurs in Africa, south of the Sahara. This is because the majority of infections in Africa are caused by Plasmodium Falciparum, the most dangerous of the four malaria parasites. It is also because the most effective malaria vector- the mosquito anopheles Gambiae- is the most wide spread in Africa and the most difficult to control. An estimated one million people in Africa die from malaria each year and most of these are children under five years old. Malaria affects the lives of almost all people living in the area of Africa defined by the southern fringes of the Sahara desert between latitude 15°North and 30°south and longitude 15°west and 40°west. Most people at risk of the disease live in area of relatively stable malaria transmission- infection is common and occurs with sufficient frequency that some level of immunity develops. A smaller proportion of people live in areas where rates of malaria are more seasonal and less predictable because of either altitude or rain fall patterns. People live in the peripheral areas north or south of the main endemic area or bordering island areas are vulnerable to highly seasonal transmission and to malaria epidemics.

In areas of stable malaria transmission, very young children and pregnant women are population groups at highest risk of malaria morbidity and mortality. Most children experience their first malaria infections during the first year or two of life, when they have not yet acquired adequate clinical immunity- which makes this early years particularly dangerous. 90% of all malaria death in Africa occurs in young children. Adult women of area of stable transmission have a high level of immunity but this is impaired especially in the first pregnancy with the result that risk of infection increases. Contrary to other tropical diseases, since the failure of the eradication efforts in the 1980's, malaria is widely described as an unavoidable effect of tropical location and natural forces such as heavy rain falls and flooding (Thuilliez, 2009).

1.5 Rationale

Malaria attributable fraction has not been done among children in Nigeria.

There is interest in knowing which method gives the best estimate out of the classical, the parametric and the non parametric approaches of estimating malaria attributable fraction.

1.6 Justification of the study

Fever caused by malaria parasite often cannot be distinguished on the basis of clinical features from fever caused by other common childhood infections such as common cold, pneumonia, influenza, viral hepatitis or typhoid fever (Hommel, 2002, Koram and Molyneux, 2007). One aid to deciding whether a fever is caused by malaria parasite is to measure the density of malaria parasite in the child's blood but even if a child has fever and has a high parasite density, the fever might still be caused by another infection (Small *et al*, 2010) hence the need for the estimation of the proportion of fever cases that is attributable to the malaria parasite is important for understanding the burden of the diseases and the changes in the burden. The findings are also expected to generate awareness which could lead to improvement in the level of government participation in the effective prevention and control of malaria.

The occurrence of fever cases due to other causes in the presence of parasitemia may well result in over diagnosis of clinical malaria thus, estimation of the proportion of fever cases attributable to malaria infection is crucial to establish a more concise definition of clinical malaria.

1.7 Objectives of the study

Broad objective

- To determine the proportion of fever cases attributable to malaria.

Specific Objectives are to:

- Determine the prevalence of plasmodium *falciparum* in children.
- Determine the prevalence of fever in children
- Estimate associated risk factors of malaria.
- Derive the malaria attributable fraction using the classical, parametric and non-parametric approaches.
- Compare the classical, parametric and non-parametric estimates of the malaria attributable proportion.

CHAPTER TWO

2.1 Background to Malaria

The World Health Organization has defined malaria as a disease caused by a parasite called plasmodium, which is transmitted via the bite of infected mosquitoes. In the human body, the parasites multiply in the liver and then infect red blood cells. In 2004, malaria was thought to have been declining in the tropics (Crump *et al*, 2013) but according to the World Malaria Report of 2011, malaria is the most widespread infection and is prevalent in 106 countries of the tropical and semi tropical world with 35 countries in Central Africa bearing the highest burden of cases and deaths. Malaria is also ranked amongst the foremost public health and development issues facing tropical countries in areas of stable malaria transmission, the population is constantly exposed to intense transmission due to frequent infective Anopheles vector bite. Under such condition significant immunity develops among the adult population. (Wagbatsoma and Omoike 2008).

Level of immunity affects not only the mortality and severity of malaria but also non-complicated malarial attacks (Thuilliez 2009). Children under five years and pregnant women are mostly affected by this intense transmission. (Wagbatsoma and Omoike 2008). The syndrome of fever is caused by a large number of infectious diseases. (Crump et al, 2013)

2.2 Identification of a malaria case

Misidentification of malaria cases can result in grave consequences and so correct identifications are necessary especially when:

1. Managing of an individual patient and incorrect diagnosis can result either in failure to treat a potentially dangerous malarial illness, or failure to seek and treat an alternative cause of the illness.

2. In enrolling "cases" to a study of pathogenesis or therapy, when false diagnoses may mask important results or bring up ones that are not genuine.

3. In identifying endpoints in preventive or therapeutic intervention trials.

4. In documenting the extent of the public health problem ("the burden of malaria") and how this changes over time, when properly identified trends may indicate the need for new efforts or the success of existing ones.

Misdiagnosis of malaria is common both in the identification of uncomplicated disease (the febrile illness) and in the diagnosis of severe or complicated malaria. Both under-diagnosis and over-diagnosis may occur. The implications of this inaccuracy depend upon whether diagnosis is being used for diagnosis or for research purposes (Koram et al, 2007).

World Health Organization (WHO) advises presumptive diagnosis as the basis for first-line treatment of uncomplicated malaria in places where a parasitological test is not possible. This policy allows uncomplicated malarial illnesses to be treated by village health workers, shopkeepers, or relatives in the home, and thus minimizes delays in treatment, especially for those living a long way from formal health facilities

2.3 Malaria in children

Malaria kills between 700,000 and 2.7 million people yearly and 75% of these deaths are of the African children (Thuilliez, 2009). In Nigeria, malaria remains the country's most important health problem. It accounts for 25% of infant mortality, 30% of under-5 mortality and 11% of maternal mortality. Between 2000 and 2010, at least 50% of the population had one episode of malaria per year, while children below 5 years had two to four attacks (Odey et al, 2013 & Uzochukwu et al, Sept. 2010). Benjamin SC et al reported that malaria has also resulted in high productivity loses. It has also been shown that In Nigeria malaria is a big contributor to the economic burden of disease in communities where it is endemic and is responsible for annual economic loss of 132 billion Naira. It is estimated that of 300,000 deaths occurring each year, 60% of outpatient visits and 30% hospitalizations are all attributable to malaria (Uzochukwu et al. Sept. 2010).

Children under five years of age are one of the most vulnerable groups affected by malaria. There was an estimated 660 000 malaria deaths around the world in 2010 of which approximately 86% were in children under five years of age. In high transmission areas, partial immunity to the disease is acquired during childhood. In such settings, the majority of malarial disease and particularly severe disease with rapid progression to death occurs in young children without immunity. Young children are much more vulnerable to all forms of malaria because their immune systems are not yet fully developed and have not yet developed effective resistance to the disease. Malaria can have a devastating effect of children's education. Repeated infections cause children to miss large periods of school and anemia, a side effect of frequent malaria attacks, interfere with children's ability to concentrate and learn and cause chronic fatigue. Repeated illnesses from malaria can also exacerbate any malnutrition which can both decrease the effectiveness of anti malaria drugs and increase children's susceptibility to the other main

killer diseases: Diarrhoea and pneumonia (malaria consortium & UNICEF). Severe anemia, hypoglycemia and cerebral malaria are features of severe malaria more commonly seen in children than in adults, (WHO, 2013). Malaria and pneumonia are both leading causes of deaths in children under-five years of age in Africa. Estimates shows that about 150 million episodes of pneumonia occur annually in under-fives in developing countries including Africa, representing more than 95% of all new cases worldwide (Nonvignon et al, 2010).

2.4 Malaria in Adult and pregnant women

Some other populations that are also at higher risk of contracting malaria and developing severe disease apart from children are pregnant women, patients with HIV/AIDS, non immune migrants, mobile populations and travelers,(WHO, 2013). Malaria infection in pregnancy is a major public health problem in tropical and sub tropical regions throughout the world. In most endemic areas of the world, pregnant women are the main adult risk group for malaria. It is estimated that each year, over 30 million women become pregnant in malaria areas of Africa with most living in area of stable malaria transmission. Malaria during pregnancy has been most widely evaluated in Africa south of the Sahara where 90% of the global malaria burden occurs. The burden of malaria infection during pregnancy is caused chiefly by plasmodium falciparum, the most common specie in Africa.

The symptoms and complications of malaria during pregnancy differ with the intensity of malaria transmission and with the level of immunity the pregnant woman has acquired. (Roll Back Malaria, 2010). Malaria in pregnancy increases the risk of maternal and fetal anaemia, still birth, spontaneous abortion and low birth weight babies which can result in neonatal death (WHO, 2013). It is estimated that in areas where malaria is endemic, around 19% of infants low birth weights are due to malaria and 6% of infants deaths are due to low birth weight caused by

malaria. The estimates imply that around 100,000 infant deaths each year could be due to low birth weight caused by malaria during pregnancy in areas of endemicity in Africa (CMR, 2004)

2.5 Attributable fraction

The attributable fraction (AF) of a disease due to an exposure is the fraction of disease cases in a population that can be attributed to that exposure. It is also referred to as the proportion of disease cases which would be eliminated if everybody's exposure was set to zero. (Wang *et al*, 2012). If members of a community are exposed to a risk factor that causes health problem or death and that risk factor is removed from the environment, we would expect the overall number of health problems or death in the community would decline. The proportional reduction in the number of health problems or deaths as a result of reducing the risk factor is known as attributable proportion. It is an important measure of the public health impact of the exposure on disease burden. (Wang et al, 2012).

2.6 Estimation of attributable fraction

A formular for the attributable fraction was first proposed by Levin in 1953 which is easy to calculate and dependent on generally easily accessible estimate regarding the underlying prevalence of risk factor in the population and the relative risk of developing the disease among those with, versus those without the risk factor (Rosen 2013). The Original formular is

$$AF = \frac{(RR-1)P(E)}{(RR-1)P(E)+1}$$

Where : p = the underlying prevalence of the risk factor in the population

RR(Relative Risk): Risk of contracting a disease in an exposed population divide by the risk of contracting a disease in an unexposed population.

MacMahon & Pugh (1970) also proposed an alternative formulation in terms of the total risk of disease and the risk of disease in the unexposed.

$$AF = 1 - \frac{P(D/E')}{P(D)}$$

The two formulations were proved to be algebraically equivalent by Leviton (1973) and it constitutes the classical definition of the attributable fraction.

2.7 Malaria Attributable Fraction

Malaria attributable fraction (MAF) is an important epidemiological quantity for measuring the burden of malaria. It is also known as the proportion of fever that is attributable to malaria. A difficulty in estimating the malaria attributable fraction is that it is difficult to diagnose a fever as being due to malaria parasite compared to other illnesses such as influenza, pneumonia, viral hepatitis or typhoid fever. Crump et al mentioned that increasing use of malaria diagnostic tests reveals a growing proportion of patients with fever who do not have malaria and they also found out in their study that malaria was over diagnosed. Microscopic examination of blood for malaria parasite helps to diagnose a fever as being due to malaria but children living in areas of high malaria endemicity often tolerate malaria parasites without developing any signs of the disease, consequently, a fever may not be attributable to malaria even if the child has malaria parasite in his or her blood (Small, 2007). Breslow et al, discussed that in some areas where malaria is endemic, Over 80% of the "asymptomatic" general population less than 10 years old have peripheral parasitemia. In such areas, parasitemia accompanied by clinical symptoms of malaria

does not necessarily imply that clinical malaria is present. An illness that includes fever may be confused with clinical malaria because of accompanying parasitemia which all contributes to the complexity involved in the diagnosis of malaria in endemic areas (Mwangi *et al.* 2005). In the past, the usual approach to this problem was to base definitions of clinical disease on parasitemia above certain thresholds accompanied by fever. This was done because high-level parasitemia was assumed to be more likely to cause fever than low-level parasitemia. However, such cutoff values for parasite density may lead to an unquantifiable level of misdiagnosis of malaria. The fraction of fevers attributable to parasitemia can also be used to calculate the number of fevers that would be eliminated if malaria was eradicated .

This classic method of calculating the fraction of fevers attributable to parasitemia compares the proportion of the population that is febrile and has parasitemia with the proportion of the population that is afebrile and has parasitemia. In areas of high endemicity, this method is not useful, because most of the afebrile population will have parasitemia. To overcome this problem, logistic regression has been used to model the risk of fever as a continuous function of the parasite density.

2.8 Estimation of malaria attributable fraction

Smith *et al 1994* proposed a methodology to estimate the attributable proportion of fever using a logistic regression of the fever on a monotonic function of the parasite density (Mabunda et al, 2009). Different methods can also be used to estimate the attributable fraction when the exposure is semi continuous i.e a clump of people have zero exposures and the rest of the people have continuously distributed positive exposures.

If there are no confounders of the exposure-disease relationship (or if we are considering the AF within a stratum of confounders), then the AF is the following. (Benichou, 2005.)

$$AF = \frac{P(Disease) - P(D/E')}{P(Disease)}$$

The classical estimate of AF is given by plugging sample proportions of P(Disease) and P(Disease|Exposure=0) into the equation above. Smith, Schellenberg, and Hayes (1994) pointed out that when the proportion of subjects with zero exposure is small, it will be hard to estimate P(Disease|Exposure = 0) and the classical estimate of AF will have wide confidence limits. For the exposure of malaria parasites in a malaria endemic area, parasite prevalence in young children may exceed 80 percent so that the proportion of children with zero exposure is small. When the proportion of people with zero exposure is small, one way to improve precision is to assume that low exposure is equivalent to zero exposure and estimate P(Disease|Exposure = 0) by the sample proportion of people with disease with zero or low exposure. However, the resulting estimate may strongly rely on the definition of low exposure.

To borrow strength in estimating P(Disease|Exposure = 0) without assuming that P(Disease|Exposure=0) = P(Disease|Exposure is 0 or low), regression models for P(Disease|Exposure) can be used to estimate P(Disease|Exposure=0). Logistic regression is a frequently applied regression method to estimate the AF (Wang *et al*, 2012). In practice, the mechanism of the exposure on the disease is usually unknown and can be very complicated, and so the true model is not necessarily in a logistic form. Power models extend logistic regression by considering transformations of the exposure variable such as logarithm and fractional polynomials (Royston *et al* 1999; Royston *et al*, 2010; Smith *et al*., 1994). An alternative to parametric regression for estimating the AF is nonparametric modeling of

P(Disease|Exposure), particularly when no prior knowledge about the shape of the true curve is available. It improves efficiency to incorporate any known shape constraints on the regression function.

CHAPTER THREE

METHODOLOGY

3.1 Study area

The study was conducted in Ona Ara Local Government Area, Oyo state. It is located southeast of Ibadan, the capital of Oyo state Nigeria. Ibadan, with a population of 1, 338,659 according to the 2006 census, is the third largest metropolitan area by population in Nigeria, after Lagos and Kano. Ibadan is also the largest metropolitan geographical area. At independence, Ibadan was the largest and most populous city in the country and the third in Africa after Cairo and Johannesburg. The city is naturally drained by four rivers with many tributaries. Ona river in the north and west: Ogbere river towards the east; Ogunpa river flowing through the city and kudeti river in the central part of the metropolis.

Ibadan has a tropical wet and dry climate, with a lengthy wet season and relatively constant temperatures throughout the course of the year. Ibadan's wet season runs from March through October, though August sees somewhat of a lull in precipitation. This lull nearly divides the wet season into two different wet seasons. November to February forms the city's dry season, during which Ibadan experiences the typical West African harmattan. The mean total rainfall for Ibadan is 1420.06mm, falling in approximately 109 days. There are two peaks for rainfall, June and September. The mean maximum temperature is 26.46°C while minimum is 21.42°C and the relative humidity is 74.55%. There are 11 local governments in Ibadan Metropolitan area consisting of five urban local governments in the city and six semi-urban local governments in the rural areas.

Ona Ara being the local government where the study was carried out covers a total land area of 425.544 square kilometers with a population density of 707 persons per square kilometer. There are about 56,406 children under the age of five years and 12,515 infants according to data from

National Programme on Immunization 2007. Older children were about 124,999 and adults are 100,630.

3.2 Study design

This study utilized secondary data analysis. The data used was collected and used by a student of the Department of Epidemiology and Medical Statistic of the University of Ibadan on the 'Epidemiology of malaria-intestinal helminth co-infection among children in Ona-Ara local government area in 2011.

3.3 Study period and population

The study period was from February 2011 to June 2011. Participants who have been residing in the community for up to six months or more who gave written or verbal informed consent (for children whose Caregiver provided written or verbal informed consent) were enrolled into the study.

3.4 Target population

The target population are children under twelve years of age. Children in this age group are more at risk of having malaria than the adults because young children are without immunity or still developing their immunity and have not yet developed effective resistance to the disease (CDC, 2012). All children who were present for the study were used and none was beyond the age of twelve years.

3.5 Sampling technique

A comprehensive list of the 6 rural wards and the comprising villages were located at the Local Government Headquarters. Thereafter 43 villages in the rural wards were recruited by convenience based on largest population size, accessibility of road and the informed consent and assistance of the village heads.

3.6 Collection of samples

Research assistants visited all households with the eligible in the villages selected. In case no one was available for the survey or no one was at home when a research assistant visited, or there was no eligible child or the household head refused to give consent, the research assistant proceeded to the next household.

For each child recruited, firstly, data such as age, sex and auxiliary temperature were obtained and recorded in a structured questionnaire (Fever was defined as auxiliary temperature of ≥37.5°C). Also capillary blood from a finger prick was used for the preparation of thick blood films and filling of a heparinized capillary tube for the determination of packed cell volume. Thick blood smears were made on slides which were air-dried and taken to the research Laboratory in the Institute of Advanced Medical Research and Training, College of Medicine, University of Ibadan for microscopy. Parasiteamia densities were grouped into three categories: None (without the parasite), 1-999/µl and ≥1000/µl as was done by Prybylski et al, (1999).

3.7 Analysis plan

Descriptive statistics such as means, medians, ranges and standard deviations were used to present quantitative variables while categorical variables were presented with proportions and percentages. The Chi square test was used to compare proportions and to investigate associations

between parasite density and other variables such as presence of fever, headache, chills and other reported signs and symptoms. Logistic regression as a parametric estimate of attributable fraction was used to model parasitemia as a continuous function of fever. The model used was

$$logit\ (\pi_i) = \alpha + \beta(X_i)^T$$

which represents a logistic regression model where π_i is the probability that observation i with parasite density X_i is a fever case. The relationship between *P. falciparum* parasite density and clinical signs and symptoms of malaria was calculated. Parasitemia densities was grouped into three categories. The prevalence of malarial signs and symptoms within the parasite density strata was calculated. Multiple binary logistic regression was used to estimate the associations between parasite density and various signs and symptoms of malaria that achieved significance in the bivariate analysis.

Another means for estimating the AF is nonparametric modeling of P(Disease|Exposure), it is useful particularly when no prior knowledge about the shape of the true curve is available. Under certain circumstances, it is often thought that P(Disease|Exposure) is a monotone increasing function of the exposure level i.e higher level of malaria parasite density leads to an increase in risk of fever. According to (Wang *et al*, 2012), non parametric regression method has not being used to estimate the attributable fraction previously but has been used to analyze medical or health related data and it improves efficiency to incorporate any known shape constraints (i.e the monotonicity constraints) on the regression function. Parametric and non parametric approaches of estimating attributable fraction helps to compare performances of these methods in estimating the attributable fraction for a semi continuous exposure i.e an exposure to which a group of people have zero exposure and the rest have positive exposures. Malaria in children has been identified as a semi-continuous exposure (Wang *et al*, 2012) which agrees with the data used.

3.7.1 Estimation of attributable fraction

Let $y = \begin{cases} 1 & \text{Presence of disease} \\ 2 & \text{Absence of disease} \end{cases}$.

The conditional probability of disease at exposure level X is P(Y = 1|X = x). The attributable fraction of a semi- continuous exposure is being considered i.e an exposure to which a group of people have zero exposures and the rest of the people have continuously distributed positive exposure. Estimation of the attributable fraction involves estimating the conditional probability of having the disease given the exposure. We assume that there are no confounders of the disease-exposure relationship or that we are considering the AF within a stratum of confounders. Under the assumption of no confounders, the AF is:

$$\frac{P(Y=1)-P(Y=1|X=0)}{P(Y=1)} = P(X > 0|Y = 1)\left(1 - \frac{1}{R}\right) \quad \ldots(3.1)$$

Where R is the relative risk of disease with exposure greater than zero compared to zero exposure. The classical estimate of the attributable fraction is to plug the sample proportions $\widehat{P}(Y = 1)$ and $\hat{P}(Y = 1|X = 0)$ into the left hand side of the equation (3.1).

To estimate the attributable fraction using regression methods, the above equation can be written as:

$$\text{AF} = \int \left[1 - \frac{P(Y=1/X=0)}{P(Y=1/X=x}\right] dF(x/Y = 1) \quad \ldots(3.2)$$

Where F(x/Y=1) is the conditional distribution of the exposure in the subpopulation of people with the disease.

Based on equation (2) from a random sample of size N from the population, one can estimate AF as:

$$\widehat{AF} = \frac{1}{\sum_{i=1}^{N} I(y_i=1)} \sum_{i=1, Yj=1}^{N} \left[1 - \frac{P(Y \neq 1|X=0)}{P(y_i=1|X_i \neq 0)}\right] \quad \ldots(3.3)$$

Where $\hat{p}(Yi = 1/Xi = xi), \widehat{P}\ (Yi = 1/Xj = 0)$, i=1,...N are estimates from a regression model of the conditional probability of disease at exposure levels.

The approaches that would be used in estimating the probability functions are

1) Classical method
2) Parametric regression method such as logistic regression model
3) Non parametric regression method such as local linear smoothing

3.7.2 Determination of attributable fraction estimates using classical methods

This approach estimates the frequency of clinical malaria by using information on parasite levels in children with individual symptoms and signs and those without symptoms and signs to estimate the proportion of individual symptoms and signs that are attributable to malaria. The overall estimate (λ) of the fraction of episodes attributable to a given exposure is given by

$$\lambda = P(R-1)/R$$

where P is the proportion of parasitemic individuals who presented with symptom/sign in question and R is the relative risk of the sign or symptom associated with the exposure.

The overall estimate of λ will be calculated using only two categories(with/without parasitaemia), P is the proportion of parasitemic individuals who presented with the symptom or sign in question and R is the relative risk of the sign or symptom associated with the exposure. R is estimated by the adjusted odds ratio of the symptom/sign in question for the parasitemic group (relative to the baseline aparasitemic group) derived from the fitted logistic regression

3.7.3 Determination of Attributable fraction estimates using the logistic regression method:

Separate logistic models would be constructed to examine the parasite density-specific malaria attributable fraction (λ_j) $=P_j(R_j - 1)/R_j$ associated with each of the parasite density categories where R_j is the adjusted OR of the various symptoms/signs for the j^{th} category, relative to the baseline category j = 1,which is based upon observations on aparasitemic patients, and P_j is the proportion of patients with the symptom/sign in question with parasites in the j^{th} category(there are three different categories: those without the parasite, those with <1000µl and those with ≥1000µl)

3.7.4 Determination of attributable fraction estimates using local linear smoothing method:

Local linear smoothing is an approach to fitting curves and surfaces to data by smoothing. The underlying model for local regression is

$$E(y_i) = f(x_i), i = 1, \dots n$$

Where the y_i are observations of a response variable and x_i are observations of the independent variable that form the design space for the model.

Loess (locally weighted scatter plot smoothing) is a method that is usually used for local linear smoothing. It is a non parametric regression method that combines multiple regression models in a k-nearest neighbor-based meta-model. Loess fits simple models to localized subsets of data to build up a function that describes the deterministic part of the variation in the data point by point.

Given a random sample $(X_1, Y_1),\ldots,(X_n, Y_n)$ of the covariate and the response, the association between the variable are usually compared using regression analysis i.e estimating $m(x) = E(Y/X = x)$ which is the best predictor in mean squared error. Local linear smoothing consists of using weighted local linear regression which has advantages over other linear smoothers.

Loess specifically denotes a method that is also known as locally weighted polynomial regression. At each point in the data set a low-degree polynomial is fitted to a subset of the data with explanatory variable values near the point whose response is being estimated. The polynomial is fitted using weighted least squares giving more weight to the point near the point whose response is being estimated and less weight to the points further away. The value of the regression function for the point is then obtained by evaluating the local polynomial using the explanatory variable values for that data point. Its advantages among others include that it does not require specification of a function to fit a model to all the data in the sample. The smoothing parameter and the degree of the local polynomial only needs specification and it is always very flexible making it ideal for modeling complex processes for which no theoretical models exist.

In the Loess method, weighted least squares are used to fit linear or quadratic functions of the predictors at the centers of neighborhood. The radius of each neighborhood is chosen so that the neighborhood contains a specified percentage of the data points. The fraction of the data called the smoothing parameter in each local neighborhood controls the smoothness of the estimated surface. Data points in a given local neighborhood are weighted by a smooth decreasing function of their distance from the centre of the neighborhood.

For each data point, the regression weights are computed and are given a tricube function given below

$$w_i = \left(\left|\frac{x - x_i}{d(x)}\right|^3\right)^3$$

Where x is the predictor value associated with the response value to be smoothed, x_i are the nearest neighbors of x as defined by the span and $d(x)$ is the distance along the abscissa from x to the most distant predictor value within the span. A weighted linear least squares regression is performed and a second degree polynomial is used for the regression then the smoothed value is given by the weighted regression at the predictor value of interest.

Where x is the predictor value associated with the response value to be smoothed, x_i are the nearest neighbors of x as defined by the span and $d(x)$ is the distance along the abscissa from x to the most distant predictor value within the span. A weighted linear least squares regression is performed and a second degree polynomial is used for the regression then the smoothed value is given by the weighted regression at the predictor value of interest.

CHAPTER FOUR

4.0 RESULTS

4.1 Socio demographic characteristics

Three hundred and forty five records were available for analysis. The mean age of the respondent was 5.6±3.2 years. About a third of the respondents ≤3 years of age (31.9%), 164 (47.5%) were males and 181 (52.5%) were females. Table 1 shows the frequency distribution of socio demographic characteristics and other variables used.

Table 4.1: Frequency table of respondent's characteristics.

Characteristics	N	%	Total
SEX			
Male	164	47.5	345
Female	181	52.5	
AGE (in years)			
≤ 3	110	32.2	
4 – 6	91	26.2	230
7 – 9	84	24.6	
10-12	57	16.7	
PARASITE DENSITY CATEGORY			
No parasitaemia	163	47.2	
Parasitaemia ≤ 999µl	62	18	343
Parasitaemia ≥ 1000µl	120	34.8	
Signs & symptoms			
Bodyache			
Yes	176	53.0	332
No	156	47.0	
Yellowish eye			
Yes	77	23.2	325
No	255	76.8	
Loss of appetite			
Yes	146	44.0	332
No	186	56.0	
Skin Infection			
Yes	75	22.6	332
No	257	77.4	
Vomiting			
Yes	110	33.2	331
No	221	66.8	
Headache			
Yes	264	79.5	332
No	68	20.5	
High temperature			
Yes	225	67.8	332
No	107	32.2	
Chills and rigor			
Yes	148	44.7	331
No	183	55.3	
Temperature < 37.5	301	93.5	
≥ 37.5	21	6.5	322

4.2 Relationship between *Plasmodium falciparum* parasite density and clinical signs and symptoms:

The percentage of children that were aparasitemic was (47.2%). Eighteen percent had < 1000μl and 34.8% had ≥ 1000 μl. Of all the children presenting with headache, 47.3% were aparasitemic while 52.7% were parasiteamic i.e positive. Of those that had Loss of appetite 50.7% were without the malaria parasite while 49.3% had the malaria parasite and of the 75 children presenting with yellowish eyes 45.3% had the malaria parasite.

In addition, there was no significant associations between those with parasitemia and the symptoms: history of fever, vomiting, chills & rigors, skin infection and body ache.

Table 4.1: Malaria parasite categories and presenting signs and symptoms

Variable	N	Negative N (%)	Positive N(%)	P-value
Fever				
Yes	221	104(47.1)	117(52.9)	0.135
No	107	41(38.3)	66(61.7)	
Headache				
Yes	260	123 (47.3)	137(52.7)	0.027
No	68	22(32.4)	46(67.6)	
Chills and rigor				
Yes	146	67 (45.9)	79 (54.1)	0.613
No	181	78 (43.1)	103 (56.9)	
Vomiting				
Yes	109	48 (44.0)	61 (56.0)	0.937
No	218	97 (44.5)	121 (55.5)	
Skin infection				
Yes	75	38 (50.7)	37 (49.3)	0.200
No	253	107 (42.3)	146 (57.7)	
Loss of appetite				
Yes	146	74 (50.7)	72 (49.3)	0.034
No	182	71(39.0)	111 (61.0)	
Body ache				
Yes	174	80(46.0)	94 (54.0)	0.493
No	154	65 (42.2)	89 (57.8)	
Temperature				
<37.5	298	136 (45.6)	162 (54.4)	0.355
≥ 37.5	20	7 (35.0)	13 (65.0)	
Yellowish eye				
Yes	75	41 (54.7)	34 (45.3)	0.038
No	253	104 (41.1)	149 (58.9)	

4.3 Prevalence of Fever and Malaria

Overall, fever prevalence (Auxiliary temperature of > 37.5°C) among children was 6.6%. Table 3 shows the prevalence of parasite and fever in different age groups. The prevalence of fever decreased with increasing age with children in the age group of less than three years old having the highest fever prevalence of 9.6%. The lowest fever prevalence of 3.9% was recorded among children ten years and above. According to age group, the proportion of children with fever increased during the first 3 years of life and thereafter decreased but was not significant with age.

The prevalence of parasitemia also decreased with increasing age but those in the age category of 4-6 years of age had the highest and those with age greater than or equal to ten years had the lowest (39.3%).

Table 4.3: Prevalence of fever and parasiteamia across different age groups.

Age group	N	Parasite (%)	Fever (%)	*Fever and parasite (%)
≤ 3	110	56.4	9.6	4.5
4-6	91	57.8	5.8	4.4
7-9	84	55.4	5.1	4.8
≥10	57	39.3	3.9	1.8
Total	342	53.7	6.6	4.1

*(Those with temperature ≥ and have the malaria parasite)

4.4 Association between fever and parasite density categories

The risk of having fever increased with increasing parasite density, particularly from parasite density category ≥1,000 parasites/µl. High *P. falciparum* parasite densities were not significantly associated with fever.

Table 4.4: Proportion of fever cases according to parasite density categories

Parasite density (parasite/µl)	Fever cases (%)
No parasite count	4.7
< 1000	5.2
≥ 1000	9.5

Table 4.5: Distribution of malaria parasite densities and fever rates in children.

Parasite density (parasite/µl)	Number of observations	Fever rate
0	148	0.0437
1 - 3 000	105	0.0667
3 001 – 7 000	41	0.0244
7 001 – 15 000	13	0.0769
15 001 - 30 000	8	0.375
30 001 – 130 000	7	0.4

In Table 7, the fever rates continued to increase as the parasite density Increased after the third interval of 3 001–7 000/µl. In Figure 1, the fever rate was plotted against each interval of the parasite density. The plot suggests the fever rates increases sharply for low exposures and also approaches 1 for high exposures. The plot also suggests a monotone pattern of the conditional probability of $P(Y = 1/X = x)$

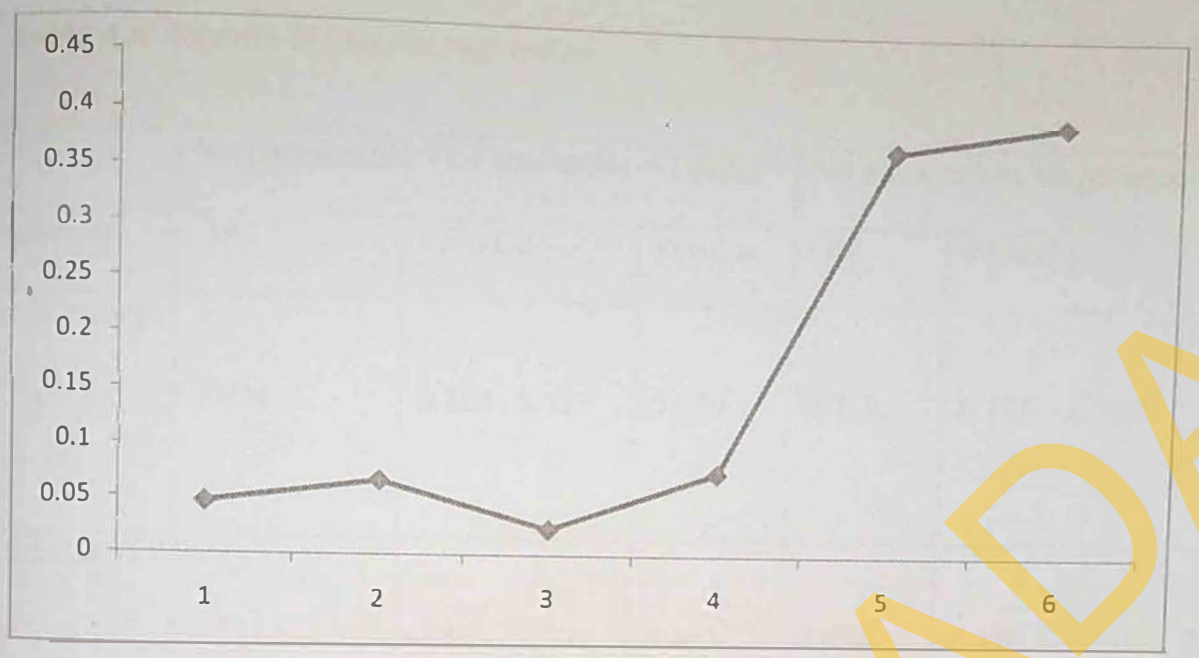

Figure 4.1: Fever rates for the parasite density intervals in table 4.5.

4.5 Relationship between parasitaemia and clinical signs and symptoms

A multivariable logistic regression analysis was conducted to examine the extent to which common signs and symptoms such as headache, loss of appetite, yellowish eye and temperature presented in children are associated with the presence of parasitaemia. There was no significant association of the signs and symptoms on those that have parasite count <1000. For those that have parasite count ≥1000 temperature was the only significant symptom. Those with temperature < 37.5°c are about 3 times less likely to have malaraia parasite count greater than 1000 compared to those that have their temperature greater than or equal to 37.5°c. (OR=0.319, 95% C.I= 0.103 – 0.984).

Table 4.6: Results of logistic regression

	No parasitemia Vs Parasitemia < 1000µl			No parasitemia Vs parasitemia ≥ 1000µl		
Predictors	OR	95% C.I	P-value	OR	95% C.I	P-value
Temperature < 37.5 ≥ 37.5*	0.934	0.164- 5.323	0.939	0.319	0.103 – 0.984	0.047
Headache Yes No*	0.731	0.314 - 1.701	0.467	0.654	0.340 – 1.257	0.202

*Reference level

4.6 Attributable fraction estimates for malaria: The classical method.

The classical method of estimation gives the overall MAF(λ) for temperature. The estimated overall attributable fraction for temperature ≥ 37.5^{O}C was 26.52% (95% CI=17.84%- 35.20%).

Table 4.7: Overall Malaria attributable fraction estimate

Symptom	n of P&S	N of S	P of P&S	R	Const	R-1	P(R-1)	$\lambda=\frac{P(R-1)}{R}$	OverallMAF(%)
Temp	13	20	0.65	1.689	1	0.689	0.4478	0.2652	26.52

Where:

N of P&S = number of parasitaemic children who presented with a particular sign/symptom.

N of S = number of those that present with the sign/symptom whether parasitaemic or non-parasitaemic.

P of P&S = Proportion of children who are parasitaemic and presented with the sign/symptom in question.

R = odds ratio of a particular sign/symptom relative to the baseline(non – parasitaemic children)

λ = malaria attributable fraction estimate.

4.7 Attributable fraction estimates for malaria: Logistic regression method.

The logistic regression method gives the parasite density – specific MAF (λ_j) of the sign and symptom across the parasite density categories. The density-specific MAF for temperature ≥37.5^{O}C was 3.85%(1.05% – 6.65%) in the category ≤999µl and 32.15%(27.38% - 36.91%) in the category ≥1000µl. (Table 5). For children with parasite count <1000µl, the proportion of fever cases that can be attributed to malaria was 3.85% which is lower, compared to children with parasite count ≥1000µl with proportion of fever cases that can be attributed to malaria as 32.15%. For those with parasite density ≤999/µl, it show that the proportion of fever cases that

we can attribute to malaria is small. Only about 4% of fever cases for those in this category can be safely attributed to malaria.

Table 4.8: Parasite density-specific attributable fraction estimates for Logistic method

PD category	Symptom	n of P&S	N of S	P of P&S	R	Const	R-1	P(R-1)	$\lambda = \frac{P(R-1)}{R}$	PD-specific MAF(%)
≤999µl	Temperature	3	10	0.4286	1.0987	1	0.0987	0.0423	0.0385	3.85
≥1000µl		11	18	0.6111	2.1102	1	1.1102	0.6784	0.3215	32.15

4.8 Attributable fraction estimates for malaria: Local linear smoothing method.

The attributable fraction using the local linear smoothing method was given as 0.2447 (0.1775 - 0.3119). This method shows that the proportion of fever cases that can be attributed to malaria was 24.47%. The line fitted to the graph in figure 2 is a locally weighted regression fitted by loess. In table 8, different estimators were displayed with their confidence intervals. The logistic regression estimator for those with parasite density ≤999µl had the smallest confidence interval. The nonparametric regression estimator i.e Local linear smoothing also had a smaller confidence intervals than the classical nonparametric estimator.

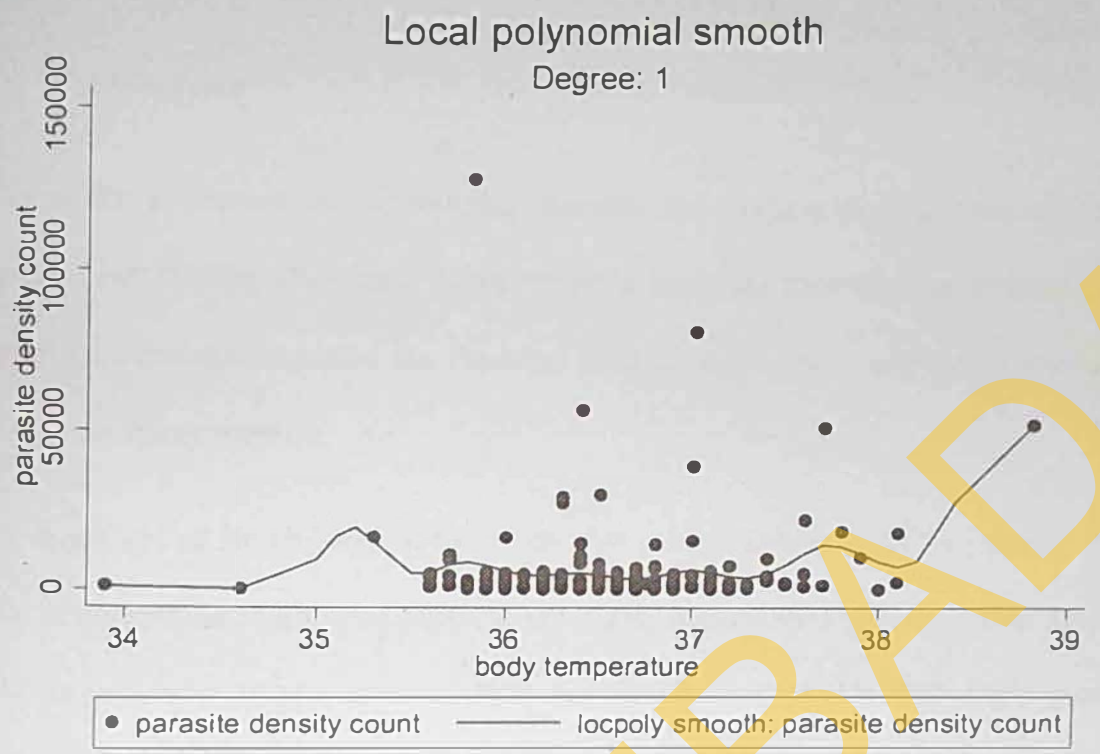

Figure 4.2: Local linear smoothing graph

Table 4.9: Estimates of attributable fraction and 95% CI for different estimators

Estimator	Classical estimate	Logistic estimate ≤999µl	Logistic estimate ≥1000µl	Local linear smoothing estimate
AF	0.2652	0.0385	0.3215	0.2447
Lower CI	0.1784	0.0105	0.2738	0.1785
Upper CI	0.3520	0.0665	0.3691	0.3119
Length of CI	0.1736	0.056	0.0953	0.1334

CHAPTER FIVE

5.1 Discussion

This study estimated the attributable fraction for malaria among children in Ona-ara local government, Ibadan, Oyo state. Three different methods were used in obtaining the estimates of malaria attributable fraction: the classical method, the logistic regression method and the local linear smoothing method.

The mean age of the children in this study was comparable to those in a study of children in the rural communities of Edo and Cross River states, Nigeria in which the mean ages were 5.67 and 6.48 respectively (Osazuwa Et al, 2010 and Ekong et al, 2013). Since the studies had similar geographical settings, it is expected that the reported mean age should not be too different from one another. Studies carried out in other parts of Africa such as Mozambique (Mabunda Et al, 2008) and Ghana (Abdul-Aziz et al) had mean age different from the one reported in this study as 3.5years and 3.69years respectively.

This study observed a higher percentage of children with malaria parasite (52.8%) as was also observed in the study by (Wang et al, 2012) with malaria parasite of 71.56%. Other studies (Nwaorgu et al and Mabunda et al, 2008) showed lower percentages of children with the parasite density. The reason for the observed low percentage might be as a result of the large sample of children that were observed in their study.

Among the signs and symptoms suggestive of malaria in children, headache and report of high fever were the commonest symptoms in this study which corroborate with the first sets of symptoms stated by WHO 2014. The signs and symptoms that were significant with malaria parasite in the bivariate analysis were headache, loss of appetite and yellowish eye, although the

symptoms of malaria are non- specific and can vary from one individual to the other. Consequently accurate diagnosis may not be possible without a blood test (Public Health Agency of Canada, 2012). In regions where malaria is present, people who get infected many times may have the disease but have few or no symptoms and the severity of malaria symptoms can vary depending on general health of the individual.

The prevalence of fever decreased with increasing age with children in the age group of less than three years old having the highest fever prevalence of 9.6% and thereafter decreased. A similar result was observed by (Mabunda et al, 2008). The prevalence of parasitemia also decreased with increasing age as those with age 4-6years had the largest and those with age greater than or equal to ten years had the lowest (39.3%) which was consistent with findings from other studies (Nwaorgu et al 2011, Hozhabri et al, 2000 and Ekong et al, 2013). High parasitemia in younger age category can be attributed to lack of strong immunity against the disease and also for the fact that during the first few months, newborns are protected by antibodies transferred from their mothers through the placenta and this immunity decreases over time. Children gain protective semi-immune status after surviving repeated infections at an older age say around 5years (CDC). The overall malaria prevalence of 53.7% observed in this study was found to be in the same range as that of Mabunda et al of 48.6% and the overall fever prevalence was 6.6% was found to be a little lower than that of Mabunda of 9.4%.

In this study, the majority of parasitized children were asymptomatic carriers, and not all fever episodes were associated with malaria parasites, hence very few fever episodes associated with asexual *P. falciparum* infections were observed. Additionally, the risk of fever among parasitized children was age-dependent, and increased with increasing parasite density.

In this study, temperature i.e fever was found to be the only significant symptoms which correlates with other findings that high fever is the commonest clinical presentation in any species of malaria (Rajkumar et al, 2012) although Bouvier et al concluded that most children with high parasite density do not develop fever subsequently and that the association between parasite density and fever varies according to age and season.

The association between malaria infection and body temperature varies significantly among children. Despite the fact that definition of clinical malaria have been related to fever episode and presence of parasites in the blood stream in endemic-malaria areas, manifestations of clinical malaria have a wide spectrum and the parasite density required to trigger fever differs significantly from one individual to another (Rogier *et al*, 1996) however, children with fever in the absence of malaria parasites are not necessarily non-malaria cases, since parasitaemia is a fluctuant variable and a child with malaria may have parasitaemia at undetectable levels at a given time.

The classical estimate of the attributable fraction of 0.2652 was obtained as the proportion of fever cases that can be attributed to malaria for the whole population of children which was similar to that obtained by Wang *et al* 2012) of 0.2939. For the study carried out in Kenya, overall malaria attributable fractions were quite higher. The two areas that were considered were referred to as area of low and low-moderate transmission of malaria and this might just explain the reason for the reported high MAF. For parasite density-specific malaria attributable fraction, the malaria attributable fraction increased as the parasite density increased as was found in the study by Prybylski *et al* (1999). Koram *et al* (2007) is of the opinion that in a population of whom a large proportion are parasitemic but not ill, it is usually found that the likelihood of being ill increases with the density of parasitemia and this observation has led to many attempts

to identify a threshold level of density of peripheral parasitemia that makes it likely that malaria is the cause of a fever.

The logistic estimates had the smallest confidence interval followed by the local linear estimate and the classical estimate performed the worst as it had the largest confidence interval.

Of the three estimates of malaria attributable fraction that was observed, the highest was about 32%. Among those who reported fever, about one third had no malaria parasite and this finding has significant implications on the treatment policy, particularly in rural areas where in the absence of laboratorial diagnosis, all fever cases would be considered as clinical malaria episodes. Moreover, even among children with the malaria parasite who had fever the highest of the estimates of attributable attributable fraction was less than 40%.

5.2 Conclusion

The prevalence of malaria disease and fever during childhood remains high and it constitutes a major health problem in this community. Signs and symptoms for malaria vary among children and remains non-specific in regions where malaria is endemic but fever remains the most reported symptom for malaria. The different proportion of fever cases that were attributed to fever were not as high as the prevalence of the disease. So it is still important to have a clinical diagnosis before any fever case is reported as malaria.

This study also confirms that malaria infection remains a major cause of febrile illness during childhood. However, other causes of fever should be considered in case management of febrile illnesses during childhood.

The logistic estimate for parasite density category of ≥1000µl gave the highest malaria attributable fraction and had the smallest confidence interval followed by the local linear

estimate. It can be concluded that logistic method is a better estimate while classical method behaved the worst.

5.3 Recommendation

The classical estimate can be improved upon by regression estimators, in particular when the change in the probability of disease given exposure at zero exposure is not steep. Nonparametric regression estimator worked well and improve considerably on the classical estimate.

There should be adequate training on malaria diagnosis and other associated causes so that not all fever cases are treated as malaria and individuals with signs and symptoms related to malaria should be advised to get a malaria test before treating malaria.

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