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Analysis of Risk Factors for Mortality Due to Malaria Infection: Case Study in Arsi Negele Health Centers, Ethiopia

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Abstract
Background: Malaria epidemiology remains a major problem of health of the majority of the population of Ethiopia as particularly in Arsi Negelle woreda. Evidences from retrospective study of the magnitude of malaria admission and death review in Oromia revealed that out of total 302,035 admissions, 16,061 deaths were registered from 1995 to 2000. Accordingly, malaria accounted for 11.2% of all admissions and 14.26% of all deaths. The main objective of this study was to evaluate the risk factors for mortality of patients from human malaria disease in the study area. **Methods**: The data for this study were abstraction from the records of malaria positive patients card reviewed or visited in Arsi Negelle major health center and Meti health center from 2010/11(2003 E.C) to 2011/12 (2004 E.C) in Arsi Negelle Woreda (retrospective cohort study). The data were analyzed using multiple binary logistic regression. **Results**: The results of the study showed that 412(76.87%) of malaria positive patients were found to be discharged while the rest 124(23.13%) have died of malaria in the health centers. The odds of death for malaria positive patients at the clinic residing in rural area were 2.933 times that of one who resides in urban. *Plasmodium vivax* has a 92.1% less chance of experiencing death due to malaria in the health center than those patients with *plasmodium falciparum*. **Conclusion**: It can be concluded from the results of this study that the most contributing risk factors of malaria epidemic related mortality in health centers were: rural resident, longer time(days) of patients stay with disease before getting treatment, *P.falciparum* types of plasmodium species, shorter time(days) of stay in health centers, immigrant patients, and patients referred to health centers.
Keywords: Malaria, Risk factors, Mortality in-health centers
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Background

The malaria disease remains one of the most important causes of human mortality with enormous medical, economic and emotional impact in the world (WHO, 2005). Malaria is governed by a large number of environmental factors, which affect its distribution, seasonality and transmission intensity. The peak in mortality is generally obtained in the rainy season, the time when malaria transmission is at its peak, and the number of deaths during this period has been shown to be over threefold higher than in the rest of the year (Jaffar S., Leach A., Greenwood A.M. *et al.*, 1997).

Malaria contributed 2.05% to the total global deaths in 2000, it was responsible for 9.0% of all deaths in Africa (WHO, 2002). The World Health Organization also estimated that the total cost of malaria to Africa was US$ 1.8 billion in 1995 and US$ 2 billion in 1997 (WHO, 1997). Malaria is therefore a massive problem, which plagues all segments of the society.

The disease is directly responsible for one in five childhood deaths in Africa and indirectly contributes to illness and deaths from respiratory infections, diarrheal disease and malnutrition (World Health Report, 1999). In Sub-Sahara Africa (SSA) alone, an estimated 0.9-2.3 million annual child deaths are attributed to malaria (Villamor *et al*., 2003).

The study on malaria admissions and deaths in Oromia region provides estimates of burden of the disease. Evidences from retrospective study of the magnitude of malaria admission and death review in Oromia revealed that out of total 302,035 admissions, 16,061 deaths were registered from 1995 to 2000. Accordingly, malaria accounted for 11.2% of all admissions and 14.26% of all deaths (Deressa *et al*., 2004).

Malaria morbidity also depends on occurrences of mosquito/parasite appearance. *P.falciparum* and *P.vivax* are the main species accounting for 60% and 40% of malaria cases. *Anopheles arabiensis* is the major malaria vector followed by *An. pharoensis* and other secondary vectors include *An.funestus* and *An. nili* (MOH, 1999 & 2002). *Plasmodium falciparum* malaria is the world's most common parasitic disease and a major cause of morbidity and mortality in Africa. However, figures on malaria morbidity and mortality are very uncertain, since reliable risk level of the distribution of malaria transmission and the numbers of affected individuals are not available for most of the African countries. Accurate statistics on the estimation of distribution of different endemicities of malaria, on the populations at risk, and on the implications of given levels of endemicity for morbidity and mortality are important for effective malaria control programs. These estimates can be obtained using appropriate statistical models which relate infection, morbidity, and mortality rates to risk factors, measured at individual level, but also to factors that vary gradually over geographical locations (Smith, 2003).

There are over 400 species of plasmodium, of which four of them occur in humans: *Plasmodium falciparum,* *P. vivax, P. ovale,* and *P. malariae*. Among these species of *Plasmodium*, the most damaging type of malaria is caused by *Plasmodium falciparum*, which represents a growing threat and burden to human health and welfare. *Plasmodium falciparum* is justifiably regarded as the greater menace because of the high levels of mortality with which it is associated, its widespread resistance to anti-malaria drugs, and its dominance in the world's most malarious continent, Africa (Deponte and Becker; Mayxay *et al*., 2004).

All four species of *Plasmodium* are known to occur in Ethiopia (Krafsur and Armstrong, 1982). However, *Plasmodium falciparum and P. vivax* are the most dominant malaria parasites in the country, accounting for 60% and 40% of malaria cases respectively. *Plasmodium malariae* accounts for less than 1% and *P. ovale* is rarely reported (Tulu, 1993).

Malaria is one of the leading causes of illness and death in the world. Nine out of ten of these deaths occur in Africa and the rest occur in Asia and Latin America. Being the world's most prevalent vector-borne disease, it is endemic in 92 countries, with pockets of transmission in an additional eight countries (Martens and Hall, 2000).

Study done in Ontario, Canada shows that the regression results are consistent with univariate analyses: case-patients were more likely to be male (odds ratio [OR] 2.24, 95% CI 1.24–4.05) and live in neighborhoods with high levels of immigration from malaria-endemic countries (OR 1.09, 95% CI: 1.06–1.12) (*Emerging Infectious Diseases Journal*, Volume 18, Number 5—May 2012).

Study done in Malawi (Paediatric ward register data from Zomba district, Malawi, between 2002 and 2003 were used, as a case study) using bivariate logistic regression analysis of the burden of malaria shows: Children aged 1–4 years were at reduced risk of dying in hospital relative to children aged 5–14 years (OR = 0.78, 95% CI: 0.68, 0.89). Children referred to the district hospital from networking health facilities were at increased risk of dying in hospital relative to non-referred children (OR: 1.18, 95% CI: 1.08, 1.35). Children hospitalized during the wet season were at reduced risk of dying in hospital relative to those hospitalized during the dry season (OR: 0.88, 95% CI: 0.79, 0.99). Length of hospital stay was also associated with the risk of hospital death.

In Ethiopia, the disease is one of the country's foremost health problem top ranking in the list of common communicable diseases (MOH, 2005). In 2002/03 the disease has been reported as the first cause of morbidity and mortality accounting for 15.5% outpatient consultations, 20.4% admissions and 27% in-patient deaths (FMOH, 2004). Even in 2004/05, it was reported to be the leading infectious disease followed by helminthiasis and tuberculosis (MOH, 2005).

From various malaria related study done in Ethiopia, there were some studies that used statistical method to analyze data that are related to malaria. These include a study done in Hawasa city on statistical analysis of risk factors of malaria related in hospital mortality from June 1, 2007 to June 1, 2010. This study indicates that female exceeds male in hospital mortality from malaria and high mortality in age group <5 years and 15-44 years. The odds of death for malaria positive patients with *P.vivax* and mixture of malaria species were 0.036 and 0.051 times less compared to those with *P.falciparum*, respectively (Chala, 2011). Another study in Adama district on spatial modeling of malaria risk reported that normalized difference vegetation index and rainfall were significantly affect malaria prevalence (Fekadu, 2012). The objective of this study is to identify the risk factors for malaria infection that leads the population to death due to malaria and to know whether the immigrant of population within woreda raises death of population from malaria disease.

Importance of the Study

The study has virtuous importance regarding the provision of necessary information regarding the mortality of patients from malaria disease in the study area.

- For further eradication of the mortality due to malaria epidemic of that area, the study may also contribute through extending the awareness of the concerned bodies of fix targets and properties.
- In addition, it also gives a certain vision about the problems for further investigation of the area.
- It also help to identify the bottle necks of factors that leads human to morbidity and mortality which the researchers and policy makers can make use (i.e. it helps policy makers that design the policy for prevention and controlling the burden of malaria and help to other researchers who have a need to do further on this field since it will fill the information gap).

METHODS

Description of Study Area

The study was conducted in Arsi Negelle major Health center and Meti health center found in Arsi Negelle Woreda, Oromia, Ethiopia. The location where Meti health center found is surrounded by natural and human made forest and mountains. This place has greater rainfall than that of where Arsi Negelle major health center was located. Therefore, it is located in wet area than Arsi Negelle major health center.

Data

For this study, secondary data was used from retrospective cohort study that reviews or visits patients' card of malaria patients in Arsi Negelle major health center and Meti health center. A form was prepared by investigator and given to the enumerators. Then the enumerators were collected information of selected malaria positive patients from their history cards.

Sampling Design

The health center gives services to all types of patients. Retrospective cohort study was done in order to conduct this research. There were about five health centers in Arsi Negelle woreda. From these five health centers two health centers were selected depending on their location area (wet area and dry area). However, the selected heath centers were Arsi Negelle major health center which was found in dry area and Meti health center which was found in wet area. The other health centers found in the woreda were located between dry and wet area. The target population for this study was all recorded malaria patients (patients only affected by malaria disease) in Arsi Negelle major health center and Meti health center from 2010/2011 (2003 E.C) to 2011/2012 (2004 E.C). Here, inclusion criteria were only malaria positive patients and exclusion criteria was mortality of patients due to combination of malaria and other endemic diseases. The sampling design used for this study to select participants is stratified random sampling. For this study, the population is divided into two none overlapping units (N_1, N_2) called strata based on stratification location of health centers. From each stratum a sample of pre-specified size is drawn independently in different strata. Then these drawn samples constitute a stratified sample. If a simple random sample selection scheme is used in each stratum then the corresponding sample is called a stratified random sample.

Sample Size Determination

The total sample size for this study was determined using the statistical formula is given as (Cochran, 1977):

$$n = \frac{\sum_{i=1}^{2} \frac{W_i^2 N_i \mathrm{P}(1-\mathrm{P})}{W_i (N_i - 1)}}{V + \frac{\sum_{i=1}^{2} \frac{W_i N_i \mathrm{P}(1-\mathrm{P})}{(N_i - 1)}}{N}}$$

, where $V = \left(\frac{d}{Z_{\alpha/2}} \right)^2$, $W_i = \frac{N_i}{N}$ is the stratum weight

$Z_{\alpha/2}$ =1.96 is the critical value for a 95% confidence interval in a normal probability table.

$N_{i=}$ total number of malaria patients admitted to Arsi Negelle major health center and Meti health center from 2010/2011 (2003 E.C) to 2011/2012 (2004 E.C).

N_1 = total number of malaria patients from Wet area (N_1=1004)

N_2= total number of malaria patients from Dry area (N_2=1066)

P= proportion of mortality of malaria patients in the health centers from 2010/2011 (2003 E.C) to 2011/2012 (2004 E.C). $N=N_1+N_2$

The sample size selected from each stratum was determined using proportional allocation as:

$n_i = \left(\frac{N_i}{N} \right) n$, where i=1, 2. Thus, $n_1+n_2=n$

Simple random sampling method was adopted as an appropriate sampling design for selecting a representative sample of patients based on their admission card number from each area to obtain the data.

Chala (2011) reported 21.52% in-hospital death due to malaria at Bushulo major health center, Hawassa, Ethiopia. Therefore, p=0.2152 was taken as the probability of being died of malaria to occur in each stratum because of the prevalence of malaria infection around Hawassa city and the prevalence of malaria infection in Arsi Negelle Woreda were similar. The level of precision taken for this study was 3.0 %(i.e. d=0.03). This is the maximum error that the investigator assumed to tolerate it in the study.

Finally, in this study the total population 2070, total number of malaria patients from wet area (Meti health center) (N_1=1004), total number of malaria patients from dry area (Arsi Negelle major health center) (N_2=1066), the level of precision, d=0.03, the probability of death for malaria positive patients in-hospital, p=0.2152, level of significance, α=0.05 were used in the calculation of sample size. The total required sample size was 536. The size of the sample in each stratum was determined by proportional allocation wet area (Meti health center) =260 and dry area (Arsi Negelle major health center) = 276). Finally, using patient's admission cards of their unique identification number a simple random sample of laboratory confirmed malaria positive patients was selected from each stratum to get information.

Variables Considered in the Study

Response Variable: The response or dependent variable in this study was a dichotomous response variable which is known as death-discharge status of malaria positive patients in health centers.

Independent variable: The variables that are considered in this research and expected to be the risk factors of death for malaria positive patients in the study area were: Sex of patient, Age of patient, Residence of patient, Duration of patients' stay with disease before going to health center, Types of plasmodium, Patient's total stay in health center, Season when the patient diagnosed, Is diagnosed patient immigrant?, Referral status, and Location of health center.

METHODS OF STATISTICAL ANALYSIS

Data were entered and analyzed by using SPSS version 20. After data were entered to SPSS, then the data were manipulated to clean it from irrelevant information. Descriptive statistics was generated as frequency and percentage while inferential statistic was performed using logistic regression tools.

Multiple binary logistic regression analysis applied when there is a single dichotomous outcome and more than one independent variable. The outcome in logistic regression analysis is often coded as 0 or 1, where 1 indicates that the outcome of interest is present, and 0 indicates that the outcome of interest is absent. The logistic regression model was used in order to address the issues under the objectives of this study. And in this case, it can be represented that $Y_i = 1$ if the i^{th} patient has died in health centers and $Y_i=0$, if recovered.

The conditional probability that the outcome of interest in a study "is present" (in this case, the patient died of malaria) can be written as:

$$P(Y_i = 1/X_i) = \frac{e^{\beta_0+\beta_1 X_{i1}+\beta_2 X_{i2}+\ldots+\beta_p X_{ip}}}{1+e^{\beta_0+\beta_1 X_{i1}+\beta_2 X_{i2}+\ldots+\beta_p X_{ip}}} = \frac{e^{X\beta}}{1+e^{X\beta}} = \frac{1}{1+e^{-X\beta}}$$

where i= 1, 2,….n and $P(Y_i = 1/X_i)$ is the expected probability that the i^{th} patient has died of malaria given X_i the vector of explanatory variables or the expression for P (x_i) provides (for an arbitrary value of β) the conditional probability that Y is equal to 1 given x is P(Y=1/x). It follows that 1-P_i gives the conditional probability that Y is equal to 0 given x, P(Y=0/x).

The logistic regression which is also known as logistic regression model is the logit transformation of P(x_i), and it is given as:

$$\log it(Y_i = 1/X_i) = \log\left(\frac{P(x_i)}{1-P(x_i)}\right) = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2} + \ldots\ldots + \beta_p X_{ip}$$

RESULTS

Results of Descriptive Analysis

Table 1: Percentages and counts of death-discharge status of malaria patient with respect to the sex, age and residence of patients, and location of health centers.

Variable	Category	Death Discharge Status				Total	
		Discharge		Death			
		Count	%	Count	%	Count	%
Sex of patient	Male	226	77.4	66	22.6	292	54.5
	Female	186	76.2	58	23.8	244	45.5
Age of patient	<5 years	66	77.6	19	22.4	85	15.9
	5-14 years	142	76.8	43	23.2	185	34.5
	15-44 years	185	77.4	54	22.6	239	44.6
	≥45 years	19	70.4	8	29.6	27	5.0
Residence of patient	Urban	165	87.8	23	12.2	188	35.1
	Rural	247	71.0	101	29.0	348	64.9
Location of health center	Wet	180	69.2	80	30.8	260	48.5
	Dry	232	84.1	44	15.9	276	51.5

Within the study period, out of the 536 patients considered, 412 (76.87%) patients were found to have recovered while 124 (23.13%) were dead. From the above table 1, 54.5% of laboratory confirmed malaria positive patients were male and the remaining 45.5% were female. From the location of health centers 48.5% patients were from wet area and 51.5% patients were from dry area. Depending on the residence of the patients diagnosed in health centers, 35.1% were urban residents and 64.5% were rural residents.

The explanatory variables which were found to be significantly associated with death-discharge status of malaria positive patients were: residence of patient, duration of patients stay with disease before going to health center, types of plasmodium, patient's total stay in health center, immigration of patients, referral status, and location of health center.

On the other hand, the explanatory variables that have no association with patients' health status (death-discharge status) were: sex of patient, age of patient, and season when the patients were diagnosed.

The proportion of malaria positive patients who died in health centers from rural area was 29% and from urban area was 12.2%. The probability of that a patient died increased with time from symptom seen to diagnoses and patients with late diagnoses after symptom appearance were died than those diagnosed at early stage. The proportions of malaria positive patients that die due to *P.falciparum, P.vivax* and mixed were 43.5%, 6.6% and 47%, respectively.

Binary Logistic Regression Analysis

The results from the bivariate analysis between each explanatory variable and the response variable showed that out of ten explanatory variables, four predictor variables such as: sex of patient, age of patient, location of health center and the season when the patients were diagnosed have no significant association with the response variable (malaria positive patient's death-discharge status). From those ten covariates six predictor variables such as: residences of patient, duration of patients stay with disease before going health center (days), types of plasmodium, patient's total stay in health center (days), and immigration of patient and referral status have significant association with the response variable (malaria positive patient's death-discharge status).

The following table 2 presents the predictor variables in the final logistic regression model.

Explanatory Variables	$\hat{\beta}$	**S.E($\hat{\beta}$)**	**Wald**	**df**	**Sig.**	**Exp($\hat{\beta}$)**	**95% CI for Exp($\hat{\beta}$) Lower**	**Upper**
Residence of patients								
Urban(Ref)								
Rural(1)	1.076	0.252	18.242	1	0.000	2.933	1.790	4.807
Duration of patients stay with disease before going health center								
<3 days(Ref)			24.302	2	0.000			
3-5 days(1)	1.035	0.380	7.431	1	0.000	2.814	1.337	5.920
>5 days(2)	2.566	0.525	23.886	1	0.000	13.013	4.650	36.413
Types of Plasmodium P.falciparum(Ref)			68.605	2	0.000			
P.vivax (1)	-2.537	0.335	57.301	1	0.000	0.079	0.041	0.152
Mixed (2)	0.320	0.410	0.608	1	0.435	1.377	0.616	3.075
Patient's total stay in health center								
<1 days(Ref)			56.463	2	0.000			
1-2 days (1)	-1.146	0.385	8.834	1	0.003	0.318	0.149	0.677
>2 days (2)	-5.062	0.675	56.316	1	0.000	0.006	0.002	0.024
Is patient immigrant?								
No(Ref)								
Yes(1)	1.230	0.340	13.108	1	0.000	3.422	1.758	6.661
Is patient referred?								
No(Ref)								
Yes(1)	1.149	0.329	12.217	1	0.000	3.154	1.656	6.007
Constant	-0.991	0.320	9.596	1	0.002	0.371		

Ref; in the brackets indicates the reference category of each explanatory variables, $\hat{\beta}$**;** regression coefficient, **S.E($\hat{\beta}$)**; standard error of $\hat{\beta}$**, df;** degrees of freedom, **Sig.;** significance (P-value), **Exp($\hat{\beta}$);** exponent of $\hat{\beta}$, **CI for Exp($\hat{\beta}$);** confidence interval of **Exp($\hat{\beta}$).**

The risks of death for malaria positive patients at the clinic residing in rural area were 2.933 times that of one who resides in urban. This indicates that the death event is more likely to occur for rural than urban residing patients in the study area.

The risks of death for malaria positive patients whose 3-5 days duration of malaria positive patients stay with disease before going to health center were 2.814 times that of malaria positive patients diagnosed with in less than 3 days. Furthermore, the risks of death for malaria positive patients whose > 5 days duration of malaria positive patients stays with disease before going to health center were 13.013 times that of malaria positive patients diagnosed with in less than 3 days.

The results of odds ratio for the types of plasmodium diagnosed also indicates that patients with *plasmodium vivax* have a 92.1% less chance experiencing death due to malaria in the health center than those patients with *plasmodium falciparum*. The risk of malaria positive patients for immigrant indicates that immigrant patients are 3.422 times more likely to die of malaria in health centers than non-immigrant malaria positive patients. This was to showed us that the risk of death due to malaria for immigrant patients was greater than that for non-immigrant malaria positive patients.

The results also showed that the risk of death of malaria positive patients significantly increases as patient's total stay in health centers decreases. The risk for the patients' total stay in health centers indicated that patients stay in health centers for 1-2 days and >2 days have a 68.2% and 99.4% less chance experiencing death due to malaria in the health centers than those length of stay in health centers was ≤ 1 day, respectively. From the results we can also say that patient's referral status to health centers was significantly associated with the death of malaria positive patients in health centers. The risk of death for malaria positive patients those referred to health centers were 3.154 times that of reference category (non referred malaria positive patients to health centers). This implies that, the risk of death of referred malaria positive patients was three times greater than the non-referred malaria positive patients to health centers.

DISCUSSION

This study provides evidence of the predictors which significantly influence mortality of malaria positive patients in Arsi Negelle Woreda health centers. These predictors were: residence of patient, duration of patients stay with disease before going health center (days), types of plasmodium, patient's total stay in health center (days), immigration of patients, and referral status.

Total lengths of stay in health centers have significant impact and relationship with malaria positive patient death-discharge status. As the total length of stay in health centers increases the risk of death of malaria positive patients decreases. The outcome variable malaria positive patient's death-discharge status is also determined by the duration of malaria positive patients stay with disease before getting treatment in health centers. These results have similarities with the results from the study done in Bushulo major health center, Hawasa city by Chala (2011) and Zomba district, Malawi.

The risk of death of malaria positive patients for rural resident was greater than that of urban resident. This is because of odds of death for malaria positive patients at the clinic residing in rural area were 2.933 times that of one who resides in urban. This result was in parallel with the results of the studies done in Bushulo major health center, Hawassa city by Chala (2011) and in Equatorial Guinea Malabo sites. The risk of death of referred malaria positive patients to Arsi Negelle health centers was greater than that of non-referred. From the types of plasmodium, P. falciparum was the most determinant for the death of malaria positive patients (because it was common cause for death) in Arsi Negelle woreda health centers than other types of plasmodium found in this Woreda. This result is in line with the results of the studies done in Bushulo major health center, Hawassa city by Chala (2011), (MOH, 1999 & 2002), (Zomba district, Malawi), and the world's most malarious continent, Africa (Deponte., and Becker., 2004; Mayxay et al., 2004).

CONCLUSION

This study was attempted to identify the risk factors of malaria related in health centers mortality at Arsi Negelle Woreda Health Centers. From the results of this study out of ten predictor variables, six explanatory variables were statistically significantly determined death-discharge status of malaria positive patients in the study area. These predictor variables were: residence of patient, duration of patients stay with disease before going health center (days), types of plasmodium, patient's total stay in health center (days), immigration of patients, and referral status. The odds of death of malaria positive patients for immigrant were 3.422 times higher as compared to that of non-immigrant patients. The death of malaria positive patients in health centers decreases as the length of times of stay in health centers increases. The risk of death of referred malaria positive patients was around three times greater than the non-referred malaria positive patients to health centers.

Limitations of the Study

The study focused on identifying some of the factors that were expected to be associated with risk factors of malaria related in health centers mortality at Arsi Negelle Woreda based on available data on patient's card. However, the study could not incorporate some other important risk factors that may leads to death of patients in health centers due to lack of data, such as socio-economic status of patients, educational status, awareness of patients about the disease, proper utilization of different ant-malarial treatments and other related issues. In spite of these limitations, the model derived in this study may give a more accurate prediction of risk factors of malaria related death-discharge status by taking into account available data on patient's card of laboratory confirmed malaria positive patients.

List of abbreviations

E.C Ethiopian calendar.
MOH Ministry of Health.
NDVI Normalized Difference Vegetation Index.
OR Odds Ratio.
SSA Sub-Saharan Africa.

DECLARATIONS

Ethics approval and consent to participate

The study was ethically approved by Ethical Review Committee of Department of Statistics, Faculty of Natural and computational science, Gondar University. Written consent/assent was obtained from guardians of the study participants prior to data collection and confidentiality was maintained.

Competing interests

The author has declared that there are no competing interests.

Authors' contributions

The author (Shumi Negawo) participated in all phases of the study including designing of the study, data collection and monitoring, data analysis, and write-up of the manuscript. Authors read and approved the final manuscript.

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