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EFFICACY DETERMINATION OF SULPHADOXINE-PRYMETHAMINE IN THE PREVENTION OF MALARIA IN INFANT UNDER FIVE YEARS IN THE EJISU-JUABEN DISTRCT OF THE ASHANTI REGION

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ABSTRACT

Malaria is not only a threat to pregnant women but to their newborn babies as well. It accounts for 1-3 million deaths yearly worldwide, with most of this burden occurring in children under 5 years of age in Sub-Saharan Africa. Around 90% of these deaths occur in Africa, mostly in young children. Malaria is Africa's leading causes of under-five mortality (20%) and constitutes 10% of the continent's overall disease burden. The treatment and control of malaria have become difficult with spread of drug-resistant strains of parasites leading to the discovery of sulfadoxine - prymethamine. However, the efficacy of the sulfadoxine - prymethamine is yet to be confirmed. The objective of this study was to determine the efficacy of sulfadoxine - prymethamine using the Cox regression model and the Poisson model. From the analysis of the Cox model the estimated hazard ratio for sulfadoxine - prymethamine compared to placebo is 0.94(95% Cl; 0.82-1.08, P=0.37). With a P-value of 0.37, there was no significant difference between the placebo and the treatment. Alternative treatments should be sort for since the treatment (sulfadoxine - prymethamine) is not very effective enough.

INTRODUCTION

Malaria is the most important tropical disease remaining widespread throughout the tropics, but also occurring in many temperate regions (Spielman, 2003). It exacts a heavy toll of illness and death especially amongst children and pregnant women. (Schellenberg *et al*, 2001). It also poses a risk to travelers and immigrants with imported cases increasing in non-endemic areas (Wongsrichanalai *et al*, 2002). Malaria is not only a threat to pregnant women but to their newborn babies as well. It accounts for 1-3 million deaths yearly worldwide, with most of this burden occurring in children under 5 years of age in Sub-Saharan Africa (Smith *et al*, 1993). There are at least 300 million acute cases of malaria each year globally, resulting in more than a million deaths. Around 90% of these deaths occur in Africa, mostly in young children. Malaria is Africa's leading causes of under-five mortality (20%) and constitutes 10% of the continent's overall disease burden. It accounts for 40% of public health expenditure, 30-50% of inpatient admissions, and up to 50% of outpatient visits in areas with high malaria transmission (Nimo *et al*, 1981). There are several reasons why Africa bears an overwhelming proportion of the malaria burden. Most Malaria infections in Africa south of the Sahara are caused by *Plasmodium falciparum,* the most severe and life threatening form of the disease. It is the main cause of severe clinical malaria. This region is also home to the most efficient, and therefore deadly, species of the mosquitoes which transmit the disease. Moreover, many countries in Africa lack the infrastructures and resources necessary to mount sustainable campaigns against malaria and as a result few benefited from historical efforts to eradicate malaria. (Browne *et al*, 2001). Malaria also presents major obstacles to social and economic development. It has been estimated to cost Africa more than US$12 billion every year in lost GDP. Treatment and control have become difficult with spreads of drug-resistant strains of parasites and insecticide-resistant strains of mosquito vectors. (Bland, 2000) Drug resistance in malaria is a vitally important public health concern. Each year, an estimated 0.7-2.7 million people dies of malaria, and over 75% of them are African children (Betty *et al*, 2003). National malaria control programmes continue to rely on effective case management whiles deploying insecticide-treated bed nets on large -scale

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Table 4.1. Table indicating the various covariates

studyno	Dob	sex	group	mothcat	Parity	maritalstatus	religion	Education	Occup	Malaria status
2	23Apr01	female	3	30-39	>3	Married	Christian	None	Salary Worker	0
3	22Apr01	male	1	20-29	1	Married	Christian	Jss	Farming	0
5	17Apr01	male	1	20-29	2	Married	Christian	Primary	Salary Worker	0
7	15Apr01	male	1	20-29	2	Married	Christian	Primary	Farming	0
9	21Apr01	male	1	20-29	1	Married	Christian	Primary	Apprenticeship	0
.	.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.	.
816	01Sep01	female	3	<19	2			Primary	Unemployed	
817	08Aug01	male	1	>39		Married	Nonchristian			0
818	01 Jul 01	male	1	20-29	>3	Married		secondary	Farming	0
820	11Aug01	male	3	20-29	>3	Married	Christian	None	Farming	0
822	01Aug01	male	1	20-29	1			None	Farming	

and waiting for an effective and affordable vaccine. The discovery of sulfadoxine - prymethamine a major breakthrough, given on two or three occasions during pregnancy has been more effective at preventing infection of the placenta than chemoprophylaxis with chloroquine. Intermittent preventive treatment in pregnancy (IPTp) has provided a protection for the pregnant woman against malaria and low birth weight. Researchers are working harder to find a similar intermittent preventive treatment for infants in the early stages of their life. Intermittent Sulphadoxide-pyrimethamine treatments have undergone extensive pre-clinical and clinical tests and have been shown to be safe and immunogenic and protective against Plasmodium falciparum in population humans living in low endemicity areas (WHO, 2002-2005). In areas of stable malaria transmission, very young children and pregnant women of the population are groups at high risk for 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 these early years particularly dangerous. Adult women in areas 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. (Netmark, 2000). Malaria is a major cause of morbidity and mortality in Ghana, directly contributing to poverty, low productivity, and reduced school attendance. According to the MOH, between 3-3.5 million cases of malaria are reported each year, over 900,000 of which are children under five. Malaria is reported to account for 61% of under-five hospital admissions and 8% of admissions of pregnant women. However, the malaria statistics captured by health facility data are well recognized to greatly underreport the extent of malaria morbidity and mortality. Given that the under-five mortality rate of 111/1000 is well documented, and assuming that malaria is responsible for an estimated 22% of under-five mortality and 9% of maternal deaths in Ghana (WHO 2005), one can conservatively estimate that 20,000 children under five die from malaria in Ghana each year.

MATERIALS AND METHODS

The data for the study was a secondary data from Ejisu Government hospital. The children were observed for a period of one year. The event for this study is the presence of malaria parasite. The data collected was on malaria treatment in children less than five years for the period, 2007–2008, indicating their sex, mothers' age, marital status of mothers, parity, religion and level of education. To achieve the objectives of this paper, Cox regression analysis was employed as the main statistical methodology for analyzing the data. Also the Poisson model was used in the analysis of the data to determine the rate of occurrence of malaria in the children. The response variable, in the case of the Cox model is the hazard rate of malaria incidence in the children. This hazard rate was regressed on the other factors (sex, mothers' age, marital status, parity, level of education and religion) as the predictor variables for the modeling process.

RESULTS

The figure in table 4.1 below is a snapshot of the data used for this paper which is made up of 822 mothers. 421 of them were given the placebo treatment and the remaining 401 were given the sulfadoxine- pyrimethamine treatment for their children. The columns are 11 representing the study number, date of birth (DOB), sex of child, group, mothers age category, parity (number of children), marital status, religion, Educational level, Occupation (Occup) and Malaria Status as shown below. In the data there were three drugs administered. These are:

i) Placebo treatment represented by the number 1
ii) Arthemitrine-lumifantrine represented by the number 2
iii) Sulfadoxine - prymethamine represented by the number 3

Table 4.2. Descriptive analysis of data

VARIABLE	PLACEBO	SULFADOXINE - PRYMETHAMINE
Age		
<19	14(3.19)	17(3.79)
20-29	185(42.14)	204(45.54)
30-39	137(31.21)	118(26.34)
>39	103(23.46)	109(24.33)
Parity (children)		
1	83(18.86)	98(21.78)
2 & 3	158(35.91)	159(35.33)
>3	199(45.23)	193(42.89)
Occupation		
Farming	170(47.49)	167(45.38)
Apprenticeship	73(20.39)	74(20.11)
Salary worker	115(32.12)	127(34.51)
Marital status		
Married	355(98.61)	361(97.57)
Single	5(1.39)	9(2.43)
Education		
None	50(13.89)	53(14.36)
Primary	87(24.17)	90(24.39)
Jss	185(51.39)	192(52.03)
Secondary	38(10.56)	34(9.21)
Religion		
Christian	315(87.50)	331(89.70)
Non Christian	45(12.50)	38(10.30)

For the analysis on the data only the placebo and the Sulfadoxine - prymethamine are used ie 1 and 3. Table 4.2 below is made up of three (3) columns; the first column is the variable column which is made up of the Mothers information categories (age, Parity, Occupation, Marital Status, Education and Religion). The other columns contain the number of individuals in each sub-group and their corresponding percentages which are in brackets. The results from the various analyses performed was obtained using the STATA software package (version 10.0) which implements both the Cox model and the Poisson model.

Cox Univariate Analysis

The Cox proportional hazards model can be written as follows:

$$hazard\ \text{ratio} = \frac{h(t;X)}{h_0(t)} = e^{\sum_{i=1}^{p} \beta_i X_i} \quad (1)$$

Where h_0 (t) is the baseline hazard, h (t; X) is the hazard at time t, X_i is explanatory or predictor variable.

From the equation above we have

$$h(t,x) = h_0(t)e^{(\beta_1 x_1 + \beta_2 x_2 + ... + \beta_p x_p)} \quad (2)$$

To see the proportional hazards property analytically, we consider the hazards h (t; x) for two different covariate values:

x_i and x_j respectively for the placebo treatment (PLC) and the sulfadoxine - prymethamine treatment (TRT) as shown below

$$h_{PLC}(t,X_i) = h_0(t)\exp[\beta_1 X_1 + \beta_2 X_2] \quad \text{And}$$
$$h_{TRT}(t,X_j) = h_0(t)\exp[\beta_1 X_1 + \beta_2 X_2].$$

For i=1,2 and j=1,2.

For a single dichotomous covariate, say $X_i = 0$ for i= 1 and X_j =1 for j=1 then the hazard ratio is given by:

$$\frac{h_{TRT}(t,X_1=1)}{h_{PLC}(t,X_1=0)} = \frac{h_0(t)\exp[\beta_1 + \beta_2 X_2]}{h_0(t)\exp[\beta_2 X_2]} = e^{\beta_1} \quad (3)$$

Table 4.3 below seeks to test the efficacy of sulfadoxine - prymethamine with placebo as control. The table is the combination of the outputs of the STATA program on the various categories. The table is made up of six (6) columns: the variable column, the hazard ratio column which compares the hazards ratio (h_{TRT}/h_{PLC}) for sulfadoxine - prymethamine, standard error column, P-value column, and the confidence interval.

Cox Multivariate Analysis

At this stage of the analysis the other factors like mothers' age, marital status, education, group, parity and religion were considered leading to a multivariate analysis of the Cox model. There were three statistical objectives to be considered. One was to test for the significance of the treatment status variable by using the p-value, adjusted for the other variables. Another was to obtain a point estimate (hazard ratio) of the effect of treatment status of sulfadoxine - prymethamine, adjusted for the variables. And a third was to obtain a confidence interval for the effect of the treatment. We can accomplish these three objectives using the output provided in Table 4.4 below.

The Cox model at this stage can be written as;

$$h(t,X) = h_0(t)e^{\sum_{i=1}^{p} \beta_i X_i}$$

Where i = 1, 2, 3 ….p; representing explanatory variables like mothers age, marital status, religion, parity etc.

$$h(t,X) = h_0(t)\exp[\beta_1 X_{Group} + \beta_2 X_{Sex} + \beta_3 X_{Mothcat} + ... + \beta_p X_{Religion}]$$

Table 4.3. Cox univariate analysis on the efficacy of sulfadoxine-pyrimethamine

VARIABLE	HAZARD RATIO	STD. ERR	P>|Z|	Z	95% CI
Group					
Placebo	1		-	-	-
Sulfadoxine	0.94	0.65	0.35	-0.93	0.82- 1.08
Sex					
Male	1		-	-	-
Female	0.90	0.13	0.45	-0.76	0.69- 1.18
Marital status					
Married	1		-	-	-
Single	0.72	0.51	0.64	-0.47	0.18- 2.89
Parity					
1	1		-	-	-
2	1.15	0.23	0.49	0.69	0.78-1.72
3	1.22	0.24	0.30	1.03	0.83-1.79
Education					
None	1		-	-	-
Primary	0.90	0.21	0.64	-0.46	0.56- 1.43
JSS	0.74	0.16	0.16	-1.40	0.49- 1.13
Secondary	0.48	0.17	0.04	-2.09	0.24- 0.97
Religion					
NoneChristain	1	-	-	-	-
Christain	1.37	0.30	0.15	1.43	0.89- 2.09

Table 4.4. Cox Multivariate analysis on the efficacy of sulfadoxine - prymethamine

VARIABLE	HAZARD RATIO	STD. ERR	P>|Z|	Z	95% CI
Group					
Placebo	1	-	-	-	-
Sulfadoxine	0.93	0.07	0.39	-0.86	0.80-1.09
Sex					
Male	1	-	-	-	-
Female	0.92	0.14	0.59	-0.53	0.68- 1.25
Mothers category	1	-	-	-	-
<19	0.72	0.30	0.43	-0.79	0.31-1.65
20-29	0.66	0.31	0.37	-0.89	0.27-1.64
30-39	0.66	0.36	0.44	-0.77	0.23- 1.91
>39					
Marital status					
Married	1	-	-	-	-
Single	0.74	0.53	0.67	-0.43	0.18- 3.02
Parity					
1	1	-	-	-	-
2	1.27	0.29	0.29	1.06	0.82-1.98
3	1.25	0.34	0.42	0.81	0.73- 2.15
Education					
None	1	-	-	-	-
Primary	1.02	0.27	0.95	0.06	0.61-1.70
JSS	0.83	0.20	0.46	-0.74	0.52- 1.35
Secondary	0.56	0.21	0.12	-1.56	0.27- 1.16
Religion					
NoneChrist	1	-	-	-	-
Christain	1.22	0.30	0.42	0.81	0.76- 1.98

Table 4.5. Poisson Univariate analysis

VARIABLE	HAZ RATIO	STD. ERR	P>|Z|	Z	95% CI
group					
Placebo	1	-	-	-	-
Sulfadoxine	0.97	0.06	0.65	-0.45	0.85- 1.11
Sex					
Male	1	-	-	-	-
Female	1.01	0.14	0.95	0.06	0.77- 1.32
Mothers category	1	-	-	-	-
<19	0.95	0.37	0.89	-0.14	0.44- 2.05
20-29	0.89	0.36	0.78	-0.28	0.41- 1.96
30-39	1.21	0.49	0.64	0.47	0.55- 2.66
>39					
Marital status					
Married	1	-	-	-	-
Single	0.65	0.46	0.55	-0.60	0.16- 2.63
Parity					
1	1	-	-	-	-
2	1.11	0.22	0.63	0.49	0.74- 1.645
3	1.30	0.25	0.18	1.33	0.89- 1.89
Education					
None	1	-	-	-	-
Primary	0.97	0.23	0.88	-0.15	0.61-1.54
JSS	0.84	0.18	0.40	-0.85	0.55-1.27
Secondary	0.52	0.18	0.06	-1.86	0.26- 1.04
Religion					
NoneChrist	1	-	-	-	-
Christain	1.34	0.29	0.17	1.36	0.88- 2.056

Table 4.6. Multivariate analysis (Poisson)

VARIABLE	HAZ RATIO	STD. ERR	P>|Z|	Z	95% CI
Group					
Placebo	1	-	-	-	-
Sulfadoxine	0.97	0.08	0.73	-0.34	0.84-1.14
MotherS' age					
<19	1	-	-	-	-
20-29	0.85	0.36	0.70	-0.38	0.37-1.94
30-39	0.74	0.34	0.51	-0.65	0.30- 1.82
>39	0.68	0.36	0.47	-0.73	0.23- 1.95
Marital status					
Married	1	-	-	-	-
Single	0.68	0.49	0.59	-0.54	0.17- 2.78
Parity					
1	1	-	-	-	-
2	1.21	0.27	0.41	0.83	0.78- 1.87
3	1.27	0.35	0.39	0.86	0.74- 2.16
Education					
None	1	-	-	-	-
Primary	1.13	0.30	0.63	0.48	0.68- 1.90
JSS	0.97	0.24	0.90	-0.13	0.59- 1.58
Secondary	0.63	0.24	0.22	-1.24	0.30- 1.31
Religion					
NoneChrist	1	-	-	-	-
Christain	1.29	0.32	0.31	1.02	0.79- 2.10

Poisson Univariate Analysis

The Poisson model was used in the analysis of the data to determine the rate of occurrence of malaria in the children which gave the output below.

Poisson Multivariate analysis

When other factors were consider the analysis gave the following results

DISCUSSION

Cox univariate analysis: In Table 4.3 a trend was observed; the hazard ratios for the education category were decreasing with increasing level of education from the non-educated right down to secondary level of education. i.e., 1.0, 0.90, 0.74 and 0.48. With the group category the hazard ratio for the placebo and the sulfadoxine - prymethamine was from 1.0 to 0.94. Overall no P-value was statistically significant except for the secondary level of education which had a value of 0.04. This is an indication that as mothers becomes enlighten the better they are able to protect their children from getting malaria. This implies that the sulfadoxine - prymethamine is not an effective first line treatment drug of uncomplicated malaria in children under five years old. The hazard ratio for male child compared to the female was 0.90 (95% CI; 0.69- 1.18, P=0.45), this was statistically non significant indicating a 1.1% efficacy. This indicates that there is no significant difference in the efficacy of the treatment on both sexes.

Cox Multivariate analysis

When other factors were considered the trends remained unchanged for all the variables and still the overall P-value was not statistically significant as shown in table 4.4.

Poisson Univariate analysis

The hazard ratio for the mothers' age was decreasing until age greater than 39 years where there was a jump from 0.89 to 1.12. Also the hazard ratio for the level of education was decreasing with increasing level of education. Overall the P-value was not significant for any of the categories.

Poisson Multivariate analysis

When the other factors were considered trends did not changed from that of the univariate analysis and the overall P-value was still not significant. Since the only variable that is significant is the mothers' level of education under the Cox univariate analysis, a model can be formulated for it.

Model Formulation

Using the formula

$$HR = e^{coefficient\ of\ \text{variables}(\beta)}$$

can lead to the determination of the coefficients of the variables.

$$\log_e(HR) = coefficient \text{ of the variables}(\beta)$$

$$\text{i.e. } \log_e(HR_{primary,jss,and\ secondary}) = \beta$$

Where HR= Hazard ratio.

Finally the Cox univariate model can be modeled using the variables and their corresponding coefficients for the level of education since it is the only significant variable.

Therefore the model is given by:

$$h(t,X) = h_0(t)\exp[-0.11X_{Primary} - 0.30X_{Jss} - 0.73X_{Secondary}]$$

Under the level of education, only the secondary level is statistically significant which brings the model to:

$$h(t,X) = h_0(t)\exp[-0.73X_{Secondary}]$$

Conclusions

Cox model

The treatment had no significant effect (hazard ratio= 0.94, CI= 0.82-1.08 and P=0.37) meaning that the efficacy of sulfadoxine - prymethamine was only 6% which is very small. When other factors were considered there was still no significant difference (hazard ratio=0.93, CI= 0.80-1.09 and P=0.39) which gives an efficacy of 7%. This indicates that there was no significant effect of the treatment (sulfadoxine - prymethamine). The mothers' age did not show any pattern but when other factors were considered, it showed a decreasing efficacy of the treatment with mothers' age of the mother. This could be that as the mother gets older her attention on the children decreases. Education showed a significant effect for mothers with secondary level of education (hazard ratio=0.48, CI= P=0.04) which gives a 52% efficacy. This gives a corresponding model:

$$h(t,X) = h_0(t)\exp[-0.11X_{Primary} - 0.30X_{Jss} - 0.73X_{Secondary}]$$

The more the mother of the child is educated the less likely for the child to get the event (malaria). When other factors were considered the trend did not change much only that the p-value change indicating that there is no significant difference in the education level this could be as a result of a wider confidence interval (hazard ratio=0.56 CI=0.27-1.16 and P=0.12). The Poisson model also gave similar results: Education, (hazard ratio=0.97, CI: 0.61-1.54.p=0.88) for primary, (hazard ratio=0.84, CI: 0.55-1.27,P=0.40) for Jss and (hazard ratio= 0.52, CI: 0.26- 1.04 P=0.06) for secondary. This reveals that the rate of occurrence of the event over the period decreases with increasing level of education; meaning as one's level of education increases, one becomes conscious of malaria and steps are taken to prevent the event (occurrence of malaria in our case). We can conclude that in reducing malaria infection in children under five years old the level of education of the mother plays an important role.

$$h(t,X) = h_0(t)\exp[-0.73X_{Secondary}]$$

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