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Exponential Model in Clinical Efficacy of Cryptolepis Sanguinolenta on Faciparum Malaria Treatment

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Abstract:
Cryptolepis Sanguinolenta is one of the many anti-malaria herbal medicines in Africa, particularly in Ghana. The plant contains Cryptolepis alkaloids when taken orally indicates efficacy in clearing Plasmodium falciparum parasites more than chloroquin. A tea bag of cryptolepis contain 2.5 grams was administered to 50 malaria patients in 5 independent stages. Each stage consist of 10 new patients. An exponential model was used to access probability of healing from uncomplicated malaria within WHO stipulated time for remission. Considering the probability values derived in the assessed overall survival probabilities, we conclude that a patient that faces treatment in stage one will have a 0.6 chance of survival, whereas stages two and three have 0.653 and 0.669 chances of survival respectively. Stages four and five had their overall survival probabilities to be above 0.7 and hence a patient chance of being cured of malaria fever in that stage is 0.7 which is a very high chance of success. It is obvious that uncomplicated malaria has very high chances of being cured with cryptolepis sanguinolenta and hence people affected with malaria are advised to resort to this herbal plant for treatment.

Keywords: *Cryptolepis Sanguinolenta, uncomplicated malaria, least square estimates*

1. Introduction

Access to quality health care is said to be a fundamental human right but the numerous challenges faced by modern health care system makes this a reality for only a section of the Ghanaian populace. Inadequate number of the already ill-equipped health facilities coupled with the unavailability of adequate trained personnel at the facilities makes traditional medicine and medical practitioners an important part of the health care system in Ghana. The tendency for Ghanaians to patronize both indigenous and modern systems simultaneously also makes the subject an issue of great public health concern.

Despite the efforts of government and its development partners to make modern health services accessible, available and acceptable to all people, most of these institutions are distances away from the communities they serve and the road network system linking some of the communities to the health facilities are mainly inaccessible, especially during the rainy seasons. This and other factors make it difficult to access quality health care and undoubtedly make traditional medicine an obvious choice for the rural people. As health care gets increasingly expensive and sometimes ineffective in many African countries, a growing number of people are turning to traditional medicine. In many countries however, these drugs are not certified and their uses raises safety concerns (VOA News, 2006). appropriate use of traditional medicines and practices can have a positive effects on treating malaria. For instance, the herb cryptolepis sanguinolenta is traditionally used in Ghana to treat malaria. In the United States, the herb was marketed as dietary aid, where correct effective dosage led to at least a good number of patients recovery.(WHO, 2003).

Studies have also shown that about 3,000 herbal formulations have been documented as being efficacious for specific conditions in Ghana, out of which over 600 are circulating as herbal medicine products and 60 of which have undergone preliminary phyto-chemical analysis and safety test at the centre for Scientific Research into plant Medicine and through MSc project works (CulturalNews, 2007). It is worth noting that three hundred of these herbal products have also been given market authorization by the Food and Drugs Board in which malaria herbal drugs form a greater portion.

2. Cryptolepis Sanguinolenta

The root of cryptolepis, also known in Ashanti language as nibima, delboi in Fulani language is an important herbal medicine in Ghana especially in rural communities. Ghanaian herbal clinics have developed this plant into tea formulation as phyto-Laria based on

this plant. *Cryptolepis sanguinolenta* is a slender, thin-stemmed climbing shrub with orange-coloured juice in the cut stem(Paulo and Houghton, 2003). The leaves are glabrous, oblong-elliptic or ovalate, shortly acuminate apex, rounded, sometimes acutely cuneate base. The flowers are greenish-yellow, the fruit is a follicle, linear 17–31 cm long, and the seeds are 10–12 mm long with a tuft of silky hairs at the end. The roots are rather tortuous and branched with little or no rootlets, with longitudinal ridges apparent in the dried samples. The root is distinctly yellow in colour and breaks with a short fracture exposing a smooth transverse surface which is yellow in colour (**Iwu 1993).**

Figure 1: Roots of C. sanguinolenta *Figure 2: Cut roots of C. sanguinolenta*

3. Material and methods

A herbal tea bag prepared from 2.5grams dried ground root of cryptolepis sanguinolenta was studied on 50 malaria patients in 5 independent stages. This means that each stage consist of new groups of patients. Each stage of the trial consists of 10 new patients with clinical features of uncomplicated malaria. The study excluded potential patients who had taken chloroquine and chloroquine related drugs within the previous two to four weeks. The patients were dosed three times daily for five consecutive days under the WHO extended 7 days test and followed for 28 days post-treatment. The proportions of patients who were totally cleared of plasmodium falciparum parasitaemia within 72 hours in each stage are as follows.

Stage i	x_i/n_i
1	$6/10$
2	$6/10$
3	$7/10$
4	$8/10$
5	$9/10$

Where

x_i is the proportion of patient cleared from P falciparum parasitaemia and n_i is the total number of patients in each stage of the trial.

4. Statistical analysis, procedures and models

The data collected was a research conducted in 5 (five) stages such that at the *ith* stage n_i patients enter the study each with a probability p_i of surviving the *ith* stage. At each stage a new group of patients is entered; thus stages are assumed to be independent as well as identical in their time periods. After the *ith* stage, the probability there are x_i survivors (number of patients healed) is

$$pr\{X = x\} = \binom{n_i}{x_i} p_i^x (1 - p_i)^{n_i - x_i}$$

To assess the growth in survivability of patients and the reliability of the cryptolepis sanguinolenta herbal drug in recovery of malaria patients in a stage to stage clinical trial; we discuss the distribution of the number of survivors at the end of a clinical trial and the effects of modifications in the clinical trial on the new groups of patients with respect possibly to increase the proportion of survivors.

Suppose a clinical trial is conducted in k stages such that at the $\boldsymbol{i^{th}}$ stage, $\boldsymbol{n_i}$patients after the study, each with a probability $\boldsymbol{p_i}$ of surviving the $\boldsymbol{i^{th}}$ stage..

After the $\boldsymbol{i^{th}}$stage, $\boldsymbol{p_i}$ is the probability that there are $\boldsymbol{x_i}$ survivors out of $\boldsymbol{n_i}$patients. The exponential growth model is assumed by $\boldsymbol{p_i}$ for measuring survivability growth and the reliability of the drug in recovery of patients from stage to stage.

The proportion of survivors from the data, increases from stage to stage. $p_i$is a function of two parameters as well as the stage number i. The exponential model is given by

$p_i = 1 - \alpha_1 exp(-\alpha_2 i)$

α_2 is the efficacy of cryptolepis sanguinolenta herbal drug

where $0 < \alpha_1 < e^{\alpha_2}, \alpha_2 > 0$ are the parameters of the model, $i = 1,2,3,4,\dots,k$. Two methods commonly used to estimate α_1 and α_2 are least squares and maximum likelihood. Maximum likelihood estimators are generally preferred to least squares estimators because of the desirability of large sample properties of maximum likelihood estimator. On the other hand least square estimators are often obtainable in closed form and are a good first approximation to the maximum likelihood estimator.

5. Least Squares

Let us define $\psi(\alpha_1, \alpha_2)$ as

$$\psi(\alpha_1, \alpha_2) \equiv \sum_{i=1}^{k} \left[\frac{x_i}{n_i} - p_i(\alpha_1, \alpha_2)\right]^2 \quad (1)$$

The least squares estimator α_1^* and α_2^* are the values of the parameters $\alpha_1$and α_2, respectively, that simultaneously minimize $\psi(\alpha_1, \alpha_2)$. Assuming that $p_i(\alpha_1, \alpha_2)$ is differentiable in $\alpha_1$and α_2, $i = 1,2,\dots,k$, and that the minimum is obtained by differentiation, we find α_1^* and α_2^*as the solution of

$$\sum_{i=1}^{k} \left[\frac{x_i}{n_i} - p_i(\alpha_1, \alpha_2)\right]^2 \frac{\partial p_i(\alpha_1^*, \alpha_2^*)}{\partial \alpha_1^*} = 0$$

and

$$\sum_{i=1}^{k} \left[\frac{x_i}{n_i} - p_i(\alpha_1^*, \alpha_2^*)\right]^2 \frac{\partial p_i(\alpha_1^*, \alpha_2^*)}{\alpha_2^*} = 0 \quad (2)$$

where

$$\frac{\partial p_i(\alpha_1^*, \alpha_2^*)}{\partial \alpha_j^*} \equiv \left.\frac{\partial p_i(\alpha_1, \alpha_2)}{\partial \alpha_j}\right|_{\substack{\alpha_1=\alpha_1^* \\ \alpha_2=\alpha_2^*}} \quad j = 1,2.$$

That is, α_1^* and α_2^* are the least squares estimators ofα_1 andα_2, respectively.

6. Maximum Likelihood

Given the probability that x_i patients of n_i on trial at stage i survive, $i = 1,2,\dots,k$.Thus the k stages being statistically independent, the likelihood function for all k stages is given by

$$L(\alpha_1, \alpha_2) = \prod_{i=1}^{k} \binom{n_i}{x_i} [p_i(\alpha_1, \alpha_2)]^{x_i} [1 - p_i(\alpha_1, \alpha_2)]^{n_i - x_i} \quad (3)$$

Assuming that the parameter vector (α_1, α_2) can be maximized with respect to the observations by maximum likelihood procedures, the maximum likelihood estimator $\hat{\alpha}_1$ and $\hat{\alpha}_2$ are the values of the parameters $\alpha_1$and α_2, respectively, that simultaneously maximize $L(\alpha_1, \alpha_2)$ or equivalently $log_e L(\alpha_1, \alpha_2)$. The vector $(\hat{\alpha}_1, \hat{\alpha}_2)$ is then the simultaneous solution of

$$\sum_{i=1}^{k} \frac{x_i}{p_i(\hat{\alpha}_1, \hat{\alpha}_2)} \frac{\partial p_i(\hat{\alpha}_1, \hat{\alpha}_2)}{\partial \hat{\alpha}_1} - \sum_{i=1}^{k} \frac{n_i - x_i}{1 - p_i(\hat{\alpha}_1, \hat{\alpha}_2)} \frac{\partial p_i(\hat{\alpha}_1, \hat{\alpha}_2)}{\partial \hat{\alpha}_1} = 0$$

and

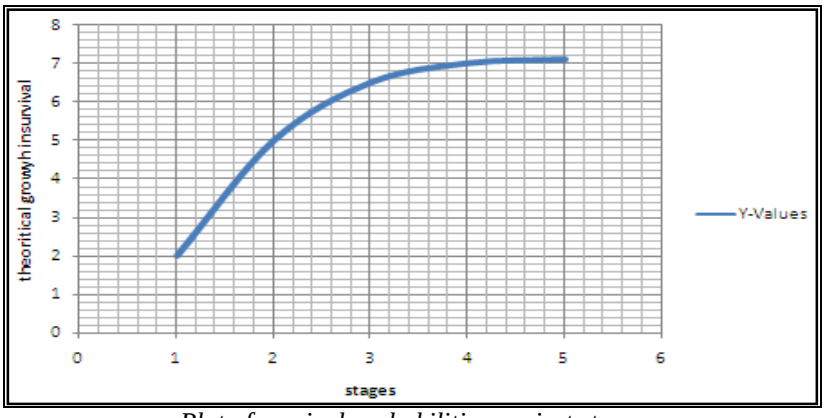
$$\sum_{i=1}^{k} \frac{x_i}{p_i(\hat{\alpha}_1, \hat{\alpha}_2)} \frac{\partial p_i(\hat{\alpha}_1, \hat{\alpha}_2)}{\partial \hat{\alpha}_2} - \sum_{i=1}^{k} \frac{n_i - x_i}{1 - p_i(\hat{\alpha}_1, \hat{\alpha}_2)} \frac{\partial p_i(\hat{\alpha}_1, \hat{\alpha}_2)}{\partial \hat{\alpha}_2} = 0 \quad (4)$$

that maximizes $L(\hat{\alpha}_1, \hat{\alpha}_2)$, where

$$\frac{\partial p_i(\hat{\alpha}_1, \hat{\alpha}_2)}{\partial \hat{\alpha}_j} \equiv \left.\frac{\partial p_i(\alpha_1, \alpha_2)}{\partial \alpha_j}\right|_{\substack{\alpha_1=\hat{\alpha}_1 \\ \alpha_2=\hat{\alpha}_2}} \quad j = 1,2. \quad (5$$

7. Estimation for the Exponential Growth Model

The exponential model was chosen for this research after plotting the survival probabilities at each stage of the trial.



Plot of survival probabilities against stages

This model depicts a slower growth in the early stages which sustains itself in the later stages.
Let $p_i(\alpha_1, \alpha_2)$ be defined by the exponential growth model. That is

$$p_i(\alpha_1, \alpha_2) = 1 - \alpha_1 exp(-\alpha_2 i), \qquad i = 1,2, \dots, k. \tag{6}$$

Since for this model

$$1 - p_i(\alpha_1, \alpha_2) = \alpha_1 exp(-\alpha_2 i), \qquad i = 1,2, \dots, k, \tag{7}$$

the least squares estimator α_1^* and α_2^* are obtained in the following ways. First

$$E\left(\frac{n_i - x_i}{n_i}\right) = \alpha_1 exp(-\alpha_2 i), \qquad i = 1,2, \dots, k, \tag{8}$$

Where $x_i \leq n_i - 1$.
As a result of this a least squares fit on the logarithm is used to obtain $\alpha_1^*$and α_2^*. The least squares equation$*$ is then

$$\psi(\alpha_1, \alpha_2) = \sum_{i=1}^{k} \left[log_e \frac{n_i - x_i}{n_i + 1} - log_e \alpha_1 + \alpha_2 i \right]^2. \tag{9}$$

Let us set $z_i \equiv log_e\{(n_i - x_i)/(n_i - 1)\}$. Differentiating $\psi(\alpha_1, \alpha_2)$ with respect to α_1 and α_2 and setting the resulting equations equal to zero we obtain

$$\sum_{i=1}^{k} i z_i - k log_e \alpha_1^* + \frac{k(k+1)}{2} \alpha_2^* = 0 \tag{10}$$

and

$$\sum_{i=1}^{k} i z_i - \frac{k(k+1)}{2} log_e \alpha_1^* + \frac{k(k+1)(2k+1)}{6} \alpha_2^* = 0. \tag{11}$$

Solving in terms of $log_e \alpha_1^*$ and α_2^* we find

$$log_e \alpha_1^* = 2[k(k-1)]^{-1}\{(2k+1) \sum_{i=1}^{k} z_i - 3 \sum_{i=1}^{k} i z_i\} \tag{12}$$

and

$$\alpha_2^* = 6[k(k-1)]^{-1} \left\{ \sum_{i=1}^{k} z_i - 2 \frac{\sum_{i=1}^{k} i z_i}{k+1} \right\} \tag{13}$$

These are used as the least squares estimators of the exponential growth model. The maximum likelihood function for the exponential growth model. Let $L(\alpha_1, \alpha_2)$ be the likelihood function for all k stages of the trials.
Then we have

$$L(\alpha_1, \alpha_2) = \prod_{i=1}^{k} \binom{n_i}{x_i} \left(1 - \alpha_1 exp(-\alpha_2 i)\right)^{x_i} \left(\alpha_1 exp(-\alpha_2 i)\right)^{n_i - x_i} \tag{14}$$

Taking logarithms and then differentiating with respect to $\alpha_1$and α_2, the maximum likelihood estimators $\hat{\alpha}_1$ and $\hat{\alpha}_2$ are obtained as the unique solution to

$$-\sum_{i=1}^{k} \frac{x_i}{[exp(\hat{\alpha}_2 i) - \hat{\alpha}_1]} + \frac{\sum_{i=1}^{k} (n_i - x_i)}{\hat{\alpha}_1} = 0 \tag{15}$$

And

$$\hat{\alpha}_1 \sum_{i=1}^{k} \frac{i x_i}{[exp(\alpha_2 i) - \hat{\alpha}_1]} - \sum_{i=1}^{k} i(n_i - x_i) = 0. \tag{16}$$

Therefore taking the logarithm and differentiating with respect to $\alpha_1$and α_2, we have

$$\frac{\partial^2 log_e L}{\partial \alpha_1^2} = -\left[\sum_{i=1}^{k} \frac{x_i}{[exp(\alpha_2 i) - \alpha_1]^2} + \sum_{i=1}^{k} \frac{n_i - x_i}{\alpha_1^2} \right], \tag{17}$$

$$\frac{\partial^2 log_e L}{\partial \alpha_1 \partial \alpha_2} = \sum_{i=1}^{k} \frac{i x_i exp(\alpha_2 i)}{[exp(\alpha_2 i) - \alpha_1]^2}, \tag{18}$$

and

$$\frac{\partial^2 log_e L}{\partial \alpha_2^2} = -\alpha_1 \sum_{i=1}^{k} \frac{i^2 x_i exp(\alpha_2 i)}{[exp(\alpha_2 i)-\alpha_1]^2} \quad (19)$$

8. Confidence regions and intervals for the exponential growth model

An approximate (1-α)100 percent elliptical confidence region for the parameter vector $\begin{pmatrix}\alpha_1\\ \alpha_2\end{pmatrix}$ is

$$\sigma^{11}(\hat{\alpha}_1 - \alpha_1)^2 + \sigma^{22}(\hat{\alpha}_2 - \alpha_2)^2 + 2\sigma^{12}(\hat{\alpha}_1 - \alpha_1)(\hat{\alpha}_2 - \alpha_2) = \chi^2(1-\alpha;2) \quad (20)$$

Where $\chi^2(1-\alpha;2)$ is the (1-α)100 percentage point of the chi-square distribution with 2 degree of freedom and

$$\sigma^{ij} = -E\left[\frac{\partial^2 log_e L}{\partial \alpha_i \partial \alpha_j}\right], \qquad i,j = 1,2. \quad (21)$$

For this model

$$\sigma^{11} = \alpha_1^{-1} \sum_{i=1}^{k} \frac{n_i}{exp(\alpha_2 i)-\alpha_1}, \quad (22)$$

$$\sigma^{12} = -\sum_{i=1}^{k} \frac{i n_i}{exp(\alpha_2 i)-\alpha_1}, \quad (23)$$

and

$$\sigma^{22} = \alpha_1 \sum_{i=1}^{k} \frac{i^2 n_i}{exp(\alpha_2 i)-\alpha_1}. \quad (24)$$

We obtain an appropriate $(1-\alpha)100$ percent lower confidence limit $p_{L_i}(\hat{\alpha}_1, \hat{\alpha}_2)$ for the exponential growth model. We have

$$p_{L_i}(\hat{\alpha}_1, \hat{\alpha}_2) = (1 - \hat{\alpha}_1 \exp(-\hat{\alpha}_2 i)) - Z(1-\alpha)\sqrt{V\hat{a}r(1 - \hat{\alpha}_1 \exp(-\hat{\alpha}_2 i))}, \quad (25)$$

Where

i. Var$(1 - \hat{\alpha}_1 \exp(-\hat{\alpha}_2 i))$ is given as

$$Var(1 - \hat{\alpha}_1 \exp(-\hat{\alpha}_2 i)) = \exp(-2\alpha_2 i)\left[\sigma^2_{\hat{\alpha}_2} + i^2\alpha_1^2\sigma^2_{\hat{\alpha}_2} - 2\alpha_1 i \sigma_{\hat{\alpha}_1\hat{\alpha}_2}\right] \quad (26)$$

ii. The values $\sigma^2_{\hat{\alpha}_1}, \sigma^2_{\hat{\alpha}_2}$ and $\sigma_{\hat{\alpha}_1\hat{\alpha}_2}$ are elements of the matrix

$$\begin{bmatrix} \sigma^2_{\hat{\alpha}_1} & \sigma_{\hat{\alpha}_1\hat{\alpha}_2} \\ \sigma_{\hat{\alpha}_1\hat{\alpha}_2} & \sigma^2_{\hat{\alpha}_2} \end{bmatrix} = \begin{bmatrix} \sigma^{11} & \sigma^{12} \\ \sigma^{12} & \sigma^{22} \end{bmatrix}^{-1} \quad (27)$$

9. Assessment model for the overall probability of success in the clinical trial

Patients' response to treatment in clinical trials is classified as "success" or "failure". Models developed have been concerned in estimating the probability of success (failure) at each stage for clinical trials conducted in stages. We are to assess the overall probability of success at the end of each stage of the clinical trial conducted in k stages. At the first stage of the trial, $\tilde{R}_1$ the estimate for patient response is given by

$$\tilde{R}_1 = r_i = \frac{X_i}{n_i} \quad (28)$$

Where, n_i = patients under stage i, X_i = patients are those who respond for stage i, $i = 1,2,..,k$

The overall assessed probability of patient response after each stage the model is

$$\hat{R}_i = \widehat{\propto_i^0}\, r_i + (1 - \widehat{\propto_i^0})\hat{R}_{i-1} \quad (29)$$

Where, r_i proportion of patient respond at the ìths stage

$\widehat{\propto_i^0}$ is the smoothing constants of each stage

Using the empirical approach or method discussed by Gross [1971b] in determining the smoothing constant, we make the following assumptions,

- $\hat{R}_i$ is an unbiased estimator of R_i, where R_i is the theoretical assessment of the overall probability of success after the i^{th} trial, $i = 1,2,..,k$
- $P_i = \epsilon(r_i)$, thus P_i is the probability that a patient on study during the i^{th} stage responds.
- All patients within a stage have the same independent probability of response. Furthermore, the stages are independent.

The criterion for the choice of each smoothing constant $\hat{\propto}_i$ is to minimise the variance $\hat{\sigma}_i^{-2}$ of its associated value $\hat{R}_i$ by assumption 1 through 3.

$$\hat{\propto}_i^0 = \frac{\hat{\sigma}_i^{-2}}{\sum_{j=1}^{i} \sigma_i^{-2}} \quad (30)$$

$$\hat{\sigma}_i^2 = \frac{r_i(1-r_i)}{n_i - 1} \quad (31)$$

Hence

$\hat{\sigma}_i^{-2} = \frac{n_i - 1}{r_i(1-r_i)}$ (32)

$\hat{\boldsymbol{\sigma}}_i^{-2}$ = inverse estimated variance for each stage

$\hat{\alpha}_i^{0}$ = smoothing constant for each stage

10. Results and Discussion

This presents the details of the analysis and results of the research. This consists of presentation of data collected, numerical analysis (least square estimates and maximum likelihood estimates), confidence region and interval at each five stages of the of the clinical trial, assessment of the overall probability of success in the clinical trial and discussion of the results.

10.1. Presentation of Data Collected

Analysis on this study began with the data collected from the Amen Scientific Herbal Clinic. The data collected was a clinical trial which was conducted in five (5) stages. The clinical trial was conducted with the aim of improving the probability that patients suffering from uncomplicated malaria fever will be cured after receiving treatment with cryptilepis sangiunolenta. The data, which was made up of ten patients in each stage of the clinical trial adding up to fifty (50) patients. Out of the fifty patients, twenty two (20) were male and twenty eight (30) were females.

The five staged clinical trial, has in each stage a total of ten patients who underwent the trials. In each stage of the clinical trial some of patients were unable to be cured of the disease, others did. The patients, who after two weeks, are supposed to be cured of the disease, were grouped into healed and not healed. That is, those patients that were cured of the disease were grouped under healed and those that were not cured, placed under not healed. Stage one of the clinical trial had six patients healed and four patients not healed. Stage two and stage three had seven patients healed and three patients not healed each. Stage four had eight patients being healed and two patients not healed. Stage five had nine patients out of ten healed.

The proportion of patients being cured at each stage of the clinical trial is derived. This is done by dividing the total number of patients that were healed in the stage by the total number of patients in that stage of the clinical trial. This proportion of patients also depicts the survival probabilities of each stage. The table below shows the details of the data collected.

Stages	Total number of patients	Number of males	Number of females	Number of patients healed	Number of patients not healed	Survival probability
1	10	3	7	6	4	0.6
2	10	3	7	7	3	0.7
3	10	5	5	7	3	0.7
4	10	5	5	8	2	0.8
5	10	4	6	9	1	0.9

Table 4.1 stage by stage clinical trial with survival probability of each stage

The table above shows an improvement in the number of patients that are healed from stage-to-stage. Plotting the survival probabilities of each stage aids in determining the exponential model used in the analysis of the data. The graph below shows the graphical display of the survival probabilities.

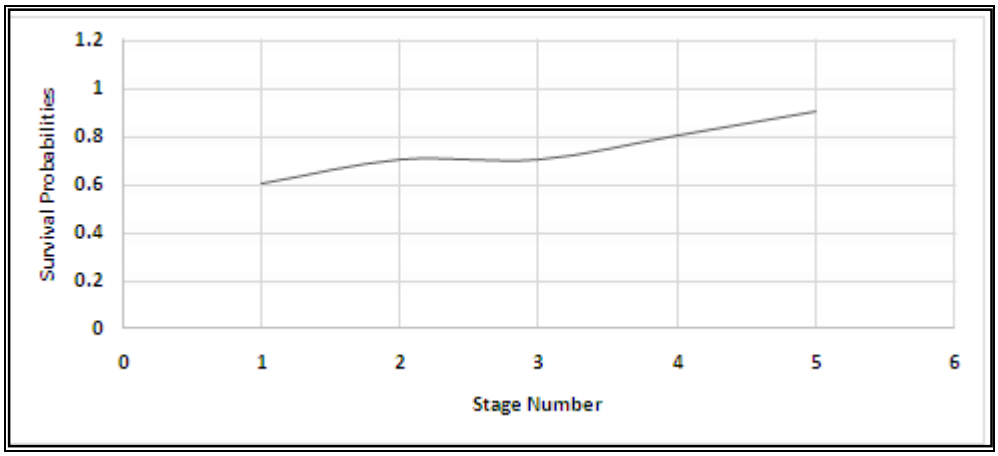


Figure 4. 1: Graph of Survival probabilities as a function of the stages (i) for uncomplicated malaria remission with cryptolepis sanguinolenta

X-axis = stages
Y-axis = survival probabilities
The graph above shows the survival probabilities having a slower growth in the early stages which sustains itself in the later stages. This determines the use of the exponential model in the analysis of the data. The exponential model is used when at the early stages of the clinical trial the survival probabilities show a slow growth and later sustains itself.

10.2. Numerical analysis
Two methods are commonly used in the estimation of $\alpha_1$and α_2. These are the maximum likelihood and least squares. Maximum likelihood estimators are generally preferred to least squares estimators because of the desirability of the large sample properties of maximum likelihood estimators. On the other hand, least square estimators are often obtainable in closed form and are good first approximation.

10.3. Least square estimates
The exponential model as given in equation (6), computes $\hat{\alpha}_1$and $\hat{\alpha}_2$, the maximum likelihood estimates of α_1 and α_2 respectively, where
α_1= the growth in the healing process (survivability growth)
α_2= the drug intervention (reliability of the cryptolepis sanguinolenta herbaldrug)
To this end, we obtained the initial estimates $\hat{\alpha}_{10}$ and $\hat{\alpha}_{20}$ by least square equations (12) and (13). The estimates $\hat{\alpha}_{10}$ and $\hat{\alpha}_{20}$ were obtained from the layout in table 4.2

Stages **i**	**Number of cured patients** $\mathbf{x_i}$	$\frac{\mathbf{n_i - x_i}}{\mathbf{n_i + 1}}$	$\mathbf{z_i = \log_e \frac{n_i - x_i}{n_i + 1}}$	$\mathbf{iz_i}$
1	6	4/11	-1.01160	-1.01160
2	7	3/11	-1.29928	-2.59856
3	7	3/11	-1.29928	-3.89784
4	8	2/11	-1.70475	-6.81899
5	9	1/11	-2.39790	-11.98948
Totals			-7.71281	-26.31647

Table 4.2 Least square computation layout

From the table 4.2 and equations (12) and (13), it follows that our initial estimates $\hat{\alpha}_{10}$ was 0.55480 and $\hat{\alpha}_{20}$ was 0.317805. These initial estimates are our least square estimates.

10.4. Maximum likelihood estimates

The initial estimates were used in the computation for the Newton-Raphson procedure. This procedure was used to obtain the maximum likelihood estimates of $\hat{\alpha}_1$and $\hat{\alpha}_2$. By the Newton-Raphson procedure, the maximum likelihood estimates was obtained by going through series of iterations for the Newton-Raphson procedure to converge at an estimate.

To facilitate the computation of the Newton-Raphson procedure, table 4.3.1 is given. In this table we let$\hat{g}_{10i}$, $\hat{g}_{20i}$, $\widehat{-f}_{110i}$, $\hat{f}_{120i}$ and $\widehat{-f}_{220i}$ be, respectively,

$$-\frac{x_i}{[exp(\hat{\boldsymbol{\alpha}}_{\mathbf{20}}i)-\hat{\boldsymbol{\alpha}}_{\mathbf{10}}]}+\frac{\sum_{i=1}^{k}(n_i-x_i)}{\hat{\boldsymbol{\alpha}}_{\mathbf{10}}},$$

$$\frac{\hat{\boldsymbol{\alpha}}_{\mathbf{10}}ix_i}{[exp(\hat{\boldsymbol{\alpha}}_{\mathbf{20}}i)-\hat{\boldsymbol{\alpha}}_{\mathbf{10}}]}-i(n_i-x_i),$$

$$-\left(\frac{x_i}{[exp(\hat{\boldsymbol{\alpha}}_{\mathbf{20}}i)-\hat{\boldsymbol{\alpha}}_{\mathbf{10}}]^2}+\frac{n_i-x_i}{\hat{\boldsymbol{\alpha}}_{10}^2}\right),$$

$$\frac{ix_i exp(\hat{\boldsymbol{\alpha}}_{\mathbf{20}}i)}{[exp(\hat{\boldsymbol{\alpha}}_{\mathbf{20}}i)-\hat{\boldsymbol{\alpha}}_{\mathbf{10}}]^2},$$

and

$$-\hat{\boldsymbol{\alpha}}_{\mathbf{10}}\frac{i^2x_i exp(\hat{\boldsymbol{\alpha}}_{\mathbf{20}}i)}{[exp(\hat{\boldsymbol{\alpha}}_{\mathbf{20}}i)-\hat{\boldsymbol{\alpha}}_{\mathbf{10}}]^2}.$$

For the first iteration we used the initial estimates in the computation.

Stages i	$\hat{\mathbf{g}}_{\mathbf{10i}}$	$\hat{\mathbf{g}}_{\mathbf{20i}}$	$\widehat{-\mathbf{f}}_{\mathbf{110i}}$	$\hat{\mathbf{f}}_{\mathbf{120i}}$	$\widehat{-\mathbf{f}}_{\mathbf{220i}}$
1	-0.1134454	0.06293951	-21.933657	12.28224	-6.814186
2	0.1575125	-0.17477582	-13.683755	14.86847	-16.498054
3	1.9755692	-3.28813741	-11.428942	13.09562	-21.796356
4	0.9474480	-2.10257666	-7.380420	12.58884	-27.937144
5	-0.2692907	0.74701253	-3.725733	11.68164	-32.404857
Total	2.697794	-4.755538	-58.15251	64.5168	-105.4506

Table 4.3 First iteration

The values $\hat{\alpha}_{11}$ and $\hat{\alpha}_{21}$were then found by solving the matrix equation

$$\begin{pmatrix}\hat{\boldsymbol{\alpha}}_{\mathbf{11}}\\ \hat{\boldsymbol{\alpha}}_{\mathbf{21}}\end{pmatrix}=\begin{pmatrix}\mathbf{0.5548}\\ \mathbf{0.317805}\end{pmatrix}-\begin{bmatrix}-58.15251 & 64.5168\\ 64.5168 & -105.4506\end{bmatrix}^{-1}\begin{pmatrix}2.697794\\ -4.755538\end{pmatrix}.$$

Solving the matrix $\hat{\alpha}_{11}$ = 0.5435and $\hat{\alpha}_{21}$ = 0.2658. $\hat{\alpha}_{11}$and$\hat{\alpha}_{21}$ were used in the second iteration. The iteration is continued since the Newton-raphson procedure did not converge to maximum likelihood estimates.

Stages i	$\hat{\boldsymbol{g}}_{\mathbf{11}i}$	$\hat{\boldsymbol{g}}_{\mathbf{21}i}$	$\widehat{-\boldsymbol{f}}_{\mathbf{111}i}$	$\hat{\boldsymbol{f}}_{\mathbf{121}i}$	$\widehat{-\boldsymbol{f}}_{\mathbf{221}i}$
1	-0.5249250	0.2852968	-23.902550	13.51596	-7.345925
2	-0.5243284	0.5699450	-15.374736	17.76099	-19.306201
3	1.3438211	-2.1911004	-12.647220	16.58983	-27.049715
4	0.2786689	-0.6058263	-8.216665	16.74835	-36.410921
5	-0.9432078	2.5631673	-4.245978	16.25448	-44.171559
total	**-0.3699712**	**0.6214824**	**-64.38715**	**80.86962**	**-134.2843**

Table 4.4 Second iteration

The values $\hat{\boldsymbol{\alpha}}_{\mathbf{12}}$and $\hat{\boldsymbol{\alpha}}_{\mathbf{22}}$were then found by solving the matrix equation

$$\begin{pmatrix}\hat{\boldsymbol{\alpha}}_{\mathbf{12}}\\ \hat{\boldsymbol{\alpha}}_{\mathbf{22}}\end{pmatrix}=\begin{pmatrix}0.5435\\ 0.2658\end{pmatrix}-\begin{bmatrix}-64.38715 & 80.86962\\ 80.86962 & 134.2843\end{bmatrix}^{-1}\begin{pmatrix}-0.3699712\\ 0.6214824\end{pmatrix}.$$

Solving the matrix $\hat{\alpha}_{12}$ = 0.5438and $\hat{\alpha}_{22}$ = 0.2706. $\hat{\alpha}_{12}$and $\hat{\alpha}_{22}$ were used in the third iteration. The iteration was continued since there was no convergence of the maximum likelihood estimates.

Stages i	$\hat{\mathbf{g}}_{12i}$	$\hat{\mathbf{g}}_{22i}$	$\widehat{-\mathbf{f}}_{112i}$	$\hat{\mathbf{f}}_{122i}$	$\widehat{-\mathbf{f}}_{222i}$
1	-0.4675435	0.2542502	-23.726761	13.37016	-7.270691
2	-0.4444299	0.4833620	-15.221282	17.44353	-18.971579
3	1.4187522	-2.3145523	-12.543850	16.20778	-26.441373
4	0.3555019	-0.7732877	-8.142917	16.29047	-35.435021
5	-0.8676804	2.3592230	-4.195555	15.74612	-42.813689
Total	**-0.005399756**	**0.008995103**	**-63.83036**	**79.05804**	**-130.9324**

Table 4.5 Third iteration

From table 4.5 $\hat{\alpha}_{13}$ and $\hat{\alpha}_{23}$were found by solving the matrix

$$\begin{pmatrix}\hat{\boldsymbol{\alpha}}_{\mathbf{13}}\\ \hat{\boldsymbol{\alpha}}_{\mathbf{23}}\end{pmatrix} = \begin{pmatrix}0.5438\\ 0.2706\end{pmatrix} - \begin{bmatrix}-63.83036 & 79.05804\\ 79.05804 & -130.9324\end{bmatrix}^{-1}\begin{pmatrix}-0.005399756\\ 0.008995103\end{pmatrix}.$$

Solving the matrix,$\hat{\alpha}_{13}$ = 0.5438 and $\hat{\alpha}_{23}$ = 0.2707 and were then used in the fourth iteration to verify the convergence of the maximum likelihood estimates.

Stages i	$\hat{\boldsymbol{g}}_{13i}$	$\hat{\boldsymbol{g}}_{23i}$	$\widehat{-\boldsymbol{f}}_{113i}$	$\hat{\boldsymbol{f}}_{123i}$	$\widehat{-\boldsymbol{f}}_{223i}$
1	-0.4662067	0.2535232	-23.723275	13.36692	-7.268933
2	-0.4426859	0.4814652	-15.218312	17.43681	-18.964272
3	1.4203726	-2.3171958	-12.541953	16.19982	-26.428394
4	0.3571305	-0.7768302	-8.141565	16.28101	-35.414452
5	-0.8661063	2.3549430	-4.194608	15.73567	-42.785292
total	**0.002504157**	**-0.004094581**	**-63.81971**	**79.02024**	**-130.8613**

Table 4.6 Fourth iteration

From table 4.6, $\hat{\alpha}_{14}$ and $\hat{\alpha}_{24}$ was found by solving the matrix

$$\begin{pmatrix}\hat{\alpha}_{14}\\ \hat{\alpha}_{24}\end{pmatrix} = \begin{pmatrix}0.5438\\ 0.2707\end{pmatrix} - \begin{bmatrix}-63.81971 & 79.02024\\ 79.02024 & -130.8613\end{bmatrix}^{-1}\begin{pmatrix}-0.004094581\\ -0.004094581\end{pmatrix}.$$

Solving the matrix, $\hat{\alpha}_{14}$ = 0.5438 and $\hat{\alpha}_{24}$ = 0.2707. The iteration was stopped since the Newton-Raphson procedure converged to the maximum likelihood estimates. Table 4.7 shows the results at each step of the iteration. The third iteration was chosen since further iterations gave the requisite maximum likelihood estimates and does not change the result.

Iteration j	$\hat{\boldsymbol{\alpha}}_{1j}$	$\hat{\boldsymbol{\alpha}}_{2j}$
0	0.5548	0.317805
1	0.5435	0.2658
2	0.5438	0.2706
3	0.5438	0.2707
4	0.5438	0.2707

Table 4.7 Values of $\hat{\alpha}_{1j}$ and $\hat{\alpha}_{2j}$ at each iteration of the Newton-Raphson procedure

Table 4.7 shows clearly that after the second iteration, the estimates begin to become the same, that is, they converge.
It is intrusive to compare the observed and expected relief probabilities at each stage using both least squares and maximum likelihood estimates. These comparisons appear in table 4.10.

Stages i	Observed Probability	Expected Maximum Likelihood Estimate probability	Expected Least Squares likelihood Estimate probability
1	0.6	0.5851647	0.5962472
2	0.7	0.6835448	0.7061711
3	0.7	0.7585937	0.7861676
4	0.8	0.8158443	0.8443846
5	0.9	0.8595177	0.8867517

Table 4.8 Expected and observed relief probabilities for the patients at each stage when the clinical trial is conducted

Table 4.8 indicates the growth in survivability at each stage of the clinical trial. The table also indicates that the least square estimates tend to overestimate and the maximum likelihood estimates tend to underestimate the observed probabilities of relief at each stage. Thus the least square estimates are somewhat optimistic whereas the maximum likelihood estimates are somewhat conservative.

10.5. Confidence region and interval for the probability of relief

We obtained an appropriate (1-α) 100 percent lower confidence limit $p_{L_i}(\hat{\alpha}_1, \hat{\alpha}_2)$ for the model by means of (3.7.1). Thus the values of $\sigma^2_{\hat{\alpha}_1}, \sigma^2_{\hat{\alpha}_2}$ and $\sigma_{\hat{\alpha}_1\hat{\alpha}_2}$ was obtained by inverting the matrix of $\sigma^{11}, \sigma^{12} and \sigma^{22}$ as by equations (3.7.3), (3.7.4) and (3.7.5), respectively. Thus, using the maximum likelihood estimates, we found $\sigma^{11} = 63.5497$, $\sigma^{12} = -79.2504$ and $\sigma^{22} = 131.2249$.

Thus we see that $\begin{bmatrix} \sigma^2_{\hat{\alpha}_1} & \sigma_{\hat{\alpha}_1\hat{\alpha}_2} \\ \sigma_{\hat{\alpha}_1\hat{\alpha}_2} & \sigma^2_{\hat{\alpha}_2} \end{bmatrix} = \begin{bmatrix} 63.5497 & -79.2504 \\ -79.2504 & 131.2249 \end{bmatrix}^{-1} = \begin{bmatrix} 0.0637 & 0.0385 \\ 0.0385 & 0.0309 \end{bmatrix}$.

By through equations (3.7.6) through to (3.7.8), we found that

$p_{L_i}(\hat{\alpha}_1, \hat{\alpha}_2) = (1 - 0.5438\exp(-0.2707i)) - (1.645)\sqrt{\exp(-0.5414i)[0.0637 + 0.01138516i^2 - 0.01680342i]}$

is a 95 percent lower confidence limit for $p_{L_i}(\hat{\alpha}_1, \hat{\alpha}_2)$, $i = 1,2,\ldots,6$, noting that 1.645 is the upper 95th percentage point of the standard normal distribution.

Stages i	$p_{L_i}(\hat{\alpha}_1, \hat{\alpha}_2)$
1	0.3340049
2	0.5299582
3	0.6604890
4	0.7432562
5	0.7957258
6	0.8324348

Table 4.9 95 percent lower confidence limits for the probability of relief from malaria at each of the five clinical trial, plus predicted sixth stage lower limit

Table 4.9 indicates the values of $p_{L_i}(\hat{\alpha}_1, \hat{\alpha}_2)$ for the exponential model at each of the five stages of the clinical trial and in addition, the predicted value $p_{L6}(\hat{\alpha}_1, \hat{\alpha}_2)$ with confidence 0.95.

10.6. Assessing the overall probability of success in the clinical trials

Assessing the overall probability of success at each stage of the clinical trial, the values of $\hat{\sigma}_i^{-2}$, α_i^0 and $\hat{R}_i$ was found.

stage i	r_i	$\hat{\sigma}_i^{-2}$	$\hat{\alpha}_i^0$	$\hat{R}_i$
1	0.6	37.5	-	0.600
2	0.7	42.86	0.533	0.653
3	0.7	42.86	0.348	0.669
4	0.8	56.25	0.313	0.710
5	0.9	100.00	0.358	0.778

Table 4.10 Assessed overall survival probabilities at each stage of the clinical trial

Table 4.10 contains the overall assessed probability of patients' response after each stage as well as the inverse estimated variance and smoothing constant for each stage. The estimated variances were found to be 37.5, 42.86, 42.86, 56.25 and 100.00. Our smoothing constants were found to minimize the variances of its associated value$\hat{R}_i$. The smoothing constant were 0.533, 0.348, 0.313 and 0.358. $\hat{R}_i$was our overall remission probabilities from malaria fever at each stage.

11. Conclusion

11.1. Summary

Malaria fever is one of the top 10 out-patient diseases in Ghana according to the Ghana health service.It is rated among the top killer diseases in Ghana. Based on reliable information gathered from the Herbal clinics in Ashanti Region(the second largest Region in Ghana) depicting a rise in the number of malaria fever cases recorded from 2011, 2012 to 2013. The figures recorded by Amen Scientific clinic were 322, 772 and 1000. These indicate an increase from year to year. The increase was amounted to the fact that the residents in the community expecially those in rural settlements had bad hygienic practices which has contributed to the spread of the disease in the vicinity. Many of the affected patients find it difficult to access facilities in orthodox hospitals due to poverty. Even though many are aware of the efficacy of some of the traditional medicines around them, negative perception attached to these drugs prevent them from usage. In this regard, the research was interested in assessing the survivability growth and reliability of the efficacy of cryptolepis sanguinolenta as an alternate malaria drugs in place of chlorogiun.

The main objectives of the research was to assess the survivability growth and reliability of cryptolepis sanguinolenta as a herbal drugs and also the overall probability of survival in each stage of the clinical trial. The methodology employed to assess the survivability growth was to find least squares and maximum likelihood estimates of the exponential model chosen to analyze the data collected from the Herbal Clinic. The exponential model was chosen after the data collected from the hospital was plotted on a graph. The graph showed a slow survivability growth in the early stages which sustained itself in the later stages of the clinical trial.

The maximum likelihood estimates and the least squares estimates were used to find expected maximum likelihood estimate probabilities and expected maximum likelihood probability estimates, respectively, which was compared with the observed probability estimates. The confidence interval and region for the probability of relief at each stage was also calculated. The overall probability of success at each stage of the clinical trial was calculated for by finding the inverse estimated variance and smoothing constants for each stage. These in turn aid in assessing the overall probability of success in each stage of the clinical trial.

The Least squares estimates were found to be the initial estimates of the maximum likelihood estimates. These initial estimates $\hat{\alpha}_{10}$ was 0.55480 and $\hat{\alpha}_{20}$ was 0.317805. The initial estimates was used in the computation for the Newton-Raphson procedure for the calculation of the maximum likelihood estimates. By the Newton-Raphson procedure, the maximum likelihood estimates was obtained by going through series of iterations for the Newton-Raphson procedure to converge at an estimate. After the second iteration, the Newton-Raphson procedure converged at $\hat{\alpha}_{12} = 0.5438$and $\hat{\alpha}_{22} = 0.2706$. The third iteration was chosen since further iterations gave the requisite maximum likelihood estimates and does not change the result. The observed and expected relief probabilities at each stage using both least squares and maximum likelihood estimates was compared.

A 95 percent lower confidence limit for $p_{L_i}(\hat{\alpha}_1, \hat{\alpha}_2)$, $i = 1,2, \ldots ,6$, noting that 1.645 is the upper 95th percentage point of the standard normal distribution was constructed. Each stage with its lower limit was found to be 1=0.3340049, 2=0.5299582, 3=0.6604890, 4=0.7432562, 5=0.7957258 and 6=0.8324348. A predicted value $p_{L6}(\hat{\alpha}_1, \hat{\alpha}_2)$ with confidence 0.95 was also calculated for.

Finally, in finding the assessed overall probability of success, the smoothing constants were calculated for and was used in assessing the overall probability of success. The overall remission probabilities for stage 1 through to five were 0.600, 0.653, 0.669, 0.710 and 0.778, respectively.

From the analysis made and estimates derived in the Newton-Raphson procedure, we conclude that since $\hat{\alpha}_2 > 0$, the drug is reliable and very useful in the healing process of malaria.

On whether the healing process is improving, conclusion was made on the observed survival probabilities derived from the data collected from the Clinic. The observed probabilities showed an increase in the number of survivors at each stage of the clinical trial. This depicts improvement in the healing process. This is further confirmed by the expected least squares estimates probabilities and maximum likelihood estimates probabilities derived for each stage which show increasing probabilities from stage to stage. Noting that $p_i$is a function of α_1 and α_2, and also since α_2 is increasing that is, the drug reliability increase from stage to stage, this in turn affects the survivability growth and hence we conclude that there is improvement in the healing process. Considering the probability values derived in the assessed overall survival probabilities, we conclude that a patient that faces treatment in stage one will have a 0.6 chance of survival, whereas stages two and three have 0.653 and 0.669 chances of survival respectively. Stages four and five had their overall survival probabilities to be above 0.7 and hence a patient chance of being cured of malaria fever in that stage is 0.7 which is a very high chance of success.

It is obvious that uncomplicated malaria has very high chances of being cured with cryptolepis sangiunolenta and hence people affected with malaria are advised to resort to this herbal plant for treatment.

12. References

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