Original article

A Bayesian approach in agreement analysis: An application in Artemisin Combination Therapies (ACTs) for malaria patients

Atanu Bhattacharjee[1], Dibyojyoti Bhattacharjee[2]

[1]Department of Statistics, Gauhati University, Guwahati-14, [2]Department of Business Administration, Assam University, Silchar-11, India.

Correspondence: Atanu Bhattacharjee Email: atanustat@gmail.com

ABSTRACT

The World Health Organization (WHO) announced phasing out artemisinin as a single drug therapy for oral treatment of malaria from the market and has started advising prescription of Artemisin Combination Therapies (ACTs) in 2010. The objective of this work is to study the ACTs practice pattern by the doctors and selling pattern by the chemist in Varanasi city market. A Bayesian approach is used to perform agreement analysis between doctors and chemists drug practice in this regard. It has been found that the agreement level between doctors and chemist towards ACTs is higher in case of pregnant mothers in comparison to the other population.

INTRODUCTION

The drug malpractice is one of the greatest problems in the control of malaria. To deal with such problem, WHO in 2010[1] has announced phasing out the single-drug artemisin for oral treatment of malaria from the market and recommended Artemisin Combination Therapies (ACTs). The reason was that single-drug artemisin treatment (monotherapy) generates resistance in the malarial parasites whereas ACT is nearly 95% effective to curing complicated malaria. The WHO has appealed to all companies to stop marketing single drug oral artemisin and to re-direct their production towards the ACTs.

In last few decades agreement analysis has become one of the important statistical tools for data analysis [Coleman (1966), Light (1969), Von and Eye Mun (2005) and Liebetrau (1983). It is a widely applied tool in categorical data analysis where the different raters provide different rating to the same subject. The analysis is performed to study the level of agreement between two performers. In this work, we observed the drug prescription and selling pattern on the same patients by doctors and chemist respectively. We performed the agreement analysis to compare the prescription pattern and selling pattern between doctor and chemist. The small sample size observed was due to the limitation of funding. The Bayesian approach in the agreement analysis has been applied to overcome the small sample size observation. In the Bayesian approach, the MCMC simulation techniques has been used and compared with doctors and chemist practice pattern.

OBJECTIVES AND STUDY DESIGN

The objective of this study was to compare the prescribing and selling practice pattern by the doctors and chemist towards the ACT versus artemisinin monotheraphy. The WHO has strictly recommended stopping the artemisin monotheraphy in the pregnant women. What is practiced in reality by chemists and the doctors is a matter of concern. This work is a cross sectional study design and the data has been collected from the patients who visited three dispensaries in Varanasi city during the period between December 2009 and November 2010. The patient prescription and the drug-purchase record of the same patient was scrutinized from the chemist. The Bayesian approach has been applied in this work to overcome the bias due to small sample size.

DATA METHODOLOGY

The secondary data was obtained from the cross sectional study by Insitute of Medical Science, Banaras Hindu University, Varanasi in 2010. A period of 12 months was taken to study the artemisin monotherapy and combined therapy practice pattern by the health care professionals. The calculated sample size to conduct the study was 54. A total of 54 prescriptions and chemist practice pattern were studied. The Bayesian approach with Markov Chain Monte Carlo (MCMC) technique was applied to obtain the statistical inferences.

METHODS OF THE STUDY

Over the last four to five decades, the agreement analysis has become one of the most explored and useful area in statistical science. The agreement analysis is dependent on the identification of the raters and subjects. Belloso et al. (2003) have applied the agreement analysis to obtain the abnormalities in the body fat in HIV patients.

McNicholas et al. (1999) have applied the kappa statistics to assess the inter and intra-observer agreement on the osteoarthritis patients. Planche et al. (2001) compared the results of application of one touch glucose meter with reference glucose meter in malaria patients with agreement analysis. In the designing stage, it is very important to look into the relationship between two groups' raters and subjects. It is assumed that there is no difference between the two raters and if the differences exist, some steps need to be used to take care of it. To find out the inter and intra observation between two raters, the Bayesian approach in the agreement analysis can be useful. It is well accepted that difference between two health professionals will always exist due to the difference of experiences and training but many times this differences creates inescapable problems in drug practice. In the categorical observation, the well accepted indicator is the kappa statistics. The expected proportion of chance of agreement between the observed frequencies can be denoted by,

$$\frac{a+c}{n} \times \frac{a+b}{n} \times \frac{c+d}{n} \times \frac{b+d}{n} \qquad (1)$$

The kappa statistics can be formulated by,

$$k = \frac{simple\ agreement - expected\ agreement}{1 - expected\ agreement} \qquad (2)$$

with the simple agreement by

$$\frac{a+d}{n} \qquad (3)$$

Scott (1955) defined the Kappa through the marginal distribution of k by

$$k = [(\theta_{00} + \theta_{11}) - (\theta_{0.}\theta_{.0} + \theta_{1.}\theta_{.1})]/[1 - (\theta_{0.}\theta_{.0} + \theta_{1.}\theta_{.1})] \qquad (4)$$

where θ_{ij} stands for the two different rater dichotomous rating.

The Kappa statistics further has been modified from the ordinal scoring to multiple scoring. Fleiss et al. (1966) have used the indices A_1 and A_2 in agreement analysis by

$$A_1 = \frac{\left(\frac{\theta_{00}}{\theta_{.0}} + \frac{\theta_{00}}{\theta_{0.}} + \frac{\theta_{11}}{\theta_{1.}} + \frac{\theta_{11}}{\theta_{.1}}\right)}{4} \qquad (5)$$

$$A_2 = \frac{\theta_{11}}{(\theta_{1.} + \theta_{.1})} + \frac{\theta_{00}}{(\theta_{0.} + \theta_{.0})} \qquad (6)$$

In the null hypothesis, it is assumed that $A_1 = A_2 = 1/2$. If the both raters have independent scores by $\theta_{ij} = \theta_{i.}\theta_{.j}$.

For the two indices, $0 \leq A_1, A_2 \leq 1$

In this work, we have computed the posterior mean of A_1 and A_2 with the uniform prior assumption. The data structure has been selected at random from the multinomial experiment. The concept of conditional agreement have been proposed by Coleman (1966) and there after by Light (1969), Von and Eye Mun (2005) and Liebetrau (1983). Here, the Bayesian approach has been applied to get the posterior distribution of the conditional kappa. Kappa is considered as one of the popular indicator in agreement analysis and it is comprehensive for both ordinal scores and for multiple raters and scores and it is unavoidably present in medical sciences.

APPLICATION

The Bayesian approach in agreement analysis has been used to find out the prescription of the doctors and drug marketing pattern by chemist to the same patients having malaria. 50 subjects have been selected randomly from the population in the presence of multinomial experiment structure. The outcomes of the experiment are mutually exclusive and distributed with uniform prior. As a result, the Dirichlet distribution has been found in place of posterior. In different categories of outcomes, gamma prior has been proposed. The score is interpreted by 1="ACT given" and 2=" ACT Not-given". The Bayesian approach with a uniform prior for θ_{ij}, i and $j = 1, 2$ has been observed with posterior mean (20, 6, 14, 14) respectively. The above description of the posterior analysis is based upon the 24,000 observations with a burn of 1000 observations with a refresh of 100.

The kappa statistics is 0.26 with posterior mean and the indices A_1 has a posterior mean of 0.5555 and the indices A_2 has the posterior mean of 0.49. Overall agreement is fair but not considered strong for the general population. The plot of the posterior density of conditional kappa for the score of 1 implies only a fair agreement for the Non ACT category. The kappa statistics and the indices A_1 and A_2 have been applied through Bayesian approach. In both the cases, uniform gamma prior has been assumed for different cell values in the contingency table. The posterior mean and standard deviation based on 24,000 observations have been generated by WINBUGS. In the sample of 10 pregnant women, 6 women have received ACT therapy from both doctors and chemist followed by 2 women who received non-ACT therapy from both chemist and

doctors and one woman who received "ACT" from chemist in place of "non-ACT" prescribed by doctor and inversely one woman received "non-ACT" by chemist that was prescribed by doctors in "ACT" therapy.

The results through the contingency table for the general population and pregnant women on the prescribed drug are given in the Table I and Table III respectively. The WINBUGS program has been originally developed to make the Bayesian analysis of the data to provide the statistical analysis of the drug prescribed pattern among the population of Uttar Pradesh.

TABLE I: CONTINGENCY TABLE PRESCRIPTION PATTERN

	Doctors	Chemist	Total
ACT given	20	6	26
Non ACT given	14	14	28
Total	34	20	54

The summary statistics for the parameter of interest in the model has been applied after discarding 24,000 initial updates. The required amount of iteration has been finalized by the MC error of the parameters and the iteration was continued until the MC error dropped down to less than 5% of the sample standard deviation. Three chains have been run for each parameter in the program. The monitored values of six nodes are given in the Table II. The posterior mean value of the kappa statistics is found to be 0.26 and for the pregnant women it is raised in 0.36. The higher kappa statistics value confirmed the strong agreement of same drug practice by doctors and chemists.

TABLE II: ESTIMATED PARAMETER FOR THE SAMPLE SIZE 54.

Parameter	Mean	SD	HPD (2.5%, 97.5%)
Kappa	0.26	0.12	(0.01, 0.49)
A_1	0.63	0.06	(0.45, 0.75)
A_2	0.49	0.01	(0.36, 0.54)

TABLE III: ESTIMATED PARAMETER FOR THE PREGNANT WOMEN.

| Parameter	Mean	SD	HPD (2.5%, 97.5%)
Kappa	0.38	0.26	(-.12, 0.87)
A_1	0.68	0.12	(0.43, 0.71)
A_2	0.67	0.12	(0.42, 0.89)

The confidences of the convergences has been taken from the three chains for all the nodes in this model that is shown in Figures I to VI by trace plot. The trace plot gives the value of the convergences for all six parameters. The posterior density of the different nodes become asymptotically normal.

DISCUSSION

Poor awareness about the effective and useful drug treatment among health care provider in the country is a hindrance in the control of Malaria in spite of several efforts from the government and NGOs. The Varanasi City's status on malaria drug treatment practice has been covered with the application of agreement analysis. Such city wise malaria drug treatment practice can be helpful in providing necessary guidelines for planning the course of action for the State specific malaria control programme.

However, in case of pregnant women, the posterior mean of the A_1 and A_2 obtained are 0.68 and 0.67, respectively and in general population, the posterior mean of A_1 and A_2 generated are 0.63 and 0.49. It can be concluded that the level of agreement between doctor and chemist for drug practice on the pregnant women is better in comparison to the general population. The comparative posterior mean value of the kappa statistics can be seen in Table I and Table II. It can also be confirmed that the agreement level is higher in case of pregnant women as compared to general population.

However, in both the cases (pregnant women and general population) the kappa statistics value is not found sufficient enough to say that the doctors and chemists follow the same strategy for ACT. It can be confirmed that the specific strategy is required to stop Artimisin monotherapy. It is also important to promote the prescribing and selling of ACT to the malaria patients.
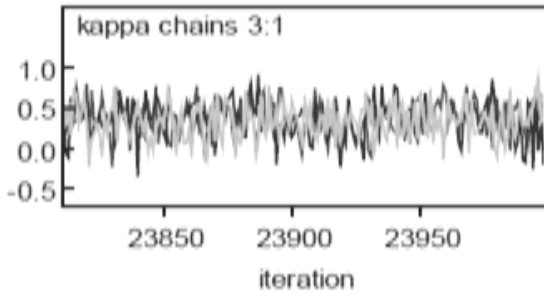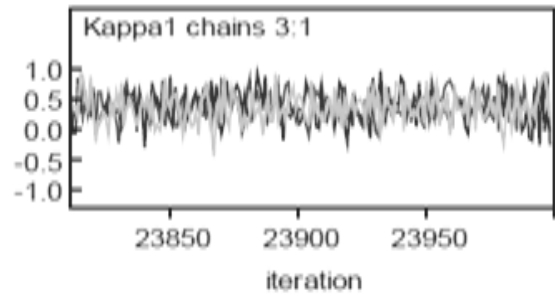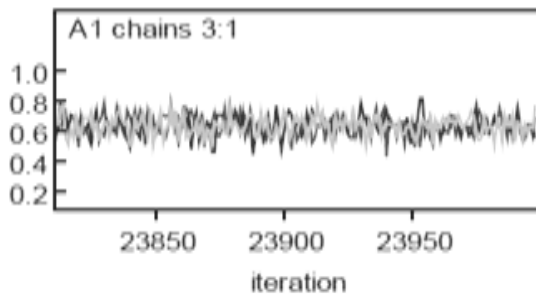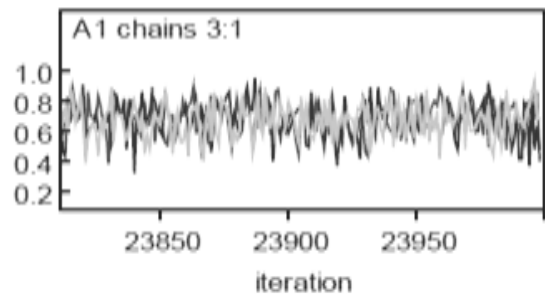
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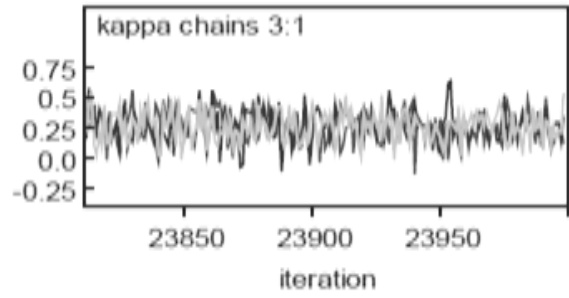
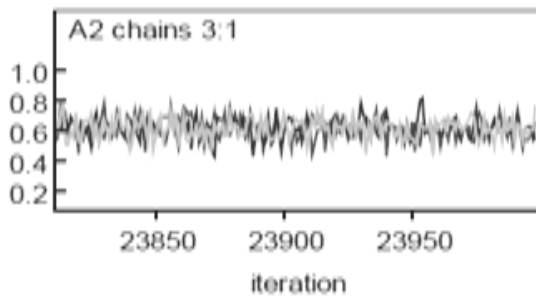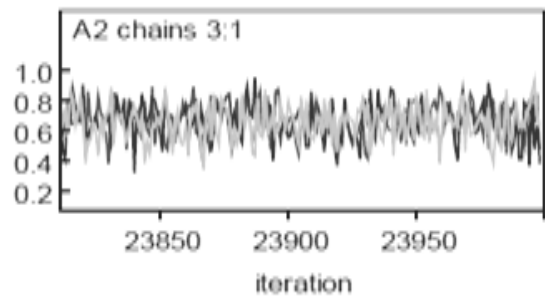
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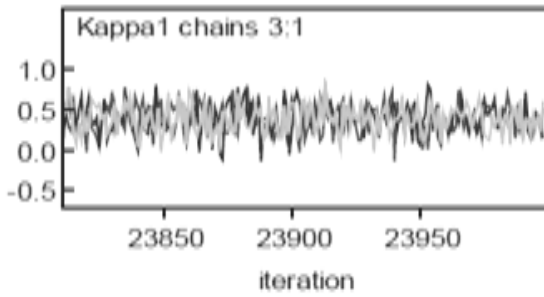
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> **Health can be defined negatively, as the absence of illness, functionally, as the ability to cope with everyday activities, or positively, as fitness and well-being. It has also been noted that in the modern world, health still has a moral dimension.**
> **Blaxter, Mildred (1990), Health and lifestyles. London (Routledge), 14**

> **Health is something which should be enjoyed, not abused. A long painless life to a ripe old age, culminating in a death replete with life, is still outstanding, has constantly been planned. As if newborn: this is what the outlines of a better world suggest as far as the body is concerned. But people cannot walk upright if social life itself still lies crooked.**
> **Bloch, Ernst (1995), The principle of hope. Cambridge, Mass. (MIT Press), 471**