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Bayesian Analysis of Adverse Effects Data Using Dirichlet Prior

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Abstract
A generalization of beta distribution is theDirichlet distribution.It is commonly used in various fields, such asthe categorical response modeling and prior distribution in Bayesian statistics. The distribution of Dirichlet belongs to the conjugate family and to multinomial and categorical distributions prior to it. In this case, the previous model of the adverse effect of ArtesunateAmodiaquine in Nigeria was adapted as the Dirichlet distribution. The reactions are divided into three: the neurologicaleffect, musculoskeletal effect and the and the dietary effect.Through the MCMC Gibbs Sampling techniques, we determine the posterior density.The posterior estimate for neurological adverse incidents encountered is close to 28.8 percent, 43.5 percent for the Musculoskeletal and 27.7 percent for the Dietary effect, from the findings using symmetric Dirichletprior. Using the previous distribution of the Non-Symmetric Dirichlet, the neurological adverse effectsencountered by the patients taking malarial medication is 24.9 percent, for the Musculoskeletal effect about 40.3 percent of the patients were observed and 34.8 percent is for the Dietary effect.

Keywords: *Bayesian Modelling,Dirichlet Prior, MCMC, Gibbs Sampling*

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I. Introduction

In determining the adverse drug effects, the conclusion and policy consequences of drugs in circulation, statistical methodology plays a critical role. In the 20th century,Laplace thoroughly introduced the Bayesian approach to inference.Due to its simplicity and easy calculation (Classical Statistical Inference), different methodology was introduced, but the Bayesian method of inference only exists for simple models (O'Hagan, 1994), with the advent of high-speed supercomputers,the Bayesian approach to inference has become possible for complex models such as Bayes multi-level modeling, hierarchical Bayes models and Bayesian dynamic model etc.

The distribution of Dirichletis a generalized beta distribution, whichhas been used to model disjoint effects. In Bayesian simulation for categorical and multinomial distribution theDirichlet distribution is a conjugate prior. In this analysis, the Dirichlet distribution will be combined with three classifications prior to the multinomial distribution to assess the prevalence or incidence of adverse effects experienced in Nigerian patients treated with ASAQ combination therapy.

Pharmacovigilance is a pharmaco-epidemiology division that deals with study of drug adverse reactions and drug safety (Bateman, 2003). For example, chloroquine was banned due to its hyper-sensitivity and non-adherence to the full prescription by patients to establish tolerance to the organisms in the body, so several clinical studies have carried out on the determination of adverse drug effects. For that reason, new malaria drugs called Artemisinin combination therapy have been developed, including ArtesunateAmodiaquine (ASAQ) and ArtemeterLumefatrin (AL) for malaria treatment. The adverse effects associated with the new drugs in circulationhave been studied by several nations, including Nigeria in partnership with international agencies. Adverse drug reactions have been categorized according to the site of reaction, adverse effects of have been classified into three groups of reaction in the study: Neurological reaction (Headache, Dizziness, Insomnia, Fever), musculoskeletal reaction (e.g. Body weakness, Body pains, Joint pains) and Alimentary effect (e.g. Vomiting, Nausea, Diarrhea, Bitter taste and Sour mouth).

Madigan *et al.* (2011) applied the Bayesian pharmacovigilance survey methodology. The research focused on two forms of observational studies, one being the review of disproportionality in spontaneous drug adverse reactions and the Randomized Control research, whichprovides data on adverse effects,demonstrating that the Bayesian approach to drug adverse reactions contributes to the understanding of drug safety problems and drug

interactions. Murphy (2006) also studies the distribution of probability that are useful for modeling discrete (categorical) data using a DNA sequence mixture of Dirichlet priors. Rita *et al.* (2012) Elicits the information of an expert on a set of proportion as a distribution of Dirichlet, as this is by far the simplest multivariate distribution suitable for such a set of proportions. It is also the most convenient, particularly when the prior expertiseof the expert is to be combined with a multinomial sample, since the Dirichlet is the previous conjugate family. Several techniques are mentionedin the literature to produce beliefs in the form of a distribution of Dirichlet, usually involving obtaining enough judgements from the expert enough to define the hyper-parameters of Dirichlet uniquely.

Penttinen and Piche' (2010) developed a Bayesian model with six choicesusing the data for opinion survey.As the data model,the generalized binomial (multinomial) model was used, the generalized beta (Dirichlet) model was adopted as the previous density with six different concentration parameters, and WinBUG14 was used to obtained the posterior density. De-Campos and Benavoli (2009) investigate inference from multinomial data and consider the problem of prior selection using Dirichlet prior density under Mean Square Error (MSE) criterion. In the analysis, the maximum probability estimator and the most widely used Bayesian estimatorswere compared. Underthis criterion, MLE becomes more superior to the non-informative prior parameters than the Bayesian estimators, with the increase in number of multinomial categories due to non-informative Bayesian estimators causing a region where they are dominant that shrinks rapidly with the increase in the categories.

Using MLE estimator, by probability is maximized. Sincethe multinomial is a member of the exponential family in the Bayesian aspect, the Dirichletdistributionis its natural conjugate prior. Thus, the Dirichlet prior to is assumed and the Bayes rule is applied to the multinomial-Dirichlet conjugate model to obtain the subsequent summaries. Analternative approach based restricted minimization of a minimum squares objective function is proposed by Kelly and Atwood (2011), which leads to a minimally informative prior distribution of Dirichlet. In the finite normal mixture model,Ishwaran and Zarepour (2011) previously used finite dimensional Dirichlet,which has the effect of acting like Sieves Bayesian process.Theuniform Dirichlet before leads to an inconsistent posterior in the analysis. Adjustment to the parameterswas made by inducing a random measure of probability that approximates the Dirichletmethod and generates a posterior that is strongly compatible with the density and weakly consistent for the unknown mixing distribution. The Gibbs Samplerwas used to sample the posterior distribution of the mixture. in non-parametric Bayesian inference, Ghosal (2010) discusses the Dirichletmethod and refers to posterior distribution. One of the basic considerations in the analysis is the statistical properties such as the asymptotic properties of the posterior distribution, the estimation of the post-convergence rates, the adaptation of the posterior rate, consistency of the Bayes factor and the selection of the model.

Hankin (2010) addressed the issues surrounding the generalization of the distribution of Dirichlet,the hyper-Dirichlet in which different kinds of incomplete observations can be integrated. When any findings are censored, It is correlated to the multinomial distribution. Minka (2000) discussed the distribution of Dirichlet distribution and its compound variants; it is commonly used for proportional data such as the percentage of individuals with the different skin colours. This research describes simple and powerful iterative schemes for using the Newton-Raphson iteration toobtaining parameter estimates for the Dirichlet multinomial. Nhama et al. (2015) conducted research on the in-vivo efficacy of ArtemeterLumefantrin (AL) and ArtesunateAmodiaquine (ASAQ) in Mozambique for the study of uncomplicated falciparum malaria in children. The research carried out is a clinical surveillancestudy with multi-site and two-Cohort trials.

AL was issued to four hundred and thirty nine (439) children, 261 were given AA, and the period lasted for 28 days. During the follow up, the majority of recurrent cases of parasitaemiawere re-infected. Both medications were well tolerated, with vomiting becoming the most common adverse effect (AL 4.5 percent [20/439]; ASAQ 9.6 percent [25/261]) and no major incidents considered linked to the medications studied. There was no space for integrating previous beliefs about the drug regiment regimen on the patients with malaria with the methods used being strictly classical frequentist statistical methods.The Cohort Event Monitoring (CEM) on large African Urban cohort (n=2,831) of outpatients receiving antimalarial medication was adopted by Dodoo*et al.* (2007). During the following week, the cohort was systematically surveyed to monitor adverse effects using follow-up phone calls, paper notes, and voluntary return clinic visits to the clinic

Of the number studied, 29.5 percent of the patients observe adverse effects in subject older than 12years and in patients prescribed Artesunate-Amodiaquine combination therapy, they used the classical approach to determine the prevalence rate of patients with adverse drug reactions without considering previous studies and expert's opinion regarding the prevalence rate of the adverse reaction on patients with malaria.

In this analysis,before collecting our previous knowledge on the prevalence rate, we will apply the Bayesian method of inference on data on adverse drug outcomes using Dirichlet and update our previous belief by determining the posterior for the posterior distribution. To evaluate the subsequent summaries for the adverse drug effects of ASAQ in Nigeria,we will use the MCMC process.

II. Material And Methods

Before using Dirichlet in 3-Dimensional response groups, we will consider the Bayesian approaches for reactions to adverse drug effects;the Multinomial distribution is a generalization of the binomial distribution in which we will follow the density as the data model based on the method of data generation. It would be good approximation for the MCMC simulation techniques to sample the parameters from the posterior distribution. One of the conditions in the MCMC system is the convergence of the limiting or equilibrium distribution $P(\theta|y)$ defined as the target density to a density function instead of a single point (Cogdon, 2003).

Bayes Model

Consider a general problem in which we have data y and require inference aboutψ. In Bayesian analysis, ψ is unknown and viewed as a random quantity. Thus, it possesses a density function$\theta(\psi)$. From Bayes theorem, we have the relation:

$$\theta(\psi|y) = \frac{\theta(y|\psi)\theta(\theta)}{\theta(y)} \propto \theta(y|\psi)\theta(\psi) \tag{1}$$

where$\theta(\psi|\mathcal{Y})$ is the posterior density, $\theta(\psi)$ is the prior density and $\theta(y|\psi)$ is the likelihood (Congdon, 2003)

Hypothesis

The probability that a hypothesis such as $H: \psi > 0$ is true which is known in the Orthodox frequentist statistics called p-value is at least conceptually, easily computed from the posterior:

$$P(H|y) = P(\psi > 0|y) = \int_0^\infty \theta(\psi|y)d\psi \tag{2}$$

Point Estimates

The posterior is a full summary of your state of knowledge aboutθ, so in this case the distribution is the estimate, but we also want summarize the information using a single number for each parameter in realistic circumstances, common alternatives are:

The posterior mode is obtain by finding:

$$argMax_\theta[\theta(\psi|y)]$$

i.e. Parameter ψ with maximum aposteriori probability (MAP), The Posterior median for ψ is obtain by finding

$$argMin_r E(|\psi - r||y)$$

The Posterior mean for θ is determined using the equation

$$E(\psi|y) = \int \theta(\psi|y)d\theta = \text{argMin}_r E[(\psi - r)^2|y] \tag{3}$$

Predictive Distribution

Before an observation (data) y is obtain, it is an unknown quantity let denote ity_π. Its distribution is call the prior predictive distribution or marginal distribution of the data. The densityis derivedusing the likelihood and the prior:

$$P(y_\pi) = \int \theta(y_\pi, \psi)d\psi = \int \theta(y_\pi|\psi)\theta(\psi) \tag{4}$$

In comparison to the parameter space, the predictive distribution is defined in the data space$\mathcal{Y}$, which is where the prior and posterior distribution are define.To test the validity of the model it is possible to use the previous predictive distribution. If the prior predictive density looks incorrect, the precedence and probability must be reexamined.

The next observation is an unknown quantity, which we defined by y_{n+1}.After observations $y_1, y_2, \ldots y_n$ are obtainedand processed.Its distributionis called posterior predictive distribution and can be estimated from the density

$$P(y_{n+1}|y_{1:n}) = \int \theta(y_{n+1}|\psi, y_{1:n})\theta(\psi|y_{1:n})d\psi \tag{5}$$

If y_{n+1} is independent of $y_{1:n}$givenψ, then the formula becomes

$$\theta(y_{n+1}|y_{1:n}) = \int \theta(y_{n+1}|\psi)\theta(\psi|y_{1:n})d\psi \tag{6}$$

Computation of Posterior Density and Summaries

In Bayesian Inference,the calculation of the posterior distribution.is one of the most challenging aspects. Different methods, including MCMC method, Numerical Computation such as Quadrature method, Lindley's Approximation (1980), Standard Approximations, Optimization technique and Lindley-Smith Iteration etc., O'Hagan (1994) have been proposed with the advent of supercomputers we will limit our emphasis to the MCMC approach for the purpose of this work.

MCMC Simulation
Gibbs Sampler
The Gibbs sampler, is use to produce samples from posterior distribution $f(\theta|y)$ with multidimensional parameter vectorΘ. The samples are produce by random walk in A Markov Chain that has stationary distribution$f(\theta|y)$.

Gibbs Algorithm
θ_{-i}: denote the vector θ with the i^{th} component removed i.e.
$\theta_{-i} = [\theta_1, \theta_2, \dots \theta_{i-1}, \theta_{i+1}, \dots, \theta_d]$
$\theta^0 \leftarrow$ Some vector in the parameter space for t from 1 to N
Choose a dimension $i_t \in \{1,2, \dots d\}$ at random ($withPMF[r_1 r_2 \dots r_d] say$)
$\theta^t_{-i_t} \leftarrow$a sample drown from $f(\theta_{i_t}|\theta^t_{-i_t}, y)$

$$\theta^t_{-i_t} \leftarrow \theta^{t-1}_{-i_t}$$

End.
Update is perform by cycling through the indices i instead of choosing indices in random order.When $\theta^{t-1}$is drawn from the distribution$f(\theta|y)$, the probability of transition from $\theta to \theta'$ via update of the i^{th} component is.

$$P(\theta^{t-1} = \theta, \theta^t = \theta', i_t = i|y) = P(\theta^t = \theta'|\theta^{t-1} = \theta, i_t = i, y) * P(\theta^{t-1} = \theta, i_t = i|y) =$$

$$\begin{cases} r_i f(\theta|y) f(\theta'_i|\theta_{-i}, y), & if \theta_{-i} = \theta'_{-i} \\ 0 & otherwise \end{cases} \quad (7)$$

Thus, the probability of transition from$\theta to \theta'$, is given by the expression

$$P(\theta'|\theta_{-i}, y) = P(\theta'_i|\theta'_{-i}, y) = \frac{P(\theta'|y)}{P(\theta'_{-i}|y)} \quad (8)$$

and

$$P(\theta_i|\theta'_{-i}, y) = P(\theta_i|\theta_{-i}, y) = \frac{P(\theta|y)}{P(\theta_{-i}|y)} = \frac{P(\theta|y)}{P(\theta'_{-i}|y)} \quad (9)$$

where$\theta_{-i} = \theta'_{-i}$, because their joint distribution is symmetric and $\theta^{t-1}|y and \theta^t|y$ have the same marginal distributions. It follows that the distribution of $\theta|y$ is a stationary distribution for this Markov Chain.

Bayesian Model for Proportion using the Dirichlet Prior in k-Response Space

Data Model: Multinomial Distribution
Multinomial model, is a generalization to the binomial model, it is described as

$$\theta(\mathcal{Y}|\psi) = \frac{\Gamma(n+1)}{\prod_{i=1}^k \Gamma(m_v+1)} \prod_{v=1}^k \mathcal{Y}_v^d \quad (10)$$

This is a multinomial distribution with k Response classes as generalization to binomial distribution.
Prior Density: Dirichlet distribution

The Dirichlet prior distribution is the generalization of the beta distribution for explaining the probabilities of k-dimensional disjoint effects. The Dirichlet density is define as

$$\theta(\psi) = \frac{y_1^{\psi_1-1}y_2^{\psi_2-1}y_3^{\psi_3-1}(1-y_1-y_2-y_3)^{\psi_4-1}}{\mathrm{B}(\psi_1,\psi_2,\psi_3,\psi_4)} \tag{11}$$

where the simplex

$$y = \{(y_1,y_2,y_3)\epsilon\mathbb{R}^2: y_1 + y_2 + y_3 < 1, \quad y_k > 0, \forall k\}$$

WithKernel

$$\theta(y|\psi) = y_1^{\psi_1-1}y_2^{\psi_2-1}y_3^{\psi_3-1}(1-y_1-y_2-y_3)^{\psi_4-1}$$

Posterior Density:

In Bayesian Inference, the posterior density can be obtain using the Bayes' theorem

$$\theta(\psi|y) = \frac{y_1^{\psi_1+d-1}y_2^{\psi_2+d-1}y_3^{\psi_3+d-1}(1-y_1-y_2-y_3)^{\psi_4-1}}{\mathrm{B}(\psi_1,\psi_2,\psi_3,\psi_4)} \tag{12}$$

Where $\theta(y)$ is the marginal distribution of y that makes the posterior density a density function

$$\theta(y) = \int \theta(y|\psi)\theta(\psi)d\psi \tag{13}$$

III. Results

Table 1: Distribution of adverse effects among patients with Malaria whom were administered AtesonateAmodiaquine (AA) combination therapy.

AdverseEffects	**No. Patients**	**θ(proportion)**
Neurological effects	368	0.288
Musculoskeletal effect	556	0.435
Alimentary	354	0.277
Total	**1,278**	**1.000**

Table 2: Summary statistics for Symmetric Dirichlet (1, 1, 1) prior

$AdverseEffects$	$rE(\theta)$	$Mode(\theta)$		$Var(\theta)$	
Neurological effects	1	0.333	Undefined	0.056	
Musculoskeletal effect	1	0.333	Undefined	0.056	
Alimentary	1	0.333	Undefined	0.056	

Table 3: Summary statistics for Non-Symmetric Dirichlet (100,200,300) prior

$AdverseEffects$	$rE(\theta)$	$Mode(\theta)$		$Var(\theta)$	
Neurological effects	100	0.167	0.166	0.000231	
Musculoskeletal effect	200	0.333	0.333	0.000462	
Alimentary	300	0.500	0.500	0.000693	

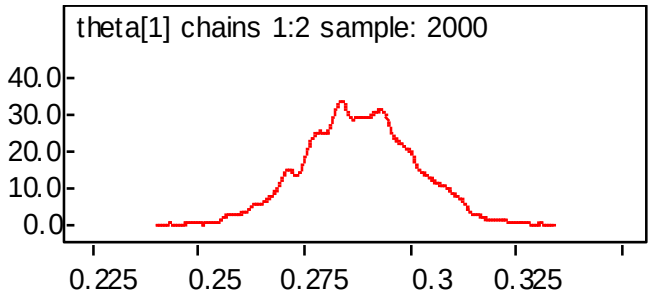

Fig 1. Posterior Density Summary Plot using MCMC Simulation via Gibbs Sampler for Neurological Adverse Effects using Dir (1, 1, 1) prior

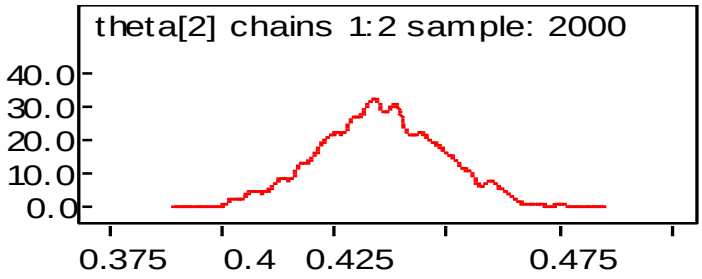

Fig 2. Posterior Density Summary Plot using MCMC Simulation via Gibbs Sampler for Musculoskeletal Adverse Effects using Dir (1, 1, 1) prior

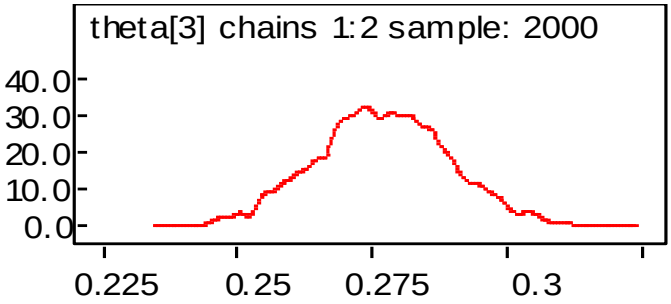

Fig 3. Posterior Density Summary Plot using MCMC Simulation via Gibbs ampler for Alimentary Adverse Effects using Dir (1, 1, 1) prior

For the proportion of different adverse drug reactions using the symmetricDir (1, 1, 1) prior, the figures 1-3 displays the posterior density maps. To obtain the posterior density maps, the MCMC Simulation through Gibbs Sampler was adopted. Figure 1 displays the posterior summary for the proportion of patients that encountered Neurological adverse effects which shows the maximum posterior mean to be 0.288 (28.8 percent) and that of Musculoskeletal adverse effects obtained in Figure 2 to be 0.435(43.5 percent), for the dietary effect the posterior mean is located at 0.277 (27.7 percent).

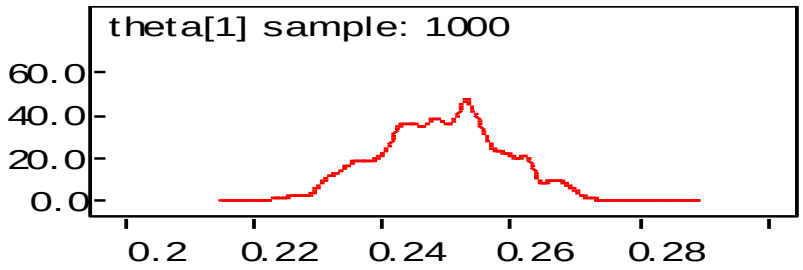

Fig 4. Posterior Density Summary Plot using MCMC Simulation via Gibbs Sampler for Neurological Adverse Effects using Dir (100,200,300)

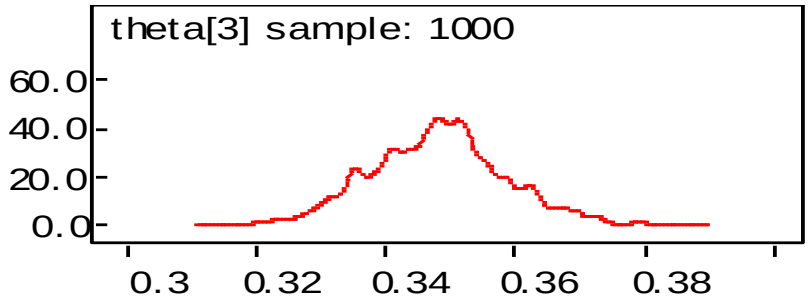

Fig 5. Posterior Density Summary Plot using MCMC Simulation via Gibbs Sampler for Musculoskeletal Adverse Effects using Dir (100,200,300)

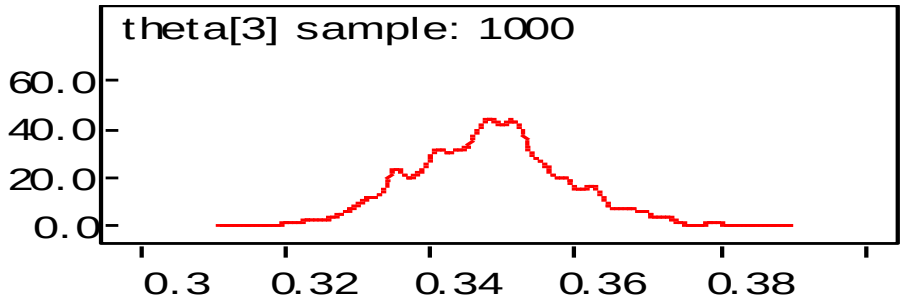

Fig 6. Posterior Density Summary Plot using MCMC Simulation via Gibbs sampler for Alimentary Adverse Effectsusing Dir (100,200,300)

The Figures 4-6displays the posterior density plot using the preceding symmetric Dir (100,200,300) for the proportion of different adverse drug reactions. To obtain the posterior density map,the MCMC Simulation through Gibbs Sampler was adopted. Figure 4 displays the posterior summary for the proportion of patients who suffered Neurological adverse effects with a median posterior mean of 0.288 (28.8 percent) and 0.435(43.5 percent) for Musculoskeletal adverse effects obtained in Figure 5, with a posterior of 0.277 (27.7 percent) for the dietary impact Figure 6.

IV. Discussion

For distribution of order statistics, the Dirichlet distribution plays a critical role in Bayesian inference;it is a generalization to the beta distribution.In this case, we use the Dirichlet distribution as the previous model of the adverse effect of ArtesunateAmodiaquine in Nigeria, the Dirichlet distribution is a conjugate prior to the multinomial distribution and categorical distributions. The responses were categorized into groups of 3-response: the Neurologic effect, Musculoskeletal and the dietary effect. In order to estimate the response rate for the three adverse drug effectsencountered by patients involved in the active surveillance of malaria medication using the MCMC techniques through the Gibbs Sampler and the posterior predictive distribution for the adverse drug effects,the posterior density summaries and the density plots are calculated.Therate for neurological adverse effects suffered is approximately 28.8 percent, 43.5 percent for the Musculoskeletal and 27.7 percent for the Alimentary effect.The Response-rate for neurologic adverse effects encountered by patients taking malarial medication is 24.9 percent using the non-symmetric Dirichlet prior distribution, for the musculoskeletal effect the response rate is approximately 40.3 percent of the patients and 34.8 percent for the dietary effect. The response rate for the data model's neurological effect (Multinomial) is 28.8 percent, which is similar to the response rate obtained using Symmetric Dirichlet prior from the posterior point estimate, 43.5 percent for the Musculoskeletal effect is also the same, and 27.7% for the dietary effect.

We know in this situation that the symmetric Dirichlet gives the same estimate for the response rate.Beforehand The Posterior summaries for the previous non-symmetric Dirichletindicatethat after the previous update, the response rate for the neurological effect decreased from 28.8 percent to 24.9 percent, musculoskeletalrate decreases from 43.5 percent to 40.3 percent and the dietary effect increased from 27.7 percent to 34.8 percent.

V. Conclusion

In conclusion, using Dirichlet prior and multinomial probability for 3-dimensional responses, the Bayesian model for estimation of response rateestimation utilizes the prior information and updates the data to obtain modified subsequent response rate estimates. We could deduce that the symmetric prior is equivalent to the proportional frequentist estimation, but the non-symmetric Dirichlet modified the previous distributionwith the data obtained from the Cohort Event Monitoring System.Finally, the MCMC techniques include the simulated values for the parameters after 1000 iterations through the Gibbs sampler,and the posterior predictive distribution can be used to further update the response rate estimate for other ASAQ studies in Nigeria.

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