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Bayesian Meta-Analysis for Randomized Controlled Trials in Anti-Tuberculosis Chemotherapy: A Comprehensive Approach

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ABSTRACT

Meta-analysis enables researchers to combine the results of several studies to get a reliable estimate. This paper examines the reviews and findings of sixteen randomized tuberculosis clinical trials and each reporting results from several independent trials. Each finding pools the results from the relevant trials in order to evaluate the efficacy of a certain treatment for a specified medical condition. These studies require consistent assessment of homogeneity of treatment effect before pooling. This paper outlined some innovations in Meta-analysis using Markov chain Monte Carlo (MCMC) techniques for implementing Bayesian random effects models. Additionally we compared the Bayesian approach with frequentist random effects model. We discuss more in a random effects approach to combining the evidence from a series of experiments particularly comparing two treatments. This approach incorporates the heterogeneity of effects in the analysis of the overall treatment efficacy. The model can be extended to include relevant covariates which would reduce the heterogeneity and allow for more specific therapeutic recommendations. We suggest a simple non iterative procedure for characterizing the distribution of treatment effects in a series of studies. These techniques allow different aspects of variation to be incorporated into descriptions of the association between studies. This work attempts to discuss the application of MCMC algorithm for high dimensional clinical trial tuberculosis data.

Keywords: *Meta-analysis, Heterogeneity, Bayesian models, Fixed effect model, Random effect models, Markov chain Monte Carlo*

1. INTRODUCTION

Meta-analysis provides an objective way of combining information from independent studies looking at the same clinical questions and has been applied most often to treatment effects in randomized clinical trials. Almost more than two decade Meta-analysis is more popular in medical research where information on efficacy of a treatment is available from a number of clinical studies with similar treatment protocol [7]. [16] investigate the effect of two treatments conducting a meta-analysis of randomized, double-blind, placebo-controlled trials. In patient care, meta-analytical summaries are used primarily to describe the average treatment effect and summarize its statistical significance and secondarily to predict likely clinical benefit for future groups of patients. Fixed effect analyses have been undertaken using the Mantel–Haenszel method and random effects analyses were performed according to the [7] approach. [6], [9] emerges the consistency of effect for study selection before performing meta-analysis [10]. The effect measures can be the difference between proportions and sometimes called the risk difference. Analyses were undertaken using the metan procedure in Stata [2] and Cochran's Q was used to assess heterogeneity. We understand meta-analysis as being the use of statistical techniques to combine the results of studies addressing the same question into a summary measure. Standard meta-analysis methods for providing an overall estimate of the treatment effects rely on certain assumption [23]. Meta-analysis is the term given to retrospective investigations in which data from all known studies of a particular clinical issue are assembled and evaluated collectively and quantitatively. It differs in important ways from traditional narrative reviews, in that there is a commitment to scientific principles in assembling and analyzing the data, via protocol-driven library searches and data abstraction, in addition to the formalism of statistical analysis. There is a need for more empirical work on methodology, properties and limitations of underlying statistical methodology [8]. A determined criticism is heterogeneity of study outcomes. Meta-analysis has responded by exploring statistical methods to understand and explain the heterogeneity. Heterogeneity,[11],[14],[20] by which we mean variation among the results of individual trials beyond that expected from chance alone, is an important issue in meta-analysis. Heterogeneity may indicate that trials evaluated different interventions or different populations [9], [5]. It is clear that when there are substantial differences among trial results, and in the face of heterogeneity, a single estimate may be misleading and should be avoided [19]. Most of the arguments presented against random effects model could be considered as explanations of the limitations of using covariates to explain the heterogeneity in trial results [11]. There is limited empirical experience comparing results from random effects and fixed effects models [22], particularly when the results are heterogeneous [19]. The random effects model incorporates the heterogeneity of treatment effects across studies in the analysis of the overall treatment efficacy [7]. We present an empirical investigation from meta-analysis of randomized clinical trials included in systematic reviews as well as reports conducted in the area of tuberculosis infected patients; we compare the two approaches with regards to statistical significance, summary relative risk, and confidence intervals. The results of any individual trial must be absorbed and debated by the scientific community before wholesale recommendations regarding treatment practice

are observed. Randomized trials and meta-analyses have distinct but complementary goals[21]. Meta-analysis can be used productively in planning new clinical trials, and in supplying updated information to study monitors in the course of a trial. This process of debate necessarily involves the weighing of evidence from different sources, and meta-analysis can and does play an important role in this process [1]. [20] explains some of the heterogeneity of results in meta-analysis are becoming more common. A Bayesian meta-analysis of hierarchical random-effects model was used by [3],[4],[12],[17] to synthesize the results.

2. Fixed effects and Random effects meta-analysis models

There are 16 independent studies each comparing the treated group with control group. The parameter representing the measure of treatment difference is denoted by θ. It is assumed here that θ equals zero when the two treatments have equal effect. $\hat{\theta}_i$ is an estimate of θ from the i[th] study. The fixed effect model is given by $\hat{\theta} = \theta + \varepsilon_i$ for i=1,2,…,16, where ε_i is error terms. $\hat{\theta}_i \sim N(\theta, \xi_i^2)$. In a random effects model it is assumed that the treatment difference parameters in the 16 studies $(\theta_1,...,\theta_{16})$ are a sample of independent observations from $N(\theta, \tau^2)$. The random effect model is given by $\hat{\theta}_i = \theta + \nu_i + \varepsilon_i$ for i=1, 2,…,16, where $\nu_i \sim N(0, \tau^2)$, the term ν_i and ε_i are assumed to be independently distributed. It follows that $\hat{\theta}_i \sim N(\theta, \xi_i^2 + \tau^2)$

2.1 Estimation of the treatment difference via fixed effects approach

Generally, the estimated variance of $\hat{\theta}_i$, $\text{var}(\hat{\theta}_i)$, is treated as if it were the true variance ξ_i^2. Let w_i be the estimated inverse variance of $\hat{\theta}_i$, $w_i = 1/\text{var}(\hat{\theta}_i)$; $\hat{\theta}_i \sim N(\theta, w_i^{-1})$, for i=1,2,…,16, under the null hypothesis that the treatment difference in each study is equal to zero. $\hat{\theta}_i w_i \sim N(0, w_i)$, for i=1, 2,…, 16, and as the study estimates are independent $\sum_{i=1}^{16} \hat{\theta}_i w_i \sim N(0, \sum_{i=1}^{16} w_i)$. The comprehensive null hypothesis that the treatment difference in all studies is equal to zero is tested by comparing the statistic $U = (\sum_{i=1}^{16} \hat{\theta}_i w_i)^2 \Big/ \sum_{i=1}^{16} w_i$ with chi-squared distribution with one degree of freedom. Assuming that there is a common treatment difference in all studies, $\sum_{i=1}^{16} \hat{\theta}_i w_i \sim N(\theta \sum_{i=1}^{16} w_i, \sum_{i=1}^{16} w_i)$ and over all fixed effect θ can be estimated by $\hat{\theta}$, where $\hat{\theta} = \sum_{i=1}^{16} \hat{\theta}_i w_i \Big/ \sum_{i=1}^{16} w_i$ Then the standard error of $\hat{\theta}$ is given by $se(\hat{\theta}) = \sqrt{1/\sum_{i=1}^{16} w_i}$ and the approximate 95% confidence interval for θ is $\hat{\theta} = 1.96\sqrt{1/\sum_{i=1}^{16} w_i}$.

2.2 Estimation of the treatment difference via random effects approach

In a random effects model it is assumed that the treatment difference parameters in the 16 studies $(\theta_1,...,\theta_{16})$ are a sample of independent observations from $N(\theta, \tau^2)$. The general random effect models is $\hat{\theta}_i = \theta + \nu_i + \varepsilon_i$, for $i = 1,2,...,16$, where the $\nu_i \sim N(0, \tau^2)$. The terms ν_i & ε_i are assumed to be identically. The term $\hat{\theta}_i \sim N(\theta, \xi_i^2 + \tau^2)$.

The variance of τ^2 is unknown and must be obtained and estimated from the data. Therefore the distributional assumption $\hat{\theta}_i =\sim N(\theta, w_i^{-1} + \hat{\tau}^2)$ where $\hat{\tau}^2$ is an estimate of τ^2. By setting $w_i^* = (w_i^{-1} + \hat{\tau}^2)^{-1}$ it follows that $\hat{\theta}_i \sim N(\theta, (w_i^*)^{-1}$ treating the term $(w_i^*)^{-1}$ as if it were the true variance of $\hat{\theta}_i$ provides the test statistic $U^* = (\sum_{i=1}^{16} \hat{\theta}_i w_i^*)^2 \Big/ \sum_{i=1}^{16} w_i^*$ which follows a chi-squared distribution with one degree of freedom under the null hypothesis of no treatment difference $(\theta = 0)$, if $(w_i^*)^{-1}$ is the true variance of $\hat{\theta}_i$, then the ML estimate of θ is given by $\hat{\theta}^*$, where $\hat{\theta}^* = \sum_{i=1}^{16} \hat{\theta}_i w_i^* \Big/ \sum_{i=1}^{16} w_i^*$ now $\hat{\theta}_i$ is asymptotically unbiased for θ, with variance approximately equal to. $1/\sum_{i=1}^{16} w_i^*$ The standard error is given by $\sqrt{1/\sum_{i=1}^{16} w_i^*}$ when $\hat{\tau}^2$ is small then the modified weights w_i^* will close to the original weights w_i . Moreover the standard error, confidence interval and overall estimate of treatment difference from the random

effects model will also similar to those from the fixed effects model. If $\hat{\tau}^2$ is large then the standard error and confidence interval will be larger from the random effects model.

The τ^2 can be estimated using the method of moments based on the following consideration under the random effects model. The θ is the fixed effects estimate and $\hat{\theta} = \sum_{i=1}^{16} \hat{\theta}_i w_i \Big/ \sum_{i=1}^{16} w_i$

2.3 Testing for heterogeneity across studies

To test for heterogeneity in the treatment difference parameter across the studies, a large-sample test is used. This is based on the statistic $Q = \sum_{i=1}^{r} w_i (\hat{\theta}_i - \hat{\theta})^2$, which is a weighted sum of squares of the deviations of individual study estimates from the overall estimate (Cochran, 1954).When treatment difference parameters are homogeneous, Q follows a chi-squared distribution with r − 1 degrees of freedom. An easier and equivalent formula for calculation is given by $Q = \sum_{i=1}^{r} \hat{\theta}_i^2 w_i - U$.

When using efficient score and Fisher's information statistics, Q can be written as

$$Q = \sum_{i=1}^{r} V_i \left(\frac{Z_i}{V_i} - \frac{\sum_{i=1}^{r} Z_i}{\sum_{i=1}^{r} V_i} \right)^2 = \sum \left(\frac{Z_i^2}{V_i} \right) - \frac{(\sum_{i=1}^{r} Z_i)^2}{\sum_{i=1}^{r} V_i} \quad ,$$

where $\hat{Q}_i = Z_i / V_i$

3. A meta-analysis of sixteen randomized clinical trials

For the present analysis we scrutinize sixteen clinical trials were same both in direction of treatment effect and in statistical significance. All these trials had been carried out at the same centre each reporting results from several independent trials over a period between 1956 and 1995. All the sixteen trials have been categorized into two groups based on their duration segment. The application is illustrated using the data from sixteen randomized controlled clinical trials which investigate the efficacy of tuberculosis treatment of both long-term and short-term regimens conducted at TRC (ICMR) over a period of 25 years. These studies have been followed up for a period of 24 months and relapse cases are accounted within that period after completion of treatment. The main approach to estimate relative efficacy is considered as a general parametric approach. The results are provided based on different component of meta-analysis including Meta regression, fixed effects and random effects models in frequentist approach and random effects model in Bayesian approach. Each study pools the results from the relevant trials in order to evaluate the efficacy of a certain treatment of anti-tuberculosis for a specified condition. We discuss both fixed effects and random effects in frequentist approach to combining evidence from a series of experiments comparing two treatments where as we discuss the random effects alone in Bayesian approach. [15] argued elaborately about the Bayesian approach for meta-analysis particularly for the randomized clinical trials, Bayesian approach as a basis for using external evidence and also provides a rational way for dealing with ethics of randomization, treatment equivalence, data accumulation and prediction about the consequences of a study. Studies are categorized according to the characteristics of the study, the characteristics of the subjects in the study and a summary estimate of effect is estimated in each of the categories [14]. [18] demonstrated that the treatment effects of same data between the Bayesian analysis and the frequentist analysis are similar to only when the inclusion of previously excluded data did differences become known between the Bayesian and frequentist approaches.

Table 1: Tests of heterogeneity for both fixed effects and random effects models for log-term and short-term treatment trials using frequentist approach

Trials	N	Pooled estimate in the meta-analysis		Test of Heterogeneity		No. of Trials in meta-analysis	Moment -based estimate of studies Variance
		REM	FEM	Q statistic	P value		
Long Term	2449	0.985	1.156	21.6(9df)	P<0.05	10	0.325
Short Term	3496	0.778	0.774	6.6(5df)	P>0.05	6	0.036
Combined	5955	0.193	0.251	45.3(15df)	P<0.001	16	0.313

The table1 shows the magnitude of the change in the pooled estimate given by the random and fixed effects models to the trials between long-term and short-term treatment trials and also their combination in the calculation of the meta-analysis of tuberculosis care for infected individuals. The tests of the heterogeneity are statistically significant in long-term trials and combined trials of long-term and short-term. Even though, it is arguably sufficient, not possible to examine the null hypothesis that all studies are evaluating almost same effect. The fixed and random effect in frequentist approach incorporates the heterogeneity of effects in the analysis of the overall treatment efficacy.

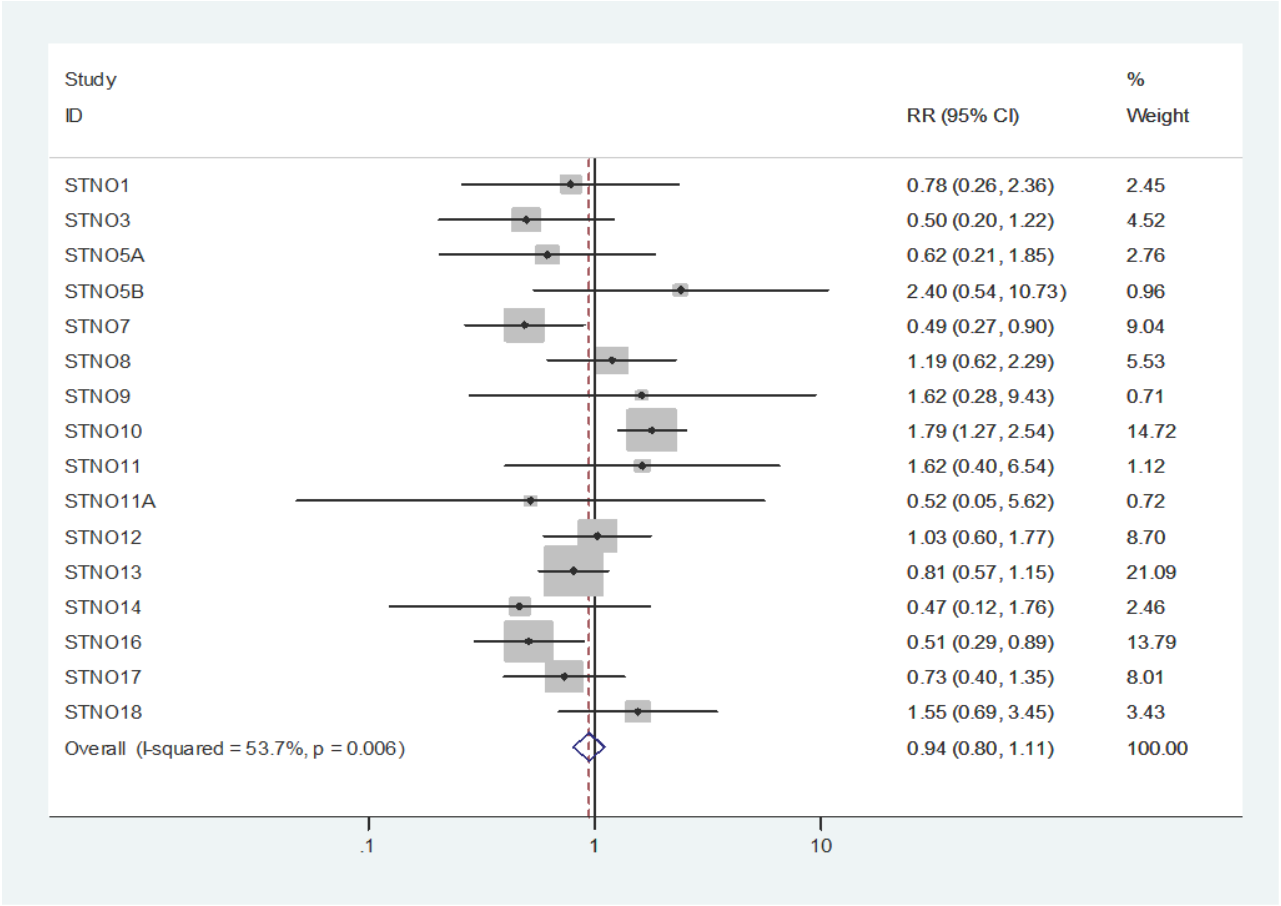

Figure 1: Forest plots of summary of treatment effect with relative, risk 95% confidence interval and the percentage weight contributed to the overall meta-analysis

In the forest plot the contribution of each study to the meta-analysis (its weight) is represented by the area of a box whose centre represents the size of the treatment effects estimated from that study. The summary treatment effect is shown by a middle of a diamond whose left and right extremes represent the corresponding confidence interval.

Both the output and the graph show that there is a clear effect of treatments curing tuberculosis among patients. The meta-analysis dominated by the large study13, study10 and study16 trials which contribute around 50% of the weight in this analysis. Moreover the I-squared is constructed the inconsistency is 53.7 %(P=0.006).

Table 2: The effect estimates with 95% confidence interval and weights for each study

Study	Treated group		Control group		Weights		Est	95% CI	
	Cured	Relapse	Cured	Relapse	FEM	REM		Lower	Upper
Short-term treatment trials									
STNO1	67	5	72	7	2.69	1.46	0.17	0.05	0.57
STNO3	133	8	78	10	4.08	1.79	0.19	0.07	0.50
STNO5A	68	5	56	7	2.66	1.45	0.20	0.06	0.66

STNO5B	96	9	54	2	1.56	1.05	0.13	0.03	0.63
STNO7	216	19	91	18	8.08	2.29	0.29	0.14	0.57
STNO8	148	18	150	15	7.37	2.23	0.22	0.11	0.46
STNO9	72	3	79	2	1.16	0.85	0.07	0.01	0.41
STNO10	177	76	189	38	19.84	2.75	0.63	0.41	0.98
STNO11	69	5	69	3	1.78	1.14	0.13	0.03	0.50
STNO11A	74	1	76	2	0.66	0.54	0.04	0.00	0.45
Long-term treatment trials									
STNO12	261	24	269	24	11.00	7.86	1.03	0.57	1.86
STNO13	219	42	257	64	20.88	11.86	0.77	0.50	1.18
STNO14	111	3	117	7	2.03	1.89	0.45	0.11	1.79
STNO16	294	15	495	52	10.95	7.83	0.49	0.27	0.88
STNO17	562	25	259	16	9.25	6.92	0.72	0.38	1.37
STNO18	182	15	174	9	5.29	4.44	1.59	0.68	3.74

Note that remarkable differences between the fixed and random effects summary estimates in the long term and the combination of long term and short term trials, which arises because the studies are weighted much more equally in the random effects analysis.

Table 2a: The fixed effect estimates of log-odds ratio with 95% confidence interval and weights for each study

Study Name	Fixed effects method					95%CI		Random effects method			
	$\hat{\theta}_i$	w_i	$\hat{\theta}_i \times w_i$	$\hat{\theta}_i^2 \times w_i$	$se(\hat{\theta}_i)$	Lower	upper	w_i^*	$\hat{\theta}_i \times w_i^*$	$\hat{\theta}_i^2 \times w_i^*$	$se(\hat{\theta}_i)^*$
STNO1	0.264	2.690	0.711	0.188	0.61	-3.36	3.06	2.48	0.65	0.174	0.63
STNO3	0.756	4.076	3.084	2.334	0.50	-4.1	3.8	3.63	2.74	2.08	0.52
STNO5A	0.530	2.663	1.413	0.750	0.61	-3.34	3.04	2.46	1.30	0.694	0.63
STNO5B	-0.928	1.562	-1.451	1.347	0.80	-2.59	2.29	1.49	-1.38	1.287	0.81
STNO7	0.810	8.077	6.545	5.304	0.35	-5.72	5.42	6.50	5.26	4.269	0.39
STNO8	-0.195	7.372	-1.443	0.282	0.37	-5.47	5.17	6.03	-1.18	0.231	0.40
STNO9	-0.498	1.163	-0.579	0.288	0.93	-2.26	1.96	1.123	-0.55	0.278	0.94
STNO10	-0.758	19.835	-15.050	11.419	0.22	-8.87	8.57	12.43	-9.43	7.159	0.28
STNO11	-0.510	1.778	-0.908	0.464	0.75	-2.76	2.46	1.68	-0.86	0.44	0.76
STNO11A	0.666	0.655	0.436	0.291	1.24	-1.73	1.43	0.64	0.42	0.285	1.24
STNO12	-0.030	11.003	-0.332	0.010	0.30	-6.24	6.76	8.27	-0.24	0.007	0.34
STNO13	0.261	20.880	5.454	1.424	0.22	-8.69	9.21	12.83	3.35	0.875	0.27
STNO14	0.794	2.025	1.609	1.278	0.70	-2.52	3.04	1.90	1.51	1.205	0.72
STNO16	0.722	10.950	7.908	5.711	0.30	-6.22	6.74	8.24	5.95	4.299	0.34
STNO17	0.328	9.247	3.036	0.997	0.33	-5.7	6.22	7.23	2.37	0.78	0.37
STNO18	-0.465	5.290	-2.464	1.148	0.43	-4.24	4.76	4.56	-2.12	0.99	0.46
U	63.5/109.3=0.58							61.02/81.57=0.75			
Q	33.24-0.58=32.3							25.06-0.75=24.21			
$\hat{\tau}^2$	(32.3-15)/((109.3-(1345.9/109.3))=0.03							(24.21-15)/((81.58-(643.7/81.58))=0.015			

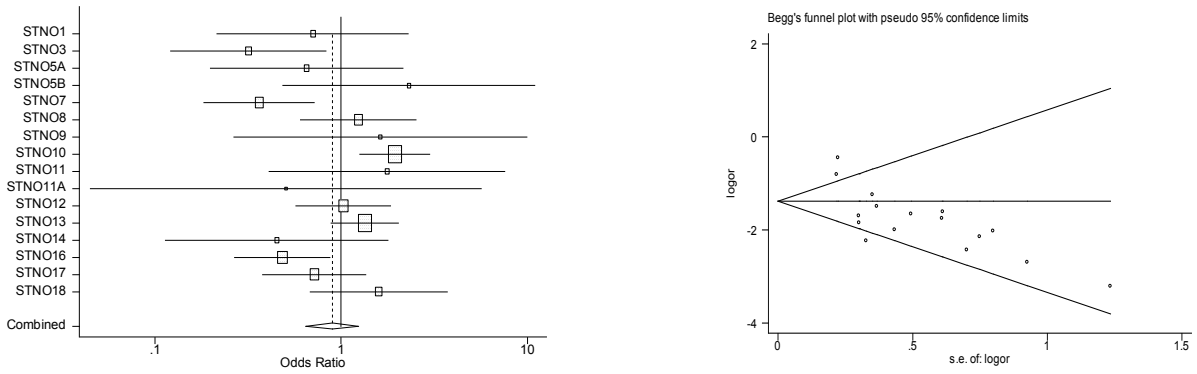

Figure 2: Forest Plot (it performs both fixed and random effects analyses & Funnel Plot with pseudo 95% confidence limits

This shows the accountability of heterogeneity is comparable more in random effects than in the fixed effects method. Figure2 shows the overall performances both fixed and random effects analyses. It is clear that the smaller studies such as study 12 and study 13 are given relatively more weight in the random effects than with the fixed effect model. The method of assessing the effect of bias is using funnel plot as given below. In which the effect sizes form a study is plotted against the study's sample size. There is evidence of bias using the Eggar test based on weighted regression method (p=0.004) but not using the Begg such as rank correlation method. It is assuming that there is no heterogeneity but here there are three studies are significantly differing due to heterogeneity. Odds ratios are an attractive means of combining studies that have differing follow-up times; however, as a relative measure, odds ratios do not take into account absolute differences and may thereby obscure the clinical importance of an intervention.

4. BAYESIAN APPROACH

Bayesian approach is entirely different from frequentist approach to estimate the unknown parameter and it is being treated as random variable which could be treated as fixed value in the frequentist approach. The Bayesian approach has two important aspects. The first approach is the expression of subjective opinion as the previous evidence through prior distributions about quantities of interest. As the posterior distribution for quantities of interest is influenced by the choice of the prior distribution and can then be obtained. The second approach is the method of combining and updating evidence. Because all unknown parameters are treated as random variables, the combination of diverse information is facilitated. The Bayesian framework also allows calculation of the probability that the odds ratio is as small as, which cannot be done in the classical framework. The posterior density of Bayesian approach is fully evaluated and exact posterior standard deviations and credibility intervals can be obtained from the posterior distributions for each model parameter. In the frequentist approach, the standard errors and confidence intervals are computed based on the assumptions of the variance components are known. Bayesian formulation initiates in the relation to the random effects meta-analysis model, for which the data consists of the study estimates of treatment difference. Within the Bayesian setting, the fixed effect parameters will be treated as random, and will usually be given non-informative prior distributions.

4.1 Bayesian approach to the random effects model

Bayesian approach to the random effects meta-analysis, parameters θ_i become random variables. The data consists of study estimates of treatment differences, $\hat{\theta}_i, \mathrm{i} = 1,\ldots,\mathrm{r}$, where $\hat{\theta}_i \sim N(\theta_i, \xi_i^2)$. The parameter θ_i is given the prior distribution $\theta_i \sim N(\theta, \tau^2)$. The θ_i 's are exchangeable and may be expected to be different, but there is no prior belief about their ordering. Consider the situation in which θ and τ^2 are known. In this case the posterior distribution for ψ, obtained using Bayes' theorem, would be given by

$$P(\psi \mid y, \theta, \tau^2) = \frac{P(y, \psi \mid \theta, \tau^2)}{P(y \mid \theta, \tau^2)} = \frac{f(y \mid \psi) P(\psi \mid \theta, \tau^2)}{\int f(y \mid u) P(u \mid \theta, \tau^2) du}, \quad \text{3.1}$$

where

$$\int f(y \mid u) P(u \mid \theta, \tau^2) du = \int\int \ldots \int f(y \mid u) P(u \mid \theta, \tau^2) du_1 du_2 \ldots du_r,$$

The equation (3.1) can be expressed in a more shortened form, as

$$P(\psi \mid y) \propto f(y \mid \psi) p(\psi) \quad \text{3.2}$$

The posterior is proportional to the likelihood multiplied by the prior. Substituting the appropriate normal density functions into the right-hand side of (3.2) gives

$$P(\psi \mid y) \propto \exp\left[-\frac{1}{2} \left\{ \sum_{i=1}^{r} w_i (\hat{\theta}_i - \hat{\theta}_i)^2 + \frac{\sum_{i=1}^{r} (\theta_i - \theta)^2}{\tau^2} \right\} \right] \quad \text{3.3}$$

It can be shown that this posterior distribution is multivariate normal, with means and variance of the θ_i given by

$$E(\theta_i \mid y) = \frac{\hat{\theta}_i \tau^2 + \theta w_i^{-1}}{\tau^2 + w_i^{-1}} = \frac{\hat{\theta}_i w_i + \theta \tau^{-2}}{w_i + \tau^{-2}} \quad and \quad \text{var}(\theta_i \mid y) = \frac{\tau^2 w_i^{-1}}{\tau^2 + w_i^{-1}}$$

The Bayesian model, we assume initially that each arm of each study independently estimates the probability p_{ij} of relapse case where i indexes each study and j indexes the study regimen group, that is j = 0 for the control regimen group and 1 for the trial regimen group. Since the follow-up period varied greatly among trials, we initially used the odds ratio as a measure of the effect size. In a random effects meta-analysis we assume the true effect (on a log-odds scale) μ_i in a trial i is drawn from some population distribution. The prior we used here is non-informative priors for over all mean effect across studies μ and study to study variations d. The graph for this model is shown in below. We want to make inferences about the population effect d, and the predictive distribution for the effect δ_{new} in a new trial. If d=0, the model reduces to a fixed-effects model, whereas larger values of d^2 represent increasing evidence of heterogeneity between the studies. We used non-informative diffuse prior distributions for τ and d^2, so that all parameter estimates are almost entirely determined by the observed data. In a random-effects model, we assume that the effect of the treatment varies from setting to setting.

Table 3: Impact on posterior inference within reasonable modification of priors

Prior specification	Posterior inference						
	Node	Mean	SD	MC	2.5%	Median	97.5%
Mu[i] ~ Normal((0.0,1.0E-5) d ~ Normal((0.0,1.0E-6) tau ~ gamma(0.001,0.001)	d delta.new sigma	-0.1017 -0.1010 0.5989	0.1994 0.6546 0.1785	0.0011 0.0021 0.0014	-0.5028 -1.4280 0.3180	-0.0995 -0.0974 0.5764	0.2879 1.2060 1.0120
Mu[i] ~ Normal((0.0,1.0E-5) d ~ Normal((0.0,1.0E-6) tau ~ gamma(0.1,0.1)	d delta.new sigma	-0.1024 -0.1040 0.6204	0.2033 0.6757 0.1752	0.0011 0.0023 0.0012	-0.5099 -1.4650 0.3478	-0.1002 -0.1008 0.5969	0.2945 1.2480 1.0300
Mu[i] ~ Normal((0.0,1.0E-3) d ~ Normal((0.0,1.0E-4) tau ~ gamma(0.001,0.001)	d delta.new sigma	-0.1015 -0.1014 0.5985	0.1993 0.6544 0.1785	0.0011 0.0022 0.0014	-0.5027 -1.4300 0.3176	-0.0993 -0.0979 0.5759	0.2877 1.2050 1.0120
Mu[i] ~ Normal((0.0,1.0E-3) d ~ Normal((0.0,1.0E-4) tau ~ gamma(0.1,0.1)	d delta.new sigma	-0.1029 -0.1043 0.6205	0.2032 0.6758 0.1752	0.0011 0.0023 0.0012	-0.5103 -1.4660 0.3478	-0.1006 -0.1009 0.5970	0.2939 1.2470 1.0300
Mu[i] ~ Normal((0.0,1.0E-3) d ~ Normal((0.0,1.0E-4) tau ~ gamma(0.01,0.01)	d delta.new sigma	-0.1022 -0.1014 0.6005	0.1994 0.6557 0.1781	0.0011 0.0022 0.0014	-0.5029 -1.4320 0.3216	-0.0997 -0.0983 0.5776	0.2871 1.2100 1.0130

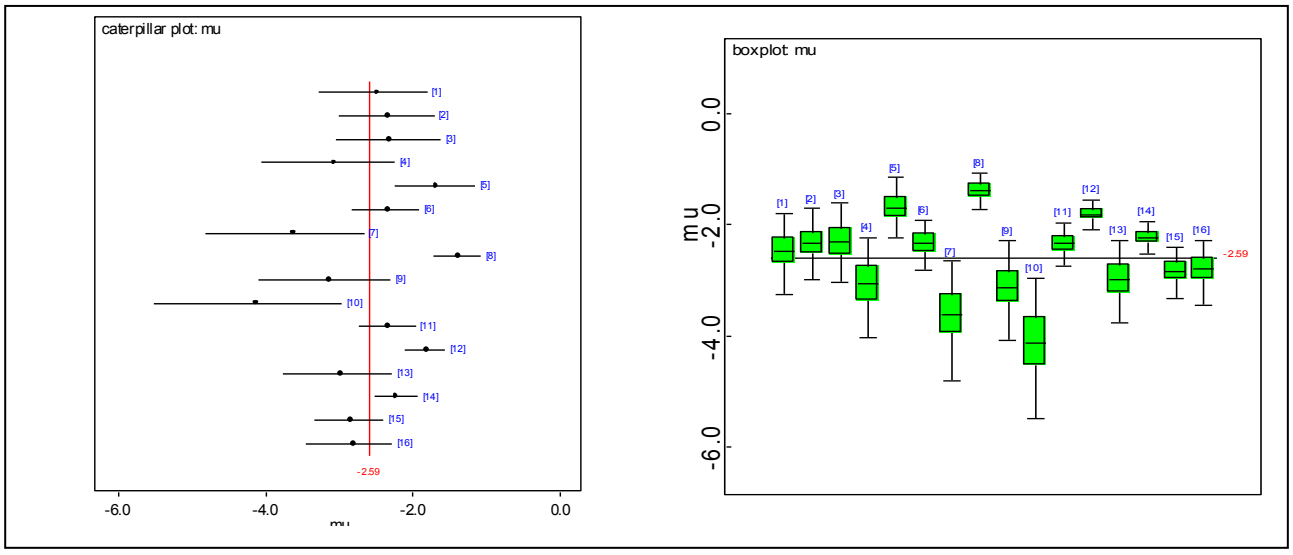

Figure3: Error bar and Box plot

5. DISCUSSION

The frequentist approach, the assumptions of a fixed and random set communicate the basis of estimation for each approach for a general measure of effect size. The fixed effect model is conditional on the stronger assumption that there is no true heterogeneity between studies also they are all estimating the same true effect and only differ because of sampling variation, where as the random effects method attempts to incorporate statistical heterogeneity into overall estimate of an average effect. The random effects model predicts better than the fixed effects model also to conclude that the modeling would be improved by an increase in use of random effects model than the fixed effects model. There are many manuscripts available and focused the meta-analysis using reviewed articles or published materials over a period or even in the several fields. But here we illustrated the meta-analysis applied for clinical trials in a particular centre and embossed the less heterogeneity among all the independent trials. Bayesian method gives high precision estimates for the relative risk. Both Bayesians and frequentists alike lament the unreliability of prior information in many clinical trials.

However, only Bayesians are required to formally incorporate it into their measure of efficacy. Even though frequentists must also build an effect size into the study, it does not directly affect the research data's estimate of that effect. Yet, prior information for Bayesians directly affects the estimate. There are many tools at their disposal permitting them to distance themselves from faulty prior information with the use of vague and uninformative priors. However, the level to which Bayesians distance themselves from prior information is the level to which they enter the land of the frequentist, where the strict rule is to completely separate a priori belief from the evidence-based product of the research effort.

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