# Bayesian Inference for Meta-analysis of 2X2 Contingency Tables

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**Abstract**

Meta-analysis has been widely used for synthesizing safety and efficacy treatment effect information from multiple clinical trials to support landmark decision-making during drug development. Bayesian meta-analysis approach offers a very flexible modeling strategy. In this paper, several fixed and random effect meta-analysis approaches under Bayesian framework are critically reviewed and applied to binary data (2X2 binary response contingency table). Simulations are used to evaluate the performance of different Bayesian meta-analysis approaches under the challenges of rare events, data heterogeneity, and unbalanced randomization by design.

**Key Words:** Bayesian, Meta-analysis, 2X2 contingency table, rare event, heterogeneity

## 1. Introduction

Meta-analysis generally refers to methods, in particular, statistical methods, focusing on contrasting and combining results from different sources, in the hope of identifying patterns, sources of disagreement, or other interesting relationships that may come to light in the context of multiple studies and pipeline of information sources [6]. Or, in short, as defined in Cochrane handbook, meta-analysis refers to the statistical combination of results from two or more separate studies. In clinical trial setting, the aim of a meta-analysis is to more powerfully estimate the true magnitude of the safety or efficacy treatment effect (e.g. risk difference of a certain adverse event of special interest between two treatment options, hazard ratio of two treatment options in terms of overall survival, etc.) as opposed to a less precise estimation derived from a single study. Normally, such synthesized/integrated estimator of the parameter of interest as well as its confidence interval is obtained by a weighted average across individual studies in the meta-analysis. The weights in the meta-analysis might be related to sample sizes or the standard error of the parameter of interest within individual studies. When the studies in the meta-analysis can be reasonably considered homogeneous in terms of treatment effect (e.g. same study population, similar study conduct, etc.), then it is appropriate to apply fixed-effect meta-analysis method, which assumes a true common effect size among studies. When the studies in the meta-analysis involve varying study population or other factors which may potentially impact the treatment effect, then a random-effect meta-analysis method, which assumes the true treatment effect varies among studies but follows a relevant distribution, should be considered to incorporate the between-study variability (heterogeneity).

Besides conventional meta-analysis methods, Bayesian methods become to gain popularity in meta-analysis area [1, 12, 13, 4, 14]. Bayesian meta-analysis approach naturally incorporates all sources of variability and relevant quantifiable external information. It provides a more informative summary and allows direct probabilistic inference of the parameters of interest, such as the overall treatment effect, the between-study variance, etc. However, regardless which meta-analysis method is used, it is always a challenge when facing rare events, data heterogeneity, or unbalanced randomization by design among studies. In this paper, three meta-analysis approaches under Bayesian framework — Leonard's

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Bayesian Mantel Haenszel (MH) fixed-effect method, Abrams' approximated Bayesian random-effect model method, and Scott Berry's Bayesian method — are critically reviewed and applied to dichotomous data ($2X2$ binary response contingency table). Statistical simulation study is conducted to evaluate their performance under either one or a combination of the aforementioned challenges. The paper is organized in the following way. The Methods section will give a brief review of each of the three methods as well as the setting of the simulation study including how the simulation data are generated. The Results section will summarize our findings by different challenging situation, such as rare events, heterogeneity, imbalanced sample size, or some combinations of the challenging factors, etc. The conclusion and discussion section will conclude our comparison among each methods studied in the paper and point directions for future research.

## 2. Review of the Three Selected Bayesian Meta-analysis Methods

### 2.1 Leonard (2002)'s Bayesian Mantel-Haenszel Fixed Effect Method

The Mantel-Haenszel (MH) model assumes that the common constant measure of association between the treatment and outcome across all studies exists. Leonard and Duffy [8] proposed the Bayesian analysis of the Mantel-Haenszel model when applied to meta-analysis. This analysis allows to check the plausibility of the Mantel-Haenszel model and to draw inferences on the common measure of association, odds-ratio. In addition, the authors provide formulae for the estimates of posterior mean and variance of the odds-ratio. We investigated the performance of the method regarding the bias and coverage of 95 % confidence intervals versus the performance of the classical MH, at the same time checking the plausibility of the MH method performance. The Bayesian analysis of $2X2$ contingency table was also studied by [2] and [9]. We are interested in the analysis of several contingency tables. Adopting notations from the Leonard and Duffy in the Table 1, consider $m$ contingency $2X2$ tables with rows representing treatment or control and columns representing positive or negative outcome in the study $i, i = 1, \ldots, m$. The totals in the rows are fixed. The number of the patients with positive outcomes is defined by frequencies $y_{ki}$; $n_{ki}$ denotes total number of patients in the treatment and control groups, $k = 1, 2; i = 1, ..., m$.

**Table 1**: Notations for $2X2$ contingency table of the $i'$th study

| | Outcome | | Totals |
|---|---|---|---|
| | Positive | Negative | |
| Treatment | $y_{1i}$ | $n_{1i} - y_{1i}$ | $n_{1i}$ |
| Control | $y_{2i}$ | $n_{2i} - y_{2i}$ | $n_{2i}$ |
| Total | $y_{1i} + y_{2i}$ | $n_{1i} + n_{2i} - y_{1i} - y_{2i}$ | $n_i$ |

The frequencies $y_{1i}$ and $y_{2i}$ are assumed to be binomially distributed with probabilities $p_{ki}$, so that

$$y_{ki} \sim B(p_{ki}, n_{ki}), \quad k = 1, 2; \quad i = 1, \ldots m \tag{1}$$

and all observed frequencies $p_{ki}$ are assumed to be independent and to have Jeffreys' priors. Then the posterior density of the logit

$$\theta_{ki} = \log p_{ki} - \log (1 - p_{ki}) \tag{2}$$

$$\pi(\theta_{ki}) \propto \frac{exp\{\theta_{ki} y^*_{ki}\}}{(1+e^{\theta_{ki}})^{n^*_{ki}}} \tag{3}$$

where $y^*_{ki} = y_{ki} + \frac{1}{2}$, $n^*_{ki} = n_{ki} + 1$. According to the assumptions of Mantel and Haenszel model, the log-measures of association

$$\eta = \theta_{1i} - \theta_{2i}, \quad i = 1, \ldots, m \tag{4}$$

are constant across $m$ tables. The formula for posterior density of $\eta$ obtained by Leonard and Duffy (details can be found in their work [8]) allows to calculate the posterior mean of the logarithm of odds-ratio

$$\hat{\eta} = \frac{\sum_{i=1}^{m} v_i^{-1} l_i}{\sum_{i=1}^{m} v_i^{-1}} \tag{5}$$

where

$$l_i = \log y^*_{1i} - \log\left(n^*_{1i} - y^*_{1i}\right) - \log y^*_{2i} + \log\left(n^*_{2i} - y^*_{2i}\right) \tag{6}$$

and

$$v_i = \frac{1}{y^*_{1i}} + \frac{1}{(n^*_{1i} - y^*_{1i})} + \frac{1}{y^*_{2i}} + \frac{1}{(n^*_{2i} - y^*_{2i})} \tag{7}$$

The posterior variance of the logarithm of the odds-ratio is equal to

$$w = \left(\sum_{i=1}^{m} v_i^{-1}\right)^{-1} \tag{8}$$

The Bayesian approach is contrasted by the classical Mantel-Haenszel estimate of the odds-ratio [10], the measure of association

$$\hat{\lambda} = \frac{\sum_{i=1}^{m} y_{1i}(n_{2i} - y_{2i})/(n_{1i} + n_{2i})}{\sum_{i=1}^{m}(n_{1i} - y_{1i}) y_{2i}/(n_{1i} + n_{2i})} \tag{9}$$

and the variance estimate given by Robins, Breslow, and Greenland [11]

$$\begin{aligned}
\hat{\sigma}^2 = & \frac{\sum_{i=1}^{m}(y_{1i} + n_{2i} - y_{2i}) y_{1i}(n_{2i} - y_{2i})/n_i^2}{2\left(\sum_{i=1}^{m} y_{1i}(n_{2i} - y_{2i})/n_i\right)^2} \\
& + \frac{\sum_{i=1}^{m}\left[(y_{1i} + n_{2i} - y_{2i})(n_{1i} - y_{1i}) y_{2i}\right]/n_i^2}{2\left(\sum_{i=1}^{m} y_{1i}(n_{2i} - y_{2i})/n_i\right)\left(\sum_{i=1}^{m}(n_{1i} - y_{1i}) y_{2i}/n_i\right)} \\
& + \frac{\sum_{i=1}^{m}\left[(n_{1i} - y_{1i} + y_{2i}) y_{1i}(n_{2i} - y_{2i})\right]/n_i^2}{2\left(\sum_{i=1}^{m} y_{1i}(n_{2i} - y_{2i})/n_i\right)\left(\sum_{i=1}^{m}(n_{1i} - y_{1i}) y_{2i}/n_i\right)} \\
& + \frac{\sum_{i=1}^{m}(n_{1i} - y_{1i} + y_{2i})(n_{1i} - y_{1i}) y_{2i}/n_i^2}{2\left(\sum_{i=1}^{m}(n_{1i} - y_{1i}) y_{2i}/n_i\right)^2}
\end{aligned} \tag{10}$$

where $n_i = n_{1i} + n_{2i}$.

### 2.2 Abrams et al. (1998)'s Random Effect Method

A random effects model is more appropriate if considerable degree of heterogeneity is present in the data. Bayesian methods in meta-analysis are common when the effect is assumed to be random. In general, Bayesian inference requires extensive complex computational techniques. Abrams and Bruno [1] adopted a Bayesian hierarchical model, which is the Bayesian version of the DerSimonian and Laird method [5], and proposed approximations for the first and the second moments of the Bayesian random effect model parameters for meta-analysis. The proposed model adopted a hierarchical modeling approach, which directly models on the study level summaries, i.e. mean difference, odds ratio, etc., and can be applied to both continuous and binary data. By assuming a Gaussian error structure, the following random effect model is obtained for the odds ratio estimation

$$z_i \sim N\left(\eta_i, \sigma_{\eta_i}^2(1/n_{1i} + 1/n_{2i})\right), \eta_i \sim N(\mu_\eta, \tau^2) \quad i = 1, \ldots, m, \tag{11}$$

where $z_i$ and $\eta_i$ are the observed and unknown true log odds ratio for study $i$, respectively, $\mu_\eta$ is the population mean of the random log odds ratio with $\tau^2$ as the population variance. This model can accommodate cases with little prior information as well as with substantial a priori information. To save the time needed for MCMC sampling, approximation formulae are provided in equations (2)-(7) of [1]. The approximation is claimed to be accurate for moderate to large study sample sizes. But its performance is not well understood for the rare event scenario. Thus, we examine its performance under rare event scenario in our simulation study.

### 2.3 Berry (1998)'s Bayesian Methods for Fixed Effect and Random Effect

Berry (1998) proposed a framework of Bayesian meta analysis methods for estimation of the common odds ratio under both fixed effect and random effect scenarios. For random effect scenario, he models the log odds as from a bivariate normal distributions in (12) and derives the common odds ratio from the posterior distribution of the mean of the log odds.

$$\begin{pmatrix}\theta_{1i}\\ \theta_{2i}\end{pmatrix} \sim N\left(\begin{pmatrix}\mu_1\\ \mu_2\end{pmatrix}, \begin{bmatrix}\sigma_{\theta_1}^2 & \rho\sigma_{\theta_1}\sigma_{\theta_2}\\ \rho\sigma_{\theta_1}\sigma_{\theta_2} & \sigma_{\theta_2}^2\end{bmatrix}\right) \tag{12}$$

In (12), $\mu_{\theta_1}$ and $\mu_{\theta_2}$ represent the population mean of the random log odds of the treatment group and the placebo group, respectively. Thus, the log odds ratio is $\eta = \mu_{\theta_1} - \mu_{\theta_2}$. The credible intervals and point estimates of log odds ratio can be derived from the posterior distribution of $\eta$. For hyper priors of the parameters in the normal distribution in (12), please refer to [3]. The fixed effect model is a simplification of the random effect model. Since it is assumed there is a fixed common odds ratio, the log odds of the treatment group can be derived from that of the treatment group, that is $\theta_2 = \theta_1 + \eta$. So, the fixed effect model is

$$\theta_{1i} \sim N(\mu_{\theta_1}, \sigma_{\theta_1}^2), \theta_{2i} = \theta_{1i} + \eta \tag{13}$$

The posterior distribution of $\eta$ yields the credible interval and the point estimate of the fixed effect odds ratio. The hyper priors of parameters in (13) can be found in [3].

## 3. Simulated Data Sets for the Meta-Analysis

Data sets for trials with balanced designs (randomization ratio 1:1) were generated to compare the performance of the three methods under two scenarios, non-rare event situation, where the incidence rates of placebo arms follow uniform distribution of U(0, 20%), and

rare event case, where the incidence rates of placebo arms follow uniform distribution of U(0, 0.2%). For each scenario, we generated 50 studies with equal sample sizes in active and placebo arms. The sample sizes of each arm in each study were set to range from very small to very large ($n$ = 8, 10, 12, 14, 16, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120, 126, 132, 138, 144, 150, 170, 190, 210, 230, 250, 270, 290, 310, 330, 350, 370, 390, 410, 430, 450, 470, 490, 510, 530, 550, 800, 1000, 1500, 2000, 2500). We investigated OR at 6 levels: 1, 1.3, 1.5, 1.8, 2 and 5. Let $p_{1i}$ and $p_{2i}$ be the incidence rates for the treatment and placebo arms in the $i$th study, respectively. For each given OR, we generated $p_{2i}(i = 1, 2, \ldots, 50)$ randomly from the uniform distribution specified above. Then we calculated $p_{1i}$ using: $p_{1i} = p_{2i}OR/(1 - p_{2i} + p_{2i}OR))$. We then generated number of events of each treatment arm for each study assuming binomial distribution with the corresponding sample size and incidence rate. The procedure is repeated $10^4$ times to generate $10^4$ datasets. We also generated data sets for trials with unbalanced designs (randomization ratio 2:1) to evaluate the Abrams (1998)'s method. All datasets were generated using R.

## 4. Simulation Results

### 4.1 Leonard (2002)'s Bayesian Mantel-Haenszel Method and Classical Mantel-Haenszel

We used (5) to calculate the average of posterior odds-ratios from $10^4$ simulations of meta-analysis generated from the balanced with no rare events and with rare events data sets from the section 3 . Both (8) and (5) were utilized to calculate $10^4$ 95 % confidence intervals for the coverage evaluation. Logarithm of (9) and (10) were used in a similar way to calculate the same statistics for classical Mantel-Haenszel model. The results, when both methods were applied to the balanced data sets without rare events are presented in the Table 4.

**Table 2**: Simulation Results: MH and Bayesian MH (Model 1 )

| | $p_{2i} \sim U(0, 20\%)$ | | $p_{2i} \sim U(0, 20\%)$ | |
|---|---|---|---|---|
| True | $n_{1i} : n_{2i} = 1 : 1$ | | $n_{1i} : n_{2i} = 1 : 1$ | |
| Odds Ratio | MH Estimate | Coverage % | BMH Estimate | Coverage % |
| 1 | 1.00 | 95.16 | 1.00 | 95.53 |
| 1.3 | 1.30 | 94.97 | 1.29 | 95.13 |
| 1.5 | 1.50 | 95.19 | 1.49 | 94.86 |
| 1.8 | 1.80 | 94.87 | 1.78 | 94.20 |
| 2 | 2.00 | 94.62 | 1.98 | 94.25 |
| 5 | 5.00 | 94.87 | 4.91 | 90.81 |

The results, when both methods were applied to the balanced data sets with rare events are presented in the Table 5.

The results on the odds ratio estimates and coverage of 95 % confidence intervals of the classical MH and Bayesian MH methods are to a great extent similar. In the case of non-rare events and balanced treatment and control groups in the meta-analysis, the estimates of odds ratio from both methods are close to the true odds ratio and the coverage is close to the nominal one. The classical MH method showed slightly better performance suggesting that there is no advantage to use Bayesian MH method. In the case of rare events in the balanced treatment and control groups of the meta-analysis data sets, both classical MH and Bayesian MH underestimated all odds ratios where the treatment effect was assumed to be present (i.e odds ratio is greater than 1) and respectively showed coverage below nominal

**Table 3**: Simulation Results: MH and Bayesian MH (Model 1 with Rare Events )

| True Odds Ratio | $p_{2i} \sim U(0, 0.2\%)$ $n_{1i} : n_{2i} = 1 : 1$ MH Estimate | Coverage % | $p_{2i} \sim U(0, 0.2\%)$ $n_{1i} : n_{2i} = 1 : 1$ BMH Estimate | Coverage % |
|---|---|---|---|---|
| 1 | 1.01 | 99.77 | 1.01 | 99.97 |
| 1.3 | 1.15 | 97.34 | 1.12 | 98.66 |
| 1.5 | 1.24 | 92.56 | 1.19 | 93.8 |
| 1.8 | 1.38 | 81.08 | 1.30 | 76.62 |
| 2 | 1.47 | 72.28 | 1.38 | 61.59 |
| 5 | 2.90 | 9.67 | 2.41 | 0.13 |

when treatment effect is large (i.e. odds ratio is above $1.3$) and coverage close to $100\%$ when there is a negligible or no treatment effect (odds ratio is close to one).

### 4.2 Abrams et al. (1998)'s Random Effect Method

The approximation formulae (2)-(7) in [1] allow us to calculate odds ratio estimates and respective confidence intervals without a computational burden. The $10^4$ simulations of meta-analysis data as described in 3 were generated. The Table 4 odds ratio estimate and 95 % confidence intervals coverage were calculated using the data without rare events; the results from the data with balanced treatment and control groups were compared with the results from the data with the unbalanced groups.

**Table 4**: Simulation Results: Approximate Bayesian Method: Additive Heterogeneity (Non-rare events)

| True Odds Ratio | $p_{2i} \sim U(0, 20\%)$ $n_{2i} : n_{1i} = 1 : 1$ Estimate | Coverage % | $p_{2i} \sim U(0, 20\%)$ $n_{2i} : n_{1i} = 1 : 2$ Estimate | Coverage % |
|---|---|---|---|---|
| 1 | 1.0113 | 96.05 | 1.0836 | 93.26 |
| 1.3 | 1.3543 | 95.50 | 1.4345 | 91.19 |
| 1.5 | 1.5852 | 95.24 | 1.6708 | 90.27 |
| 1.8 | 1.9355 | 94.16 | 2.0225 | 88.76 |
| 2 | 2.1694 | 93.47 | 2.2580 | 87.42 |
| 5 | 5.7108 | 85.31 | 5.7800 | 81.94 |

The results showing the performance of the method when applied to the balanced data set without rare events versus with rare events are presented in the Table 5.
The application of the method to both balanced and unbalanced data sets without rare events showed that the method overestimates the odds ratio and the overestimation increases with the size of the effect. However the coverage is closer to the nominal when the method is applied to the balanced data set. When comparing the performance of the method applied to the meta-analysis with balanced data without rare events versus the data with rare events, the odds ratios are highly overestimated for the rare events setting in comparison to the without rare events set-up, and the coverage is respectively much lower in the case of rare

**Table 5**: Simulation Results: Approximate Bayesian Method: Additive Heterogeneity (Non Rare vs. Rare events)

| True | $p_{2i} \sim U(0, 20\%)$ $n_{2i} : n_{1i} = 1 : 1$ | | $p_{2i} \sim U(0, 0.2\%)$ $n_{2i} : n_{1i} = 1 : 1$ | |
|---|---|---|---|---|
| Odds Ratio | Estimate | Coverage % | Estimate | Coverage % |
| 1 | 1.0113 | 96.05 | 1.2990 | 93.75 |
| 1.3 | 1.3543 | 95.50 | 1.9070 | 92.81 |
| 1.5 | 1.5852 | 95.24 | 2.3668 | 91.19 |
| 1.8 | 1.9355 | 94.16 | 3.0530 | 88.81 |
| 2 | 2.1694 | 93.47 | 3.5333 | 86.47 |
| 5 | 5.7108 | 85.31 | 10.4396 | 57.60 |

**Table 6**: Simulation Results: Scott Berry Bayesian Hierarchical Methods

| $n_{1i}$ :$n_{2i}$ | $p_{2i}$ | OR | Random Effect Model | Coverage (%) | Fixed Effect Model | Coverage (%) |
|---|---|---|---|---|---|---|
| 1:1 | U(0,20%) | 1 | 1.02 | 93.4 | 1.00 | 93.5 |
| | | 2 | 1.76 | 75.5 | 1.99 | 93.6 |
| | | 5 | 3.95 | 36.3 | 4.95 | 91.9 |
| | U(0,0.2%) | 1 | 1.60 | 94.5 | 0.97 | 86.4 |
| | | 2 | 1.81 | 82.5 | 1.85 | 88.2 |
| | | 5 | 2.07 | 34.1 | 4.42 | 82.7 |

events.

### 4.3 Berry (1998)'s Bayesian Method for Fixed Effect and Random Effect

The understand the performance of Berry (1998)'s method in the rare event and fixed effect scenario, we performed $10^3$ simulations using the dataset created in §3. Because of the computation burden, only the odds ratio 1, 2, and 5 scenarios are selected for the simulation, which is sufficient for us to understand the frequentist property of this method.
Table 6 tabulates the posterior mean estimates and the coverage rates of the 95% credible intervals. When the true odds ratio is great than 1, the fixed effect model works better than the random effect model in terms of both the bias of the point estimates and the coverage rates. The reason is that the simulated datset does not have random effect, which violates the assumption of the random effect model. Thus, in practice, random effect model should be used with caution if there is not strong evidence of a random effect. For the rare event scenario ($p_{2i} \sim U(0, 0.2\%)$), the coverage rates of the fixed effect model are about $13\%$ to $10\%$ lower than the nominal $95\%$, which suggests the normal priors for the log odds may be improper for the rare event scenario.

## 5. Conclusion and Discussion

Bayesian approach offers an appealing methodology framework to conduct meta-analysis by naturally incorporating all sources of variability and relevant quantifiable external information. It allows direct probabilistic inference on the overall treatment effect and quantification of the between study heterogeneity. In particular, Leonard et. al. (2002)'s Bayesian Mantel-Haenszel Fixed Effect Method offers a Bayesian alternative for Mantel-Haenszel method. The performance of the Bayesian MH method and the classical MH method is comparable for non-rare event case, but both methods do not perform well for rare event case and the treatment effect is from moderate to large (e.g. odd ratio $> 2$). Abrams et. al. (1998)'s approximate Bayesian random effect approach uses first and second moments to obtain an approximation of the parameters. Simulation studies have revealed that the approximate Bayesian inference for random effect method is fine with non-rare event and unbalanced sample size among treatment groups, but may not be appropriate for rare events, especially when treatment effect is large (e.g odd ratio $> 5$). Berry (1998)'s method provides a Bayesian framework for meta-analysis and uses Bayes factor to automate the selection between fixed effect or random effect model. However, regardless under either rare or non-rare event case, the performance of the fixed model is better than the one from the random model, since the simulation data are not generated with random effect component. This also suggests that incorporation of heterogeneity should be taken with caution if there is no strong evidence of random effect.

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