Bayesian Meta-analysis of Studies on Corticosteroid Therapy on Neonatal Death

Introduction

This paper will discuss a meta analysis with Bayesian approach on the data collected from seven randomized trials that evaluate the effect of corticosteriod therapy on neonatal death. The data are from the rmeta package in R:

```
> library(rmeta)
> data(cochrane)
> cochrane
```

	name		ev.trt	n.trt	ev.ctrl	n.ctrl
1	Auckland	36	532	60	538	
2	Block	1	69	5	61	
3	Doran	4	81	11	63	
4	Gamsu	14	131	20	137	
5	Morrison	3	67	7	59	
6	Papageorgiou	1	71	7	75	
7	Tauesch	8	56	10	71	

The Bayesian model for the study is based on the model proposed by Smith et al. (1995). This paper will discuss the model's strength and limitation, frequentist property as well as the results of the meta analysis.

Methods

In 1995, Smith et al. proposed a Bayesian random-effects model for meta analysis in contrast to the pooled estimate from a fixed-effect model. The model was used for the meta-analysis of the effectiveness of decontaminating treatment on respiratory tract infections, which has a very similar data category and structure as well as analysis objective as the neonatal data from the current study. Taking random-effects into the model could be very helpful in terms of explaining the potential biased estimations given that different trials could be conducted on different populations with different medical conditions and health profiles. For the current study, we adopted the Bayesian random-effect model proposed by Smith et al. which can be written:

$$r_i^c \sim Binomial\left(p_i^c, n_i^c\right)$$

$$r_i^t \sim Binomial(p_i^t, n_i^t)$$

$$logit(p_i^c) = \mu_i + \delta_i/2$$

$$logit(p_i^t) = \mu_i - \delta_i/2$$

$$\delta_i \sim Normal(d, \sigma^2)$$

In notation, r_i^c denotes the number of neonatal death in the control group in trial i, arising from n_i^c cases, each assumed to have probability of p_i^c of the neonatal death. Adopting an equivalent notation for the treatment group, we assume that δ_i is the true treatment effect (on a log-odds scale) in trial i, so that $\delta_i = logit(p_i^t) - logit(p_i^c)$. The 'average' neonatal death in the i^{th} trial is denoted as μ_i, which $\mu_i = (logit(p_i^t) + logit(p_i^c))/2$. The model also assume that the individual trial effects are drawn from some Gaussian population with mean d and variance σ^2.

In this study, the value of d will be the estimator for the effectiveness of the treatment. If $P(d<0)<1/11$, null hypothesis will be rejected and alternative hypothesis, the treatment is effective, will be accepted.

For the prior selection, Smith et al. suggested to use uninformative natural priors on μ_i, d, σ^2. Specifically, they used priors:

$$\mu_i \sim Normal(0, 4)$$

$$d \sim Normal(0, 10)$$

$$\sigma^2 \sim InvGamma(3, 1)$$

When determining the prior parameters, we need to define a procedure to make sure the parameters make the prior uninformative and appropriate, especially in the case that the terms are in the logit format. For μ_i, Smith et al. made a conservative assumption that the overall response rate $1/(1+e^{\mu_i})$ is 95% likely to lie within a range of 0.02 to 0.98, which lead to a normal prior for μ_i with mean 0 and precision 0.25. For $p(d)$, they assumed a extremely conservative assumption that the underlying odds ratio is unlikely to exceed 500 in favor of either arm of the trial, which can be translated into a 0.95 chance that d is between $[-6.2, +6.2]$. Hence the prior distribution for d was specified as normal with mean 0 and variance of $(6.2/1.96)^2 = 10$. Finally, the decision for σ^2 was based on two assumptions: First, the spread of the odd ratio between studies should be within one order of magnitudes, which means the 0.975 percentile of the distribution of odds ratios is ten times the 0.025 percentile, or equivalently that a 0.95 interval for δ_i has width of 2.3. This gives a prior estimate for σ^2 of $(1.15/1.96)^2 = 0.34$. Second, it is very unlikely that the spread is over two order of magnitudes, which can be finally translated into a 'high' value for σ^2 of $(2.3/1.96)^2 = 1.38$

. A gamma(3, 1) distribution is a good approximation under such assumptions. The assumptions behind the model proposed by Smith et al. also fit well with the current study. Hence, this study decide to adopt the same distribution family as well as the parameters for the priors.

By using uninformative priors, this analysis assumes no background knowledge about the subject. More specifically, for this study, we assume no information available regarding the 'average' neonatal death. However, such information could be available from government reports, peer studies etc. Using a more informative prior could lead to a more accurate estimation.

Simulation Study

Simulation study was conducted to test the frequentist properties of the Bayesian model. 1000 simulated datasets with event probability of 0.1 for both control and treatment groups was generated and tested on the proposed Bayesian model and also with a frequentist approach, two sample t-test, as a performance reference.

The null hypothesis (H_0) is that the treatment does not have significant effect on reducing neonatal death. For the Bayesian model, in order to achieve a good frequentist property (low Type I error), the model will reject the null hypothesis and accept the alternative hypothesis (treatment can significantly reduce the neonatal death) if $P(d<0)<1/11$. For the two sample t-test, if the P-value < 0.1, reject the null hypothesis and accept the alternative hypothesis.

Computation

All the computations were implemented and executed in JAGS and R 3.5.1. For the Bayesian model, MCMC sampling was used to summarize the estimations. The MCMC sampling used 2 chains with 5000 iterations for the burning and 20000 iterations for the sampling. Gelman–Rubin convergence diagnostic was adopted for convergence test (acceptable CI <= 1.1).

Results

According to the result of the simulation study (Table 1), the Bayesian model achieved a Type-I error rate that less than 5%, which is even slightly better than the two sample t-test.

Table 1: Result of the Simulation Study

	Two Sample t-Test	Bayesian Model
Type I Error (%)	8.8	2.4

According to the MC sampling, the probability of the mean true treatment effect d less than 0 is $0.0065 < 1/11$ (Figure 2). So the null hypothesis was rejected and the alternative hypothesis,

treatment can significantly reduce the neonatal death, was accepted. Figure 2 shows the posterior distribution for the pulled mean neonatal death rates for the control and treatment groups.

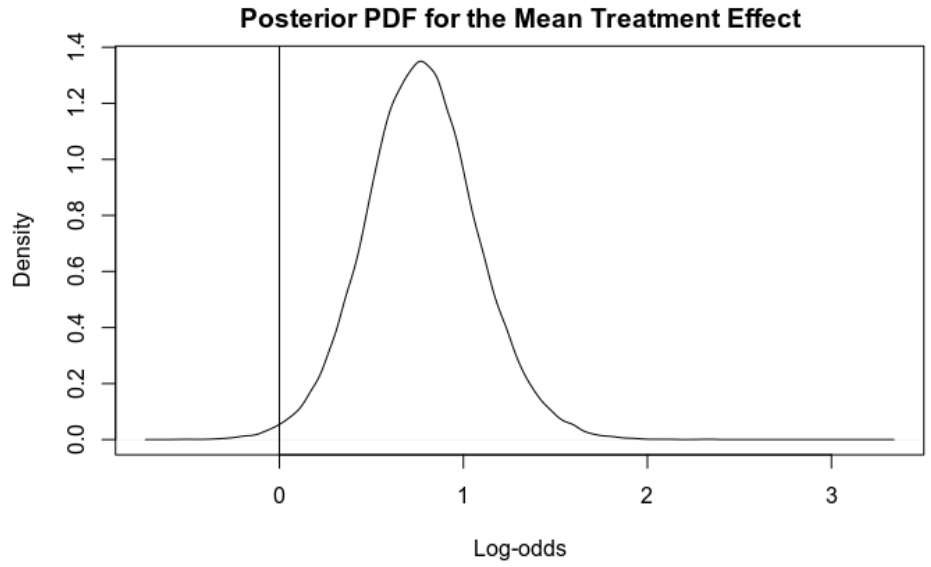

Figure 1: Posterior PDF for the Mean Treatment Effect (Log-odds)

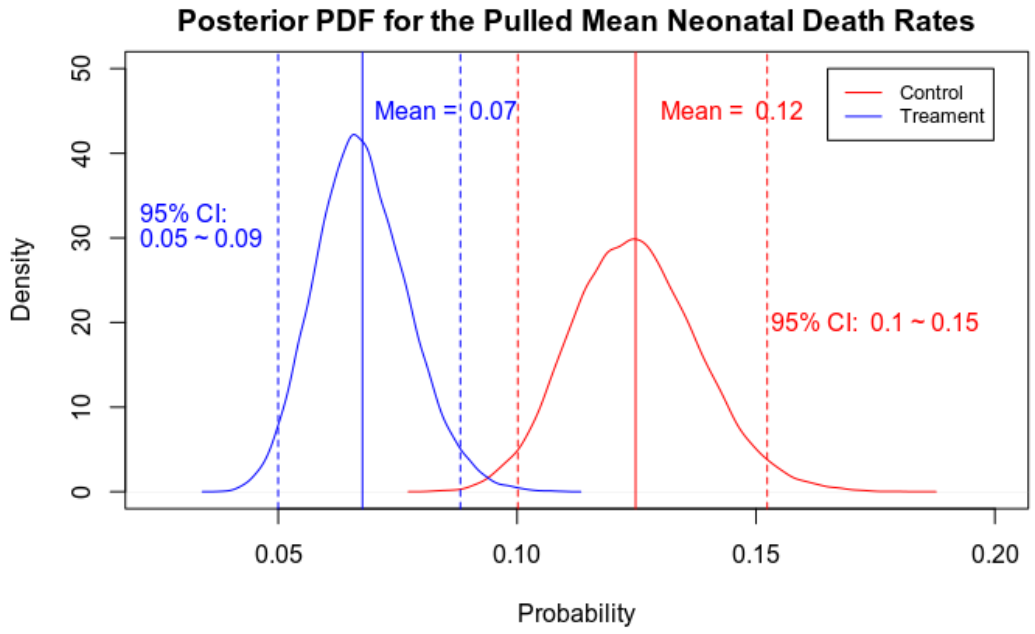

Figure 2: Posterior Distribution for Pulled Mean Neonatal Death Rates for Control and Treatment Groups

Reference

Smith, T. C., Spiegelhalter, D. J., & Thomas, A. (1995). Bayesian approaches to random effects meta analysis: a comparative study. *Statistics in medicine*, *14*(24), 2685-2699.

APPENDIX: JAGS Code for Bayesian Model

```
"model{
        # likelihood
        for (i in 1:7) {
                rc[i] ~ dbinom(pc[i],nc[i])
                rt[i] ~ dbinom(pt[i],nt[i])
                logit(pc[i]) <- mu[i] + delta[i]/2
                logit(pt[i]) <- mu[i] – delta[i]/2
                delta[i] ~ dnorm(d, tau)
        }
        # priors
        for (i in 1:7) {
                mu[i] ~ dnorm(0, 0.25)
        }
        d ~ dnorm(0, 0.1)
        tau ~ dgamma(3, 1)
  }"
```