Meta-analysis of rare events with few studies

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Introduction

Meta-analyses are commonly based on few studies. Additional issues arise for binary outcomes when only few or no events are observed in some of the studies or study arms. These problems are common when secondary or safety endpoints are considered, since the studies were not powered for these.

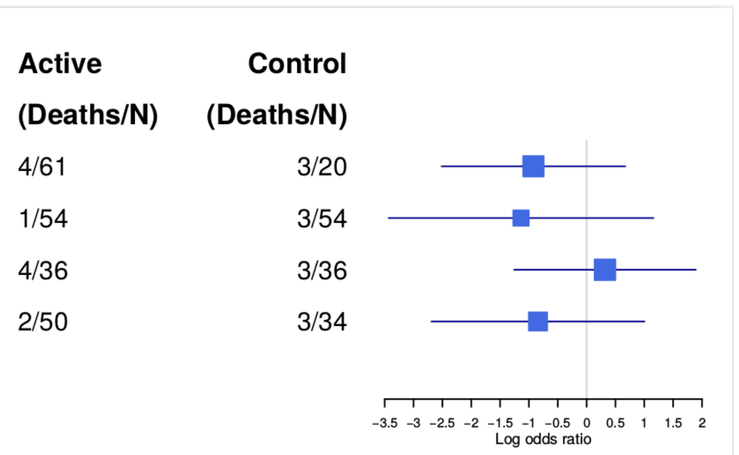

Figure 1: An example of a review reporting mortalities for 4 studies in paediatric immunosuppression [1].

Data model

We use the Binomial-Normal hierarchical model (BNHM), a generalized linear mixed model (GLMM) [2]. For study i and treatment arm k:

- event counts : $y_{ik} \sim \text{Bin}(\pi_{ik}, n_{ik})$
- probabilities : $\text{logit}(\pi_{ik}) = \mu_i + \theta_i \, x_{ik}$
- random effects : $\theta_i \sim \mathcal{N}(\theta, \tau^2)$

where x_{ik} is a treatment indicator, μ_i are the baseline risks, θ_i are the (random) treatment effects, and τ denotes the amount of heterogeneity. BNHM is a random effects meta-analysis model which uses binomial data directly, does not rely on normal approximations.

Weakly informative priors

For meta-analysis of few studies, weakly informative priors (WIPs) for τ, eg half-normal $\mathcal{HN}(1)$, are suggested [3]. Inspired by the penalization ideas in the context of logistic regression [4], we investigate WIPs for θ. We choose BNHM, since it explicitly includes the parameter of interest, θ, which can, therefore, be penalized directly.

To construct a WIP for θ, assume a priori that with 95% the underlying odds ratio (OR) lies between δ_l and δ_u:

$$\exp(\mu \pm q_{0.975} \cdot \sigma) = [\delta_l, \delta_u]$$

Assuming a priori neutral effect ($\delta_l = \frac{1}{\delta_u}$), the degree of the information is linked to prior standard deviation σ. If we chose a normal prior:

$$\sigma = \frac{\log(\delta_l) - \log(\frac{1}{\delta_l})}{2 \cdot 1.96}.$$

Conservatively, $\delta_l = 250$ resulting in $\sigma = 2.82$.

In terms of prior's effective sample size, this is equivalent to adding 2 patients.

Empirical evidence supporting weakly informative priors

We downloaded the meta-analysis datasets from the Cochrane Database in March 2018, resulting in 37 773 meta-analysis with binomial endpoints. We re-analyzed them using BNHM via MLE.

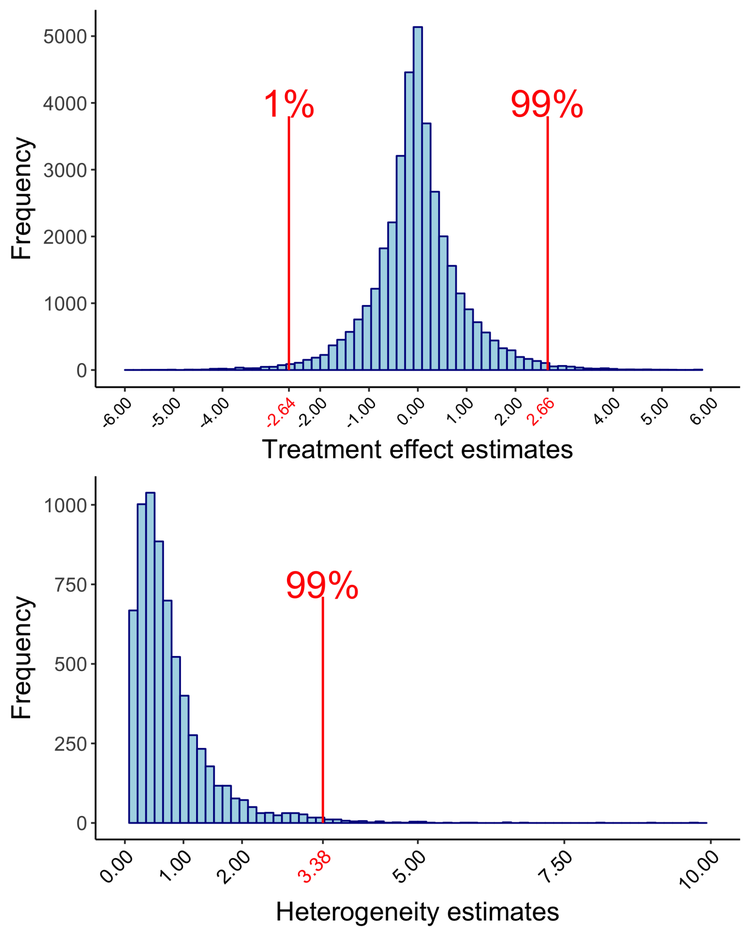

Figure 2: Estimates of treatment effect and heterogeneity (non-zero) from Cochrane database. Percentiles are indicated in red.

Suggestions of $N(0, 2.82^2)$ and $\mathcal{HN}(1)$ are consistent with estimates of θ and τ empirically observed in the Cochrane Database.

`MetaStan` R package

To use Bayesian inference, BNHM is fitted using Markov chain Monte Carlo via **Stan** [5]. An R package `MetaStan` is under development to automate the implementation.

Install `MetaStan` using `devtools`:

```
install_github("gunhanb/MetaStan")
library("MetaStan")
```

BNHM WIP can be fitted by specifying δ_l via `OR_apriori`:

```
meta_stan(ntrt = dat$exp.total,
          nctrl = dat$cont.total,
          rtrt = dat$exp.events,
          rctrl = dat$cont.events,
          tau_prior_dist = "half-normal",
          tau_prior = c(0, 1),
          OR_apriori = 250)
```

Simulations

The frequentist properties of

- BNHM vague ($\theta \sim \mathcal{N}(0, 100^2)$)
- BNHM WIP ($\theta \sim \mathcal{N}(0, 2.82^2)$)
- BNHM MLE
- BBM (Beta-binomial model) [6]

are investigated. Values for sample sizes and baseline risks are motivated from the Cochrane Data, and equal allocation is assumed. For both BNHM vague and BNHM WIP, the prior for τ is taken as $\mathcal{HN}(1)$.

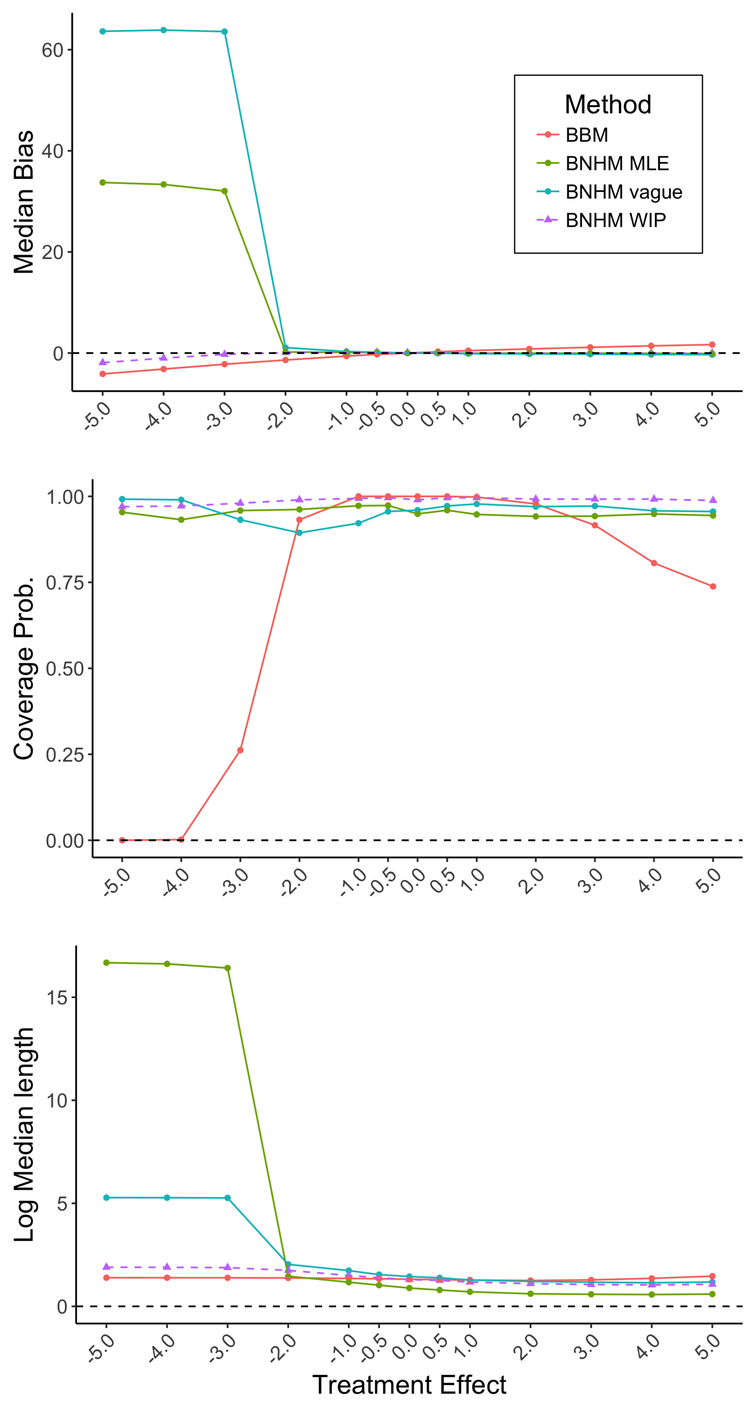

Figure 3: Results for meta-analysis datasets with three studies, and medium heterogeneity ($\tau = 0.2$).

In terms of median bias of θ, BNHM WIP outperforms all other methods. Although the bias from BBM is small, the coverage of 95% credible interval of θ from BBM for some scenarios is unacceptably low. For those scenarios, BHNM vague and BNHM MLE give poor results in terms of bias. Those scenarios correspond to the datasets in which very few or no events were observed.

Conclusions

- BNHM using WIP displays desirable properties in simulations
- Easy to apply as `MetaStan` is publicly available
- Possible extensions
  - Other endpoints, eg counts over time period
  - Network meta-analysis
  - Meta-analysis of diagnostic studies

References

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