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Review of applications of Bayesian meta-analysis in systematic reviews

Melissa Glenda Lewis [1] , *N Sreekumaran Nair* [*2]

ABSTRACT

Background: Systematic reviews are important sources of evidence in health care research. These reviews may or may not include meta-analysis as a statistical assimilation of the results of several studies in order to acquire a pooled estimate. Systematic review with meta-analysis is considered as a robust method of evidence synthesis. The methodology concerned with traditional meta-analysis does not incorporate external prior information. Hence, Bayesian methods are essential due to the natural process of incorporating the past information and updating the belief. Bayesian methods to meta-analysis have been developed with a motivation from the limitations of traditional meta-analysis such as dealing with missing data, problem with limited number of studies and problem with sparse event data in both the groups. The present article aims to unearth as to what extent Bayesian methods have been used in systematic reviews, evolution and its applications. This article also highlights the existing challenges and opportunities.

Methods: The literature search was performed in databases such as Cochrane, PubMed, ProQuest and Scopus using the keywords "Bayesian Meta-analysis" and "Bayesian Meta-analyses". All the methodology and application oriented papers specific to Bayesian meta-analysis were considered relevant for this review.

Conclusion: Bayesian meta-analysis has gained popularity in the field of evidence synthesis of clinical trials. However, it did not pick up momentum in summarizing public health interventions, owing to the fact that public health interventions are targeted to highly heterogeneous population, multi-component interventions, and multiple outcomes and influenced by the context

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[1]PhD Scholar, Department of Statistics, Manipal University, Public Health Evidence South Asia

[*2]Professor and Head, Department of Statistics, Manipal University
Director, Public Health Evidence South Asia

*Corresponding Author:
N Sreekumaran Nair
Manipal – 576104
nsknairmanipal@gmail.com
Telephone number: +918202922407

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Key messages

(1) The article provides a bird's eyes view on the extent at which Bayesian meta-analysis have been applied in systematic reviews
(2) The Evolution and applications of Bayesian methods in meta-analysis
(3) Difficulty in applying Bayesian meta-analysis in public health systematic reviews.
(4) The paper also suggests ways at which Bayesian methods can be incorporated in public health systematic reviews.

INTRODUCTION

Systematic reviews are important sources of evidence in health care research. These are considered to provide high level of evidence because they minimize bias during the review process, provide comprehensive evidence about an intervention's effectiveness and very often solve the confusions created by the conflicting results of different studies addressing the same question. Meta-analysis is a powerful quantitative technique that combines the results of several individual studies in order to obtain a single effect size.[1] Thus, Systematic review with Meta-analysis is considered to provide highest form of evidence.

The methodology concerned with traditional meta-analysis does not incorporate external prior information. Hence, a different approach to meta-analysis is developed where the past information is integrated using Bayesian principles. Bayesian approach is defined as "the explicit quantitative use of external evidence in the design, monitoring, analysis and interpretation of health care evaluation".[2] One of the requirements of Bayesian meta-analysis is the prior belief about the parameter, which should be external to data. The observed data is integrated with past knowledge to have current knowledge about the parameter of interest.

The aim of this article is to unearth to what extent Bayesian methods in meta-analysis have been undertaken, thereby providing a glimpse of methodological developments, its advantages and applications to the readers. The article also highlights the existing challenges and opportunities.

FUNDAMENTALS OF BAYESIAN METHODS

The traditional statistical inference assumes that the sample is arriving from a population with a parameter being fixed and unknown. Entire inference about the parameter is based on the sample information. In contrast, Bayesian approach considers parameters as a random variable with a probability distribution and that distribution expresses our prior information. The current data summarizes the likelihood function. Using Bayesian principles, the prior distribution and likelihood function is combined to obtain posterior distribution function.

The elements of Bayesian approach are as follows,

$$P(\theta \mid \text{data}) \propto P(\text{data}) \times P(\theta)$$

Where, $P(\theta|\text{data})$: Posterior Distribution; it is the uncertainty about the parameter after seeing the data, expressed using probability.

$P(\text{data})$: Likelihood function

$P(\theta)$: Prior Distribution; it is the uncertainty about the parameter before seeing the data: expressed using probability.

CONCEPT OF BAYESIAN META-ANALYSIS

The Bayesian meta-analysis involves four fundamental steps:

(1) Identifying appropriate Priors: Summarizing the evidence external to observed data is a first step in Bayesian meta-analysis. This summarizes the past evidence and beliefs on the relative benefits of intervention. The evidence can be from nonrandomized studies, invitro or invivo trials, laboratory studies or subjective beliefs. The prior distributions are placed on the parameters since they are considered unknown random quantities.

(2) Current Data: The observed data or effect estimates collected from different studies answering the same question will constitute likelihood function of the parameters. A full probability model is obtained for all the observable and unobservable quantities.

(3) Posterior: The external evidence is then merged with the current data to obtain a current state of knowledge regarding the effect of intervention. Thus, the posterior distribution is obtained from the combination of prior distribution and likelihood function. The posterior is also termed as the updated evidence. Further, all the inferences should be based on the posterior distribution that is in contrast to traditional Meta-analysis.

(4) Summarizing: The final step involved in Bayesian Meta-analysis is to summarize from

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the posterior distribution. Very often the posterior distribution obtained will be of high dimension and complex, hence computer based packages (BUGS and WINBUGS) are required to perform the integrations.[3] Simulation techniques like Markov Chain Monte Carlo are used to sample directly from the posterior distribution. Hence, all the summary estimates are estimated from those samples e.g. Mean, Standard Deviation, Odds Ratio, Risk Ratio etc. 95% credible intervals (which is 2.5 percentile and 97.5 percentile of the posterior distribution) are calculated rather than 95% confidence interval.

Similar to traditional meta-analysis, two models are commonly used in Bayesian meta-analysis; fixed effect model and random effects model. Consider k independent studies with i^{th} study estimating an effect size T_i, which is an estimate for the population effect size θ_i. T_i is assumed to have a normal distribution with mean θ_i and variance σ_i^2. Fixed effect model assumes that $\theta_1 = \theta_2 = \theta_3 \ldots \theta_k = \theta$ (common effect size). Using Maximum likelihood estimation method (MLE) the pooled estimate of θ is given by $\hat{\theta} = \frac{\sum_{i=1}^{k} w_i T_i}{\sum_{i=1}^{k} w_i}$ where w_i is the weights given to each study ($w_i = \frac{1}{\sigma_i^2}$), i=1, 2, 3...k.

Whereas, in random effects model we allow the true effects underlying the studies to differ, conventionally a normal distribution. We assume θ_i's are independent with $\theta_i \sim N(\mu, \tau^2)$ where μ is the pooled effect size and τ^2 is between study heterogeneity. Marginally, $T_i \sim N(\mu, \tau^2 + \sigma_i^2)$. Hence, when τ^2 is known, we use MLE to estimate μ. Therefore, the pooled estimate of μ is given by, $\hat{\mu} = \frac{\sum_{i=1}^{k} (\tau^2 + \sigma_i^2)^{-1} T_i}{\sum_{i=1}^{k} (\tau^2 + \sigma_i^2)^{-1}}$ where, $(\tau^2 + \sigma_i^2)^{-1}$ is the weights given to each study.[4]

In Bayesian Meta-analysis, the only difference to that of traditional meta-analysis is that, prior distributions are specified for the unknown parameters.

The Bayesian fixed effect model is given by;

$T_i \sim N(\theta, \sigma_i^2)$: Likelihood
$\theta[\_, \_]$: Prior

Prior distribution can also be assumed for σ_i^2 or one can assume it is known and can replace by the within study variability, which usually makes little practical difference.

The Bayesian random effects model is given by:

$T_i \sim N(\theta_i, \sigma_i^2)$: Likelihood
$\theta_i \sim N(\mu, \tau^2)$, $\mu \sim [\_, \_]$, $\tau^2 \sim [\_, \_]$: Priors

Where, T_i is the observed effect from each study, θ_i is the true effect in each study, σ_i^2 is the known within study variance, μ is the pooled effect size and τ^2 is between study heterogeneity. If the outcome is binary, then the assumption of normality does not hold hence binomial models are specified.

CHOOSING PRIOR DISTRIBUTIONS FOR THE PARAMETERS

Choosing prior distribution is a very important step in performing Bayesian meta-analysis and researcher needs to decide which distribution to place on parameters.[5] There are different types of priors: Informative, non-informative, skeptical and enthusiastic. Information derived from past literature or expert opinion is referred as informative. Such distributions have more impact on the posterior because they approach from the past data. When there is no past information or when the past information is decided to be ignored, then the distributions used are referred as non-informative. They consider all probable values of the parameter as equally likely. Skeptical priors are those which consider that there is no difference between the two groups i.e., intervention and control. Whereas, enthusiastic priors are those that initially favour one side or the other. [6-8] Non-informative priors are also termed as vague priors and they often yield similar results to that of traditional meta-analysis where the posterior pooled estimate is entirely on likelihood function. Some of the vague distributions commonly used in literature are normal distribution for μ and τ. Uniform, gamma, Inverse gamma and Pareto for τ, τ^2 and precision($1/\tau^2$).

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Binomial and beta distribution are used when the outcome is binary in nature.

In a fixed effect model with outcome assumed to be normally distributed, most of the situations the within study variability (σ_i^2) is usually known and hence it is replaced by the observed within study variance which is believed to have less impact on posterior distribution particularly when the sample size is very small. Normal distribution with a large variance is commonly used for θ and μ, if vague prior knowledge has to be specified. Jeffrey's prior (improper prior) used for τ and τ^2 will lead to a posterior which is non-integral therefore as an alternative, Sutton highlighted the use of Inverse gamma and the usage of Pareto, log Cauchy and t distribution.[9] Smith commented that working with precision (inverse variance) is easier than working with variance or standard deviation. When studies have extreme values of μ_i, the choice of prior for μ and τ will have a greater influence when estimating pooled log OR.[10] Lambert CP conducted a simulation study and looked for the impact of 13 different vague priors on between study variance and concluded that the effect size estimated was not biased, but the precision with which it was estimated was different with different priors. He found out that there was large variation in the estimates of the τ leading to different statistical inferences.[11]

Thus choosing prior is the most controversial phase in Bayesian framework. It is not always obvious which prior is the most appropriate. Hence, sensitivity analysis of the results to the choice of the prior should be examined.

EXAMPLE OF BAYESIAN META – ANALYSIS

Bayesian Meta-analysis was performed for the studies included in the systematic review "The benefits of steroids versus steroids plus antiviral for treatment of Bell's palsy: a meta-analysis". The objective of the review was to determine whether providing steroids together with antiviral provide a better degree of facial muscle recovery in patients with Bell's palsy than steroids alone. Primary outcome was proportion of patients with at least partial facial muscle recovery from Bell's palsy, [12] data are showed in Table 1.

Table 1 Facial muscle recovery outcome data for five studies evaluating Steroids plus antiviral vs Steroids in patients with Bell's palsy

	Steroids plus antivitals			Steroids					
Study	No. with recovery	No. not recover	Total	No. with recovery	No. not recover	Total	OR	ln(OR)	V{ln(OR)}
Engstrom et.al 2008	164	16	180	160	26	186	1.67	0.51	0.11
Sullivan et.al 2007	115	9	124	122	5	127	0.52	-0.65	0.33
Hato et.al 2007	110	4	114	96	11	107	3.15	1.15	0.36
Yeo et.al 2008	41	3	44	40	7	47	2.39	0.87	0.53
Minnerop et.al 2008	42	8	50	53	14	67	1.39	0.33	0.24

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BAYESIAN FIXED EFFECT AND RANDOM EFFECTS META-ANALYSIS

T_i is normally distributed with mean θ and known unequal variance σ_i^2

$T_i \sim$ Normal (θ, σ_i^2)

L gives the likelihood function $(\theta, \sigma_i^2; T_1, T_2 T_3 \ldots T_k)$ $= \prod_i^k \frac{1}{\sqrt{2\pi\sigma_i^2}} e^{-\frac{1}{2\sigma_i^2}(T_i-\theta)^2}$.

Prior distribution for θ is $\theta \sim N,(\theta_0, {\sigma_0}^2)$ which is written as $P(\theta) = \frac{1}{\sqrt{2\pi{\sigma_0}^2}} e^{-\frac{1}{2{\sigma_0}^2}(T_i-\theta_0)^2}$.

The prior was taken from a study that evaluated Steroids and antiviral vs. Steroids in patients with Bell's palsy published a decade ago.[13] i.e., θ ~ N (0.30, 0.39) Now multiplying the prior with likelihood, we obtain the posterior distribution that is normal with posterior mean and posterior variance. Bayesian fixed effect meta-analysis was carried out in WINBUGS, 5000 iterations were used for burning the sampler and 10000 iterations were used for estimation. The posterior pooled OR is 1.56 with 95% credible interval as (1.002, 2.33) suggesting that steroids plus antiviral gives no better degree of facial muscle recovery in patients with Bell's palsy than steroids alone. The Frequentist Fixed effect Meta-analysis leads to a pooled OR of 1.52 with 95% CI as (0.99, 2.34).

For the same example, random effects Bayesian meta-analysis was performed placing prior distribution on the parameters μ and τ^2. The model is given by,

$T_i \sim$ Normal (θ_i, σ_i^2)

$\theta_i \sim N(\mu, \tau^2)$

$\mu \sim$ normal (0.30, 0.39)

$\tau^2 \sim$ Inv-gamma (0.001, 0.001)

Where, μ is the pooled effect size and τ^2 is the between study heterogeneity. Since variance cannot go negative, normal distribution with mean zero and large variance is not a feasible option. Hence, inverse gamma distribution on variance is specified. The analysis was performed in WINBUGS with 5000 iterations for burning the sampler and 10,000 iterations for estimation. The posterior pooled OR is 1.58 with 95%CrI (0.86,2.66), suggesting that steroids plus antiviral gives no better degree of facial muscle recovery in patients with Bell's palsy than steroids alone. The estimate of τ^2 is 0.036 (low degree of heterogeneity i.e.$\tau^2 \leq 0.04$) with 95% CrI as (0.0009, 1.455). One of the advantages of Bayesian meta-analysis is the estimate of between study heterogeneity and its uncertainty is obtained, whereas traditional Random effects Meta-analysis leads only the pooled OR of 1.52 with 95% CI as (0.90, 2.56).

EVOLUTION OF BAYESIAN META-ANALYSIS AND ITS APPLICATIONS

Figure 1 illustrates number of Bayesian meta-analysis papers published in PubMed and Cochrane, along with methodological papers. It is clear that the number of Bayesian meta-analysis publications have been increasing over the year since 1990. One of the major reasons for this increasing trend is the development of the BUGS software and the windows achievement of WINBUGS.[14,15] Methodological papers have been much smaller in numbers. However, the first identified paper was published in 1992.[16] Carlin develops a Bayesian approach in meta-analysis similar to random effects method of Laird and DerSimonian to meta-analysis. He concludes that this method accounts for full uncertainty in estimating the parameters and terminates declaring that different prior's leads to different conclusion. Smith et al published a comparative study on Bayesian approaches to random effects meta-analysis in which they describe how Bayesian analysis can deal issues with choosing between fixed effect and random effects model, problems with small sample size and including study particular covariates.[10] "Approximate Bayesian inference for Random effects meta-analysis" a paper published by Abrams and Sanso highlights simple approximations for the first and second moments of the parameters of a Bayesian random effects model.[17]

A unique model was developed by Smith, which modelled both quality bias and publication bias simultaneously. Quality in terms of study design factors like blinding and control, sample characteristics were assessed.[18] Lun et al gives a brief note on WinBUGS, which included a Bayesian modelling framework the Concepts, structure and extensibility.[3] Voils et al developed a model in

Bayesian meta-analysis, which incorporated both qualitative and quantitative evidence. Informative prior probability was generated from qualitative data and likelihood was generated from the quantitative data.[19]

Sutton and Abraham published a review paper on use of Bayesian methods in meta-analysis and evidence synthesis. The authors suggest that one can integrate the results of RCTs and observational studies by considering the estimates from the observational studies as the prior. They also suggest that the pooled estimate obtained would be more precise than that from the RCTs and observational studies.[9] Higgins et al argued that neither fixed effect nor random effects meta-analysis is appropriate when mega-trial is included.[20] They also concluded that the Bayesian approaches to meta-analysis have the advantage of naturally allowing for full uncertainty, especially for prediction.[5] Non parametric approach of Bayesian meta-analysis based on mixtures of "conditional Dirichlet processes" was introduced in 2004 where Bayesian model was developed in which the distribution of the study-specific effects was modelled using nonparametric priors.[21] Lindley et al used the application of General Bayesian Linear Model (GBLM) theorem to obtain the posterior distribution of modelled parameters.[22] Further, in 2012 Junaidi et.al calculated the posterior distribution for a Hierarchical Bayesian Meta-analysis using the GBLM theorem where they performed simulation study to estimate parameters of interest and assess parameter stability and in 2012 where they demonstrated the validity of the Gibbs sampler in terms of estimating parameters.[23] Dias et.al (2013) introduced a series of seven tutorial papers on evidence synthesis methods for decision making where topics on Bayesian framework, Bayesian meta-regression, presentation of evidence, synthesizing of the methods and results are discussed.[24-29] Copetti et.al (2014) [30] discussed how Bayesian meta-analysis can be used as generalization for sensitivity analysis and the use of priors as a data augmentation approach which was initially developed by Greenland in 2001.[31] One of the modern developments of Bayesian methods in meta-analysis is the utilization of power prior proposed by Zhang et al (2014). The motivation of this approach comes from the notion that not all studies should be treated equivalently when estimating the pooled effect in a meta-analysis. Hence, a methodology was proposed in Bayesian meta-analysis that can control the contribution of individual study through power prior. The authors have demonstrated its application in financial and management research.[32]

ADVANTAGES AND DISADVANTAGES OF BAYESIAN META-ANALYSIS

Bayesian meta-analysis incorporates all the available, relevant past evidence external to the trial in the form of prior distribution.[33-35] They allow for all uncertainties, mainly in obtaining a predictive distribution for the true effect in a new study.[36] Bayesian meta-analysis is appropriate when there are a small number of studies included or when studies having less event data or when studies report only the summary estimate and not its variance. The posterior distribution is ideal for any decision making and the probabilities are easier to understand than p values. They also permit for interpretation of the probability of effect of intervention.[37,38] Prior probabilities can be used as a tool of sensitivity analysis and check for robustness and to investigate and quantify different hypotheses.[39-42] The major disadvantage is that, when the number of parameters grows with increase in number of studies; therefore placing vague priors on all parameters can lead to inconsistent results. Different prior distributions lead to different results. Researchers need to be careful while using informative priors since they can have huge impact on the posterior. Implementation of the software requires excellent knowledge, experience, skill and care.

CONCLUSION

This review paper focuses on to what extent Bayesian techniques are used for evidence consolidation and has provided a glimpse of methodological developments, its advantages and applications to the readers. These approaches conclude how the results of meta-analysis modify the belief held before the meta-analysis been conducted. Bayesian framework to meta-analysis provides easier solution to various issues related to missing data, limited number of studies, limited event data etc. Priors play very important role in Bayesian meta-analysis and one

need to be very careful in choosing priors. Lot of methodological developments has taken place over the past two decades, which proves that Bayesian approach is more coherent, scientific and natural.

Due to the strong methodology of incorporating external evidence in Bayesian, these methods are also widely used in the area of network meta-analysis where one makes both direct and indirect comparisons based on a common comparator and this approach results in ranking of interventions. Implementation of softwares does most of the work easier however; they require a lot of computational assistance and expertise.

FUTURE WORKS

Bayesian meta-analysis has gained popularity in the field of evidence synthesis of clinical trials. However, it did not pick up momentum in summarizing public health interventions, owing to the fact that public health interventions are targeted to highly heterogeneous population, multi-component interventions, context specific and multiple outcomes. Pooling results of such studies with traditional meta-analysis itself has not been explored fully. There has been recent attempt to study the complexity of public health interventions and develop meta-analysis for public health interventions after accounting for complexity.[43] The evidence in any of the public health intervention is usually derived based on a combination of observational and interventional studies. There is no standard mechanism to pool results of observational and that of intervention studies and in such situation; most of the systematic reviews are described narratively. Hence, a robust method of evidence synthesis is required in complex public health research. Finally reporting guidelines exclusive to Bayesian meta-analysis needs to be developed.

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