Handling uncertainty in economic evaluations of patient level data: A review of the use of Bayesian methods to inform health technology assessments

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Objectives: Due to potential advantages (e.g., using all available evidence), Bayesian methods have been proposed to assist healthcare decision making. This review provides a detailed description of how Bayesian methods have been applied to economic evaluations of patient level data. The results serve both as a reference and as a means by which to examine the appropriate application of Bayesian methods to inform decision making.
Methods: MEDLINE, EMBASE, and Cochrane Economic Evaluation databases were searched to identify studies, published up to November 2007, meeting three inclusion criteria: (i) the study conducted an economic evaluation, (ii) sampling uncertainty was incorporated using Bayesian methods, (iii) the likelihood function was informed by patient level data from a single source. Data were collected on key study characteristics (e.g., prior distribution, likelihood function, presentation of uncertainty).
Results: The search identified 366 potentially relevant studies, from which 103 studies underwent full-text review. Sixteen studies met the inclusion criteria. Half of the studies used uninformative priors; most studies incorporated the potential dependence between costs and effects, and presented cost-effectiveness acceptability curves. Results were sensitive to changes in the priors and likelihoods.
Conclusions: Limited use of informative priors, among the included studies, gives policy makers little guidance on one of the main benefits of Bayesian methods, the ability to integrate all available evidence to capture the uncertainty inherent in decision making.

Keywords: Bayes theorem, Cost-benefit analysis, Uncertainty

Economic evaluation in health care can be defined as the comparison of alternative options in terms of their costs and consequences (6). The purpose being to inform the efficient allocation of scarce resources (5). Two main approaches exist, those using patient level data and those using decision analytic modeling.

When patient level data are used, economic outcomes are the result of a single sample drawn from the population (19). However, decisions are made at the population level. Consequently, uncertainty arises from using limited samples to estimate the true (population) value of costs and effects. This source of uncertainty can be referred to as sampling variation (13). Two methods have been used regularly in the applied literature to incorporate sampling variation: the non-parametric bootstrap method and Fieller's method (6). Both methods propagate uncertainty using only the information contained in the original data.

The past 25 years have seen an increase in the prevalence of Bayesian statistics (2). In particular, the Bayesian Initiative in Health Economics & Outcomes Research was established, "to explore the extent to which formal Bayesian statistical analysis can and should be incorporated into the field of health economics and outcomes research for the purpose of assisting rational health care decision making"(15).

Under a Bayesian interpretation, parameters of interest are ascribed a distribution reflecting uncertainty concerning the true value of the parameter (4). A Bayesian analysis synthesizes two sources of information about the unknown parameters of interest. One source is the prior distribution, which represents information that is available before (or, more generally, in addition to) the data (e.g., previous trials, literature, expert opinion). In the absence of prior information, vague or uninformative prior distributions can be used. The less informative the prior, the more weight is given to the data in the analysis. The other source of information is the data, which contribute to the analysis through the likelihood function (23). The likelihood summarizes all of the information about the unknown parameters that is contained in the data (22). These two sources of information are combined through the use of Bayes' theorem. Bayes' theorem updates the prior information by taking into account, by means of the likelihood, the newly observed data. The result is a posterior distribution that represents what is now known about the unknown parameters based both on the data and the prior information (23). Posterior distributions can be generated using simulation techniques such as Markov Chain Monte Carlo.

The inferential outputs from a Bayesian analysis and the ability to make direct probability statements regarding unknown quantities provide a natural way of informing policy makers. The ability to take into account all available evidence, through the combination of the prior and the likelihood, speaks to another potential advantage. By focusing on the vital question: how does this new piece of evidence change what we currently believe? Bayesian methods present a more iterative approach to evaluation because prior beliefs can be updated as new evidence becomes available (22). Another potential advantage is the use of a likelihood function to model the underlying distribution of the data (17).

In the wake of a renewed interest in Bayesian statistics, the primary objective of this review is to describe how Bayesian methods have been used to handle uncertainty due to sampling variation in patient level economic evaluations. The results serve as a reference, detailing how these methods have been used to evaluate healthcare interventions. Specifically, the review focuses on describing the priors, the likelihoods, the presentation of uncertainty, and sensitivity analyses in these studies. Concentrating on these aspects gives a sense of how Bayesian methods have been used to incorporate additional information, accurately model the data, communicate the impact of uncertainty, and assess the robustness of the results. Findings and implications from the review are discussed.

METHODS

Data Sources and Search Strategy

We conducted a comprehensive search strategy to identify all relevant published Bayesian analyses (to the second week of November 2007). We developed the search strategy in MEDLINE and modified it for other databases. Only articles in English were considered. Ovid MEDLINE In-Process & Other Nonindexed Citations and Ovid MEDLINE (1950 to Present), EMBASE (1980 to 2007 Week 45), and Cochrane Library NHS Economic Evaluation (Issue 4, 2007) databases were searched. In addition, we searched the reference sections of relevant papers for potentially eligible studies.

Search terms were derived based on mapping keywords for Bayesian analysis (e.g., Bayesian, WinBUGS) and economic evaluation (e.g., cost, economic) to indexed subject headings within the respective databases. Terms were also derived based on investigator-nominated terms and keywords from the titles and abstracts of potentially relevant studies. Relevant keywords and subject headings were then combined allowing for alternative spellings and suffixes. Operators denoting the proximity of various search terms in relation to others were also used to derive a comprehensive retrieval strategy. The search strategy is provided in Supplementary Table 1 (which can be viewed online at www.journals.cambridge.org/thc).

Study Selection

We screened citation records in two stages. In the first stage, the titles and abstracts of retrieved articles were screened for potential inclusion or exclusion. In the second stage, those records not excluded at the first stage underwent a full-text review. Included studies met the following criteria: (i) the study conducted an economic evaluation comparing two or more healthcare interventions, (ii) the impact of uncertainty

Table 1. Description of Priors for Effects and Costs

Author(s)	Type of prior(s)[a–d]	
	Effects	Costs
Methodological papers with applications		
Heitjan 1999	Uninformative	Uninformative
Al 2000	Uninformative	Uninformative
	Empirical	Empirical
	Subjective	Subjective
Briggs 2001	Uninformative	Uninformative
	Empirical	Empirical
O'Hagan 2001a	Subjective	Uninformative
	Uninformative	
O'Hagan 2001b	Uninformative	Uninformative
	Subjective	Structural
O'Hagan 2002	Uninformative	Uninformative
Hahn 2003	Uninformative	Uninformative
Heitjan 2004a	Empirical	Subjective
		Uninformative
Heitjan 2004b	Empirical	Subjective
Vazquez-Polo 2005a	Uninformative	Uninformative
Vazquez-Polo 2005b	Subjective	Subjective
Negrin 2006	Uninformative	Uninformative
Bachmann 2007	Uninformative	Uninformative
Application papers		
Fenwick 2002	Uninformative	Uninformative
UK BEAM Trial Team 2004	Uninformative	Uninformative
Shih 2007	Uninformative	Uninformative
	Empirical	Empirical

[a] Uninformative: no information.
[b] Empirical: data based.
[c] Subjective: opinion based.
[d] Structural: relationship based.
Total number of priors for effects = 22 [uninformative = 13(59%), empirical = 5(23%), subjective = 4(18%)]. Total number of priors for costs = 22 [uninformative = 14(64%), empirical = 3(14%), subjective = 4(18%), structural = 1(5%)]. Percentages rounded to nearest whole number.

(sampling variation) on the results of the economic evaluation was incorporated using Bayesian methods, and (iii) the likelihood function was informed by patient level data from a single source (e.g., trial, study).

Excluded studies involved only patient level costs or only patient level effects, incorporated any sort of decision analytic modeling, or used Bayesian methods for purposes other than the incorporation and assessment of sampling variation (e.g., evidence synthesis, value of information analysis, heterogeneity). In both stages, a single reviewer (C.E.M.) selected articles for inclusion.

Data Synthesis and Analysis

In the context of the current analysis a descriptive synthesis of the included studies was undertaken. An abstraction form was developed to collect information on key study characteristics. To get a sense of how Bayesian methods were used to combine additional information with the data, the type of prior distribution was recorded. To illustrate how the underlying data were modeled and whether these distributions allowed for issues such as the potential dependence between costs and effects or skewness in costs, information was collected on the likelihood functions. To understand how Bayesian methods were used to inform decision makers, the presentation of uncertainty was documented. Attention was also given to whether the studies explored the sensitivity of the results to changes in the priors and the likelihoods, as this could have implications for the results. The data were then synthesized to provide an overall description of the use of Bayesian methods to handle uncertainty in economic evaluations of patient level data.

RESULTS

Literature Review

The literature search yielded 366 potentially relevant bibliographic records. From the 366 citations, 103 articles were retrieved for relevance assessment. The selection of included studies is presented in the QUORUM diagram given in Figure 1. Sixteen studies met the final inclusion criteria (1;3;4;7;9–12;14;16–18;20;26–28). Thirteen of these studies were classified as methodological papers with applications (1;3;4;9–12;14;16–18;27;28) and three were classified as application papers (7;20;26). For the purpose of this review, the former classification pertains to those papers that used applications merely for illustrative or pedagogic purposes. The latter refers to those papers whose primary objective was an economic evaluation, where Bayesian methods were used to incorporate sampling uncertainty. Supplementary Table 2 (www.journals.cambridge.org/thc) describes the included studies.

Assessment of Bayesian Methods

Prior Distributions. The most common type of prior used for either costs or effects was a vague or uninformative prior. Uninformative priors for costs were used in fourteen studies (1;3;4;7;9;11;12;14;16–18;20;26;27) and for effects in thirteen studies (1;3;4;7;9;12;14;16–18;20;26;27). These priors were incorporated either exclusively (3;7;9;12;14;17;26;27) or as part of a sensitivity analysis (1;4;11;16;18;20). Informative priors (empirical, subjective, or structural) were included in half of the studies (1;4;10;11;16;18;20;28). Priors based on empirical data were used for effects in five studies (1;4;10;11;20) and for costs in three studies (1;4;20). Data sources for the empirical priors included previous trials (1), pilot studies (10;11), the literature (4), and individual Medicare claims data (20).

Priors based on subjective opinion were applied equally to costs (1;10;11;28) and effects (1;16;18;28). Subjective priors most often reflected informal reasoning (1;10;11;16;18). However, one study (28) referred to a process of eliciting expert opinion. Experts who participated in the study were asked about the mean and the probability interval to obtain
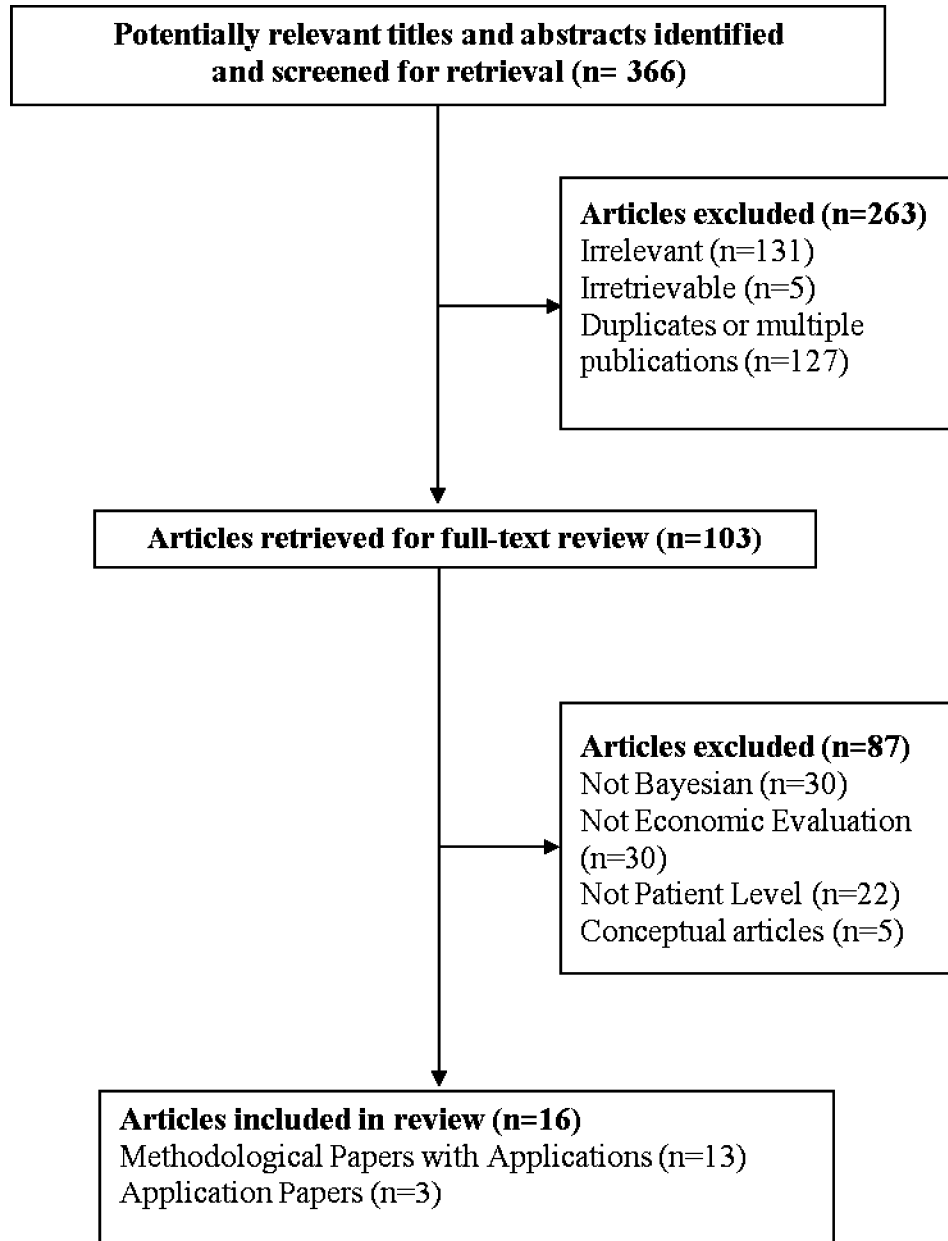
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│  Potentially relevant titles and abstracts identified │
│       and screened for retrieval (n= 366)            │
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                      │        │  Irrelevant (n=131)          │
                      │        │  Irretrievable (n=5)         │
                      │        │  Duplicates or multiple      │
                      │        │  publications (n=127)        │
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│  Articles retrieved for full-text review (n=103) │
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                      │        │  Not Bayesian (n=30)         │
                      │        │  Not Economic Evaluation     │
                      │        │  (n=30)                      │
                      │        │  Not Patient Level (n=22)    │
                      │        │  Conceptual articles (n=5)   │
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│  Articles included in review (n=16)              │
│  Methodological Papers with Applications (n=13)  │
│  Application Papers (n=3)                         │
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Figure 1. QUORUM diagram of studies considered for inclusion.

the prior mean and variance of the parameters of interest. Structural priors, denoting the relative relationship between parameters as opposed to the actual numerical values, appeared in one of the studies (16). In this case, the prior represented the belief that the variances of costs should not be too different between patient groups. The effect of this prior information was to moderate the influence of the extreme costs. Table 1 describes the prior distributions.

Likelihood Functions. Two of the applied studies (7;26) did not specify the distributional form of their likelihood functions, and one of the methodological papers

(3) analyzed the individual level data using two different approaches. Therefore, there are thirteen examples where costs and effects are modeled directly (1;3;4;9–12;14;16–18;27;28), and two examples using regression-based modeling of net benefits (3;20).

The majority of studies incorporated the potential dependence between the cost and effect data. This was achieved through the use of both multivariate normal distributions and regression analysis. Two of the studies (27;28) that applied regression analysis directly to costs and effects included covariates in their likelihood functions and assessed the resulting impact on uncertainty.

Table 2. Description of Likelihoods

Author(s)	Distributional form of likelihood[a–c]
Methodological papers with applications	
Heitjan 1999	(meanEffects, meanCosts)~Multivariate normal
	Large sample approximation
Al 2000	(meanEffects, meanCosts)~Multivariate normal
	Large sample approximation
Briggs 2001	(meanEffects, meanCosts)~Multivariate normal
	Large sample approximation
O'Hagan 2001a	(Effects, Costs)~Multivariate normal
O'Hagan 2001b	Effects~Binomial
	Costs|Effects~Lognormal
O'Hagan 2002	Effects~Weibull
	Costs~nonparametric
Hahn 2003	i. Effects~Normal
	Costs~Normal
	ii. Effects~Normal
	Cost components~Normal
	iii. Effects~Normal
	Cost components~other distributions
	iv. (Effects, Costs)~Multivariate normal
	v. (Effects, Costs components)~Multivariate normal
Heitjan 2004a	Effects~Binomial
	Costs|Effects~Gamma
Heitjan 2004b	Effects~Weibull
	Cost|Effects~Gamma
Vazquez-Polo 2005a	Effects~Normal
	Costs|Effects~Normal
Vazquez-Polo 2005b	i. (Effects, Costs)~Multivariate normal with probit model for effects
	ii. (Effects,Costs)~Multivariate normal
Negrin 2006	(Effects,logCosts)~Multivariate normal
Bachmann 2007	i. Effects|Costs~Binomial
	Costs~Gamma
	ii. Net benefit~Normal
Application papers	
Fenwick 2002	Not Specified
UK BEAM Trial Team 2004	Not Specified
Shih 2007	Net benefit~Normal

[a] (effects,costs): effects and costs determined simultaneously.
[b] cost\|effects: costs depend on effects.
[c] effects\|costs: effects depend on costs. Total number of distributions = 29 [multivariate normal = 9(31%), normal = 9(31%), binomial = 3(10%), gamma = 3(10%), weibull = 2(7%), lognormal = 1(3%), other = 1(3%), nonparametric = 1(3%)]. Percentages rounded to nearest whole number.

For three of the studies (1;4;12), the use of multivariate normal distributions was based on large sample approximations for the means of costs and effects. Where the likelihood functions allowed for a specific relationship between the cost and effect data, costs most often depended on effects: four studies (10;11;16;27) allowed costs to depend on effects, whereas only one study (3) allowed effects to depend on costs. Different distributions were used for effects based on whether the outcome measure was a continuous or discrete random variable.

Six studies (3;9;10;11;14;16) incorporated the potential skewness in the cost data. Three of these studies used gamma distributions (3;10;11) and two (14;16) used lognormal distributions. One study (9) divided total cost into three components and applied distributions (e.g., lognormal) to each of the cost components. Table 2 describes the likelihood functions.

Presentation of Uncertainty. The predominant approaches to the presentation of uncertainty were Bayesian 95 percent credibility intervals (0.95 posterior probability that the true value lies in the interval), and cost-effectiveness acceptability curves (CEAC) (posterior probability that the intervention is cost-effective given the data and willingness to pay). Almost all of the studies presented cost-effectiveness acceptability curves (1;3;4;7;9–11;16–18;20;26–28). Six studies (1;3;10;11;12;27) presented Bayesian 95 percent credibility intervals for the incremental cost-effectiveness ratio (ICER), two studies (3;10) presented credibility intervals for the incremental net monetary benefit (INMB), and

Table 3. Presentation of Uncertainty and Sensitivity Analysis

Author(s)	Presentation of uncertainty	Sensitivity analysis[a]
Methodological papers with applications		
Heitjan 1999	95% Credibility Interval ICER	No
Al 2000	95% Credibility Interval ICER	Prior
	CEAC	
Briggs 2001	CEAC	Prior
O'Hagan 2001a	CEAC	Prior
		Likelihood
O'Hagan 2001b	CEAC	Prior
O'Hagan 2002	CEAC	No
Hahn 2003	CEAC	Likelihood
Heitjan 2004a	95% Credibility Interval ICER	Prior
	95% Credibility Interval INHB	
	CEAC	
Heitjan 2004b	95% Credibility Interval ICER	No
	95% Credibility Interval INMB	
	CEAC	
Vazquez-Polo 2005a	95% Credibility Interval ICER	Likelihood
	CEAC	
Vazquez-Polo 2005b	CEAC	Likelihood
Negrin 2006	CEAPF[b]	No
Bachmann 2007	95% Credibility Interval ICER	Likelihood
	95% Credibility Interval INMB	
	CEAC	
Application papers		
Fenwick 2002	CEAC	No
UK BEAM Trial Team 2004	CEAC	No
Shih 2007	CEAC	Prior
		Likelihood

[a] Refer to paper for description of priors and likelihoods. Number of presentations of uncertainty = 24 [cost-effectiveness acceptability curves (CEAC) = 14 (58%), 95% credibility interval for incremental cost-effectiveness ratio (ICER) = 6 (25%), 95% credibility interval for incremental net monetary benefit (INMB) = 2(8%), 95% credibility interval for incremental net health benefit (INHB) = 1(4%), cost-effectiveness acceptability plane frontier (CEAPF) = 1(4%)]. Number of sensitivity analyses = 10 [Prior sensitivity = 4(40%), Likelihood sensitivity = 4(40%), Prior and Likelihood sensitivity = 2(20%)]. Percentages rounded to nearest whole number.

[b] Proposed as an alternative to the cost-effectiveness acceptability curve when considering more than one measure of effect.

one study (11) presented credibility intervals for the incremental net health benefit (INHB). Another study (14) that compared multiple treatment options and incorporated two measures of effectiveness proposed the cost-effectiveness acceptability plane frontier (CEAPF) as an alternative to the cost-effectiveness acceptability curve. Table 3 summarizes the presentation of uncertainty in each study.

Sensitivity Analysis. In addition to assessing the impact of sampling variation on the results, ten studies (1;3;4;9;11;16;18;20;27;28) considered the sensitivity of the results to changes in the prior distributions and the likelihood functions. Of those studies, four (1;4;11;16) used different priors, four (3;9;27;28) used different likelihoods, and two (18;20) changed both the priors and the likelihoods. Table 3 describes the sensitivity analyses that were conducted. The following summarizes the findings of those studies.

Priors. The study by Al and Van Hout (1) assessed the sensitivity of the results to three different prior distributions for costs and effects: an uninformative prior disregarding all information from a previous trial, an empirical prior equal to the posterior of the previous trial, and a subjective prior that uses only 50 percent of the information from the previous trial. The authors concluded that different prior distributions may lead to different decisions. For example, given a specific willingness to pay, the probability of cost-effectiveness was 0.65 for the uninformative prior, 0.80 for the subjective prior, and 0.90 for the empirical prior.

Another study (16) that assessed the impact of different priors found that varying the prior information on effects made negligible difference to conclusions, because the data quite strongly indicated an improvement in effectiveness. However, the impact of the prior information on costs was much more substantial. For smaller willingness to pay values, where cost is a real consideration, the different priors

produced quite different probabilities of cost-effectiveness. When weak prior information was used, the probability of cost-effectiveness never went below 0.70. When structural prior information was used, the probability of cost-effectiveness went from 0.45 to 0.65 for smaller willingness to pay values. The authors argued that this difference was primarily being driven by two outlying observations. The use of structural prior information, representing the belief that the variances of costs should not be too different between patient groups, effectively mitigated the impact of the outliers and resulted in a correspondingly lower cost-effectiveness acceptability curve for small willingness to pay values. In the remaining studies (4;11) the priors did not appear to be a source of sensitivity.

Likelihoods. Hahn and Whitehead (9) compared five different likelihood functions for the cost and effect data. For two of the likelihoods, only one cost was considered, namely total cost. In the other three, the total cost was broken down into three components. Four of the likelihoods used normal or multivariate normal distributions for the cost and effect data. The remaining likelihood used other distributions (e.g., lognormal) for the cost components. The cost-effectiveness acceptability curve associated with this likelihood was different from those based on the other four likelihoods. In particular, the willingness to pay value for which the probability of cost-effectiveness is 0.50 was greater than that suggested when the other likelihoods were used.

In the regression framework presented in Vazquez-Polo et al. (28), the authors assessed the sensitivity of the results to the inclusion of covariates, first using a continuous outcome and then a binary outcome. When the continuous outcome was used, the willingness to pay value at which the probability of cost-effectiveness is 0.50 was approximately 75 percent greater without covariates than when covariates were included. When the binary measure of effect was used, the control treatment dominated the new treatment. Similar results were found in the study by Vazquez-Polo et al. (27) that used only a single continuous outcome. In this study, the cost-effectiveness acceptability curve was also higher when covariates were included in the likelihood. The study by Bachmann et al. (3) compared the joint modeling of costs and effects using a binomial-gamma likelihood and a regression-based model of net benefits. Both likelihood functions produced similar results; however, the point estimate for the incremental cost-effectiveness ratio was approximately 20 percent higher for the binomial-gamma likelihood.

Priors and Likelihoods. One study (20) examined the cost-effectiveness impact of generic drug entry using two approaches to Bayesian net benefit regression analysis. One approach pooled the data from the pre- and post-entry periods and used uninformative priors to estimate the regression parameters. The second approach proceeded in two steps. In the first step, the authors assumed uninformative priors for the regression parameters and updated these with data from the pre-entry period. In the second step, the authors used the posterior distributions generated in the first step as empirical priors for the regression parameters. Information from the post-entry period formed the likelihood data and was used to update the parameter values. At a willingness to pay of $US5,000, the probabilities of cost-effectiveness for the four non-generic drugs were 96.7 percent, 77.6 percent, 96.3 percent, and 97.0 percent, respectively, in the pre-entry period in the pooled analysis. These probabilities reduced to 36.7 percent, 62.7 percent, 33.0 percent, and 60.1 percent, respectively, in the post-entry period. The probabilities became 94.1 percent, 71.9 percent, 89.1 percent, and 92.1 percent in the analysis using the pre-entry data as a prior to update the post-entry data.

In O'Hagan et al. (18), the only substantial aspect of prior information was in regard to the true mean effect. When an informative prior was used for the effect measure, the cost-effectiveness acceptability curve was uniformly higher than when a weak prior was used. On the basis of the weak prior, the uncertainty associated with the decision was much greater, although in both cases the probability of cost-effectiveness was greater than 0.50 for all willingness to pay values. To test the robustness of the conclusions to changes in the likelihood, the authors replaced the assumption of normally distributed costs with lognormal distributions. Quite substantial differences in the cost-effectiveness acceptability curve were observed, especially for small willingness to pay values. While the probability of cost-effectiveness still exceeded 0.70 for almost all willingness to pay values, it never went beyond the level of 0.90 that was reached when the informative prior was used.

The sensitivity of the results to changes in the priors and the likelihoods is discussed in terms of changes in the probability of cost-effectiveness, as represented by the cost-effectiveness acceptability curve. This measure is chosen based on the frequency of its use among the studies as well as the relevancy of the information it imparts to decision makers. However, when considering the impact of using a more informative prior distribution, estimates of the mean difference in costs and effects might be more revealing. In general, you would expect the probability of cost-effectiveness to change when using an informative prior, even if the point estimates of the mean differences in costs and effects stayed exactly the same, because the probability of cost-effectiveness is a function of both the point estimates and the uncertainties. Al and Van Hout (1) reported posterior mean differences in costs and effects of NLG 2149 and 0.098, NLG 2567 and 0.137, and NLG 2564 and 0.158 (NLG = Netherland guilders), for increasingly informative priors. The only other study to do so was O'Hagan et al. (18), which presented posterior estimates of the mean differences in costs and effects of −£574 and 1.24 (weak prior), and −£626 and 2.03 (informative prior). From the perspective of a decision maker, the issue, therefore, becomes one of whether the primary impact of the more informative prior is to reduce uncertainty, or if it

actually changes the estimated differences in costs and effects in such a way as to alter the relative cost-effectiveness.

DISCUSSION AND LIMITATIONS

The Bayesian approach allows for the ability to accurately model the data and to incorporate additional information, in the form of prior distributions. The use of priors based on previous data may be less susceptible to accusations of subjectivity than opinion based priors, but they may also fail to subscribe to the notion of a fully Bayesian analysis. Some Bayesians would argue that such an approach is not in fact Bayesian at all because no subjective beliefs are used (4). Despite the use of more informative priors among some of the included studies, the most common type of prior found in this review remains the vague or uninformative prior. This may reflect a deliberate attempt to give more weight to the data in the analysis. However, if prior information exists, the use of uninformative priors seemingly negates a fundamental feature of the Bayesian approach. The ability to incorporate genuine prior information in addition to the data in the final analysis is compromised when uninformative priors are used (23).

The rationale for choosing certain likelihoods and priors reflects the need to accurately model the data and to include all relevant prior information in the analysis. Likelihood functions, chosen based on the need to accommodate specific characteristics of the data (e.g., skewness, dependence), together with prior distributions, are intended to represent the totality of available evidence. Where the studies gave a reason for using uninformative priors (1;11;14;16;18;20;26), most stated a lack of genuine prior information. However, one study (7) commented, "vague priors ensured that the trial results had a larger influence upon the analysis than the prior beliefs." Reasons for using informative priors included the presence of preceding trial or study results, which though the populations might differ, were viewed as being informative. The study by Shih et al. (20) justified their use of prior information on the basis of preserving some of the original cost-effectiveness information in decision making.

In a Bayesian analysis of patient level data, one would assume that any estimate of the impact of sampling variation would be conditional on both the prior distribution and the likelihood function. The sensitivity of the results to changes in the priors and the likelihoods was considered in ten of the included studies (1;3;4;9;11;16;18;20;27;28). The results suggest that a failure to include sensitivity analysis could affect the estimated uncertainty and potentially lead to inappropriate inferences. Several authors (22;24;25) have recommended the use of sensitivity analysis when reporting the results of Bayesian analyses.

The results of this review are intended to provide, for the first time, a comprehensive description of the use of Bayesian methods to handle uncertainty due to sampling variation in patient level economic evaluations. The review was limited to published studies identified from three databases and relied on a single reviewer. However, the search strategy covered the largest databases and was designed in consultation with a trained research librarian. The review was limited to patient level economic evaluations using information from a single source and did not consider decision analytic models using several data sources (e.g., Fryback et al.) (8).

Despite these limitations, we believe that this review serves as a reference to those engaged in, or considering Bayesian analysis of patient level data. The decision to use Bayesian methods, rather than more traditional approaches, requires consideration of the relative advantages and disadvantages, in terms of informing healthcare policy decisions.

Potential disadvantages of Bayesian methods in healthcare evaluation include a lack of expertise, difficulty specifying and potential subjectivity of priors, as well as the additional complexity (22). Future research on the choice and elicitation of prior distributions in practical applications would seem critical to ensuring the ability of the Bayesian approach to synthesize all available evidence is fully exploited.

POLICY IMPLICATIONS

To the extent that important health policy decisions are informed by the results of economic evaluations, and that these results are subject to uncertainty, a comprehensive and robust approach is required. This would include the use of all relevant evidence to inform decision makers. The ability to combine informative priors with the data, as well as providing a natural way of handling uncertainty, suggests Bayesian methods may offer certain advantages over traditional methods.

SUPPLEMENTARY MATERIAL

Supplementary Tables 1 and 2: www.journals.cambridge.org/thc

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REFERENCES

1. Al MJ, Van Hout BA. A Bayesian approach to economic analyses of clinical trials: the case of stenting versus balloon angioplasty. *Health Econ*. 2000;9:599-609.
2. Ashby D. Bayesian statistics in medicine: A 25 year review. *Stat Med.* 2006;25:3589-3631.
3. Bachmann MO, Fairall L, Clark A, Mugford M. Methods for analyzing cost effectiveness data from cluster randomized trials. *Cost Eff Resour Alloc*. 2007;5:12.
4. Briggs AH. A Bayesian approach to stochastic cost-effectiveness analysis: An illustration and application to blood pressure control in type 2 diabetes. *Int J Technol Assess Health Care.* 2001;17:69-82.
5. Briggs AH. handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17:479-500.
6. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005.
7. Fenwick E, Wilson J, Sculpher M, Claxton K. Pre-operative optimisation employing dopexamine or adrenaline for patients undergoing major elective surgery: a cost-effectiveness analysis. *Intensive Care Med*. 2002;28:599-608.
8. Fryback DG, Chinnis JO, Ulvila JW. Bayesian cost-effectiveness analysis: An example using the GUSTO trial. *Int J Technol Assess Health Care.* 2001;17:83-97.
9. Hahn S, Whitehead A. An illustration of the modelling of cost and efficacy data from a clinical trial. *Stat Med*. 2003;22:1009-1024.
10. Heitjan DF, Kim CY, Li H. Bayesian estimation of cost-effectiveness from censored data. *Stat Med*. 2004;23:1297-1309.
11. Heitjan DF, Li H. Bayesian estimation of cost-effectiveness: An importance-sampling approach. *Health Econ*. 2004;13:191-198.
12. Heitjan DF, Moskowitz AJ, Whang W. Bayesian estimation of cost-effectiveness ratios from clinical trials. *Health Econ*. 1999;8:191-201.
13. Johnson-Masotti AP, Laud PW, Hoffmann RG, Hayat MJ, Pinkerton SD. Probabilistic cost-effectiveness analysis of HIV prevention comparing a Bayesian approach with traditional deterministic sensitivity analysis. *Eval Rev*. 2001;25:474-502.
14. Negrin MA, Vazquez-Polo FJ. Bayesian cost-effectiveness analysis with two measures of effectiveness: The cost-effectiveness acceptability plane. *Health Econ*. 2006;15:363-372.
15. O'Hagan A, Luce BR. *A primer on Bayesian statistics in health economics and outcomes research*. Bayesian Initiative in Health Economics & Outcomes Research Centre for Bayesian Statistics in Health Economics; 2003.
16. O'Hagan A, Stevens JW. A framework for cost-effectiveness analysis from clinical trial data. *Health Econ*. 2001;10:303-315.
17. O'Hagan A, Stevens JW. Bayesian methods for design and analysis of cost-effectiveness trials in the evaluation of health care technologies. *Stat Methods Med Res*. 2002;11:469-490.
18. O'Hagan A, Stevens JW, Montmartin J. Bayesian cost-effectiveness analysis from clinical trial data. *Stat Med*. 2001;20:733-753.
19. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: The ISPOR RCT-CEA Task Force Report. *Value Health*. 2005;8:521-533.
20. Shih YC, Bekele NB, Xu Y. Use of Bayesian net benefit regression model to examine the impact of generic drug entry on the cost effectiveness of selective serotonin reuptake inhibitors in elderly depressed patients. *Pharmacoeconomics*. 2007;25:843-862.
21. Skrepnek GH. The contrast and convergence of Bayesian and frequentist statistical approaches in pharmacoeconomic analysis. *Pharmacoeconomics*. 2007;25:649-664.
22. Spiegelhalter DJ, Abrams KR, Myles JP. *Bayesian approaches to clinical trials and health-care evaluation*. Chichester, West Sussex: John Wiley & Sons Ltd; 2004.
23. Stevens JW, O'Hagan A. Incorporation of genuine prior information in cost-effectiveness analysis of clinical trial data. *Int J Technol Assess Health Care*. 2002;18:782-790.
24. Sung L, Hayden J, Greenberg ML, et al. Seven items were identified for inclusion when reporting a Bayesian analysis of a clinical study. *J Clin Epidemiol*. 2005;58:261-268.
25. The BaSiS Group. *Bayesian standards in science (BaSiS)*. http://lib.stat.cmu.edu/bayesworkshop/2001/BaSis.html. 2001.
26. UK BEAM Trial Team. United Kingdom back pain exercise and manipulation (UKBEAM) randomised trial: cost effectiveness of physical treatments for back pain in primary care. *BMJ*. 2004;329:1381-1385.
27. Vazquez-Polo FJ, Hernandez MAN, Lopez-Valcarcel BG. Using covariates to reduce uncertainty in the economic evaluation of clinical trial data. *Health Econ*. 2005;14:545-557.
28. Vazquez-Polo FJ, Negrin M, Badia X, Roset M. Bayesian regression models for cost-effectiveness analysis. *Eur J Health Econ*. 2005;6:45-52.