A systematic review of the use of implicit and explicit Bayesian methods in health technology assessment

Running header: Bayesian methods in HTA

Nicola J Cooper*[1], David Spiegelhalter*[2], Sylwia Bujkiewicz[1], Pascale Dequen[1], Alex J Sutton[1]
Joint first authors

[1]Department of Health Sciences, University of Leicester, University Road, LE1 7RH, UK

[2]Laboratory Centre for Mathematical Sciences Wilberforce Road Cambridge, CB3 0WB UK

Corresponding address:
Professor Nicola Cooper
Department of Health Sciences
University of Leicester
University Road
LE1 7RH
UK
Tel: 0116 2297267
Fax: 0116 2297250
e-mail: njc21@le.ac.uk

ABSTRACT

Objectives: To examine the use of implicit and explicit Bayesian methods in health technology assessments and to identify whether this has changed over time.

Methods: A review of all health technology assessment (HTA) reports of secondary research published by the UK National Institute of Health Research (NIHR) between 1997 and 2011. Data were extracted on the use and implementation of Bayesian methods, whether defined as such by the original authors (i.e. explicit) or not (i.e. implicit).

Results: 155 out of 375 (41%) NIHR HTA reports, identified as relevant to this review, contained a Bayesian analysis. Of these 128 (83%) contained an implicit Bayesian analysis, 3 (2%) an explicit Bayesian analysis and 24 (15%) both implicit and explicit Bayesian analyses. Of the 27 reports that explicitly used Bayes theorem only 6 included prior information in the form of (informative) prior distributions. Over time, the percentage of HTA reports that used Bayesian (implicit and/or explicit) methods increased from 0% in 1997 to nearly 80% in 2011.

Conclusions: This review has shown that there has been an increase in the use of Bayesian methods in HTA, which is likely to be a result of the increase in freely available resources to implement the approach. Areas where Bayesian methods have the potential to advance healthcare evaluations in the future are considered in the discussion.

INTRODUCTION

Agencies such as the National Institute for Health and Clinical Excellence (NICE) need to both synthesise and summarise the available evidence, and assess the relative cost-effectiveness of competing clinical interventions. They also need to ensure that those conducting the necessary analyses have made use of the most appropriate, often increasingly sophisticated, quantitative methods; it turns out that many new statistical approaches are implemented under the Bayesian modelling paradigm due to the flexibility of the framework – see elsewhere[1] for a recent review.

The requirement for non-standard analytic methods arises from two main issues. First, evidence synthesis and cost-effectiveness analysis is a complex process that generally requires construction of a 'decision model'[2-4] which is a formal representation of a disease process in a heterogeneous population. The available evidence (accurately reflecting uncertainty) then needs to be used to assess how this process will be affected by different treatment options. Second, limitations in evidence due to a paucity of relevant high-quality studies means that there are inevitable gaps in the quantities necessary to populate the model, and these have to be filled with an element of judgement. It turns out that both of these issues can be addressed using Bayesian ideas. Bayesian methods were reviewed in 2000[5, 6] and a primary motivation for this current review is to establish the degree of penetration of such methods over the past decade. Before progressing to the details of our review we provide a concise description of the Bayesian paradigm and its applied use in health technology assessment (HTA).

The Legacy of Bayes

When Reverend Thomas Bayes, a non-conformist minister of Tunbridge Wells, died in 1761 he left behind a manuscript that when published posthumously (7) contained two fundamental and revolutionary ideas. He is primarily remembered for *Bayes theorem*, a formal law of probability that tells us how to learn from experience: we initially express our uncertainty as a *prior* probability distribution, which on the basis of observed evidence is revised to a *posterior* distribution using Bayes theorem (this is in contrast to the Classical approach to statistical analysis which only makes use of the observed evidence). But his other insight precedes this mathematical rule and is far more fundamental. This is the idea that probability distributions are not just applicable to predicting 'chance' phenomena such as dice and cards, but can also be placed over unknown states of the world (i.e. to represent prior opinion about proportions, event rates and other unknown quantities).

This apparently esoteric idea has immediate and important application in health technology assessment. Any assessment of the impact of an intervention requires assumptions about unknown parameters such as the average effect on a defined population, the period of effectiveness, compliance rates and so on. There is epistemic uncertainty about these parameters that can, taking a Bayesian approach, be expressed as a probability distribution. This permits 'probabilistic sensitivity analysis', in which the influence of the uncertainty about the parameters is propagated through a model to qualify any claims about the eventual cost-effectiveness of the intervention. These techniques require a Bayesian interpretation of the parameter uncertainty.

Implicit and Explicit Bayes

In the context of evaluating healthcare interventions, the Bayesian approach has been defined as "the explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation and reporting of a healthcare evaluation"(8). Within HTA both 'implicit' and 'explicit' Bayesian methods may be used(11). Implicit

Bayes refers to any analysis in which a distribution is placed on a parameter but without overtly referring to Bayesian ideas. For example, probabilistic sensitivity analysis(12) where probability distributions are placed on imprecisely-known quantities in the cost-effectiveness model, plausible values simulated from the distributions, and the resulting expected costs and effectiveness of the treatments calculated. Repeating this analysis many times (each time sampling values) allows the uncertainty about the overall cost-effectiveness to be communicated – this is known as a Monte Carlo analysis. It is then possible to use these results to perform a value of information analysis(13) to determine the expected costs of decision uncertainty predicted by the cost-effectiveness model and the maximum value that can be placed on additional research aimed at reducing this uncertainty.

Explicit Bayes refers to analyses that actually use Bayes theorem, whether the prior distributions are 'informative', in the sense of expressing substantive opinion, or 'non-informative', in the sense of trying to have as little influence as possible. (14). For example, when comparing the effectiveness of more than two treatments, or where no head-to-head trials exist, mixed treatment comparison methods (also known as network meta-analysis) may be applied(15-17); Such complex non-standard statistical methods require a flexible modelling framework and therefore are most often fitted within a Bayesian framework using 'non-informative' prior distributions(18). Explicit Bayesian methods using 'informative' prior distributions may also be applied in evidence synthesis; for example, where the overall aim is to include *all* the evidence, while allowing for different degrees of uncertainty (due to potential biases, or generalisability) associated with different studies(19).

In overview, within HTA the main advantages of Bayesian analysis, compared to the Classical approach to statistical analysis, include the more efficient use of all available data, more flexible framework to adapt to non-standard situations, and more interpretable probability results directly regarding the quantities of interest(8, 9). Barriers to the use of Bayesian methods include the use of prior distributions which may be seen as subjective (although "non-informative" prior distributions may

be defined – see above), non-trivial elicitation of prior beliefs, and computationally complex, and therefore time consuming, to implement (although this has become less of an issue with the development of freely available specialist software such as WinBUGS(10)).

Objectives

In this paper we aim to examine the use of implicit and explicit Bayesian methods in HTA and to identify whether this has changed over time. A case study will also be presented, selected from the HTA reports reviewed, to demonstrate the extent to which Bayesian methods may be used to aid the HTA process.

METHODS

All UK NIHR Health HTA Programme reports listed on their website (http://www.hta.ac.uk/) as published between 1997 and 2011 inclusively were selected for review (a subsample of these reports also informed the NICE appraisals). We decided to focus our review on these HTA reports because they provide in-depth accounts of the methods applied both within the systematic review and the economic analysis, due to no explicit word limit restrictions as imposed by many journals; thus, providing an excellent sample to explore the use of Bayesian methods in HTA. HTA reports were excluded if they were primary research (e.g. randomised controlled trials), or focused on a particular methodological issue (e.g. errors in HTA models, feasibility of value of information). The main focus of the review was to identify secondary research reports which had used Bayesian methods in their evaluation(s). Bayesian methods were classified as either implicit or explicit using the definitions specified above. In addition, data were also extracted on the software used to undertake the Bayesian analysis.

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RESULTS

Figure 1 shows a flow diagram of the identification of NIHR HTA reports for inclusion in this review. Of the 608 HTA reports published between 1997 and 2011, 375 were identified as relevant for this review. Of these, 155 (41%) contained an implicit and/or explicit Bayesian analysis; of which 128 (83%) HTA reports contained an implicit Bayesian analysis alone, 3 (2%) explicit Bayesian analysis alone and 24 (15%) both implicit and explicit Bayesian analyses. 76 out of these 155 (49%) reports identified for inclusion in our review also informed a NICE appraisal, and of these 62 (82%) contained an implicit Bayesian analysis alone and 14 (18%) contained both implicit and explicit Bayesian analyses.

Overall, of the 155 HTAs containing a Bayesian analysis, 154 (99%) developed economic decision models (i.e. 58 developed a decision tree model, 68 a Markov model, 15 a Discrete event simulation (DES) model, 6 a Decision tree and DES, and 6 a Markov model and DES), of which 152 (99%) applied probabilistic sensitivity analysis and 18 (12%) performed value of information analysis.

Twenty-seven HTAs explicitly used Bayes theorem, of which only 6 specified informative prior distributions mostly in the evidence synthesis models. 20 out of the 22 (91%) HTAs that specified 'non-informative' prior distributions (including 2 that specified both 'non-informative' and 'informative') used the Bayesian framework to undertake indirect/mixed treatment comparisons meta-analysis(15, 16). The remaining 2 performed Bayesian pairwise meta-analyses.

Figure 2 depicts how Bayesian methods have been used in the HTA reports reviewed over time. Overall, there has been an increase in the use of Bayesian (both implicit

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and explicit) methods (as indicated by the total height of each bar), although there is an unexplained drop in 2008 and 2010. The solid line shows the percentage of HTAs reviewed that also informed a NICE appraisal and the dotted line shows the percentage of these that applied Bayesian methods. After 2004 it can be observed that the number of HTAs informing NICE appraisals decreased due to the introduction of Single Technology Appraisals(20, 21) whereby pharmaceutical companies submit their own HTAs for review by NICE. However, of those HTAs that did inform NICE appraisals, a large percentage applied Bayesian methods.

In Figure 2 the bars are subdivided into the types of Bayesian analyses used over time. Overall, implicit Bayesian methods were used more often than explicit methods, and always included a probabilistic sensitivity analysis for the cost-effectiveness evaluation. It can be observed from Figure 2 that prior to 2004, less than 20% of HTAs per year applied Bayesian methods and all of these applied implicit methods in the form of probabilistic sensitivity analysis; that is none of the HTAs used any other form of Bayesian analysis. In April 2004 the first NICE guide to the methods of technology appraisal (22) was published. Although the term Bayesian analysis did not appear in the guidance, it did state that '*Probabilistic sensitivity analysis should be conducted on models to reflect the combined implications of uncertainty in parameters*' (Section 5.8.1), '*formal value of information methods are available*' (Section 5.11.2) and '*Where no head-to-head trials are available, consideration is given to indirect comparisons, subject to careful and fully described analysis and interpretation*' (Section 3.2.2.2). Figure 2 shows the likely impact this guidance had on the uptake of both implicit and explicit Bayesian methods. Focusing on the 3 components outlined in the NICE guidance, Table 1 shows a significant increase in the use of mixed treatment comparison (2005 to 2008: 11%) and value information (2005 to 2008: 8%) methods in HTAs post 2004. Updated guidance was issued by NICE in June 2008(23). Again the term Bayesian analysis did not appear in the document. Although the guidance on probabilistic sensitivity analysis and value of information remained largely the same, the guidance on the use of mixed treatment comparisons was expanded stating that "*When head-*

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to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison' (section 5.3.13). Table 1 shows an increase in the number of HTAs applying both mixed treatment comparison (2009 to 2011: 19%) and value of information (2009 to 2011: 21%) methods.

Where stated, explicit Bayesian analyses were conducted using freely available software WinBUGS (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml) and/or R (http://www.r-project.org/), whereas implicit Bayesian analyses were conducted using a variety of commercially available decision modelling and spreadsheet packages including Simul8 (http://www.simul8.com/), Data TreeAge (http://www.treeage.com/) and Microsoft Excel (http://office.microsoft.com/en-gb/excel/).

A case study, selected from the HTA reports reviewed to demonstrate the extent to which Bayesian methods may be used to aid the HTA process, is presented in the Appendix.

DISCUSSION:

This review has assessed the uptake of Bayesian methods to inform HTAs published by the NIHR HTA Programme between 1997 and 2011 inclusively. The use of both implicit and explicit Bayesian methods has increased over the time period studied. This is partly due to the publication of the method guides by NICE(22, 23) which promotes the use of relevant methods but also due to the development of freely available, more user-friendly, Bayesian specialist software packages such as WinBUGS(10) which have aided the analysis of more complex evidence synthesis structures (e.g. mixed treatment comparisons). For example, the original HTA of neuraminidase inhibitors for the treatment of influenza published in 2003(24) presented separate meta-analyses for the 2 active treatments (zanamivir and

oseltamivir) under review compared to placebo as no head-to-head trials of the 2 active treatments existed. However, the updated review, published in 2009(25), applied explicit Bayesian methods to obtain an indirect estimate of the 2 treatments compared to one another as well as placebo. Similarly, the recently published review of obesity treatments(26) collated and updated the previous 2 HTAs (evaluating the effectiveness and cost-effectiveness of Orlistat(27) and Sibutramine(28) separately) using explicit Bayesian mixed treatment comparison methods to bring the evidence together within a single analysis. The above analyses may have been possible to conduct using Frequentist statistical methods; however, the main advantages of using a Bayesian approach include the flexibility of WinBUGS to fit complex non-standard statistical models and the ability to make direct probability statements such as the probability each treatment is the "best".

Despite an observed increase in the use of Bayesian methods over time in the HTAs reviewed here, a comprehensive review of over 50 health technology assessment (HTA) and pharmacoeconomic guidelines from 38 countries revealed that only 12 HTA organisations(29) worldwide explicitly discuss the use of Bayesian methods. These include the Canadian Agency for Drugs and Technologies in Health guidelines(30), which state that Bayesian approaches are particularly "well suited" for health care assessments, identifying the most important sources of uncertainty and providing more accurate estimates. Also the Haute Autorité de la Santé (HAS) guidelines(31) that refer to the use of Bayesian methods to perform network meta-analysis to allow the complete hierarchy of evidence within a therapeutic area to be drawn upon. Health Austria(32) also presents the advantages and growing popularity of Bayesian methods in solving complex models and the Agency for Health Research and Quality in the US(33) supports "the use of Bayesian methods with vague priors in CERs [comparative effectiveness reviews]". A number of guidelines that do not explicitly use the term Bayesian, such as those published by NICE(23), Scottish Medicines Consortium (SMC)(34), and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia(35), do implicitly endorse their use by positively

advocating the use of methods such as probabilistic sensitivity analysis and mixed treatment comparisons.

The HTA process has developed as a procedure of 2 halves(36). This review has identified how explicit Bayesian methods are mostly used by statisticians to assess clinical effectiveness via evidence synthesis (e.g. mixed treatment comparisons, generalised evidence synthesis) whereas implicit Bayesian methods are mostly used by health economists/decision modellers in the economic evaluation (e.g. probabilistic sensitivity analysis, value of information). This traditional professional split is reflected in the structure of the HTA reports and can prove problematic; for example, the format of the pooled clinical outcome may not 'match' the data requirement for the economic evaluation(36, 37) (e.g. for the clinical review the most appropriate summary measure may be median survival time whereas the economic evaluation requires mean survival time), and/or the uncertainty associated with a particular outcome may not be appropriately specified when input into the decision model.

There are increasing attempts to integrate the two components of HTA, both to ensure that the results of the evidence synthesis carry through accurately and consistently into the economic model, and to allow a unified approach to sensitivity analysis(38, 39). Specifically, it is an advantage to be able to integrate probabilistic sensitivity analysis to unknown quantities, with deterministic sensitivity analysis to different assumptions about the structure of models and which data to be used. The aim being to identify and communicate to decision-makers what are the pieces of evidence and assumptions that are driving the preference for one treatment over another, so that these can be subject to particular scrutiny and possible refinement. The Transparent Interactive Decision Interrogator (TIDI), developed by Bujkiewicz et al (40) and applied in the 2011 published HTA of treatments for psoriatic arthritis(41), enables the 2 components of the HTA process (i.e. the systematic
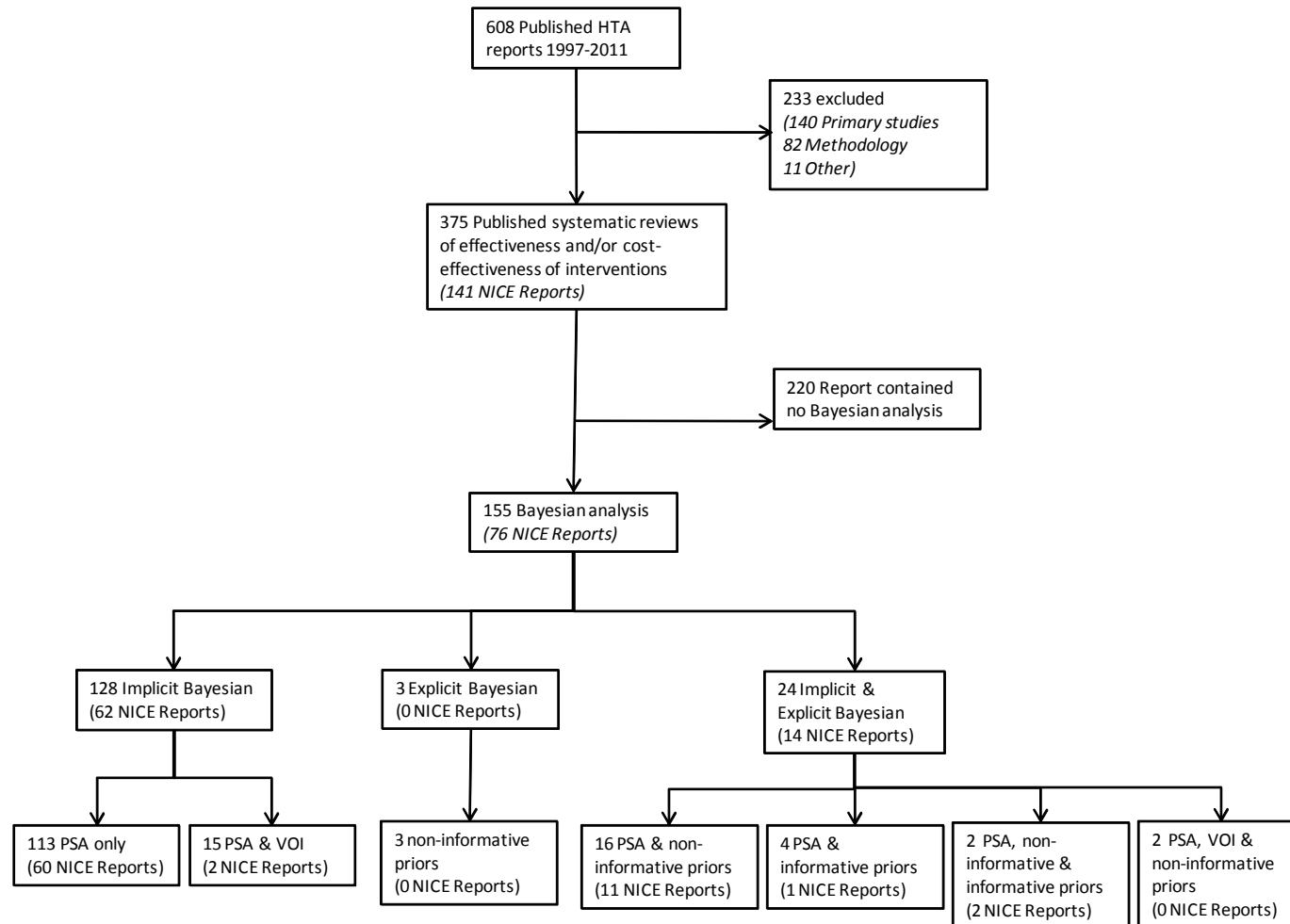
review of effectiveness and the economic evaluation) to be combined within a single coherent framework by linking different software packages (e.g. WinBUGS for evidence synthesis, Excel for decision modelling and R for graphics) together through an Excel frontend. All results from the analyses (e.g. evidence synthesis and cost-effectiveness) are clearly returned to Excel for clear presentation. The TIDI concept also facilitates more formal critique of decision models by decision makers (such as members of appraisal committees of the National Institute for Health and Clinical Excellence in the UK) by allowing advanced statistical models under different scenarios to be run in real time (including the incorporation of decision makers own beliefs about, for example, study inclusion/quality weightings, etc.), thus making the decision process more efficient and transparent. For a more detailed description of TIDI see Bujkiewicz et al (40).

Overall, we have shown that the use of Bayesian methods in HTAs has increased over time despitenot explicitly being endorsed in the guidelines published by many of the main international HTA agencies. We envisage that this increase in the uptake will be sustained into the future because, as HTA questions become more complex and demanding, and methodology evolves in response to this, the flexibility of Bayesian methods seem best suited to implement and address non-standard, often complex, approaches. For example, recent methodological developments where there is potential for Bayesian methods to make an even greater impact on healthcare evaluations in the future include i) assessing and adjusting for the relevance and rigour of evidence used in both the evidence syntheses(19); ii) addressing structural uncertainty in the economic decision model(42); iii) assessing model fit in both the evidence syntheses and economic decision model(43); and iv) incorporating beliefs of decision makers.

Acknowledgements

Figure 1: Flow diagram of identification of NIHR HTA reports for inclusion

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                    ┌──────────────────────┐
                    │ 608 Published HTA    │
                    │ reports 1997-2011    │
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                               │          ┌──────────────────────┐
                               │          │ 233 excluded         │
                               ├─────────▶│ (140 Primary studies │
                               │          │ 82 Methodology       │
                               │          │ 11 Other)            │
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          ┌────────────────────────────────┐
          │ 375 Published systematic reviews│
          │ of effectiveness and/or cost-  │
          │ effectiveness of interventions │
          │ (141 NICE Reports)             │
          └───────────────┬────────────────┘
                          │          ┌──────────────────────┐
                          │          │ 220 Report contained │
                          ├─────────▶│ no Bayesian analysis │
                          │          └──────────────────────┘
                          ▼
              ┌──────────────────────┐
              │ 155 Bayesian analysis│
              │ (76 NICE Reports)    │
              └──────────┬───────────┘
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128 Implicit Bayesian (62 NICE Reports)	3 Explicit Bayesian (0 NICE Reports)	24 Implicit & Explicit Bayesian (14 NICE Reports)

113 PSA only (60 NICE Reports)	15 PSA & VOI (2 NICE Reports)	3 non-informative priors (0 NICE Reports)	16 PSA & non-informative priors (11 NICE Reports)	4 PSA & informative priors (1 NICE Reports)	2 PSA, non-informative & informative priors (2 NICE Reports)	2 PSA, VOI & non-informative priors (0 NICE Reports)

Key: PSA=Probabilistic sensitivity analysis; VOI = Value of information

Figure 2: Stacked bar chart showing the percentage of HTA reports reviewed containing different types of Bayesian analysis.
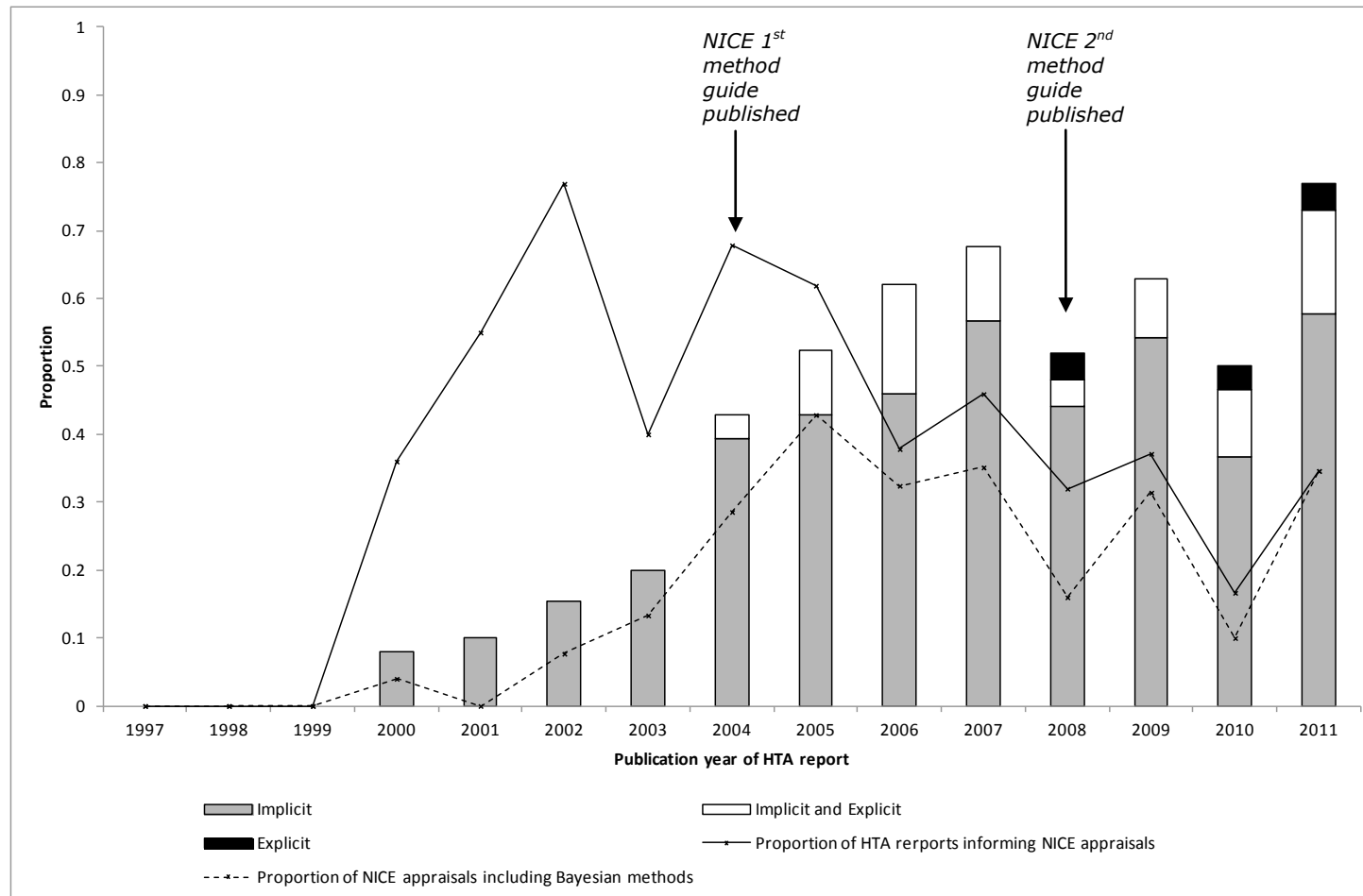
Table 1: Number of HTA reports containing Bayesian methods that used mixed treatment comparisons, probabilistic sensitivity analysis and value of information in 3 time periods

	1997-2004	**2005-2009**	**2009-2011**
Total number of HTA reports containing Bayesian methods	26	72	57
Number including Mixed Treatment Comparison	1 (4%)	8 (11%)	11 (19%)
Number including Probabilistic Sensitivity Analysis	26 (100%)	71 (99%)	55 (96%)
Number including Value of Information	0 (0%)	6 (8%)	12 (21%)

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