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**A Sensitivity Analysis Framework for Health Economic Evaluation in
Middle Income Countries: Appropriately Incorporating a
Comprehensive Approach**

“We demand rigidly defined areas of doubt and uncertainty!”

— Douglas Adams, The Hitchhiker's Guide to the Galaxy

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Abstract

When constructing a health economic decision model, it is critical to select a sensitivity analysis approach appropriate for the decision context. This point is particularly salient to Middle-Income Countries (MICs), where there is relatively heightened resource scarcity and increased opportunity-cost. MICs face acute shortages of accessible as well as high-quality evidence, resulting in a frequent imputing of data from external jurisdictions. Conversely, there are also shortages in skills and research capacity, creating a strong complementary need to consider the contextual feasibility of applying more resource demanding sensitivity analysis methodologies. Given the above, it is therefore critical to establish whether and when the technical benefits of complex and resource demanding methods result in real-world value. We apply a comparative case study using a comprehensive approach to decision-modelling, implemented in the R and JAGS languages. Specifically, the case study replicates a deterministic model originally used to inform the cost-effectiveness of adding a bivalent Human Papilloma Virus (HPV) vaccine to South Africa's public health care cervical cancer screening programme. Crucially, the case study provides critical insight into the pros and cons of implementing more complex sensitivity analysis techniques within MIC climates. Our findings indicate that the benefits of more advanced sensitivity analysis methods are nuanced; are therefore contextually beneficial according to a case-by-case basis; and, moreover, choosing a sensitivity analysis method should be guided by a conceptual 'fruitfulness' (i.e. a bang-for-buck), more than a mere desire to reduce model complexity. To aid analysts in this process, from our comparative case study we provide a framework with three core concept areas namely Decision-Maker Preferences (Decision Power, Investment, Risk Aversion), Analytical Considerations (Available resources, Indirect Evidence) and Policy Context (Knowledge of Topic, Technical Expertise). The framework intends to encourage more judicious selection of sensitivity analysis methods; help reduce the methodological variation apparent in MIC settings; and simultaneously provide decision-makers with greater methodological transparency in the selection of sensitivity analysis methods.

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1. Part A: Protocol

1.1.Rationale

1.1.1. Context and purpose

With the global shift towards Universal Health Coverage (UHC), health economic evaluations have garnered substantial recognition for their role in the establishment of health benefits packages and the sustainable provision of medical technologies¹. As middle-income countries (MICs) move toward the principles of UHC however, and thus a concomitant rise in demand for economic evaluations which inform public health care policy^{2, 3}, a critical area of methodology will be to adequately account for the uncertainty associated with a decision model's parameters^{1, 4-7}. In turn, however, MICs face a limitation in research capacity as well as funding, and, therefore, cannot be expected to allocate a significant proportion of their scarce technical skills to every decision problem they face. In light of this, it is critical to develop a framework which aids the analyst in selecting an appropriate sensitivity analysis method, given the needs of the decision space^{8, 9}. This will help to ensure the quality and complexity of an economic evaluation is preserved to be a function of the decision-problem it intends to inform^{9, 10}.

MICs face frequent limitations in accessible and quality data for many treatment effects. Collated evidence, therefore, on the relative effectiveness of treatments to be imputed in a decision-model, are regularly derived from trials and observations made outside of and then generalised to the jurisdiction of interest^{1, 10}. However, distinct population groups incur significant variation in a treatment's overall population effect⁹⁻¹¹. Moreover, the uncertainty in treatment's effects is further exacerbated by significant uncertainty surrounding system-wide health care costs associated with new technologies, as there are also regular challenges in obtaining data, which are sufficient in quality and accessibility within MIC climates¹²⁻¹⁵. This, therefore, similarly results in analysts often needing to assign a large proportion of time and effort to collecting sufficient empirical costing data for new health technologies¹⁴. Lastly, and to exacerbate these issues even further, health economic research capacity, as well as funding, is similarly stressed within many MIC settings^{16, 17}. To alleviate such issues, various methods have been proposed by the World Health Organization (WHO) and others to sustainably address the specific issue of estimating parameter uncertainty while balancing the problem of research capacity. For example, Generalised Cost-Effectiveness Analysis (G-CEA) is an often recommended approach for these contexts¹⁸. Generally, G-CEA requires the development of a league table which ranks several policy options according to their associated incremental cost-effectiveness ratio (ICER)¹⁹. The intention of this is to identify a "best buy" from a given range of treatments or intervention options, usually for a targeted geographical region or specific disease area¹⁸. Despite wide support for G-CEA to be grounded in its simplicity as well as transparency, it is explicitly intended for application within generalised contexts¹⁸. Furthermore, several methodological issues relating to the use of league tables have been admitted, including the inability to effectively communicate a decision's uncertainty¹⁹. G-CEA is thus characteristically unable to account for the specificities of a contextualised decision process – a big shortcoming considering the future needs of UHC^{15, 19}. Such evident methodological constraints have therefore resulted in limited widespread use²⁰. With particular regard to system-wide health care costs in MICs however, a tentative solution has been proposed by Adam et al. (2008), who advocate that MIC policy decisions should be solely based on studies which assess the capacity utilisation of a treatment²¹, while a method of step-down accounting has been advocated by Cunnamana et al. (2016)¹³.

These solutions, however, remain non-parsimonious, inefficient, inflexible, and data-intensive; accounting for insufficient parameter uncertainty; and, moreover, can require a large team of analysts to be conducted^{10, 16}. Given that MICs additionally incur shortages in trained researchers¹⁶, resource intensive methods are thus doubly inadequate in addressing the issues of estimating uncertainty in such data scarce climates. It is evident, then, that methods which sufficiently account for parameter uncertainty, while maintaining a relative level of parsimoniousness, persists to be a fundamental issue for economic evaluations conducted within MICs¹⁰. Identifying parsimonious and transparent methods, which fittingly deal with parameter uncertainty in MICs, has thus been identified as an important area of methodological research within health economics¹⁰. Therefore, reviewing appropriate sensitivity analysis methods within the context of MICs addresses a fundamental gap in present health economic literature. Additionally, and perhaps more importantly, developing a framework to support the application of appropriate sensitivity analysis methods for economic evaluations conducted in MICs will constructively contribute to the development of more uniform specifications and reduce the methodological disparities apparent across the MIC health economic evaluation literature^{8, 10, 12, 16, 22}.

1.1.2. Approaches and considerations

Sensitivity analysis methods can be broadly categorised as deterministic or probabilistic techniques^{1, 11}. *Deterministic sensitivity analysis* (DSA), sometimes referred to as *Scenario Analysis*, requires the analyst to manually vary a model's parameter inputs, either by one or more at a time, using their own judgement and professional experience^{7, 11}. However, the impact of parameter uncertainty on a decision-model can also be estimated by employing *Probabilistic Sensitivity Analysis* (PSA)^{1, 11, 23-26}. PSA explicitly considers parameters to be random quantities and hence it is often argued to be an inherently Bayesian exercise. PSA samples are typically obtained from an integrated probability distribution $p(\theta)$. As noted in reference [27], $p(\theta)$ can be intuitively thought of as a prior distribution, even though it may partly be based on observed data²⁷⁻²⁹. Hence, this has also been referred to as a 'likelihood-based' approach to PSA²⁹. Note that we will use the term likelihood-based to refer to this technique from hereon.

The likelihood-based approach to PSA first requires an analyst to obtain parameter estimates by means of standard statistical techniques, such as method of moments or maximum likelihood estimation^{5, 11, 23, 24, 27, 30, 31}. These estimates are subsequently used as parameter inputs to populate appropriate probability distributions, which are then sampled using *second-order*[†] Monte simulation for example (a process which, very roughly speaking, samples from a selected statistical distribution over many, many iterations at random)¹¹. Technically, for each sequence of iterations, $s = 1, \dots, S$, a value θ_s is simulated from a specified parameter distribution, $p(\theta | y)$ ^{25, 27†}. This attempts to approximate parameter uncertainty by providing an estimated range of potential values and their associated probability of being realised^{5, 32}. However, this does not account for the potential correlation between parameters and so several methods are available to estimate the potential correlation of parameters when conducting likelihood-based PSA^{33, 34}. One way to induce correlation between a set of parameters when undertaking a likelihood-based approach to obtain a PSA output is to acquire a variance-covariance matrix from a standard regression model of the parameters of interest, for example. Cholesky decomposition can then be

[†] This is distinguished from *first-order* Monte Carlo simulation, which simulates stochastic variability.

[†] Note that bootstrap sampling can also be used in place of Monte Carlo sampling for both parametric and non-parametric input parameters

applied to the variance-covariance matrix to provide a factorised covariance-matrix which, if then applied to a vector of parameters, produces a set of desired coefficients^{7, 11}. Such techniques are, however, clearly complex: several methodological and technical steps are needed, while parametric assumptions of normality have to typically be made (i.e. that the distribution is a multivariate normal)^{7, 11, 32}.

Most significant is that the likelihood-based approach contains information derived from a single probability distribution^{27, 29, 30}. Specifically, the samples obtained from likelihood-based PSA is derived from a *function* of the selected parameters given the data, which is then integrated via standard simulation techniques such as Monte Carlo sampling. Technically, samples are thus *not* sampled from a joint posterior distribution, despite the implicit assumption that they are^{25, 27, 29, 30, 35}. In contrast with the likelihood-based approach to PSA is to explicitly use Bayes' theorem. Sometimes referred to as Bayesian Posterior simulation (as well as a “comprehensive”, “fully-Bayesian”, or “decision-theoretic” approach to modelling), it necessitates the *practical* formation of a prior and likelihood function for all observed and unobserved quantities. This can be achieved by using a range of analytic and simulation methods, although sampling algorithms such as Markov Chain Monte Carlo (MCMC) are perhaps most practical^{23, 24, 27, 28, 33}. Specifically, the more explicit use of Bayes' theorem provides a more flexible approach to decision-modelling, especially in contexts with sparse data²⁸. Moreover, it enables for the decision to be naturally iterative and probabilistic, enabling for information to be continuously ‘updated’ as more information is gathered^{27, 33}.

1.2. Methodology

1.2.1. Research Questions

1. Does Bayesian Posterior simulation enable for improved parsimoniousness and application of probabilistic cost-effectiveness analysis in MIC contexts?
 - a. Does the use of Bayesian Posterior simulation provide robust sensitivity analyses outputs for the general context of MICs?
 - b. Do developments of statistical software, such as the R programming language, facilitate improved ease of use and implementation of Bayesian Posterior simulation for cost-effectiveness analysis?
2. Under what conditions should an analyst consider Bayesian Posterior simulation for health economic decision-modelling within MIC climates?

1.2.2. Objective statement

With respect to the outcomes of the above research questions, this dissertation sets out to explore and illustrate the use of a Bayesian posterior simulation approach to achieving a PSA output for health economic decision-modelling in MIC contexts. First, the associated concepts of health economic decision-modelling will be undertaken followed by a thorough review of common sensitivity analysis methods. A case study will also be included to assist in reviewing the technical application of a Bayesian posterior simulation approach to achieving PSA. Second, and in connection to the previous point, a framework for applying different sensitivity analysis methods within MIC settings will be developed, which is largely intended to aid and encourage the use of more complex sensitivity analysis methods such as Posterior simulation.

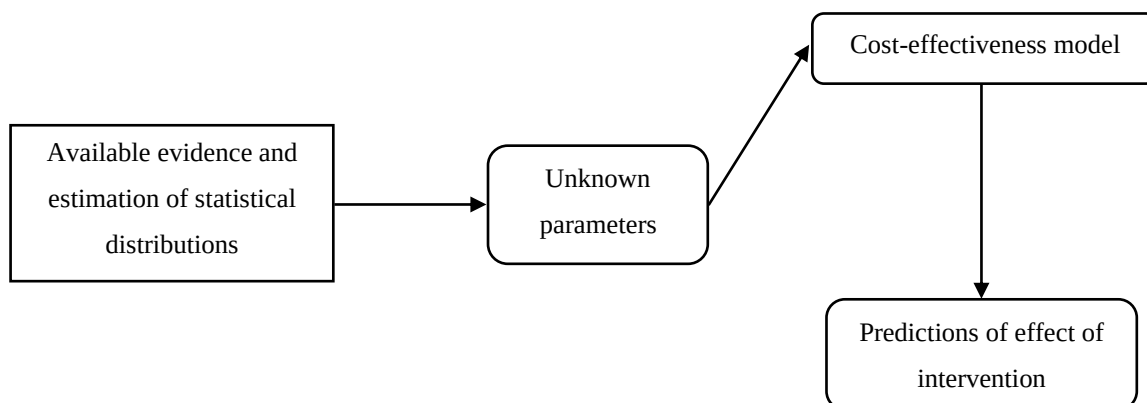


Figure 1. Likelihood-based PSA, via Monte Carlo integration (adapted from reference [37]).

The two-stage approach uses an estimate to sample from a distribution, which is in turn selected by the analyst. The spread of the subsequent samples informs the uncertainty analysis. However, as is evident from the diagram, this does not ‘update’ the distribution via the combination of a prior and likelihood to form a posterior.

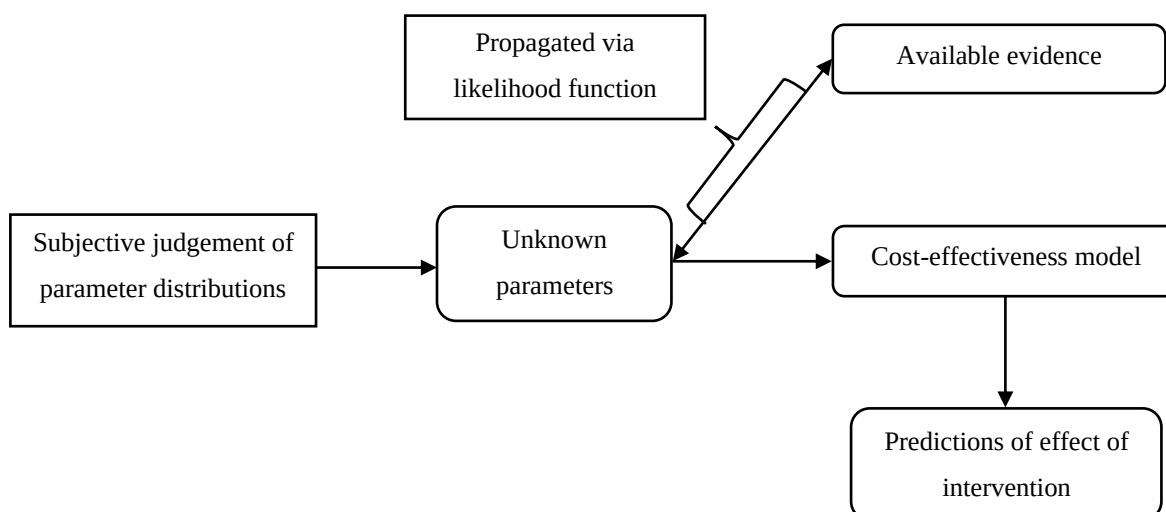


Figure 2. Fully-Bayesian, integrated via MCMC (adapted from reference [37])

In contrast, the Bayesian MCMC Simulation approach combines a prior distribution and likelihood function to form an ‘updated’ posterior distribution. This is analytically evidenced by Bayes’ theorem:

$$P(\theta | y) = \frac{P(\theta)P(y | \theta)}{\int P(\theta)}$$

1.2.1. Objective statement

With respect to the outcomes of the above research questions, this dissertation sets out to explore and illustrate the use of an MCMC simulation approach to PSA for health economic evaluations conducted in MIC contexts. First, the associated concepts of health economic decision-modelling will be undertaken followed by a thorough review of common sensitivity analysis methods. A case study will additionally be included to assist in reviewing the technical application of an MCMC simulation approach to PSA. Second, and in connection to the previous point, a framework for specific use within MICs settings will be developed. It is specifically intended to aid and encourage the use of more complex PSA methods which can account parameter uncertainty in a more comprehensive manner within MIC climates.

1.2.2. Conceptual framework

Deciding on which approach (i.e. a deterministic approach or probabilistic approach) is appropriate for the model context within an MIC rests on several core taxonomic features. We propose that the core categories essential to the choice of an appropriate sensitivity analysis method are as follows: the decision-maker's preferences, the available resources, the type of evidence used, the type of software available, and the availability of data to the analyst.

Foremost, we believe that taking into consideration the preferences of a decision-maker is critical for enabling the analyst(s) to report clearly on their incorporation of policy assumptions, given a decision-maker's policy options [5]. This is in line with the recommendations provided by general health economic literature [5, 36, 54]. Additionally, the core categories have also been conceptualised consideration with several of The Professional Society for Health Economics and Outcomes Research's (ISPOR) good modelling practice guidelines and reports [28, 38, 55-59]. Every core category then comprises several sub-features, which are founded in reflexion with the recommendations of *Section 11.8-11.10* in reference [5] by Neumann et al. (2017). Accordingly, this generally entails broadening the contextual roles of decision-makers and analysts.

In some cases, decision-makers will have limited responsibilities. This might mean that there is little to no room for reviewing past decisions or recommending additional research. Often, a simple "accept" or "reject" rule for decisions is necessary and sufficient in such contexts [5]. However, many decision-makers potentially have broader policy options, such as delaying decisions when there is significant uncertainty in the effectiveness of implementing a proposed nation-wide strategy for example [5].

In relation to the role of analysts, selecting the appropriate approach to sensitivity analysis requires a careful consideration of the constraints that might be present when undertaking a cost-effectiveness analysis. In particular, time and skill requirements compel the analyst(s) to sensibly deliberate the trade-offs that have to be made between both the practicable methodological options as well as desired modelling quality (given the overall context of the decision-problem) [5]. The constraints of the decision-problem context, therefore, inevitably lead to various analytical assumptions that might affect a model's ability to suitably reflect policy options and the associated uncertainty thereof [5]. Hence, understanding what is required but also contextually feasible is critical in developing a decision-model that is appropriate and transparent given the constraints of the decision-space [5].

All of the above compels deliberation over the opportunity-cost(s) that the decision-maker is willing to make and, in turn, the appropriate selection of a decision-model which can adequately reflect the preferences of the decision-maker given the resource constraints faced by the analyst. This, furthermore, requires a consideration of the type of evidence used and its generalisability to the decision-making space, which in turn necessitates a consideration of which type of PSA is more applicable (e.g. a DSA, likelihood-based PSA, or fully-Bayesian based PSA). This conceptual framework is briefly illustrated in Figure 4.

1.2.3. Proposed study design

The initial starting point of this study, given the above defined research questions, will be a thorough review of current health economic sensitivity analysis methods. This will include review of important concepts related to decision-uncertainty as well as a brief discussion of the differences between deterministic and probabilistic methods to sensitivity analysis, and the associated pros and cons of each broad technique. This will be followed by a deeper review of the varying approaches to PSA (i.e. the likelihood-based using Monte Carlo integration versus fully-Bayesian modelling using MCMC simulation). Thereafter, in order to illustrate the apparent parsimonious and transparent advantages associated with the MCMC approach, we will test the concept that an MCMC approach can be used to inform scarce data climates by means of an illustrative case study. Using the model structure of the MCMC simulation approach, represented in Figure 2 above, the study will be replicated in [R software](#) (R Foundation for Statistical Computing) [41], using the user interface of [RStudio](#) [60]. Furthermore, a secondary aim of replication will be to illustrate how effectively an MCMC approach can be applied to evaluation contexts where there is a considerable lack of transferable evidence. As noted previously, this is when evidence has been derived from outside of but then generalised to a specific jurisdiction [1, 10, 59].

The case study selected was conducted by Sinanovic and colleagues (2009) [61] and attempted to address the cost-effectiveness of adding a human papillomavirus (HPV) vaccine to the South African primary health system's cervical cancer prevention programme [61]. At the time, there was no HPV vaccine available within the South African public health sector. Both the *Cervarix* and *Gardasil* vaccines were considered, which target HPV16/18 and HPV 6/11/16/18 respectively. The study concluded that adding an HPV vaccine to South Africa's public cervical cancer prevention programme was a potentially "... cost-effective strategy." [61] However, there was considerable uncertainty surrounding this conclusion, which the study cited to be a result of the price of both vaccines [61].

The original study also collapsed both the *Gardasil* and *Cervarix* vaccine into a single model input efficacy parameter; this assumption was made due to both vaccines being priced at US \$120 in South Africa in 2009 [61]. However, Sinanovic et al. (2009) state that the study was primarily concerned with the prevention of cervical cancer [61]. Therefore, because HPV 16/18 are considered to be the primary viral strains which contribute to the development of cervical cancer in females [61] and *Cervarix* is the primary bivalent vaccine used for HPV 16/18 prevention, we will only incorporate data from *Cervarix* vaccine trials [61]. We assume that combining both *Gardasil* and *Cervarix* vaccine trial data will lead to inconsistencies and reduce data transparency. *Cervarix* is registered as an HPV-16/18 AS04 adjuvanted vaccine [61].

The endpoints for each of the *Cervarix* randomised controlled trials (RCTs) are, although time variable, considered to be measuring the same disease outcome. As such, we assume that the primary endpoint in each trial measures the same underlying effect, i.e. an absence or presence of HPV infection, across all collated studies. Table 1 below is a collation of

8 RCT studies, with 3 additional long-term follow-ups, all of which administered a *Cervarix* vaccine and a placebo to a trial and control arm respectively. Two studies were omitted due to concerns of bias and absent trial registration numbers. All data are only collected from the According to Protocol (ATP) cohort. All participants were female.

Table 1. Collated Cervarix vaccine Randomised Control Trials.

First author and year	Trial number	Age groups (years)	Total number in vaccine arm	Events in vaccine arm (%)	Total number in control arm	Events in control arm (%)
Apter <i>et al.</i> (2015)	NCT001226810	15-25	5406	32 (0.006)	5375	435 (0.08)
Harper <i>et al.</i> (2004)	NCT00689741	15-25	366	12 (0.03)	355	41 (0.12)
Harper <i>et al.</i> (2006)	NCT00120848	15-25	310	1 (0.003)	277	28 (0.1)
Herrero <i>et al.</i> (2011)	NCT00128661	18-25	2190	3 (0.001)	2239	38 (0.02)
Herrero <i>et al.</i> (2013)	NCT00128661	18-25	2910	61 (0.02)	2924	219 (0.08)
Konno <i>et al.</i> (2010)	NCT00316693	20-25	387	0 (0)	392	15 (0.04)
Naud <i>et al.</i> (2014)	NCT00518336	15-25	193	0 (0)	175	21 (0.12)
Paavonen <i>et al.</i> (2007)	NCT00122681	15-25	7788	2 (0.0002)	7838	21 (0.003)
Paavonen <i>et al.</i> (2009)	NCT00122681	15-25	7344	4 (0.0005)	7312	56 (0.008)
Romanowski <i>et al.</i> (2009)	NCT00120848	15-25	401	0 (0)	372	20 (0.05)
Zhu <i>et al.</i> (2014)	NCT00779766	18-25	2497	1 (0.0004)	2502	17 (0.006)
†Percentages rounded to nearest decimal point.						

Table 2 displays a dummy table of the parameters which are assumed to have contributed significant parameter uncertainty in the original study. The original case study has several different age infection rate values due to HPV having significant variation in infection rates across age groups [61]. Every parameter is associated with an appropriate probability distribution [22]. For example, a beta distribution is a suitable probability distribution for characterising proportions and is parametrised by two shape parameters, denoted α and β respectively [62]. This is in contrast to a log-Normal distribution, which is an appropriate probability distribution for parameters bounded to strictly positive values, $\theta_i \in (0, \infty)$, and heavy-right tails [37].

Estimated vaccine efficacy will be obtained through the application of an evidence synthesis. Evidence synthesis can be generally thought of as a technique to pool studies together which relate to one or more input parameters [44]. The advantage of this technique is that it enables for the pooling of studies that may be variable in time or possibly even study design [44, 63]. The technicalities of this process will be more exhaustively reviewed in the study's literature review. All other parameter distributions will be simulated using single point estimates applied to appropriate distributions and are obtained from the original study conducted by Sinanovic and colleagues (2009) [61]. Overall, the intention of the case study is to provide a comparison of sensitivity analysis techniques; an illustration of the transparency and parsimoniousness of an MCMC simulation approach; and how the choice of method can affect the outcomes of the decision-making process. After reproducing the case study, we will also review several web applications designed to provide 'point-and-click'

implementations as well as other resources intended for PSA methods. Some examples are the online web application [BCEAweb](#) and resource networks such as the [Decision Analysis in R for Technologies in Health \(DARTH\)](#) and [R-HTA](#) groups.

The case study will additionally serve as a reference to inform the development of a sensitivity analysis selection framework. A simple decision-matrix will be developed that qualitatively ranks each core criteria independently [64]. Each criterion will be associated with a prescribed ranking system ('Low', 'Medium', and 'High') [65]. The decision-matrix method is used in engineering and other fields to support the evaluation of candidate concepts and their applicability to a particular decision problem [66]. The above is thus intended to constructively contribute to more uniform specifications for economic evaluations conducted in MICs. This will arise by contributing to the development of a transparent and practical framework, which gives particular attention to contextual decision-maker preferences as well as analytical resource constraints. As a result, this will aid analyst in MICs to adopt an appropriate sensitivity analysis method given their contextual decision space and resource constraints.

1.2.1. Expected results and implications of the research

The outcome of this research will identify key criteria that guide the appropriate selection of a sensitivity analysis method for health economic evaluations conducted in MIC contexts. The expected parsimoniousness of the MCMC simulation approach will also result in the need to consider current economic evaluation capacity in MICs and the development of adequate skills to undertake such an approach to PSA, if necessary. Moreover, the development of the applied framework will contribute to the growing number of specifications for economic evaluations, enabling in particular for more transparent and conducive health economic decision-models in MICs. Lastly, we expect that this research will positively contribute to the improving the quality of health economic decision-modelling across MICs.

1.2.2. Possible difficulties and solutions

We expect that there is potential difficulty in reproducing the selected case study. The replication of the study across differing software (from TreeAge to R) is potentially problematic. Moreover, the original model was conducted in TreeAge software, which inhibits an easy replication. In order to overcome this potential barrier, we will contact the authors of the original study to better understand the structure of the model and the assumptions they incorporated into it and reasoning thereof.

1.2.3. Ethical considerations

The structure of this research presents minimal ethical risk. All data used is collated from secondary sources which do not share participant information [67]. However, there is potential benefit in how parameter uncertainty may be better handled and understood in the future, which could have positive implications for decision making and the health of society at large.

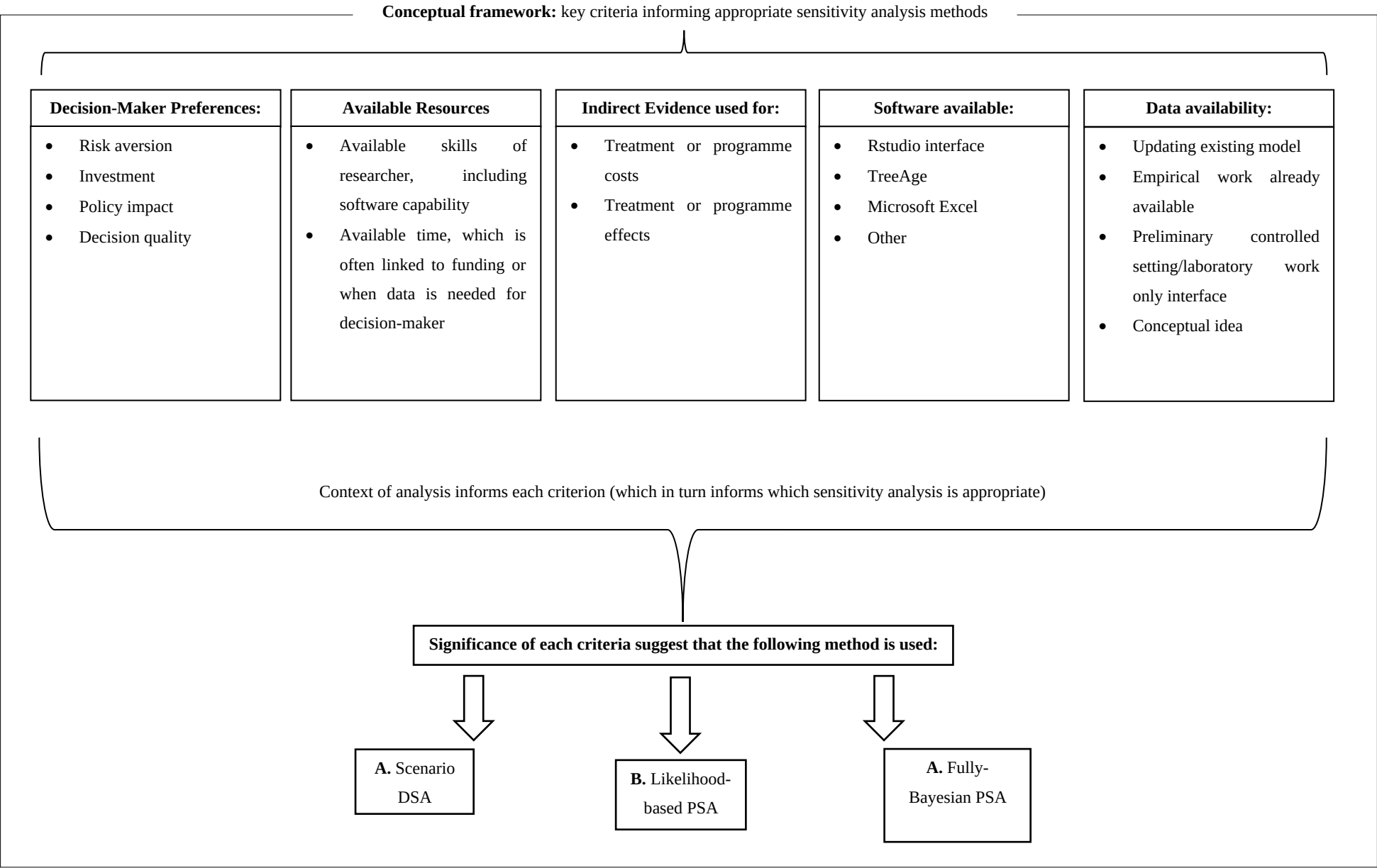


Figure 3. Structural illustration of conceptual framework

Table 2. Vaccine related variables used in model.

Variable	Description	Prior Distribution	Source
γ	Vaccine efficacy	Non-Informative Normal	[68-78]
ζ	Vaccine coverage	Informative Beta	[61]
	<i>Normal $\rightarrow$ Infection</i>		[61]
λ_a	15-16 years	Informative log-Normal	[61]
λ_a	17 years	Informative log-Normal	[61]
λ_a	18 years	Informative log-Normal	[61]
λ_a	19 years	Informative log-Normal	[61]
λ_a	20 years	Informative log-Normal	[61]
λ_a	21 years	Informative log-Normal	[61]
λ_a	22-23 years	Informative log-Normal	[61]
λ_a	24-29 years	Informative log-Normal	[61]
λ_a	30-49 years	Informative log-Normal	[61]
λ_a	≥ 50 years	Informative log-Normal	[61]
	<i>Infection $\rightarrow$ Normal</i>		[61]
δ_a	15-24 years	Informative Beta	[61]
δ_a	25-29 years	Informative Beta	[61]
δ_a	≥ 30 years	Informative Beta	[61]
δ_1	<i>Infection $\rightarrow$ LSIL</i>	Informative Beta	[61]
δ_2	<i>Infection $\rightarrow$ HSIL</i>	Informative Beta	[61]
$v_{1,1}$	<i>LSIL $\rightarrow$ Infection or Normal</i>	Informative Beta	[61]
$v_{1,2}$	<i>LSIL $\rightarrow$ HSIL</i>	Informative Beta	[61]
$v_{2,1}$	<i>HSIL $\rightarrow$ LSIL or Normal</i>	Informative Beta	[61]
$v_{2,3}$	<i>HSIL $\rightarrow$ Stage I Cancer</i>	Informative Beta	[61]
$\phi_{1,2}$	<i>Stage I Cancer $\rightarrow$ Stage II Cancer</i>	Informative Beta	[61]
$\phi_{2,3}$	<i>Stage II Cancer $\rightarrow$ Stage III Cancer</i>	Informative Beta	[61]
$\phi_{3,4}$	<i>Stage III Cancer $\rightarrow$ Stage IV Cancer</i>	Informative Beta	[61]
	<i>Probability of screening detection by stage</i>		[61]
σ_1	Stage I	Informative Beta	[61]
σ_2	Stage II	Informative Beta	[61]
σ_3	Stage III	Informative Beta	[61]
σ_4	Stage IV	Informative Beta	[61]
	<i>Probability of 1-year survival by stage</i>		[61]
$\alpha_{1,1}$	Stage I $\rightarrow$ Survived	Informative Beta	[61]
$\alpha_{1,2}$	Stage II $\rightarrow$ Survived	Informative Beta	[61]

$\alpha_{1,3}$	Stage III → Survived	Informative Beta	[61]
$\alpha_{1,4}$	Stage IV → Survived	Informative Beta	[61]
<i>Probability of 2-year survival by stage</i>			[61]
$\alpha_{2,1}$	Stage I → Survived	Informative Beta	[61]
$\alpha_{2,2}$	Stage II → Survived	Informative Beta	[61]
$\alpha_{2,3}$	Stage III → Survived	Informative Beta	[61]
$\alpha_{2,4}$	Stage IV → Survived	Informative Beta	[61]
<i>Probability of 3-year survival by stage</i>			[61]
$\alpha_{3,1}$	Stage I → Survived	Informative Beta	[61]
$\alpha_{3,2}$	Stage II → Survived	Informative Beta	[61]
$\alpha_{3,3}$	Stage III → Survived	Informative Beta	[61]
$\alpha_{3,4}$	Stage IV → Survived	Informative Beta	[61]
<i>Probability of 4-year survival by stage</i>			[61]
$\alpha_{4,1}$	Stage I → Survived	Informative Beta	[61]
$\alpha_{4,2}$	Stage II → Survived	Informative Beta	[61]
$\alpha_{4,3}$	Stage III → Survived	Informative Beta	[61]
$\alpha_{4,4}$	Stage IV → Survived	Informative Beta	[61]
<i>Probability proportion of treatment type [†]</i>			
τ_1	Hysterectomy	Informative Dirichlet	[61]
τ_2	Chemo-radiation	Informative Dirichlet	[61]

Abbreviations: *LSIL*: Low-Grade Intraepithelial lesions; *HSIL*: High-Grade Intraepithelial lesions.

[†]Following Sinanovic, et al., (2009), HPV 16 and 18 infection will be assumed to be asymptomatic and, thus, not treated.

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2. Part B: Literature Review

2.1.Objectives

The following literature review sets out to develop a broad understanding of the foundational principles underlying health economic decision-modelling. In section 1.3, the reader is introduced to the foundational philosophies of health technology assessment. Then, in section 1.4., this is followed by a discussion of the statistical foundations which underpin much of decision-modelling in general, though a more precise argument concerning the advantages of Bayesian inferences within the realm of decision making under uncertainty as well as its relation to the health economics is also provided. Then, in section 1.5., the concept of sensitivity analysis is brought forward, supported by a brief discussion of differences between the deterministic and probabilistic sensitivity analysis methods commonly used within the health economics today. Lastly, due to the technical scope of probabilistic sensitivity methods, section 1.6 provides a more technical review of the notable differences between using likelihood-based and fully-Bayesian approach to obtain a probabilistic sensitivity analysis output. Opening, however, is section 1.2, which begins by introducing the reader to the core foundations of the health economics.

2.2.Health Economics: a brief overview

Health economics is a relatively new and multifaceted discipline, characterised by several diverse areas of expertise which encompass fields such as medical research, epidemiology, and statistics [1, 63]. More generally speaking, however, health economics can be thought of as the application of economic theory to *health* (where health is defined as “... a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [79]) and *health systems* (which are “... all the activities whose primary purpose is to promote, restore or maintain health” [80]). The application of economic theory entails the following broad conventions: consideration for scarcity of societal resources; the assumption that humans are rational decision-makers; market changes are understood to be marginal (i.e. infinitesimal and thus differentiable); and that abstract quantitative and qualitative models can be used to make sense of complex socio-economic systems [81]. Despite being an ever growing necessity, it is remarkable to note the lack of association made between the topics of health and economics [20].

Health care services continually accrue substantial shares of capital investment within many countries [20]. Individuals are purchasing more and more health services; increases in life expectancy result in a continually growing demand for health and health care; and new health technologies and services frequently enter the market which entail rising costs and a potential reduction in an individual’s ability to access health care [20]. Moreover, the inflation rate of health care is evidenced to be higher than the general inflation rate of the economy, posing considerable difficulty for the sustainable maintenance of many health care programmes [20]. But how does economic theory relate to the specific *production* of health?

Most discernible, like many sectors of the economy, health care necessitates the allocation of resources to be made between diverse and competing demands whilst markets are simultaneously constrained by the reality of finite resources [20, 81]. Thus, decisions have to be made regarding where to allocate these finite resources for the production of health and health care [20]. Moreover, a holistic understanding of health production requires consideration for resource inputs beyond the health care sector, as health is also produced from goods and services obtained from outside of the health care market [81].

For example, variation in the quality of basic needs, such as food, education, and housing, can contribute significantly to differences within a population's overall health [81]. The production of health care is, therefore, in this sense, like many other goods and services that we purchase on a daily basis, and, despite its distinctive features, it is not entirely unique in how it functions [20, 81-84].

However, the production of health and health care is influenced by a range of other contextual factors too, such as governmental policies and the values we may give preference to as a society [5, 84-86]. How much resources are allocated to a country's health system; the market share between private and public services; how a health care system is generally financed (from private insurance or public taxes, for example); as well as the types of health care treatments a system provides can vary widely both within and between countries [20, 81]. Hence, the application of economic theory to health and health care provides public policymakers with a more refined understanding of when to intervene in, and possibly correct, market processes [20, 81]. Public good theory can provide an especially germane insight [20, 81, 83].

For example, though some health care services can - technically - be categorised as private and arguably luxury goods, the regulation and public provision of health care services are, more often, socially valuable [81, 87-89]. This is especially relevant when the health care markets succumb to various types of market failure. Market failure encompasses various dimensions, though it broadly implies an inadequate reflection of the true social costs and benefits and externalities generated by market activities [1, 83]. Therefore, the provision of health care to non-health care payers can substantially improve social well-being by mitigating welfare loss incurred as a direct result of private market inefficiencies [20, 85]. For instance, the poor health of a person evokes a feeling of concern from others (one of the many distinguishing features of health and health care in comparison to other goods and services) [20, 84]. Likewise, the large role of insurance - which used to hedge against the existence of the acute uncertainty associated with health and well-being - is predominantly unique to the health care market [1]. This is often cited to be a result of the significant uncertainty surrounding the time and the extent to which an individual will experience meaningful bouts of ill-health [20]. Furthermore, due to this uncertainty surrounding ill-health, the role of expertise within the health care market produces a pronounced information asymmetry between principals and agents, i.e. doctors and patients [15]. Individuals rely on health care agents to act in their best interest (such as when being prescribed medicine) [20, 81]. However, health care agents may have incentive to act in discord with the interests of their patients - for instance, by prescribing non-essential treatments with the intent to increase profits [81]. This is known as the 'principal-agent' problem and, although it occurs in various other sectors of the economy, its presence is of particular worry within health care [86, 90].

An additional point regarding public and private provision is that - while individuals who do not pay for information can be excluded - the marginal cost of providing information to another individual is usually small. There is, however, little incentive to do this within a private market [91]. Consequently, a state of imperfect information for health care consumers can occur, despite the *neoclassical* assumption that individuals have 'perfect information' whenever they purchase goods and services [20]. In these instances, government intervention can, in fact, help to stem losses incurred to a society by disseminating knowledge or regulating the role of health care agents, for example [81]. This may occur directly (through direct public provision of health services) or indirectly (by regulation and subsidisation of the private market, for example) [20, 90]. Governments can also take on more active roles in expanding scientific knowledge by funding research

endeavours which, potentially, have positive payoffs for public welfare, such as research funding for rare and chronic disease treatments [20, 81].

Consequently, a similarly important concept within the health economics field is the idea redistribution (with specific relation to *welfare* economic theory) [15, 81]. The interests of the individual might differ to the aggregated interest of a society and thus what may give utility to the individual may not necessarily benefit a collective citizenry [15, 81]. Governments often need to transfer resources from those who are able to forgo their own resources to those who are in need of resources, from high-income groups to lower-income groups (which, interestingly, emerges in *both* private and public sectors from the cross subsidization of health insurance) [1, 86]. However, this raises several problems: should we prioritise specific individuals in receiving certain health benefits, or should we allocate more resources to treating diseases which increase in incidence with age? Perhaps we should rather allocate more resources to preventative health programmes? While coupled with the reality of scarcity, such questions reflect a prioritisation of needs, into those that will be met and those that will not, and, ultimately, represent how the competing demands of different groups of a society are valued as well as measured by decision-makers [1, 3]. Thus, when collective decisions are made by public agents, it arguably demands the use of explicit principles and values to make public decisions manifestly transparent and accountable [1, 81]. Considering the issues of economic efficiency, resource allocation, and equity factors which pertain to health care systems, we are therefore presented with a common thematic problem: the need to make effective, equitable, and transparent decisions. It is, therefore, in relation to such themes that health economic evaluation has garnered a particularly valuable role in informing the practice of resource allocation within the health care market.

2.3. Foundations of Health Economic Evaluation

Effectively, equitably, and transparently informing health care resource allocation requires a systematic and careful consideration for the potential outcomes of a decision [1, 92]. To this end, economic evaluation is particularly suited for several reasons. First, economic evaluation is primarily concerned with making a comparative analysis of the available options [22]. Second, it is a systematic process of evaluating which option is most effective, specifically in terms of the comparative *costs* and *consequences* [1, 92]. Lastly, economic evaluation systematically makes explicit the principles and values that are applied to a decision [1, 5]. Thus, it is of little surprise that the practical foundations of health economics are based upon a strong focus for the methods of economic evaluation and its specific application to the realm of health care and policy [93]. Note: the philosophies underlying the development of economic evaluation in health care are diverse and interwoven, and a detailed review is beyond the scope of this dissertation. Nonetheless, a brief overview of the foundational ideas must suffice.

A common notion informing the theoretical application of health economics, which can be traced back to the *neoclassical* school of economics, is the concept of a *Pareto-improvement* [81]. The concept derives from the idea of a *Pareto criterion*, which itself centres on the economic ideas of *marginal rates of substitution*[†] and *utility* [81]. Roughly, the idea proposes that no individual who partakes in a market can be made better off without making someone else worse-off. Following this

[†]This is defined as the rate at which an individual must give up of one good in exchange for another good while maintaining the same level of utility (subjective ‘satisfaction’). Technically, this is the slope of an individual’s indifference curve, which equals the price ratio between two goods at a specific *locus*: $MRS_{xy} = MU_x/MU_y$.

logic, Vilfredo Pareto (1848-1923) argued that, if we are to respect the rights of every sovereign individual, we can only consider a social change to be an improvement when it makes someone better off without making anyone else worse off [83]. Of course, because health care in general aims to maximise health and well-being of a society at an aggregate level, a pareto-improvement seems to be a consistent arrangement. Yet, as noted in the previous section, when we decide on which treatment or service to financially reimburse in health care, the outcomes of choosing a particular course of action over another imposes unavoidable economic consequences [20].

Making specific allocations of health care resources undeniably results in opportunity-costs having to be borne, potentially both within and outside of any given health system. An investment in one treatment programme, for example, restricts the availability of resources that can be allocated to another potential, or perhaps already existing health care programme [1, 20]. Accordingly, almost no economic activity can be conducted without the occurrence of potential losers and thus, when we apply Pareto's logic to its *ad absurdum*, it theoretically implies that no collective decision can be made for a society [83]. This despite the fact that, within the context of health care, the people, amount of time, facilities, health care equipment, as well as the expertise available to a health care system are all perennially scarce; yet we still have to make decisions on how to use our resources in a way that maximises our collective well-being [1]. Such a theoretic arrangement is, therefore, ultimately precarious [81, 94].

Moreover, some individuals are able to compensate others without a comparative loss to their well-being [1]. An 'optimal' distribution of welfare is not simply an average of a society's income or health pool; individuals differ in the extent to which they need and respond to health care and, as such, an arrangement of benefits which is allocated to those who are in greater need is perhaps more socially valuable [1, 86, 89]. Challenging the initial income distribution of society is, however, unthinkable within the strict welfarist paradigm [94]. Still, the problem arises: holistically assessing the inevitable trade-offs associated with a health care allocation decision means taking into account the variation of the costs and consequences, and its subsequent effect on the expected benefits provided to a society [55]. In this sense, people would perhaps see it as reasonable for there to be losers within a market, if the benefits of an allocation decision are satisfactory, for example if there were to be large gains in a specific population's health [81]. Such scenarios (where there are potential decreases in individual welfare but increases in the collective welfare) have been termed *potential Pareto-improvements*; a situation where the potential losers of a decision are not directly compensated for their losses [81]. Simply put, this means that the gains accrued to the winners of a collective decision must exceed the losses to those who lose [81].

While there have been notable critiques concerning the potential Pareto-improvement postulate, such as the Scitovsky paradox[95][†], it is one of the *de facto* principles that contribute to the foundations of health economic evaluation [1, 81]. In fact, we can consider the application of a cost-benefit framework to be the practical realisation of a *potential Pareto-improvement* [81]. However, there are several shortcomings to the strict welfarist approach to social decision-making. For example, utility as a measure of well-being is remarkably difficult [1]. As noted by Drummond et al. (2015), the shortcomings of the Paretian welfarist approach has led to the alternative 'extra-welfarist' approach which underpins much of the theoretic application of economic evaluation in health care today [1].

[†]Broadly speaking, the paradox demonstrates that the concept of a potential Pareto-improvement can be used to argue for both a change and a reversion to the status quo, i.e. the original position. See [95] for further reading.

An extra-welfarist approach places emphasis on the measurement of health gained as the indicator of accrued benefits, rather than on individual utility [5]. Individual health gains are generally referred to as a *quality-adjusted life year* (QALY), which is the product of an *individual's life expectancy* and their *health related quality of life in those remaining years* (HRQoL) [92, 96][†]. The advantage of using a QALY is that it captures the reduction of morbidity and mortality in a single, simultaneous unit of measurement [92]. Of course, this does not firmly imply that other inputs and outputs associated with a decision-process should be excluded from an analysis; relevant consumption commodities, such as a patient's transport costs or income loss due to ill-health, should ideally be incorporated into an economic evaluation [1, 92]. Thus, the costs and benefits deemed relevant to an economic evaluation further reflect a choice between the welfarist and extra-welfarist paradigms. Specifically, a *societal* perspective (Paretian welfarist) or *provider* perspective (extra-welfarist) can be assumed [5, 97]. Accordingly, the maximand for each perspective is distinct; utility versus health possibilities [97]. This means that, if you were to assume a *provider* perspective for example, the economic evaluation would, generally speaking, only incorporate the costs incurred by the provider of the service – and not society – while *vice versa* if assuming a *societal* perspective [97].

However, and to conclude this section, a most notable and decisive distinction that can be made between these approaches is that extra-welfarism considers the preferences, values, and criteria of the decision-maker to be the most significant factors to consider in a decision process, as they are the elected body responsible for making the decisions on a society's behalf [1, 94]. Although arguably paternalistic, extra-welfarism manifestly broadens the evaluative space for health care decision-making by incorporating criteria beyond individual utility (such as non-preference based principles) [94]. Extra-welfarism does, however, assume that public agents will uphold the values which adequately represent their general society and, most importantly, ought to clearly reveal the implications of their decisions [1, 85]. It is in this light, therefore, that, over the past several decades, accountable and transparent economic evaluation guidelines have been gradually developed [93].

2.3.1. Reporting guidelines and related concepts

Nomenclature for health economic evaluation guidelines has ubiquitously been dubbed a 'reference case' [5]. The incorporation of a reference case is regarded an essential part of any health economic evaluation report [1], which is intended to guide and standardise the methods and reporting of economic evaluations within particular jurisdictions [28]. Though this has undoubtedly aided in the reduction of *ad hoc* methodological variation [1, 5], it is important to note that a reference case is generally thought of as a set of principles rather than a strict guideline [28]. Still, as already alluded to, a strong rationale for centring resource allocation decisions on clear principles, which incorporate both methodological and social value concerns, is to increase the transparency and thus accountability of public decision-makers [8, 81].

Throughout the late 1970s and 1980s, health economic evaluation research had already begun to be steadily published within medical literature [5, 98]. However, these initial inroads into the field of health economic evaluation was

[†]Simply, an individual's remaining life years are weighted by their quality. The quality weighting can be thought as a utility measure in and of itself, as the weights associated with each year of life are derived from individual's preference weights. These weights are typically gathered by means of patient surveys, using measurement tools such as the EQ-5D or SF-6D. Moreover, it is relevant to note that the concept of a QALY is firmly grounded in decision theory.

characterised by substantial methodological variation [5, 93]. By the late 1980s, and facing perpetually increasing health care costs, numerous health care systems began to seek the development of more firm and, therefore, standardised decision-making guidelines [93].

In 1987 an amendment to Australian law stipulated the requirement of costs and benefits to be evaluated in all pharmaceutical financing considerations [5]. In the same year, the Council for Technology Assessment in Health Care was established in Sweden, and was mandated to critically review “... the scientific basis of methods used in healthcare and to evaluate their benefits, risks, and costs.” [5] Several years later, in 1993, the earlier amendment to Australian law had prompted the formation of the first country-specific pharmaeconomic guidelines. The reference case was specifically constructed to inform Australia’s then newly founded Pharmaceutical Benefits Advisory Committee (PBAC), which was missioned to evaluate the cost-effectiveness of all pharmaceutical products being placed on the publicly funded Pharmaceutical Benefits Scheme (PBS) [5]. In 1994, the Canadian health system also developed a cost-effectiveness guideline for pharmaceutical reimbursement, establishing the Canadian Coordinating Office for Health Technology Assessment (COOHTA) [5, 93]. Over the same period, a key reference case development occurred in Oregon, United States of America, between 1993-1996: the Original Health Service Panel on Cost-Effectiveness in Health and Medicine released recommendations regarding the establishment and use of a reference case, with the specific aim of assisting the standardisation of health economic evaluation methods [5, 99]. In fact, the explicit notion of a ‘reference case’ was first proposed by the Original Health Service Panel, who defined it as “... a standard set of methods to serve as a point of comparison across studies.” [1, 5].

A few years later, in 1998, the establishment of the World Health Organization’s CHOosing Interventions that are Cost-Effective (WHO CHOICE) project marked a similarly significant point, as it was the first attempt to provide integrated information and strategic assistance on the health care decision-making processes across 14 sub-regional geographic and demographic areas [5, 26, 100]. The establishment of the National Institute for Clinical Excellence (NICE) followed shortly in 1999, which was tasked with developing evidence-based evaluation guidelines for health care in both England and Wales [5, 93, 101]. By the early 2000s, the Netherlands, Portugal, Norway, and Spain had guidelines for the health economic evaluation of pharmaceuticals [102].

Despite the dominance of reference case development being across institutions within Western Europe and North America, recent progress has been made in other areas such as in South Korea (2006) [5] and Thailand (2008) [103]. Additionally, a general and consolidated reporting standards checklist was published in 2014 by a Professional Society for Health Economics and Outcomes Research (ISPOR) Task Force, aptly titled the Consolidated Health Economic Evaluation Reporting Standards (CHEERS). The report lists and discusses the steps considered essential to producing a comparative and transparent economic evaluation [55]. Furthermore, 2014 saw the commission of the Methods in Economic Evaluation Project (MEEP), by the Bill and Melinda Gates Foundation (BMGF), which culminated in the International Decision Support Initiative (iDSI) Reference Case for Economic Evaluation report in 2015 [104]. Specifically, The iDSI reference case outlined eleven key principles to support the application of health economic evaluation in Low- and Middle-Income Countries (LMICs) [28]. Thus, since the initial progress in the late 1980s, reference cases have become clearly diverse. However, several key principles can still be considered fundamental to the majority of these guidelines.

Essentially, the principles of a reference case frequently entail a consideration for 1) the perspective of the analysis and 2) the preferred health outcome measure [5]. It is generally considered best practice for the estimates of both benefits and harms of an intervention to be clearly reflected through a *societal* perspective, while the use of QALYs, as a measurement for health outcomes, is most often desirable [1]. However, the difficulty in exhaustively reflecting costs and benefits from a *societal* perspective is generally acknowledged and, thus, assuming a *provider* perspective is often accepted for the purpose of practicality [1, 5, 97].

The issue of discounting is another salient topic which is usually incorporated. This is because the rate at which costs and benefits are discounted theoretically signals a *time preference* (which is the idea that individuals and society prefer having resources in the present rather than future) [22, 81]. Basically, a payment received sooner is more valuable than a payment received later, assuming it can be profitably invested elsewhere [22, 81]. Discounting simply puts future values on a more equal footing with present values [1, 5, 20]. Technically, costs or benefits of an intervention t are typically reported in terms of its *Present Value (PV)* [20]. For example, if c_{tj} is the cost associated with intervention t at time j , and J is the length of an evaluation's time horizon, the cost of intervention t at point j can be computed as [20, 63]

$$PV_t^{(c)} = \sum_{j=0}^J \frac{c_{tj}}{(1+d)^j}$$

Equally, the type of evidence used for an evaluation is frequently determined as needing of careful deliberation, particularly with regard to the transferability of efficacy and cost evidence across jurisdictions [1, 59, 99, 105]. Several other procedural areas are also routinely advised as necessary to report. For instance, deciding on whether to account for a population's heterogeneity and how to measure health outcomes both reflect value preferences of the decision-maker. Values such as these need to be clear and within reason in order to be accountable to the public [1, 3]. In turn, how an analyst accounts for and reports uncertainty of a decision-model is a topic associated with the majority of reference case guidelines [1]. Note that (for the sake of avoiding repetitiveness) the importance and application of sensitivity analysis techniques in health economic evaluation will be comprehensively discussed at a later stage.

Notwithstanding firm establishment of multiple reference cases, it should be noted that the nature of a decision-model's consequences can, nevertheless, vary considerably [1]. As suggested, the potential benefits of an intervention can be measured and reported on either a health-gain scale – with its own variations – or a monetary scale [1, 5]. This distinction once again reflects a choice of theoretical framework, i.e. it signals a preference for either a Paretian or extra-welfarist approach [94, 97]. Besides, in order for health economic evaluation to be relevant, it should adhere to the policy context to adequately address the decision-problem it intends to inform [5]. Thus, despite firm principles, the technical structure of a health economic evaluation can take on several forms [1].

2.3.2. Types of economic evaluation

There are three key distinctive forms of applied economic evaluations which are generally considered relevant to the evaluation of new health care programmes. A health economic evaluation can therefore take on the form of either a cost-effectiveness analysis (CEA), a cost-utility analysis (CUA), or a cost-benefit analysis (CBA)[†].

Roughly speaking, CEAs use the costs and health outcomes of an intervention to calculate an incremental cost-effectiveness ratio (ICER), which is used to make multiple pairwise comparisons between treatments being considered [1][‡]. Thus, an ICER can be thought of as a relative cost-effectiveness ratio between a set of alternative options [5]. There is a critical distinction compared to other techniques. In CEAs, health outcomes are generally measured as intermediate health outcomes and, as a result, naturally vary [1]. Intermediate health outcomes can take the form of measuring, for example, cholesterol levels or blood pressure; to the absence or averting of disease; or, perhaps, even mental illness [1, 5]. CEAs are therefore often applied in contexts where the decision-maker is considering specific treatments within a given domain of health care [1, 5]. A manager who is responsible for choosing a new treatment regimen in a hypertension programme is an obvious example [1]. This, however, presents a major limitation: the use of intermediate outcome measure which restricts the ability to properly assess the opportunity cost incurred across other programmes governed by the same budget but different diseases areas[1]. Conversely, assessing the opportunity costs borne from introducing a new health programme, and thus the potential for displacing already existing programmes, requires the use of a more generic measure of health outcomes[1]. It is perhaps precisely because of this distinction that CEAs present a relatively small proportion of the applied health economic evaluation literature[1, 5].

In comparison, CUAs strictly use a generic measure for individual health outcomes [5]. Within the context of health care, these are usually *disability-adjusted life years* (DALYs)* or QALYs[106]. CUA is, therefore, by design, consistent in the way it reports the consequences of the alternatives under consideration [1, 106]. More technically however, the denominator of the ICER is calculated using incremental changes in QALYs (or DALYs), rather than using a relevant intermediate health outcome measure [106]. This means that the output of a CUA is in terms of cost per *healthy life year gained* (or, more specifically, the cost per QALY gained) [1]. Importantly, this enables for cross-comparisons of cost-effectiveness between different disease areas [1]. The ease of comparativeness of a CUA has made it a more widely published form of health economic evaluation within the contemporary medical literature [1]. Nevertheless, both CEA and CUA still demand an explicit cost-effectiveness threshold to be adopted [5]. This is what makes both techniques closely related; they centre on the idea of a constrained maximisation [1].

[†]For sake of brevity and relevance, we only review full economic evaluation techniques. As already noted, such techniques explicitly consider the relative costs and consequences of the alternative actions being considered. The detailing of simple *cost analysis* techniques is hence omitted. See [1] for further reading.

[‡]Which is calculated as $ICER = \frac{C_1 - C_2}{E_1 - E_2}$, where C_1 , C_2 and E_1 , E_2 are the costs and effects of two comparative interventions.

*DALYs are assumed to measure the gap between a population's health and a hypothetical ideal of health achievement. It is the product of a prescribed weighting for a disease or condition, for example depression, and the maximal reported life expectancy (of a given country or region) for that disease or condition.

However, it may be worthwhile to expand a budget, to incorporate a novel treatment programme (though this necessitate a direct translation of a programme's benefits into monetary units) [1]. To facilitate this particular decision-making process in health economic evaluation, the use of a CBA typically favoured [1, 5]. A CBA can be considered the practical realisation of the *potential Pareto-improvement* framework. The primary distinction of a CBA is, therefore, that all incremental consequences of a programme are valued in direct monetary units (for example, US dollars or other applicable currencies) [5]. Preferences are expressed in terms of a programme's associated market prices, rather than the preferences or utilities of the gainers and losers of the intervention [5]. Thus, the consequences of a CBA are ordinarily reported as a ratio of costs to benefits or a simple net benefit (which is the difference in benefits between two interventions) [1]. A positive net benefit means the intervention is considered to be favourable for social investment, and *vice versa* for a negative result [5]. The generality of CBA also makes it common choice in other fields - such as in transport and environmental analysis [1]. A general example is the economic evaluation on a tax of older cars, which entails consideration for cost and benefit factors such as the extra government revenue directly associated with the tax; a monetary valuation of the air quality and environmental improvements; the savings associated with reduced hospital admissions related to illnesses associated with air pollution; and, finally, the impact on the economy due to newer cars being purchased to replace aging cars [63].

Although the above techniques do provide a diverse toolbox for applied health economic evaluation, there exists a vital topic we have yet to consider; a topic which persists across all applied health economic evaluation methods. It is the omnipresent problem of uncertainty, a problem of imperfect knowledge and randomness. Most significant is that the uncertainty of a decision has a pivotal and unavoidable effect on the outcome of an economic evaluation, no matter the technique employed, or, equally, the value judgements preferred by the decision-maker. It is here that we find it necessary to digress. Before exploring the topic of incorporating decision uncertainty into health economic decision models by means of a sensitivity analysis it is first, however, critical to explore the topic of statistical inference. This provides the reader with a strong grounding for the key discussion found in section 2.5, which concerns a comprehensive review of popular sensitivity analysis methods used within health economics.

2.4. Statistical Inference

"Facts are stubborn things, but statistics are pliable."

- Mark Twain

Statistical inference comprises the Frequentist and Bayesian schools of thought respectively. There is considerable debate regarding the specific philosophical groundings of both methods, though it is beyond the range of this paper to comment. Though both share many aspects in common (such as assuming the convergence of random variables via the 'Law of Large Numbers' and parametric behaviours such as the Central Limit theorem) differences in interpretation of probability means that how uncertainty of a parameter is interpreted is notably distinct [37, 107, 108]. See references [37, 107, 108] for further reading. Regardless, the axioms of probability[‡] apply equally to both approaches and it is imperative to realise that majority

[‡]The axioms of probability provide formal measurement rules and other proofs for what constitutes a valid 'probability measure'. We refer the reader to the supplementary appendix for a deeper exploration.

of statistical analyses, regardless of applied method, are usually performed to help make conclusions and ultimately, therefore, some form of decision [62, 109].

Notably, in contrast to a Frequentist approach, Bayesian inference has regularly met suspicion due to the incorporation of *prior* information – which is argued to be a ‘*subjective*’ and thus unempirical supposition [37, 62]. Though the validity of this assertion is tenable, the ideal of impartial objectivity is perhaps equally illusive to both schools of thought [110-115]. Discussion on these points is exhaustive and multidimensional and concern a myriad philosophical and methodological issues. We refer the reader to references [37, 62, 107-120]. To this end, we do find it necessary to state that we do not view the Frequentist and Bayesian approaches as competitive, but complementary and better suited to differing statistical concerns.

2.4.1. Frequentist Inference

The Frequentist school of thought has had a longstanding history, although it was only popularised to a point of dominance by the late statistician R.A. Fisher around the 1920s (1890-1962) [37, 111, 121]. Alongside formally establishing the *likelihood* as a measure of fit, Fisher proposed the use of *p*-values as an informal summary of the evidence against the null hypothesis (where a *p*-value is the chance of getting a result equal to or more extreme as the observed result assuming no effect or difference, i.e. focusing on the unlikely ‘tail’ properties of a distribution) [37, 122, 123]. However, Frequentist techniques were vastly expanded upon by J. Neyman (1894-1981) and K. Pearson (1857-1936) sometime later in the 1930s, who introduced confidence intervals and other popular methods still used today[†] [37, 121, 122].

In essence, the Frequentist school of thought interprets probability as a *physical* property of the ‘thing’ being measured [110, 124]. From this point-of-view, therefore, probability is assumed to be a long-run frequency over a large number of ‘observable’ repetitions relating to a set of equivalent ‘experiments’ [49, 63], which implies that data are sampled from a fixed and well-defined population [45, 125]. More generally however, statistical inference about parameter θ has largely centred on the *likelihood* function, a goodness-of-fit measure for the observed data given an assumed statistical model [37, 44]. In notational form, this is often expressed as $p(y | \theta)$ or simply $L(\theta)$ [37, 45].

The intention of the likelihood is to provide a measure of support for the observed data at differing values for a model’s parameter value θ . In turn, the model θ is a distributional parametric assumption about how some observed data are potentially generated and hence, the value with the highest likelihood is known as a maximum likelihood estimate [37, 125]. Frequentist inference is, therefore, arguably concerned with quantifying the confidence in an applied ‘method’ rather than quantifying the *confidence* of a ‘decision’ problem [111, 117]. Accordingly, and notwithstanding the approach has played a pivotal role in many fields (such as the drug regulatory framework), the perspective has faced strong criticism in its applicability to areas of decision-making with limited information and infrequent events [17, 18, 37, 44, 110-112, 117-122, 124-128]. In health economics for instance, consider how one should interpret the evaluation of a ‘unique’ health technology? One can, hypothetically, repetitively and empirically interrogate the cost and effect outcomes of technology (*ad infinitum*), though this is certainly prohibitive (due to obvious time and money constraints) [17, 119]. Moreover, how

[†]Notable is that though the techniques are often taught in a combined manner today, those developed by Neyman and Pearson were a result of strong technical disagreement with Fisher and were explicitly intended as an alternative. See references [37], [111], and [121].

might we incorporate the measurement of a Paretian- or extra-welfarist-utility within a Frequentist framework (concepts that inherently or at least partly incorporate a measure of ‘personal’ belief?) [22, 37, 106]

When making decisions about things which occur with minimal repetition it is clearly reasonable to conclude that a physical interpretation of probability is often inappropriate nor even fit for purpose [111, 124, 126, 129]. This becomes self-evident when we acknowledge that the outcomes of an uncertain event are, by very definition, wholly or at least partly unobservable and therefore unmeasurable [37, 125]. In order to make systematic decisions under uncertainty we must thus often unavoidably incorporate elements which go beyond a strict concept of long-run frequencies [17, 18]. It is in such particular spaces of decision-making that the advantages of the Bayesian school of thought comes to a clear fruition.

2.4.2. Bayesian Inference

Bayesian inference is largely attributed to T. Bayes (1702-1761), a British theologian and hobbyist mathematician [130, 131]. Bayes solved the problem of “reverse” probabilities, a problem which had been earlier raised by the French mathematician A. De Moivre (1667-1754) [132]. The method was, however, later but independently generalised by P.S. Laplace (1749-1827)[†] [131, 132]. Nevertheless, in order to conceptualise this perspective proper, we must first derive Bayes’ theorem. The initial step is to realise that there are two ways of expressing the conditional probabilities between any two events, for instance A and B [132], so that

$$P(A | B) = P(A \cap B) / P(B) \text{ and } P(B | A) = P(B \cap A) / P(A)$$

From this we can express *joint* probability $P(A \cap B)$ between both events, which is, in this case,

$$P(A | B)P(B) = P(A \cap B) = P(A)P(B | A)$$

then, finally, if we solve for $P(A | B)$ we derive Bayes’ theorem:

$$P(A | B) = \frac{P(A)P(B | A)}{P(B)}$$

It seems that Bayes’ theorem permits the decomposition of complex probability problems into parts, as it can break *joint* probabilities into *marginal* and or *conditional* probabilities relatively effortlessly [49, 62]. But to be more precise, Bayesian inference combines prior knowledge with the likelihood of observed data [37, 62]. In contrast, therefore, a Bayesian approach views data to be *fixed* and model parameters to be unobserved and thus inherently uncertain phenomena [45, 125].

However, the above still fails to communicate the distinct technical nature of Bayes’ theorem and thus its supposed ease-of-application to more complex probability problems. First to note, therefore, is that a *prior* enables assignment of subjective probabilities to reasonable hypotheses or, more generally, a parameter - such as a value of 0.6 to the outcome θ

[†]This is, of course, a very superficial reading.

[111, 117]. However, the subjective uncertainty of θ can be sequentially ‘updated’ by gathering more empirical information, gradually making our estimation about θ more exact, while simultaneously providing information on the goodness-of-fit for the assumed statistical model via a likelihood measure [37, 62, 133]. In notational form, this ‘updating’ of uncertainty is generally expressed as $P(\theta | y)$ and is referred to as the *posterior* probability distribution of the parameter θ [49, 62, 132]. Thus, an unnormalized posterior distribution is proportional to the prior distribution multiplied by the likelihood [62], expressed in notational form as

$$P(\theta | y) \propto P(\theta)P(y | \theta)$$

Here, $P(\theta)$ is the prior and the function $P(y | \theta)$ is the *likelihood* of the data (although, within Bayesian lexicon, it is occasionally referred to as the *sampling distribution**) [49, 62, 132]. Similarly critical is the property of implicit summation or integration via the denominator, according to the ‘Law of Total Probability’ (LOTP), but this depends on whether the parameters of interest are discrete or continuous, respectively [49, 62]. In turn, LOTP makes conditional and unconditional probabilities relatable [49, 62]. For example, returning to the notation of the earlier example, this implies that the marginal probability of the event B can be solved, in this case, by

$$P(B) = \sum (P(A_i \cap B_i) + P(\bar{A}_i \cap B_i))$$

Likewise, LOTP normalises the posterior distribution into a standard probability distribution - which is precisely what enables for the inference of θ using direct probability statements [49, 62]. Perhaps most meaningful to this discussion however, is that it enables us to structurally incorporate any scepticism or ‘background’ information about a decision-problem via the prior value [37]. For instance, say that you are propositioned to place a bet on two coins - one fair and the other unfair. The win condition is to choose the fair coin. You are told, with certainty, that the unfair coin is biased towards Tails (T) by 0.6 and that you are allowed to choose one of the coins to flip a maximum of 5 times in order to provide you with some observed yet *limited* information [49]. Say the flip sequence is $\{H, T, H, H, T\}$, where Heads = H, what is the probability that the coin you flipped is the unfair one?

Let A represent the hypothetical event that you picked the unfair coin, and $(B | A)$ be the sequence of flips assuming the chosen coin was unfair. It is important to be aware that you are completely ignorant as to which coin is *truly* the unfair one, and thus it is reasonable to assign a prior probability to event A as $P(A) = 0.5$, based on a position of ignorance. However, you do know that the unfair coin is biased towards T by 0.6. Hence, the *likelihood* of obtaining the observed sequence (data) *assuming* that you did indeed use the biased coin is provided on the proceeding page:

$$\therefore P(B | A) = \left\{ \frac{2}{5} \times \frac{3}{5} \times \frac{2}{5} \times \frac{2}{5} \times \frac{3}{5} \right\} = \frac{72}{3125} \approx 0.023$$

To make clear, this is the same as explicitly using the binomial likelihood model [49], as

*Technical note: the term *sampling distribution* is more commonly associated with applied Bayesian modelling, whereby the analyst selects an appropriate sampling distribution to model the likelihood of the data.

$$\binom{n}{k} p^k q^{n-k} = 0.6^2 \times 0.4^3 \approx 0.023$$

In order to complete Bayes' theorem, we then need the marginal probability $P(B)$; the probability of the observed sequence *unconditional* on either of the coins [49]. This is accomplished by recognising that an event is the sum of its partitions (i.e. all possible outcomes) [49], and hence

$$P(B) = P(A \cap B) + P(\bar{A} \cap B) = P(A)(B | A) + P(\bar{A})P(B | \bar{A})$$

Assuming $P(A) = \frac{1}{2}$, then $P(\bar{A}) = 1 - P(A) = \frac{1}{2}$ is the logically partitioned complement [49]. Additionally, given that $\bar{A}$ is assumed to be a fair coin, it is reasonable to assign $\frac{1}{2}$ to both outcomes H and T. Consequently, the alternative sequence of 5 flips conditional on $P(\bar{A})$ is a sequence of equiprobable outcomes:

$$P(B | \bar{A}) = \left(\frac{1}{2}\right)^5 = \frac{1}{32}$$

From the above, it is easy to solve for $P(B)$, where

$$\therefore P(B) = \frac{1}{2} \times \frac{72}{3125} + \frac{1}{2} \times \frac{1}{32} \approx 0.028$$

which makes it trivial to solve for the probability that the chosen coin was unfair, given the observed evidence. One simply plugs the results into Bayes' theorem

$$\therefore P(A | B) = \frac{P(A)P(B | A)}{P(A)(B | A) + P(\bar{A})P(B | \bar{A})}$$

$$P(A | B) = \frac{\frac{1}{2} \times \frac{72}{3125}}{\frac{1}{2} \times \frac{72}{3125} + \frac{1}{2} \times \frac{1}{32}}$$

$$\therefore P(A | B) = \frac{2304}{5429} \approx 0.42$$

Though slight, the result implies that it is more probable the chosen coin was fair (given the observed evidence and prior state of knowledge). Obtaining more information about the coin, in order to decrease the uncertainty of your decision, would be ideal – though this is relevant to every decision problem under uncertainty [134]. Nevertheless, it is perhaps most vital to appreciate how the above has enabled you to make a systematic conclusion despite limited information and, moreover, that it has naturally quantified the uncertainty of the decision in terms of a direct probability statement.

It is therefore clear that Bayesian inference manifestly offers a natural and powerful approach to handling uncertainty across any and all potential observations and parameters of a model [135]. This makes it fitting to the health economic decision-modelling field, which – at its core - attempts to determine the uncertainty associated with the once-off incorporation of a new health technology within a health system, by using probability as a yardstick, in a systematic and transparent way [37, 62, 135, 136]. In other words, health economic decision-modelling, at its core, attempts to provide the decision-maker with an optimal decision under uncertainty [11, 12, 16, 22, 31, 35-38, 44, 48, 51, 52, 62, 129, 133, 136-147].

2.5. Modelling Decisions Under Uncertainty in Health Economics

“It ain’t what you don’t know that gets you into trouble. It’s what you know for sure that just ain’t so.”

- Mark Twain

Decision-making under uncertainty regards making choices where the consequences of our actions cannot be completely anticipated, since they are dependent on future, unknown states of the world [17, 18, 116, 148]. Thus, possible states of the world are theoretically a function of the actions we can take in the present [17, 18, 116, 148]. This makes it akin to an optimisation problem that is *as* equally concerned with logical decisions as it is with economically rational ones[†] [18]. A decision-maker faced with uncertainty thus ought to select the action which provides the highest expected utility^{*}; that is, one should select the action that provides the greatest *potential* average utility – or, more simply, the average of the action’s combined utility of each outcome weighted by the outcome’s probability of occurring [17, 18, 37, 117, 119, 149].

Consider evaluating a potential treatment t_1 versus a status-quo treatment t_2 . Here, the health care decision-maker is faced with stochastic *and* informational uncertainty (1st and 2nd order uncertainty) [17, 37]. Simply speaking, stochastic uncertainty is the variation in individual-to-individual treatment response within homogenous populations [5, 22]. Informational uncertainty is associated with potentially ‘knowable’ data, though at the time of making the decision it is partially ‘unobserved’ [5, 22]. The distinction is that stochastic uncertainty cannot be reduced by gathering more information, whereas informational uncertainty can [5, 22]. For now, it is necessary to grasp that if t_1 has a greater average expected utility than t_2 , such that $E[u_{t_1}] > E[u_{t_2}]$, we can expect the act of prescribing a treatment t_1 leads to a greater overall utility for the population, on average [17, 37]. This implies that prescribing the new treatment is preferable, such that $t_1 \geq t_2$ is a rational preference according to the general prescripts of expected utility theory[‡] [17, 119]. In terms of decision-making under uncertainty within the field of health economics, we can also consider willingness-to-pay for t_1 [22, 37]. If the decision-maker’s willingness-to-pay for incremental health benefits exceeds the relative incremental ‘costs’

[†]This should be obvious since, by the logic of uncertainty, there is still an unknown *chance* (stochastic) probability to obtain a state of the world in which the outcome fails to provide the greatest utility. Yet, because we are faced with an unresolvable uncertainty, we should *logically* choose the action which provides the greatest *chance* of obtaining a more desirable outcome overall.

^{*}See Supplementary Appendix A for a brief review of expected utility and other grounding concepts.

in prescribing the treatment, the treatment is said to be ‘cost-effective’ [1, 5]. By using the Expected Incremental Benefit framework (EIB), this is expressed in notational form as

$$EIB = kE[\Delta_e] - E[\Delta_c]$$

where k is the willingness-to-pay threshold and $E[\Delta_e]$ and $E[\Delta_c]$ are the expected increment changes in comparative benefits and costs[‡] [5, 22]. In this arrangement, the health benefits of a treatment are therefore a factor of k , i.e. a decision-maker’s willingness-to-pay threshold for that treatment [22]. Thus, similar to a utility preference, if $EIB_{t_1} > EIB_{t_2}$ (i.e. the comparative net benefit of the new treatment is positive), it is preferable to choose the new treatment t_1 given our current information and *vice versa* if negative.

Health economic decision-modelling is hence, at its most fundamental level, concerned with providing a methodological quantification for the optimal course of action, based on the current state of knowledge [1, 11, 12, 44, 129, 137, 150]. But, as noted in the opening sections of this paper, it is important to make the preference for one action over another explicit. Thus, adoption of thorough statistical decision-theory methodology has become a prerequisite for systematic health care resource allocation [22]. A cornerstone of systematic decision-modelling, however, demands the thorough assessment of uncertainty because it can provide indispensable information on a decision’s set of potential outcomes [22, 117, 145, 151]. In health economics specifically, the process of reflecting the uncertainty associated with decision has become widely known as *sensitivity analysis*.

2.5.1. Incorporating Uncertainty into Health Economic Decision Models

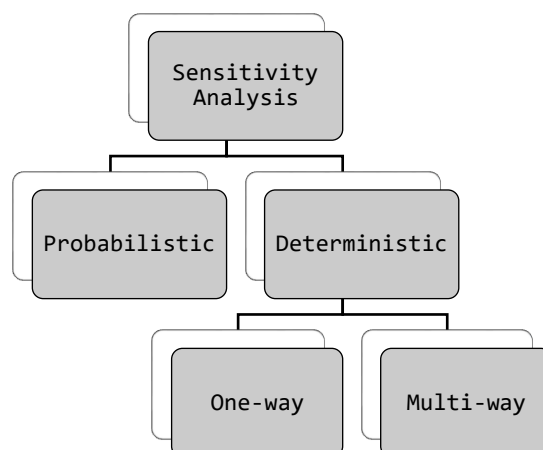
Approaches to sensitivity analysis can be technically categorised as deterministic or probabilistic in nature. Sections 2.5.1.1 - 2.5.2.2 will briefly explore this distinction. First, the simpler approaches of Deterministic Sensitivity Analysis (DSA) are examined. This is followed by a brief review of the more thorough, yet technically complex techniques that can be used to achieve a Probabilistic Sensitivity Analysis (PSA). The added complexity of PSA brings into light the important distinction between the alternative techniques that can produce a PSA output for health economic decision modelling. However, these techniques are complex, are require a relatively deeper technical knowledge compared to DSA techniques. Therefore, in Section 5, we provide a more detailed demonstration of applied PSA techniques.

2.5.1.1. Deterministic Sensitivity Analysis

At its core, DSA seeks to understand how changes in the values of one or more parameter may influence the overall decision [1, 5]. Practically, the input values of a model’s parameters are manually varied either one at a time or simultaneously, conducting a ‘one-way’ or ‘multi-way’ DSA respectively [1, 22]. For example, one may choose to change the cost of an intervention, say by 10% or more, and reduce the effectiveness of a treatment by 15% - either one-at-a-time or simultaneously. An analyst may also implement a ‘threshold analysis’, which entertains ‘even-if’ scenarios that are

[‡]This is the net benefit arrangement. It is a simple algebraic transformation of the ICER approach discussed in Section 2.2. Roughly speaking, the transformation technically scales the benefits to be on the same scale as costs, as $ICER = \frac{E[\Delta_e]}{E[\Delta_c]}$. This arrangement helps to avoid the pitfalls associated with ratios when the denominator approaches zero.

considered to be extreme [5]. For instance, increasing the cost of a treatment by 50% rather than 10%. If the extreme change in a parameter's value is found to be inconsequential to the overall decision, the model is assumed to be robust to uncertainty and thus uninfluenced by large changes in initial input parameter values [1, 5]. Although there is a qualitative distinction between DSA methods, there is no technical difference between a 'one-way' and 'multi-way' DSA (other than in the number of parameters varied) and thus, the methods can be safely categorised into a single, coherent 'Scenario Analysis' category for example [1, 5, 7, 22, 55]. Of course, it is still important for the analyst to communicate how a model's parameters were varied and whether the DSA method was a one- or multi-way analysis [55].



DSA techniques are most apt for posing specific questions about hypothetical changes to a set of parameter values and, subsequently, the sensitivity of the decision to those changes [1, 5, 22]. Nevertheless, there are several critical drawbacks to be aware of. Foremost, DSA cannot inform the decision-maker about how *probable* the decision is, in fact, the *wrong* decision [1, 5, 22, 44, 48, 63]. DSA is thus more appropriate for understanding the effects of *heterogeneity* (i.e. an observable variation, such as the changes in the costs of an intervention across different jurisdictions), rather than stochastic uncertainty [5, 44, 48].

Additionally, a rigorous account of decision-uncertainty desires an interval estimate, rather than a single point estimate [17, 151]. Moreover, all parameters ought to be assessed simultaneously, i.e. parameters are varied over suitable probability distributions concurrently [5, 151]. This is especially true regarding models with correlated parameters and or multiplicative effects [1, 5, 22, 48]. DSA is unable to account for the potential correlation or multiplicative effects that can often occur between parameters [1, 5, 22, 48]. It assumes no 'randomness' in a model's outputs and, consequently, that all parameter inputs are proportional to outputs [1, 5, 22, 48]. The output of a DSA is, often, *technically* nonmeaningful as the it cannot properly estimate relationships between the potential payoffs and health state transition probabilities within many health economic decision-models. [1, 5, 22, 48, 59, 63]. Due to shortcomings such as these, a Probabilistic Sensitivity Analysis (PSA) approach is often employed [22].

2.5.1.2. Probabilistic Sensitivity Analysis

Although uncertainty also encompasses the domain of stochastic error, the primary intention of PSA in health economics is to provide an estimation of the uncertainty associated information (i.e., the standard error of a parameter's 'true' value) [22, 137]. Therefore, a key characteristic of PSA is that the evidence on each parameter is summarised as a probability

distribution [145, 152]; arguably, this is the most significant point-of-departure between DSA and PSA methods. Furthermore, this characteristic enables (in general) for the quantification of how *probable* a decision is, in fact, the *wrong* decision [5, 36]. This is enormously beneficial to decision-makers, especially in contexts of relatively increased resource scarcity (such as MICs) [13, 59, 153]. An additional advantage of summarising evidence as a probability distribution is that it can quantify the cost of delaying a decision to gather more information (thus ultimately reducing decision uncertainty) [5, 22, 140]. Quantifying the costs of gathering more information by delaying a decision is known as Value of Information analysis (VOI) [22, 134]. Evidenced by recent ISPOR reports, VOIs powerful ability to aid decision-makers in weighting the risks of irreversible investment decisions has made it a progressively more popular tool [5, 22, 134, 140, 154, 155].

Given the above, PSA is often better at estimating uncertainty (an uncontroversial statement given the health economic literature) [1, 2, 5-7, 12, 22, 36, 48, 55, 56, 101, 129, 152, 154, 155]. Adopting a PSA approach to sensitivity analysis is thus usually recommended by established health economic evaluation agencies, e.g., NICE and CADTH, while it is also considered best practice by the ISPOR-SMDM Task Force on parameter uncertainty [1, 2, 5, 7, 101]. Nevertheless, despite obvious technical advantages, there are notable weaknesses too. First, PSA is more technically complex [5, 22]. It necessitates advanced technical skills and a broader knowledge of statistical decision theory [22]. Similarly, the relatively increased resource demands of PSA – in terms of technical and time needs – may be unfavourable within resource constrained settings. Clearly, adoption has obvious limitations. It is therefore important to consider the applicability of a PSA within context [1, 5, 7, 57]. Similarly, increased complexity and technical requirements generate a model that can be trickier to communicate to a decision-maker [1, 5, 57]. And lastly, PSA takes a significant amount of time to simulate when using standard spreadsheet programmes, such as Microsoft Excel® and TreeAge[†], and, therefore, more specialised and unfamiliar programming languages such as R is (technically) more desirable [5, 22, 37, 51, 156, 157].

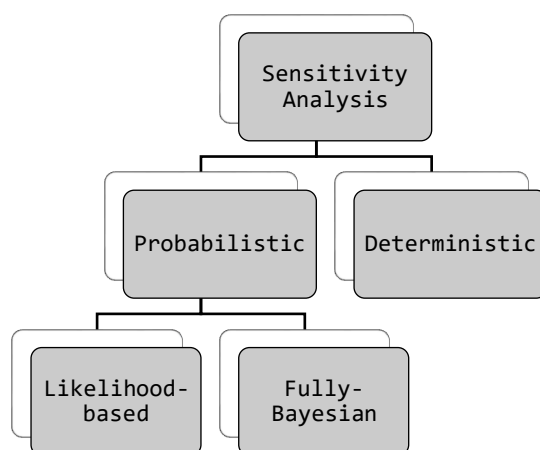


Figure 4. Varying approaches to PSA.

It is, nevertheless, meaningful to comment on the fact that there are two approaches to obtaining a health economic decision-model with a PSA output (see Figure 5 above). The contrast is described by reference [136] as a distinction between “implicit” and “explicit” Bayesian methodology. When compared to the alternative one- and multi-way DSA approaches mentioned earlier, the different PSA methods - what we hereon refer to as likelihood-based and fully-decision

[†]Relevant is that such software are the typical analytic tools used by many health economic analysts.

theoretic- are substantially more technical and, most pointedly, therefore, cannot be easily classified into a single homogenous category. Given the overarching aims of this paper, we are thus obliged to explore these nuances in greater detail.

2.5.2. Producing a Probabilistic Sensitivity Analysis Output: differences between likelihood- and fully-Bayesian approaches

The following sections set out to discuss the technical nuances between likelihood and fully-Bayesian based simulation (with the latter also referred to as comprehensive decision-modelling). The primary aim is to provide the reader with a deeper but still intuitive command of the advantages and disadvantages of both techniques.

2.5.2.1. PSA via likelihood-based simulation

A likelihood approach to PSA is widely applied across health economic literature [1-3]. It is likely a far more familiar technique to obtaining a PSA model for most health economic analysts [1-4]. Conducting PSA via a likelihood approach first requires the analyst to estimate a parameter's distribution values via more standard frequentist statistical methods, such as 'method of moments' [1, 6, 7]. As stated in reference [1], a simple example of estimating a parameter's distribution values is for a proportional set of outcomes, where the beta distribution $\theta \sim \text{dbeta}(\alpha, \beta)$ is applicable to use [1]. The first and second moments of a beta distribution are

$$E[\theta] = \frac{\alpha}{\alpha + \beta}$$

and

$$\text{var}[\theta] = \frac{\alpha\beta}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

If the analyst(s) gathers the sample moments $\bar{\mu}$ and s^2 , say from a meta-analysis, one is able to equate the known sample moments with the unknown moments of the beta distribution, so that the total proportion of outcomes $(\alpha + \beta)$ is equal to

$$(\alpha + \beta) = \frac{\bar{\mu}(1 - \bar{\mu})}{s^2} - 1$$

where alpha is

$$\alpha = \bar{\mu}(\alpha + \beta)$$

and beta is then simply

$$\beta = (\alpha + \beta) - \alpha$$

We refer the reader to reference [1] for further clarification. For now, the grounding idea is that once the estimates of a parameter's distribution values are obtained, the analyst(s) can simulate the potential values from an appropriate parametric distribution [1, 8]. Broadly speaking, this is achieved by simulating values from a probability mass function (pmf) or probability density function (pdf), depending on whether the parameter of interest is a *discrete* or *continuous* random variable (r.v.) [1, 9]. The key difference is that a pmf directly provides the probability of a discrete r.v. taking on a set of specific values, so that the probability for a r.v. X taking the value x can be simply inferred simply as [5, 9]:

$$p_x(x) = P(X = x)$$

This means that it is possible to sample the probability of a parameter's values from a pmf without any need for further statistical transformations [5, 9]. In contrast however, this does *not* hold for continuous r.v.'s, which are the more common variables used in health economic evaluation models (due the nature of cost and effect parameters) [1, 9]. Regardless, the distinction is that a pdf only provides the *relative* likelihood of parameter's values and it is thus requisite to map the simulated samples of a continuous parameter's pdf to the cumulative distribution function (cdf) by means of integration [1, 9]. More precisely, the process of integration provides the area under a curve constrained to the interval $[0, 1]$, making the cdf a valid probability measure function [1, 9]. For example, to obtain the probability of X falling within the range $a \leq X \leq b$, it is necessary to obtain the cdf of X , such that

$$P(a \leq X \leq b) = F(b) - F(a) = \int_a^b f(x)dx$$

where $f(x)$ is the original pdf [5, 9]. But analytical solutions, especially for continuous r.v.'s, are often intractable and complex [5]. More efficient computer simulation-based methods are often necessary and, perhaps, even desirable in most practical circumstances [5, 9]. Monte Carlo integration is a popular approach. Roughly speaking, Monte Carlo integration refers to the use of broad class of algorithms that simulate pseudo-random draws from a parametric distribution which then provides an estimation of a random variable's (r.v.'s) expected value, such that $E(X) \approx \frac{1}{n} \sum_{i=1}^n X_i$, where n is the number of simulated draws [5]. From there, one can integrate the samples to provide a probabilistic estimate of a parameter value. A straightforward example is *inverse transform sampling*[†] [1, 5, 9]. One may also use the option of the Box-Muller transform method. Generally, the aim is to draw random samples from a uniform distribution and then map these samples to a parameter's cdf [1, 5]. A brief example of the inverse transform method (coded in the R language) follows.

First, 20 000 random samples are drawn from the uniform distribution $x_i \sim U(0,1)$, bounded on the interval $[0, 1]$. The random samples are then transformed to the appropriate scale using the desired inverse cdf (quantile function) of the desired parameter [5]. An example of simulated random samples from a uniform distribution is coded and plotted below.

[†]Technical note: the inverse transform method *can* be applied to *both* discrete and continuous r.v.'s. However, for a discrete r.v., it is necessary to use the pmf directly and indicate each outcome value by specifying the upper and lower bounds of the uniform distribution, so that the total 'chopped' intervals of the uniform distribution sum to 1. See reference [7], specifically pages 228-229.

```
x <- runif(n = 20000)
```

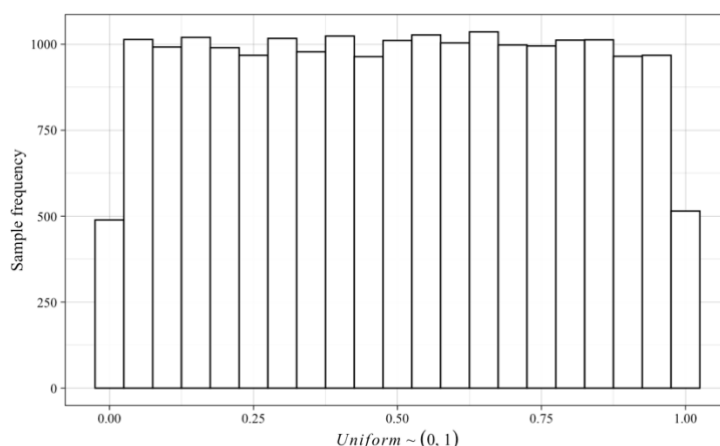


Figure 5 20,000 samples drawn from a uniform distribution at random.

For illustrative purposes, if the parameter of interest takes on the form of an exponential distribution with a rate parameter of, say, $\lambda = 0.4$, or a normal distribution with a mean $\mu = 0.65$ and variance $\sigma^2 = 0.7744$, it can then be transformed using the appropriate quantile distribution function[‡] [10], which can be coded in R using the built-in quintile functions, as shown on the proceeding page.

```
inv_cdf_exp <- qexp(p = x, rate = 0.4)
inv_cdf_norm <- qnorm(p = x, mean = 0.65, sd = sqrt(0.7744))
```

The subsequent outcome provides an estimation for the probability of a parameter taking on a range of values, given the initial parameter estimates [1, 5]. The key theme to notice, however, is that a achieving PSA using implicit Bayesian methods obtains information derived solely from a single distribution function, which, in turn, derives its support from single, deterministic point-estimates [4, 6, 7, 11, 12]. Although it assumes that this is *theoretically* equivalent to combining a ‘non-informative’ or ‘flat’ prior with a likelihood model, the method clearly does *not* practically combine a prior distribution with a likelihood function [4, 6-8, 13]. However, since the PSA framework (in general) views all model parameters to be random variables; that decisions are interpreted from an expected utility perspective; and the overarching aim of a health economic decision-model is thus to provide an optimal decision in the face of uncertainty, an MC PSA simulation approach is, in principle, grounded upon a Bayesian inferential framework [1, 8, 13-19].

[‡]In R, one could easily make use of the available random distribution functions, such as `rexp` and `rnorm`. However, this example follows the process described in several widely read health economic decision-modelling textbooks, such as reference [1]. The reason for this difference is that most standard spreadsheet programmes do not have random distribution function capabilities built-in. For example, in Microsoft Excel®, one has to first use the `RAND()` function coupled with the inverse cdf function of a desired distribution, such as `NORMINV()`. We refer the reader to reference [1] for further reading.

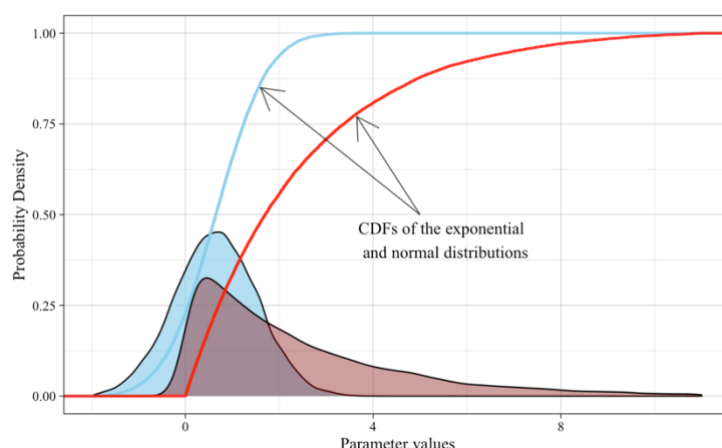


Figure 6 The probability and cumulative density (solid lines) distributions for an exponential (red) and normal distribution (blue) generated from the quantile function transformation above.

To be technically precise however, a standard likelihood-based PSA is *not* a fully integrated Bayesian data analysis approach to decision-modelling [13, 16]. In fact, as stated in reference [1], the approach is “rather informal” and, we argue, is perhaps most comparable to an ‘empirical’ Bayes method which estimates prior distribution parameter values using single, point-estimate data (by methods such as the example provided in this section’s opening paragraphs) [1, 13, 20]. Though the distinction is remarkably subtle, reference [16] provides a much sharper resolution, noting that: “... Bayesian *inference* does not actually require [a joint probability distribution for all the data and parameters]; all it needs from the data is the likelihood, and different [joint distributions] can have the same likelihood. But Bayesian *data analysis* requires [a joint probability distribution for all the data and parameters, i.e. that priors are combined with likelihood models].” Regarding health economic decision-modelling, we are more concerned with the latter, i.e. *data analysis*, which is to provide information that helps to inform decisions.

Ostensibly, the core reasoning in favour of the standard likelihood-based position is that it enables for a refined ‘empiricism’ compared to incorporating a ‘subjective’ and ‘data-less’ prior distribution which is then combined with a likelihood model [1, 8, 18]. We do not wish to discuss the philosophical contentions associated with this position, but do, however, steadfastly argue that this incurs a significant trade-off in a model’s flexibility[†] [4, 6, 7, 13, 21]. With regards to the primary focus of this paper, such a trade-off is specifically related to the concepts of *transparency* and *parsimoniousness*, as the following passage intends to further substantiate.

Foremost, a standard likelihood-based PSA approach cannot *cohesively* combine all parameter evidence by means of an evidence synthesis [6, 21]. This despite the gathering of all available evidence to be a consistent recommendation across major health economic guidelines [2, 3, 22-24]. Though a combined evidence synthesis and sensitivity analysis can be achieved using a this approach, it typically requires the use of several non-integrated software platforms, resulting in an opaque, disjointed and, most significantly, therefore, hard to replicate health economic decision-model [4, 6, 7, 21, 25-27]. This makes the decision-model *technically* non-transparent and hard to investigate in an organised fashion [4, 6]. Moreover, exporting from an initial software programme to another (that is subsequently used for the final cost-effectiveness analysis,

[†]It is not the purpose of this paper to review the technical shortcomings of MC algorithms. We therefore focus on the practical trade-offs that are relevant to MIC contexts, such as the use of all available evidence and modelling flexibility.

for example) relinquishes statistical relationships that are induced between a set of parameters as an intrinsic product of evidence synthesis – for instance, if data are obtained from a survival model [6, 21]. Statistical relationships like parameter correlation can be imputed into the final economic evaluation model by means of several methods (such as incorporating a covariance matrix directly into the MC simulation). Again, however, we argue that this is an arduous process which opens significant opportunities for errors to enter into the final model (compared to the parsimonious fully-Bayesian approach which achieves this within a single, unified manner) [3, 4, 6, 28-30]. Lastly, because parameter input values are modelled using point estimates and are not sampled from prior distributions (which enable for *random* sample paths, i.e. variation in a parameter's point estimate) the uncertainty associated with using a single point estimate for a parameter's distribution value is ignored [13, 20, 21]. This can lead to a noticeable underestimation of uncertainty. Therefore, considering the general context of MICS, which face acute shortages in adequate data and research capacity, such contexts may benefit from the more established use of the more parsimonious and integrated approach in instances of data limitations and researcher capacity.

2.5.2.2. PSA via fully-Bayesian posterior simulation

Noted in the opening sections of this paper, direct information is frequently scarce within MIC climates. Although 'empirical', point-estimate data is argued to lead to more 'objective' estimations, it has the potential to be vastly insufficient for making critical decisions when there is an inadequate amount of direct or generalisable information [13, 16, 19, 31-33]. For example, despite Randomised Control Trials (RCTs) being the 'gold-standard' of data sources, RCTs are often unsatisfactory as "... a single trial will very rarely embody the entirety of the evidence base available to inform a decision." [34]

Coupled with the fact that direct RCT data conducted within MIC jurisdictions is scant, collated RCT data are necessarily generalised from higher-income jurisdictions to the MIC context of interest [35, 36]. Relevant to note here is that a fully Bayesian data analysis (comprehensive) approach to probabilistic sensitivity analysis sufficiently accommodates uncertainties related to both patient- and country-specific variation, which occurs whenever evidence is adopted from a different jurisdictional context [4, 7, 28, 34, 37, 38]. On the other hand, it is equally critical to appreciate that the approach requires more complicated Markov Chain Monte Carlo (MCMC) algorithms as well as cohesive statistical software, such as the R language and BUGS/JAGS or STA, implemented in RStudio for instance [6, 7, 13, 21, 39, 40]. Moreover, due to this heightened complexity, MCMC algorithms are perhaps only necessary when constructing complex decision problems, using a '*hierarchical*' or '*multilevel*' modelling approach [4, 6, 7, 13, 21, 39].

Nevertheless, the power of Bayesian hierarchical modelling is that it enables for synthesis of data sources distinct in jurisdiction and study design, as well direct and indirect evidence, within a single, integrated structure [4, 6, 13, 21, 40, 41]. Therefore, the approach parsimoniously implements advanced evidence synthesis techniques, such as Indirect and Mixed Treatment Comparisons (which are useful in instances of limited direct and head-to-head trial data)* [34, 37, 42].

*An Indirect treatment comparison is useful when there is no data available comparing head-to head trials for treatments of interest. If, for instance, one is interested in the relative effects *A* versus *B*, it may, given the absence of direct data, be beneficial to combine evidence from available indirect trials between treatments *A* and *C* and *B* and *C*. Using comparative effects between *A* and *C* and *B* and *C*, one can model the relative effects between *A* and *B* via the 'indirect' results obtained from the common treatment comparison *C*. This is

Moreover, RCTs, observational studies, and even evidence summaries from meta-analyses can be combined using *generalised* evidence synthesis. Note that generalised evidence synthesis is, however, less established when compared to other network synthesis methods [7, 13, 34, 37, 38, 43]. To make the case that a comprehensive MCMC approach provides for a greater parsimoniousness tangible, we turn to a simple example below which attempts to illustrate how a fully integrated (comprehensive) Bayesian data analysis approach sufficiently accommodates the uncertainties that result from combining different sources of RCT evidence which are conducted across varying geographical regions.

The more straightforward approach to evidence synthesis is to perform a ‘Fixed Effects’ model. A Fixed Effects model, however, assumes that the variation between a set of collated studies arises from measurement error alone. Even RCTs, however, likely incur variation in treatment outcomes due to various phenomena [4, 7, 21]. For instance, the study population, geographic jurisdiction, as well as timing of each intervention can differ [4, 21]. Consequently, these differences can change the overall effect size of a given treatment and, accordingly, a ‘Random Effects’ model is typically a more appropriate choice for combining several sources of evidence from across different contexts [4, 21]. Thus, a Random Effects model implies that there is an underlying variation between all studies (statistical heterogeneity) as well as within each study’s (statistical homogeneity) treatment effect size. In other words, the ‘true’ effect size is not equal across all trials and it cannot be attributed to measurement error alone [4, 21]. But, if potential causes of variation can be identified, for instance when individual patient level data are available, it is best practice to include covariates into the equation [1, 4, 21].

Nevertheless, even if there is no identifiable covariation, say because specific characteristics have not been explicitly measured, adding a ‘random effect’ satisfactorily characterises the variability of *both* patient- and population-level stochasticity, which is achieved structurally by adding greater parameter uncertainty into the pooled population effect estimate and stochastic parameter value estimates (obtained from the prior) [4, 21]. For example, it is possible to fit a Random Effects model to several collated RCT control and treatment group data from different geographical contexts by using a Binomial likelihood model [4]. Technically, this generates a logistic model with an added ‘stochastic’ effect [4]. To repeat, if there is some information on covariation, such as age or sex characteristics, one can simply add a coefficient into the logistic function. However, in the case above, and assuming that none can be currently identified, a ‘Random Effects’ model can be conceptually structured as shown below

In the below diagram, r_{A_i} and r_{B_i} are the number of events in each arm; n_{A_i} and n_{B_i} are the total number of participants in each arm; p_{A_i} and p_{B_i} are the probabilities of an event in either arm; μ_i is the *prior* baseline population log(odds) estimate for an event in either arm; while $i = 1, \dots, k$ defines the number of collated RCTs [4]. For the average population effect prior, ψ represents some reasonable variance value; it could be 100, 1000, or even 10000, depending on the judgement of the analyst [4]. For example, assuming a variance value of 10000 implies that the analyst is *a priori* 95% certain that the ‘true’ parameter variance is between $(0 - 1.96 \times 100)$ and $(0 + 1.96 \times 100)$, where $100 = \sqrt{10^4}$. This essentially codes a ‘flat’ prior into the model which, simply speaking, means all realistic values have an equal chance of being sampled [4]. The same logic applies to the subsequent random effect priors.

especially useful for instances where Randomised Control Trials raise ethical concerns for investigating the intervention of interest. Similarly, an extension of this evidence synthesis method is Mixed Treatment Comparisons, which combines *both* direct evidence *and* indirect evidence pertaining to treatments *A* and *B*. Reference [4] provides a comprehensive and practical discussion on these topics.

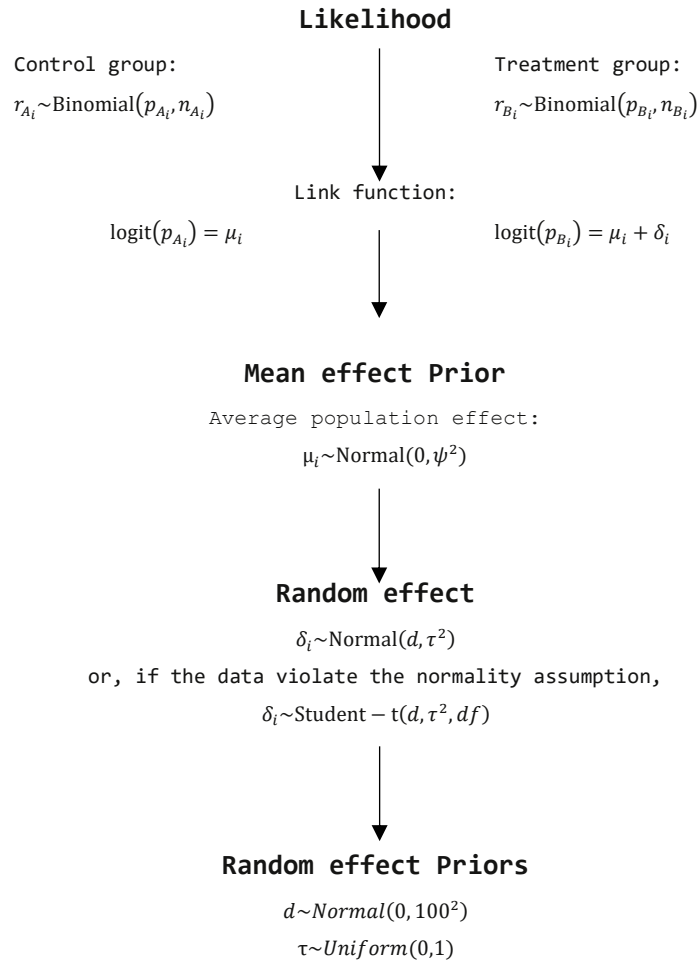


Figure 7. A structural representation of a Random Effects model

It is also important to understand the ‘random’ effect added to each study’s treatment effect size, δ_i [4]. This is because all the studies are ‘related’ as the ‘stochastic’ variation δ_i is modelled (sampled) from a common distribution –see chapter appendix for a brief note on *exchangeability* [4, 21]. Along with a prior average population effect parameter μ_i , this enables for each study to ‘borrow strength’ from the others - a consequence of the hierarchical structure of the model [4, 7]. Hence, structural dependence incurs a ‘shrinkage’ in the overall posterior population estimate and thus a reduction in the uncertainty associated with the expected overall population treatment effect [4, 7, 21, 44]. What is evident from the above illustration is that the practical incorporation of a prior and a likelihood enables the fully integrated, explicitly Bayesian approach to sufficiently model stochastic variation on the ‘individual’ level (obtained from the ‘subjective’ prior) *and* ‘population’ level, while maintaining a robust estimate of the uncertainty associated with information via the likelihood function [4, 6, 7, 21, 44].

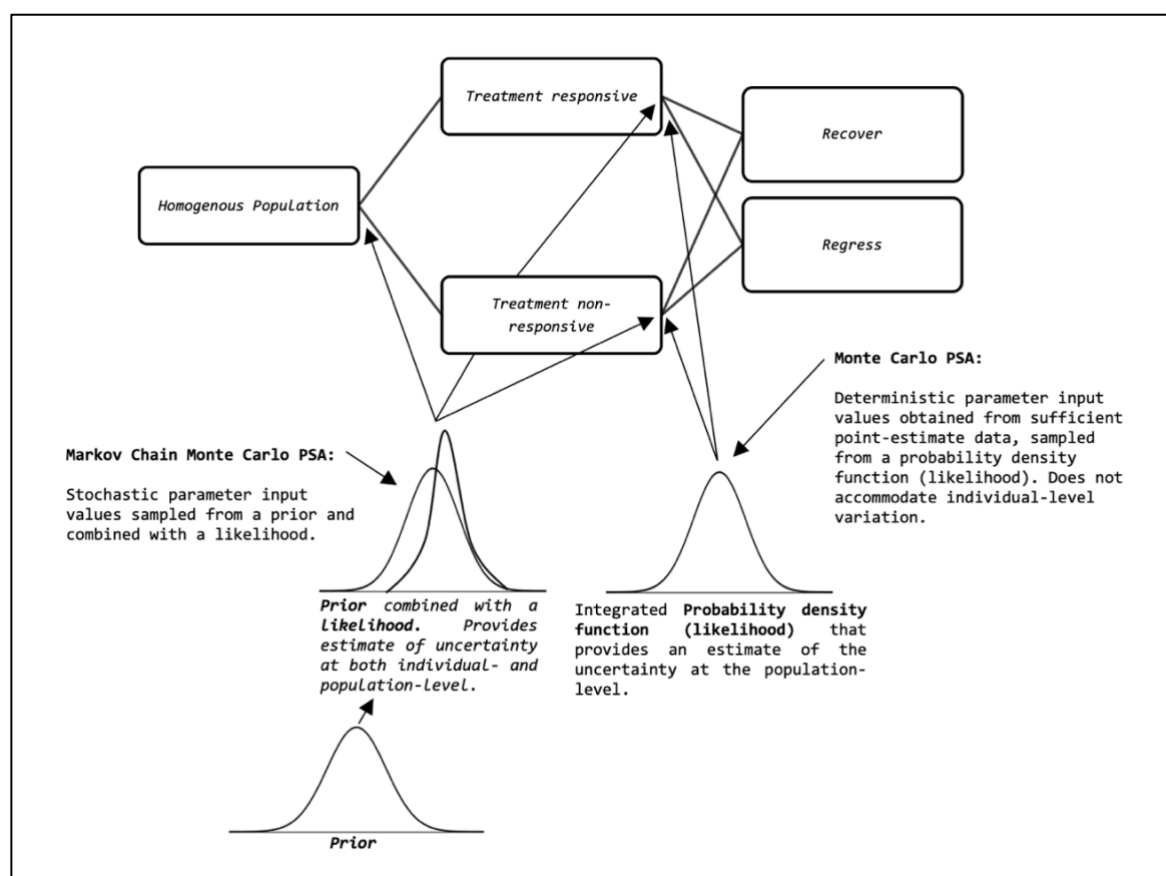


Figure 8 a structural illustration of the differences between MC and MCMC PSA.

There are, obviously, critical assumptions and trade-offs to consider when implementing such an analysis but, to maintain the focus of this paper, we must refer the reader to more in-depth reading, particularly references [4, 6, 7, 21, 45, 46]. Yet, however complex and demanding (in both time and technical skills), one is clearly compelled to consider how such flexibility and inclusiveness leads to an improved parsimoniousness (relative to the complexity of the overall model). The clear benefit is that a fully integrated (comprehensive) approach to achieving a probabilistic sensitivity analysis output enables for a *highly* flexible approach to evidence synthesis (meta-analysis), the estimation of model parameters, a sensitivity analysis, and the final evaluation of a model to be combined into a single, coherent structure (hence why it is also referred to as an ‘integrated’ approach) [6, 21]. This clear parsimoniousness is valuable within the data scarce climates of MICs. Notably, reference [27] provides a clear conceptual path for applying a fully integrated MCMC approach given an appropriate context, stating that:

“... [it] might be considered to be the preferred basis for cost-effectiveness analysis... when 1) the available trials were undertaken wholly outside the jurisdiction of interest... 2) there is more than one relevant source of evidence [i.e. difference study designs]... 3) where a trial [RCT] exists, but some other aspect of the economic evaluation is not consistent with the design of that trial [i.e. time horizon]... and 4) a decision model [i.e. a fully integrated MCMC approach] has been developed for another jurisdiction and might be adapted to support decision-making in another.”

The advantages of a fully integrated Bayesian approach to health economic decision-modelling within MIC contexts are evident. Uncertainty associated with both limited information and stochastic variation can be adequately modelled within a single, unified structure. Moreover, a wide array of different types of evidence can be systematically incorporated, which, in turn, can help reduce decision uncertainty. However, given the capacity constraints of MICs discussed earlier, it is as critical to consider that the approach is more intricate, requiring a statistical model to be embedded directly within a health economic decision-model (which, we believe, in order to be practically feasible, desires more purpose specific software languages and programmes, such as R and RStudio) [6, 45].

Therefore, there are key trade-offs given the relative precision improvement versus quality of decision-making gained from performing an explicit Bayesian approach to consider. In this light, it is critical to remember that decisions in health care are not exclusively informed by quantitative analyses [2, 3, 47]. Qualitative social values frequently, and perhaps *necessarily*, play a fundamental role in informing health care resource allocation decisions [2, 3, 47]. Health economic decision-models are not solely predictive tools, but also *communicative* tools which are used by decision-makers to weigh the possible consequences of their decision [2, 3, 47]. In other words, it is important to remember that our models do not make the final decision; this, perhaps fortunately, is ultimately in the hands of the decision-maker. Indeed, not all health care decision problems are in equal need of complex sensitivity analysis methods - on the contrary, the method applied should ideally fit the complexity of the decision problem it intends to inform [1, 8, 15, 26, 48, 49].

2.6. Conclusion

“I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail.”

- Abraham Maslow

There is little doubt that different approaches to sensitivity analysis lead to different cost and effect estimates. However, consider, for instance, a scenario where all available approaches to sensitivity analysis lead to *practically* the same cost-effectiveness decision, i.e. that the treatment under consideration is accepted or rejected as being a cost-effective intervention *regardless* of the method used to achieve said sensitivity analysis output. Surely, one may ask, in such scenarios, it more desirable to use the least complex method.

Choosing between different DSA or PSA methods clearly demands a careful deliberation of the potential trade-offs (such as the time, skills, and evidence uncertainty involved) and how such factors can ultimately influence a health resource allocation decision. This is especially true for contexts of heightened resource scarcity (such as MICs), as an efficient allocation of resources is paramount to the sustainable provision of health care services – including the proper allocation of sparse technical skills [50, 51]. Thus, perhaps equally important in such contexts is for the decision-model to aptly *communicate* the given decision-problem, i.e. that the model is interpretable for the decision-maker [52].

The presence of such conundrums provides a convincing rationale for the development of a selection framework to aid the choice of appropriate sensitivity analysis methods within MICs. However, this, without doubt, requires a more practical application of a fully integrated MCMC approach. In the proceeding section, therefore, we develop a framework for sensitivity analysis methods, supported by the practical application of a comprehensive (i.e. MCMC) approach to obtaining

a sensitivity analysis output. Specifically, we replicate a deterministic model to help understand the potential pros and cons associated with performing comprehensive approach and, after, develop a framework that incorporates the findings of the case study with the discussions of this review hereto.

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3. Part C: Manuscript

A Sensitivity Analysis Framework for Health Economic Evaluation in Middle Income Countries: Appropriately Incorporating a Comprehensive Approach

Joshua Soboil¹

3.1. Abstract

When constructing a health economic decision model, it is critical to select a sensitivity analysis approach appropriate for the decision context. This point is particularly salient to Middle-Income Countries (MICs), where there is relatively heightened resource scarcity and increased opportunity-cost. MICs face acute shortages of accessible as well as high-quality evidence, resulting in a frequent imputing of data from external jurisdictions. Conversely, there are also shortages in skills and research capacity, creating a strong complementary need to consider the contextual feasibility of applying more resource demanding sensitivity analysis methodologies. Given the above, it is critical to establish when the technical benefits of more complex and resource demanding sensitivity analysis methods result in real-world, practical value. We apply a comparative case study using a comprehensive (probabilistic) approach to decision-modelling, implemented in the R and JAGS languages. Specifically, the case study replicates a deterministic model originally used to inform the cost-effectiveness of adding a bivalent Human Papilloma Virus (HPV) vaccine to South Africa's public health care cervical cancer screening programme. Crucially, the case study provides critical insight into the pros and cons of implementing more complex probabilistic sensitivity analysis techniques within MIC climates. Our findings indicate that the benefits of more advanced sensitivity analysis methods are nuanced; are beneficial on a case-by-case basis; and, moreover, choosing a sensitivity analysis method should be guided by a conceptual 'fruitfulness' (i.e. a bang-for-buck), more than the desire to reduce a model's complexity. To aid analysts in this process, using our comparative case study we provide a framework with three core concept areas, namely: Decision-Maker Preferences (Decision Power, Investment, Risk Aversion), Analytical Considerations (Available resources, Indirect Evidence) and Policy Context (Knowledge of Topic, Technical Expertise). The framework intends to encourage more judicious selection of sensitivity analysis methods; help reduce the methodological variation apparent in MIC settings; and simultaneously provide decision-makers with greater methodological transparency in the selection of sensitivity analysis methods.

3.2. Key Points for Decision Makers

- Selecting a sensitivity analysis technique must be a thoughtful process weighted within the context of the decision-problem, especially in more resource constrained settings.
- Though more complex sensitivity analysis methods do lead to an improvement in technical precision, this does not always translate into a real-world benefit which requires a strong consideration for practical parsimoniousness.
- Therefore, weighing-up technical trade-offs versus practical trade-offs of health economic sensitivity analysis techniques is important for MICs as they seek to move closer towards the principles of Universal Health Coverage.

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3.3. Declarations

3.3.1. Funding

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3.3.2. Conflicts of interest/Competing interests

The authors declare no conflicts of interest.

3.3.3. Availability of data and material

Only secondary data sources were used in this study. Note that the original model conducted in TreeAge is not accessible to the public, though the final article report can be accessed [here](#). The Excel file containing mortality data used in the original and replicated model is available from the Github repository linked below.

3.3.4. Code availability

The code for the replicated model is freely available from the following [Github](#) repository.

3.3.5. Author contributions

Joshua Musson is the primary author. Lucy Cunnama served as primary research supervisor; Thomas Wilkinson served as secondary research supervisor.

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3.5.Introduction

As Middle-Income Countries (MICs) move closer towards the principles of Universal Health Coverage (UHC), instituting high-quality health economic decision modelling methods is essential to the provision of sustainable health care benefits packages [10, 27, 168, 170]. Therefore, health economic evaluations conducted in MICs ought to sufficiently communicate all areas of information related to a given decision problem, enabling decision-makers to make better judgements. A critical area of providing quality decision-modelling is the assessment of uncertainty [1]. Generally termed ‘sensitivity analysis’ in health economics, reflecting the uncertainty of a health care resource allocation decision is a hallmark of high-quality health economic decision-modelling as it provides indispensable information on the potential outcomes of a decision [55, 56, 172]. Nevertheless, the quality of information obtained from a sensitivity analysis is *strongly* determined by the technique employed to achieve it.

Hence, several sensitivity analysis techniques have become reputable within the health economics field, each with unique practical-technical trade-offs that are important to consider. For instance, a familiar technique to most health economic analysts is deterministic sensitivity analysis. Broadly speaking, Deterministic Sensitivity Analysis (DSA) can be stratified into one- or multi-way analysis methods respectively. These methods are often favoured for technical simplicity, and are more regularly employed within MIC settings relative to more complex and skills demanding probabilistic techniques [8, 10, 33]. Briefly, DSA requires an analyst to vary selected input parameter values either one at a time or simultaneously, post-construction of a health economic evaluation model. Despite frequent use, there are, however, notable weaknesses - especially considering the general context of MICs.

MIC jurisdictions face a frequent lack of localised costing and efficacy data. As a result, much imputed data in MIC health economic evaluations are unavoidably derived from observations made outside of and then generalised to the jurisdiction of interest [8, 10, 23, 33, 163]. But, if this is not explicitly modelled, the use of generalised evidence signals an assumption of symmetry in a treatment’s effect size between two distinct population groups, which, in turn, entails considerable uncertainty regarding a treatment’s ‘true’ effect [10, 54, 59, 153, 163, 173]. Additionally, limited costing data aggravates the uncertainty surrounding the potential system-wide health budget impacts of new technologies [25]. Concerning the above matters, DSA methods *cannot* reliably estimate such uncertainties [1, 143].

Given the above, DSA methods are largely only suited to exploring *specific* changes in parameter input values (e.g. due to *empirical* variation in costs from one jurisdiction to the next, for example) on a model’s output [1, 143]. Although novel deterministic methods have been developed to overcome these shortfalls [174], here we limit our analysis to established health economic sensitivity analysis nomenclature. In contrast, therefore, probabilistic sensitivity analysis (PSA) is, in general, substantially better at formally reflecting the uncertainty associated with randomness and limited information, although the degree to which is dependent on the PSA technique employed [1, 22]. The flexibility of current PSA techniques differ greatly and thus, it is necessary for analysts, as well as decision-makers, to understand this distinction at a basic level, at minimum. Note that due to the scope of this paper, we do not discuss the technical process of constructing either PSA technique. We refer the interested reader to references [1], [175], [7], and [22] for more detailed reading.

A standard approach to probabilistic sensitivity analysis is to perform likelihood-based PSA, using Monte Carlo simulation for integration [1, 22, 44]. Like DSA methods, likelihood-based PSA is typically conducted post-construction of a health economic evaluation model, i.e., it is typically performed once data have been collated and a model has been constructed, often in a spreadsheet software programme such as Excel® [1, 22, 37]. Technically speaking, however, likelihood-based simulation that is typically applied to health economic decision models typically only reflects parametric uncertainty [62, 135]. This technically means that stochastic (first order) uncertainty - associated with a distribution moment's (as input values are deterministic) – is ignored. This can result in the underestimation of decision uncertainty [22, 37, 63, 145, 176]. In addition, it is intrinsically fragile to the issue of data scarcity, which is a regular occurrence in MICs [177]. Regardless, if an analyst wished to impute statistical relationships – such as parameter correlation – into the decision-model, likelihood-based PSA typically requires several extra mechanical steps to be performed, conducted using several independent software tools (especially if a standard spreadsheet programme is used) [7, 22, 38, 44, 175, 177]. This clearly opens up opportunity for error and reduces transparency, as parameter input values are not captured within a single, unified structure [38, 156]. This inefficiency also extends into the realm of practical efficiency, as models with a large set of parameters can take a considerable time to simulate when conducted in common spreadsheet programmes (which are the more popular platforms in health economic decision modelling) [22, 44].

Rather than simulating first- and second-order uncertainties using standard likelihood-based simulation (which can be computationally expensive), an alternative is via fully-Bayesian modelling. When applied to health economic decision modelling, this has broadly referred to as ‘comprehensive’, ‘decision-theoretic’, or ‘integrated’ decision-modelling [37, 40, 172, 176, 177]. The primary difference is that the approach provides a natural probabilistic sensitivity analysis output. Therefore, despite being substantially more complex, fully-Bayesian modelling provides an enormously flexible approach to health economic decision-modelling, overcoming the many shortfalls associated with a standard likelihood-based, Monte Carlo simulation. Markedly, it can imbed an evidence synthesis directly into the decision-model [38, 44, 48, 177-179]. This, however, requires a statistical model to be embedded directly into a decision-model, rather than being constructed as an independent entity [16, 176].

Irrespective of the added complexity, fully-Bayesian PSA - or ‘comprehensive-modelling’ – delivers a parsimonious (resource sparing) approach when imputing statistical relationships (like parameter correlation), performing evidence synthesis (including indirect and mixed treatment comparisons), and providing a probabilistic sensitivity analysis output [44, 48, 176, 177]. Moreover, utilising the natural modelling structure associated with fully-Bayesian modelling reflects the uncertainties at both the individual- and population-level (see Figure 10 for a visual comparison of the two PSA approaches) [50, 63, 153, 163, 177]. This, therefore, accommodates the uncertainties of using cross-jurisdictional evidence more rigorously, making it visibly compelling for more established use within the broader context of MICs already discussed above [37, 44, 59, 63, 180]. Nevertheless, the approach is perhaps only efficient when exploiting specialised software, using languages such as R (with BUGS/JAGS or STAN), with an RStudio interface for example [37, 42-44, 62, 63, 180]. Moreover, this approach to PSA obviously requires an analyst to have a much broader set of theoretic as well as technical skills and can thus be doubly demanding of their valuable time and skills. Again, this is most relevant to the general context of MICs, which face notable shortages in analytic capacity [10, 33, 162]. This, then, raises a significant question, namely: when are can complex (i.e. probabilistic variants of) sensitivity analysis methods be fruitfully used within MICs contexts? As MICs shift towards implementing the principles of UHC, it will inevitably incur a rising demand for

health economic evaluations to inform public health care policy. In turn, this will evidently demand more frequent use of high-quality decision-modelling. Yet, there are, however, clear trade-offs to consider within the general MIC context, which face notable scarcity of data *as well as* research capacity [3, 10, 23, 33, 80, 168]. As a result of such issues, weighing practical trade-offs - in terms of the increased time and skills demanded – with technical trade-offs – in terms of technical precision lost – is an undoubtedly meaningful exercise which would aid in ensuring that the complexity of a decision model is maintained to be a function of the decision problem it intends to inform [168].

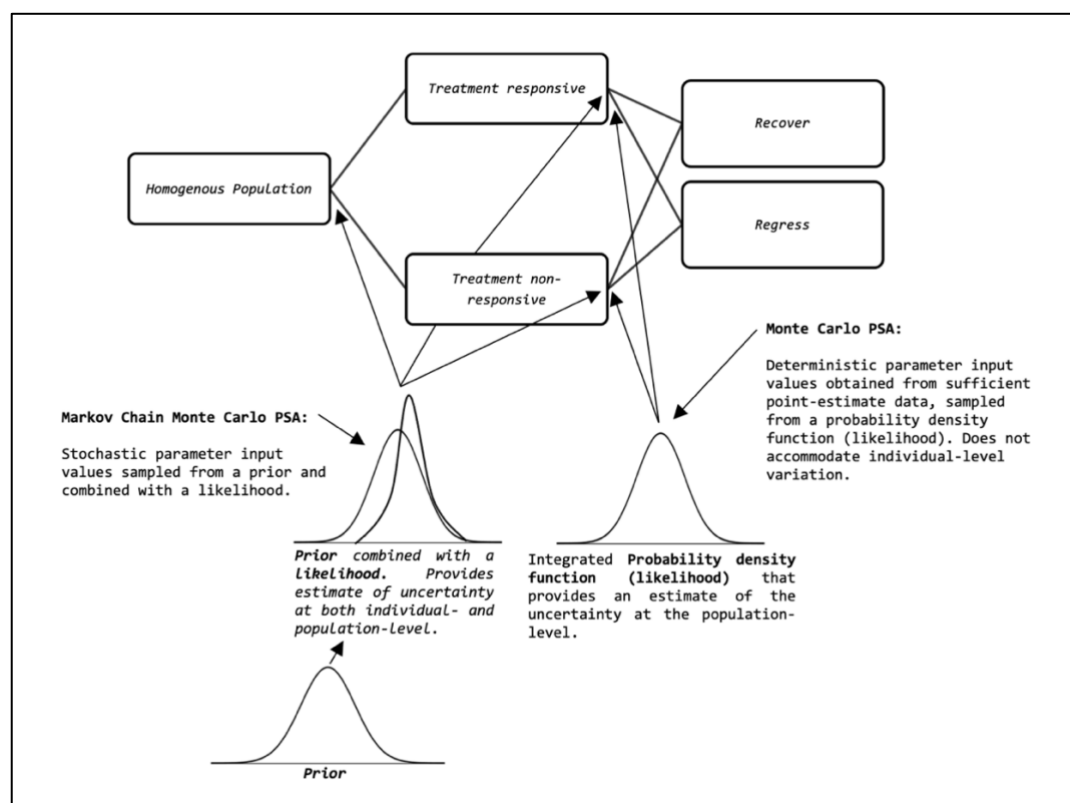


Figure 9. A structural illustration of the differences between Probabilistic Sensitivity Analysis Techniques: likelihood-based vs fully-Bayesian.

3.6. Practical Case Study

To understand the trade-offs between sensitivity analysis approaches, we develop a comparative case study and reconstruct a cost-utility model using (to our knowledge) the most complex sensitivity analysis available; viz. comprehensive modelling [40, 164]. Note that the original model was implemented in 2009 and was intended to inform the cost-effectiveness of adding a bivalent Human Papillomavirus (HPV) vaccine to South Africa's primary health care cervical cancer screening programme. The original model implemented a Markov model with 31 health states (see Supplementary Appendix 1 for depiction of Markov Model), constructed in TreeAge, and performed both one- and multi-way deterministic sensitivity analysis [61]. In contrast, we replicated the model in the R and JAGS languages, performing a comprehensive approach to PSA. We avoid discussion of the original deterministic model's assumptions and focus on the comparative outcomes of the replicated (comprehensive) probabilistic model. More explicitly, the chief purpose of the replication is to establish whether a comprehensive approach would significantly change the original study's conclusion, given its underlying assumptions. We refer the reader to the [original study](#) for a more detailed reading of its key assumptions [61].

3.6.1. Model Structure: an overview of inputs

For the majority of model parameters, we recycled point estimates of the original study and estimated the relevant distribution values respectively. Note that most of the sensitivity analysis outputs for the model parameters are, therefore, equivalent to a standard likelihood-based PSA, via Monte Carlo integration. A comprehensive model requires a prior $p(\theta)$ and likelihood distribution $p(y | \theta)$ to form a full-joint posterior distribution. See references [62] and [181]. However, to exploit the technical advantages which comprehensive decision-modelling can offer, we performed an evidence synthesis on the efficacy of the Cervarix bivalent HPV vaccine using data obtained from eight randomised control trial (RCT) studies, with three additional long-term follow-ups, to form a likelihood $p(y | \theta)$ that was then combined with uninformative priors $p(\theta)$ [68-75, 77, 78, 182]. Notably, the evidence synthesis on the vaccine efficacy parameter estimated the bivalent vaccine to be roughly 93% protective against future HPV infection (3% greater than the original model's assumption of 90% efficacy) [61]. The code of the sub-model used to estimate vaccine efficacy is shown in Figure 10 below, which was implemented using the JAGS language. Costs were evaluated in United States dollars (US \$) and Quality-Adjusted Life Years (QALYs) were the primary measure of effectiveness in both models. Lastly, the study was implemented from a societal perspective, capturing both provider and patient costs.

```
### SUB-MODEL 2: POP. LEVEL VACCINE-EFFICACY.
# Note: this is a fully integrated Bayesian model, as it combines
# evidence directly via the likelihood and a prior.
for (i in 1:Nstud.vac) {
  # Likelihood:
  rA.vac[i] ~ dbin(pA.vac[i], nA.vac[i])
  rB.vac[i] ~ dbin(pB.vac[i], nB.vac[i])

  # Logistic link function:
  logit(pA.vac[i]) <- mu.vac[i]
  logit(pB.vac[i]) <- mu.vac[i] + delta.vac[i]

  # Average effect prior for SUB-MODEL 2:
  mu.vac[i] ~ dnorm(0, 1e-4)
  # Prior for sub-model 2 (Random. pop. effect):
  delta.vac[i] ~ dt(psi.vac, prec.vac, 1)
  # if desired can be ~ dnorm(psi.vac, prec.vac)

  ### Mixed predictive check for SUB-MODEL 2:
  # Predictive likelihood:
  rA.mxd[i] ~ dbin(pA.new[i], nA.vac[i])

  # Predictive logit link function:
  logit(pA.new[i]) <- mu.vac[i] + delta.new

  # Mixed predictive p-value:
  pA.mxd[i] <- step(rA.mxd[i] - rA.vac[i]) - 0.5 *
  equals(rA.mxd[i], rA.vac[i])
}

# Hyperpriors for SUB-MODEL 2:
psi.vac ~ dnorm(0, 1.0e-4)
prec.vac <- pow(tau.vac, -2)
tau.vac ~ dt(0, 1, 1)T(0, )

# Transformations for SUB-MODEL 2:
# Convert LOR to OR
OR.vac <- exp(psi.vac)
# Convert OR to probability for vaccine efficacy
pEfficacy.vac <- 1 / (1 + OR.vac)

# Predicted average
# treatment effect:
delta.new ~ dnorm(psi.vac, prec.vac)

### END OF SUB-MODEL 2.
```

Figure 10. JAGS code used to construct an evidence synthesis assessing the efficacy of the Cervarix bivalent vaccine.

3.6.2. Results

The original study concluded adding an HPV vaccine to South Africa's public cervical cancer prevention programme was potentially a "... cost-effective strategy." [61] Given that South Africa had not established a willingness-to-pay threshold at the time of study, the authors suggested adding an HPV vaccine to treatment as usual would be "very cost effective" if a Gross Domestic Product (GDP) per capita approach was used as a yardstick, with a value of US \$5724 (at a set exchange rate of US \$1 = R6.5) [61]. However, there was considerable uncertainty surrounding the overall conclusion, which the

original study cited to be a result of costs, especially with regards to the cost of the vaccine itself. The comparative results of the original and replicated study are presented in Table 1 below. We provide three separate simulation results from the replicated model due to the inherent variation that occurs when using probabilistic modelling.

Table 3. Discounted costs, effects, and ICER output of original model from a societal perspective. Each simulation is the average of separate PSAs

Original Model			
	Cost (USD)	Effect (QALYs)	ICER
Status Quo: screening only	\$216	24.08	1078
New Programme: screening & vaccine	\$289	24.15	
Replicated Model			
PSA Simulation 1:			
Status Quo: screening only	\$181.8310	25.09503	1062.71
New Programme: screening & vaccine	\$307.9226	25.21368	
PSA Simulation 2:			
Status Quo: screening only	\$181.8801	25.09525	1062.614
New Programme: screening & vaccine	\$307.9025	25.21385	
PSA Simulation 3:			
Status Quo: screening only	\$181.9323	25.09509	1059.968
New Programme: screening & vaccine	\$307.8775	25.21391	

When comparing the overall cost-effectiveness results, the original model's underestimated both the costs and effects associated with the new programme. The original model thus overestimates the Incremental Cost-Effectiveness Ratio (ICER) value comparative to the replicated probabilistic model, as the replicated model presents a cost-effectiveness ratio of roughly \$15 per QALY-gained *less* than the original deterministic model. We believe that this is partly due to the increase in information gained from conducting an evidence synthesis on vaccine efficacy, as our evidence synthesis on the bivalent vaccine estimated efficacy to be roughly 93% protective against future HPV infection (3% greater than the original model's assumption of 90% efficacy) [61]. A comparative difference in costs and effects is expected, due to the increased technical precision of the parameter estimation resulting from performing a probabilistic (comprehensive) approach to decision-modelling. A comparative undervaluation of costs and effects is a well-known phenomenon that occurs from using a DSA approach - a consequence of the technical assumptions imbedded within these methods. Notably, a comparative underestimation of the uncertainty associated with costs and effects is particularly aggravated in instances

of non-linear parameter relationships as well as marginal treatment effects [5, 22]. We refer the reader to more in-depth reading, see references [1], [22], and [5].

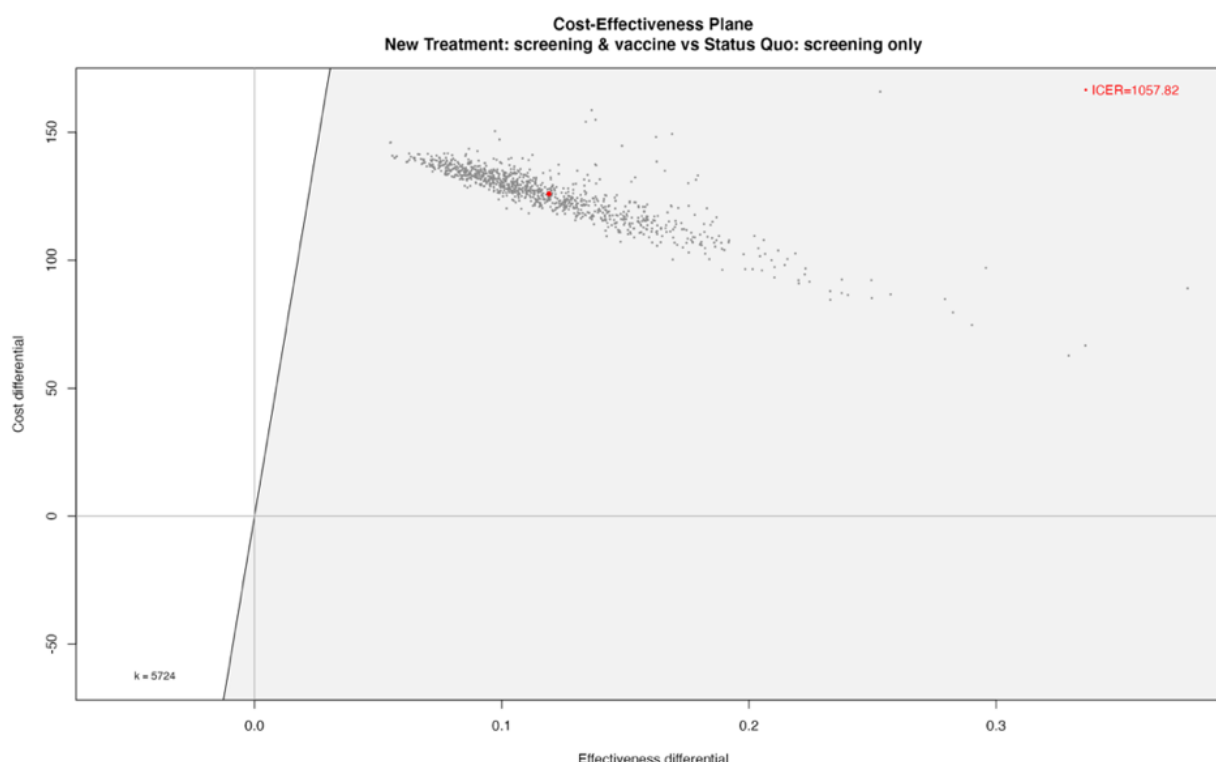


Figure 11. Visualisation of cost-effectiveness plane obtained from the 3rd simulation provided in Table 1 of the replicated case study

However, the overall results remain relatively similar, with the differences having minor practical consequence. For instance, additional simulation runs provided a range of ICER estimates as low as \$1044 and as high as \$1084 per QALY. Thus, despite a clear and anticipated difference in the results between both models - one utilising a deterministic approach and the other a probabilistic (comprehensive) one - we believe that the replicated model does not conclusively lead to a significant inversion of the original (deterministic) model's conclusion. Simply speaking, implementing a comprehensive approach would not – hypothetically - lead to any *real* practical benefit regarding this decision scenario (i.e. a tentative, yet positive decision would most likely remain given the updated results obtained from this exercise). In turn, the difference in the precision of parameter estimation is evident and, considering the technical advantages of this technique, the result would most likely be significant within a decision space given a higher uncertainty of a treatment's costs and effects [1, 2, 5, 22, 145, 183].

Therefore, we strongly believe that the difference in comparative outcomes would have, most likely, been more significant if a thorough use of available evidence had been conducted, i.e. if evidence had been collated on additional model parameters such as prevalence of HPV infection within South Africa. For example, one study estimated the overall population prevalence of HPV to be 66.7% within South Africa [184], while another study found the prevalence of high-risk HPV infection (which the authors defined as the HPV strains 16/18/31/33/35/39/45/51//52/56/58/59) to be as high as 54.1% amongst women aged 18-25 years [185]. Both estimates are considerably higher than the maximum prevalence of roughly 15.63% (for women aged 20 years) obtained from the original study conducted earlier by Sinanovic and colleagues

in 2009 [61]. Thus, hypothetically, the original study's point-estimate of HPV infection could have been used as a prior value combined with more recent data via the likelihood to form an 'updated' posterior distribution (structured in a similar way to the sub-model shown Figure 10 above). Therefore, if a comprehensive approach had been extended to include additional model parameters, it would have undoubtedly provided a more significant comparative difference compared to the original deterministic model outputs.

3.7. Framework

Given the above findings, one may advocate the principle of Occam's Razor, which states 'Entities are not to be multiplied without necessity' (or, in terms of modelling, one should limit the assumptions that are included) [186]. However, the process of selecting a sensitivity analysis method is evidently more nuanced and ought to be, as best as possible, grounded upon the constraints of the decision-context. We therefore believe that the choice of sensitivity analysis should be guided by a flexible 'bang-for-buck' ideology - rather than by a desire to purely minimise a model's complexity - and propose a more refined framework which considers the *fundamental* needs of a decision space, grounded upon a flexible and less restrictive redefinition of the principle termed *Occam's Laser*. Briefly, the philosophy of the Laser offers a higher 'precision' related to the context's decision needs, commanding: do not multiply *fundamental* entities without necessity [186]. In other words, one should ask: *is the method necessary given the fundamental needs of the current health economic evaluation?*

With this in mind, we present several categories relevant to the general health economic evaluation decision-making context. Note that these categories were conceptualised consideration with several of The Professional Society for Health Economics and Outcomes Research's (ISPOR) good modelling practice guidelines and reports [28, 38, 55-59, 165]. Every core category is additionally informed by several sub-items which have been founded in reflexion with the recommendations found in reference [5] (specifically sections 11.8 - 11.10).

Before proceeding however, we encourage the reader to review the tree-diagram (Figure 13) below as a reference to understand the differences in complexity between the DSA and PSA techniques discussed throughout this framework. This will help you to understand the differences in the complexity between popular deterministic and probabilistic sensitivity analysis methods. Additionally, we have chosen to provide a tool which qualitatively ranks the different sensitivity analysis methods presented in this framework to aid analysts in selecting a sensitivity analysis technique that is appropriate given the needs of their decision-space (see Supplementary Appendix 2) [64, 65]. If an analyst cannot implement the desirable sensitivity analysis technique, we hope that the framework will nonetheless provide the decision-maker with a clearer understanding on the choice of sensitivity analysis commonly used within the health economic evaluation field.

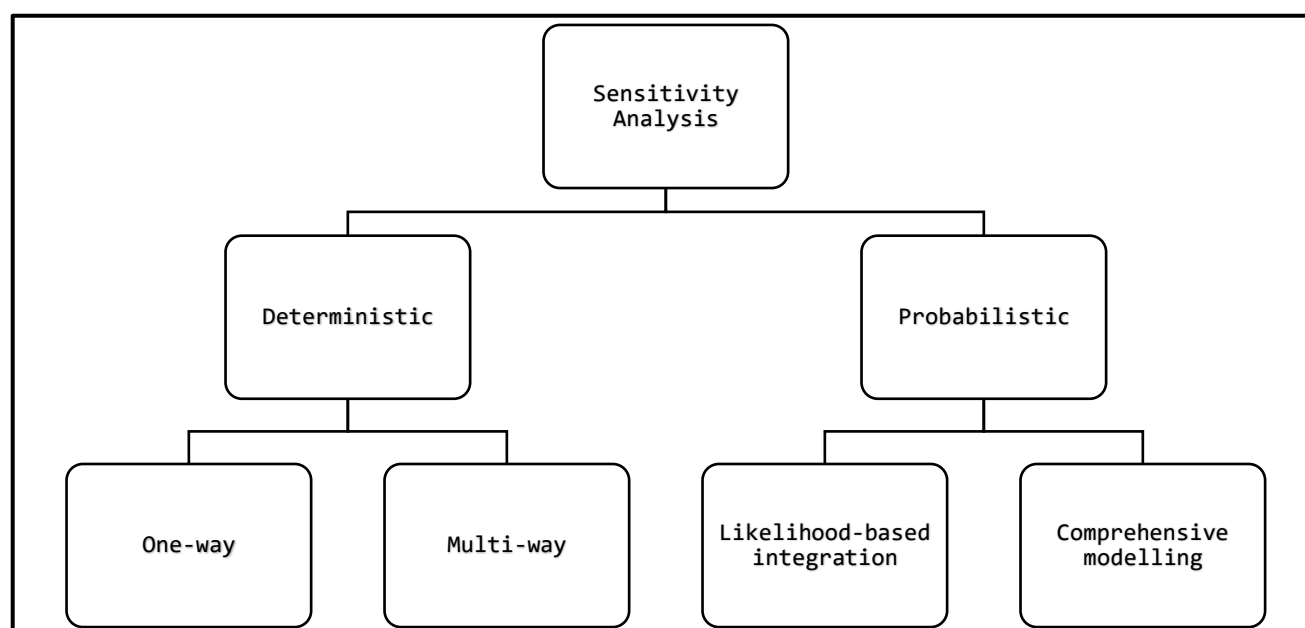


Figure 12. Tree-diagram of established sensitivity analysis methods. The simplest method is one-way, the most complex is comprehensive modelling.

3.7.1. Decision-maker preferences

The first stage in the process of selecting a sensitivity analysis method appropriate for the decision-context should be to consider the preferences of the decision-maker, as it provides for key policy assumptions to be formally incorporated ex-ante into the overall process [1, 5, 36, 54, 183]. Specifically, these preferences revolve around themes of decision-power, investment, as well as risk-aversion.

3.7.1.1. Decision Power

Although the decision-maker's ability to delay the decision should not be the most formative feature when choosing an appropriate sensitivity analysis within MICs, as DSA or PSA methods may be suitable irrespective of whether a decision-maker can delay the decision, employing a Value of Information (VOI) analysis may be valuable if the decision-maker can, in fact, defer the decision. Consider, for instance, a new treatment t_1 versus a status quo treatment t_0 , where t_1 only has an acceptable probability of being cost-effective at a willingness-to-pay (WTP) threshold above what is considered an efficient use of health care resources. Though there may be a high degree of uncertainty (variability) in the cost-effectiveness of t_1 versus t_0 , choosing t_0 over t_1 may impose an unnecessary loss to society as patients would not receive the potentially cost-effective treatment t_1 . VOI resolves this issue by providing the decision maker with an estimate on the cost of delaying a decision to gather more information. From a decision-theoretic perspective, gaining further information about t_1 reduces the uncertainty associated with the decision. If VOI analysis is indeed considered valuable given the decision-context, implementing a PSA approach is, however, requisite. Therefore, this item should be carefully considered in relation to item 2.1, as VOI desires an advanced knowledge of decision theory and modelling techniques.

3.7.1.2. Investment

Within MICs, the appropriateness of a sensitivity analysis method should be partially considered in relation to the level of fiscal space demanded by the proposed intervention. For instance, if the intervention demands a relatively small fiscal investment, and the decision uncertainty is driven primarily by individual model parameters such as overall costs or health effects, implementing probabilistic sensitivity analysis (PSA) methods - instead of one- or multi-way deterministic sensitivity analysis (DSA) - are unlikely to fundamentally change the decision.

In contrast, costly interventions, which demand higher levels of fiscal space, may desire the use of PSA methodologies, because DSA methods cannot provide an adequate understanding for the scale of the decision's uncertainty. Hence, as the potential opportunity-loss (which is the alternative the decision-maker forgoes when making the decision) increases in proportion to the level of fiscal space required by a decision, it is important to realise that the practical consequences of choosing between DSA- and PSA-based methodologies may become more acute.

3.7.1.3. Risk Aversion

Most decision-makers are assumed to be risk-neutral. In such scenarios, choosing the decision with the highest ICER or expected 'net benefit' is reasonable. If a decision-maker is indeed indifferent to decision uncertainty (i.e., is risk-neutral), the appropriateness of the sensitivity analysis method ought to be more heavily weighted against items 1.1, 1.3, 2.1, 2.2, and 3. But, within MICs especially, the assumption of risk-neutrality may not always be appropriate. Because MICs face tighter budget constraints and hence the potential for relatively greater opportunity-loss, the decision-maker may place significant value on limiting uncertainty to avoid making the wrong decision. Incorporating a risk-aversion parameter into the decision-model thus enables the analyst to reflect this preference. However, this does require a more general form of the utility function:

$$U(\theta^t) = \int \frac{1}{r} [1 - e^{-rb}] p(b | \theta^t) db$$

where $r > 0$ is the risk coefficient and b is the incremental benefit, defined as $IB(\theta) = k \times \Delta_{effects} - \Delta_{costs}$ (k is the WTP threshold). As this introduces non-linearity into the utility function, *only* PSA methods are appropriate. Furthermore, given the context of MICs, the analyst should also note that reflecting risk-aversion is perhaps more efficiently implemented via posterior simulation (comprehensive modelling) to obtain PSA, which desires more purpose-specific languages such as R coupled with BUGS/JAGS or STAN to be practical. As incorporating risk-aversion into the decision-model similarly requires an advanced knowledge of decision-theoretic concepts, this item must be deliberated in careful conjunction with the decision-maker's decision power (item 1.3) and resources available to the analyst (further discussed in item 2.1.) [1, 5, 36, 54, 183].

3.7.2. Analytical Considerations

Once the preferences of the decision-maker have been considered, the analyst should turn to the items associated with their available resources. These categories are specific to the skills toolbox of the analyst as well as the available resources available to them. More precisely, selecting an appropriate sensitivity analysis method requires careful consideration for the resource constraints of the decision-context, both individual and systemic [5, 28, 38, 55-59]. Again, the following

categories were conceptualised in consideration with several of the ISPOR good modelling practice guidelines and reports [28, 38, 55-59, 165] and every core category comprises several sub-items founded in particular reflexion with the recommendations found in reference [5] (sections 11.8-11.10).

3.7.2.1. Available Resources

We define resources in relation to the analyst, specifically their skills and the time available to them. First, an analyst ought to consider their proficiency for implementing more complex, probabilistic sensitivity analysis methods. Attempting to produce methods unfamiliar to the analyst may open significant opportunity for modelling error. This too relates to time, which has an equally significant bearing on the decision-space and thus the appropriateness of a given sensitivity analysis method. If the available time to produce a health economic evaluation is minimal, using more time-demanding probabilistic methods – especially comprehensive-modelling – may be less fruitful, (e.g., in terms of the practical and technical trade-offs that can arise and the limited time for model validation compared to more straightforward deterministic methods). It is, however, still important to consider that if the analyst has advanced their skillset and has the time to perform posterior simulation to obtain PSA, there may be an economies of scale effect which can be beneficial within MICs. For instance, if a network meta-analysis is advantageous for the given decision-problem, coupled with a desire to impute statistical relationships and provide the decision-maker with a probabilistic sensitivity analysis, posterior simulation (i.e., comprehensive modelling) offers a more integrated and practically efficient approach to performing all of these stages of the analysis within a single, unified structure (compared to the likelihood-based approach to PSA for example).

3.7.2.2. Indirect Evidence

Network Meta-Analysis (NMA) methods, also referred to as Indirect- (ITCs) and Mixed-Treatment Comparisons (MTCs), are useful if little-to-no direct (head-to head) comparisons of the alternatives being considered are available. If there is no direct evidence, an ITC may be performed to obtain relative treatment effects between two alternatives. Alternatively, an MTC is also possible if both direct and indirect evidence can be combined, which may concomitantly help to reduce decision uncertainty. However, quantitative evidence synthesis may, in fact, heighten the decision uncertainty, especially if only indirect evidence is available or, for example, there is significant heterogeneity between studies used in the analysis. It is also likely that the evidence will have to be generalised from an external jurisdiction and then applied to the MIC context of interest. If a quantitative evidence synthesis includes indirect evidence, we thus strongly encourage PSA based sensitivity analysis methods within MICs. Implementing a likelihood-based sampling approach to likelihood-based PSA via Monte Carlo integration may be sufficient, where point-estimates can be used to define functional relationships between the parameters of interest within spreadsheet software such as Microsoft Excel®. However, even if both direct and indirect evidence is used, the analyst ought to consider the strengths and efficiency of posterior simulation, as it provides a naturally coherent framework in which to conduct both a quantitative evidence synthesis and decision-model, while also simultaneously accommodating the uncertainty associated with indirect evidence by providing a natural PSA output. Again, this should be carefully considered in relation to item 2.1.

3.7.3. Policy Context

Lastly, consideration for the policy context is perhaps most meaningful [36]. An analyst must be mindful of the decision-maker's technical point-of-view, as they may not be familiar with software needed to implement more complex sensitivity

analysis methods, such as when performing fully-Bayesian modelling with BUGS/JAGS. If this is indeed the case, the analyst ought to consider if adopting complex methodologies is beneficial, or, for example, whether the model would be better received (as well as understood) by utilising popular software such as Microsoft Excel® [38] - as might have been the case with the original HPV model (created by Sinanovic et al. in 2009) [61]. On reflection, for instance, the replicated case study is constructed using over two-thousand lines of code, and although more technically transparent for analysts and decision-makers who are familiar with the R and JAGS languages, it is understandably illegible for those who are not. Moreover, concern for model interpretation must be further directed towards the inevitable variation in the cost-effectiveness values produced by probabilistic methods. For example, note the changes that occur between the three simulation runs of the replicated model, provided earlier in Table 1. Although technically insignificant if reproduced within a reasonable range of values, this may be perceived as unreliable by a decision-maker (compared to the consistency of deterministic methods).

Bearing these issues in mind, the primary aim of health economic evaluation is to provide tools which are *interpretable* for the decision-maker, regardless of technical precision [36, 171]. It is important to remember that health economic decision-models are not solely intended as predictive tools, but also *communicative* tools which are used by decision-makers to weigh the possible consequences of their decision [2, 3, 46]. Technical compromises such as these therefore embody the spirit of a ‘succussive-yet-limited’ strategy to gradually improving public health care provision [171]. As such, providing a simpler model, which is *interpretable* to the decision-maker, is perhaps better suited to the political context of the decision-problem than attempting to provide technically superior, yet substantially more complex model [171].

3.8. Conclusion

To our knowledge, this is the first paper attempting to develop a framework which supports the choice of sensitivity analysis methods within MIC climates. The framework identified and centres on the three main areas of Decision-Maker Preferences, Analytical Considerations and Policy Context. The paper contributes to closing a notable methodological gap in current health economic evaluation literature by adding to the development of more uniform specifications and tools intended for use within MIC jurisdictions. In turn, this will help reduce the methodological variations that are apparent between economic evaluations conducted within MICs, where there is a notable discrepancy in the implementation of more advanced analytical techniques. Most importantly however, by showing how a comprehensive approach to health economic evaluation has the potential for improving decision-making given the appropriate circumstances, we hope the framework will spur on further discussion for the capacity development of the technical skills required for conducting such analyses within MIC jurisdictions.

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3.10. Supplementary Appendix 1: Markov Model

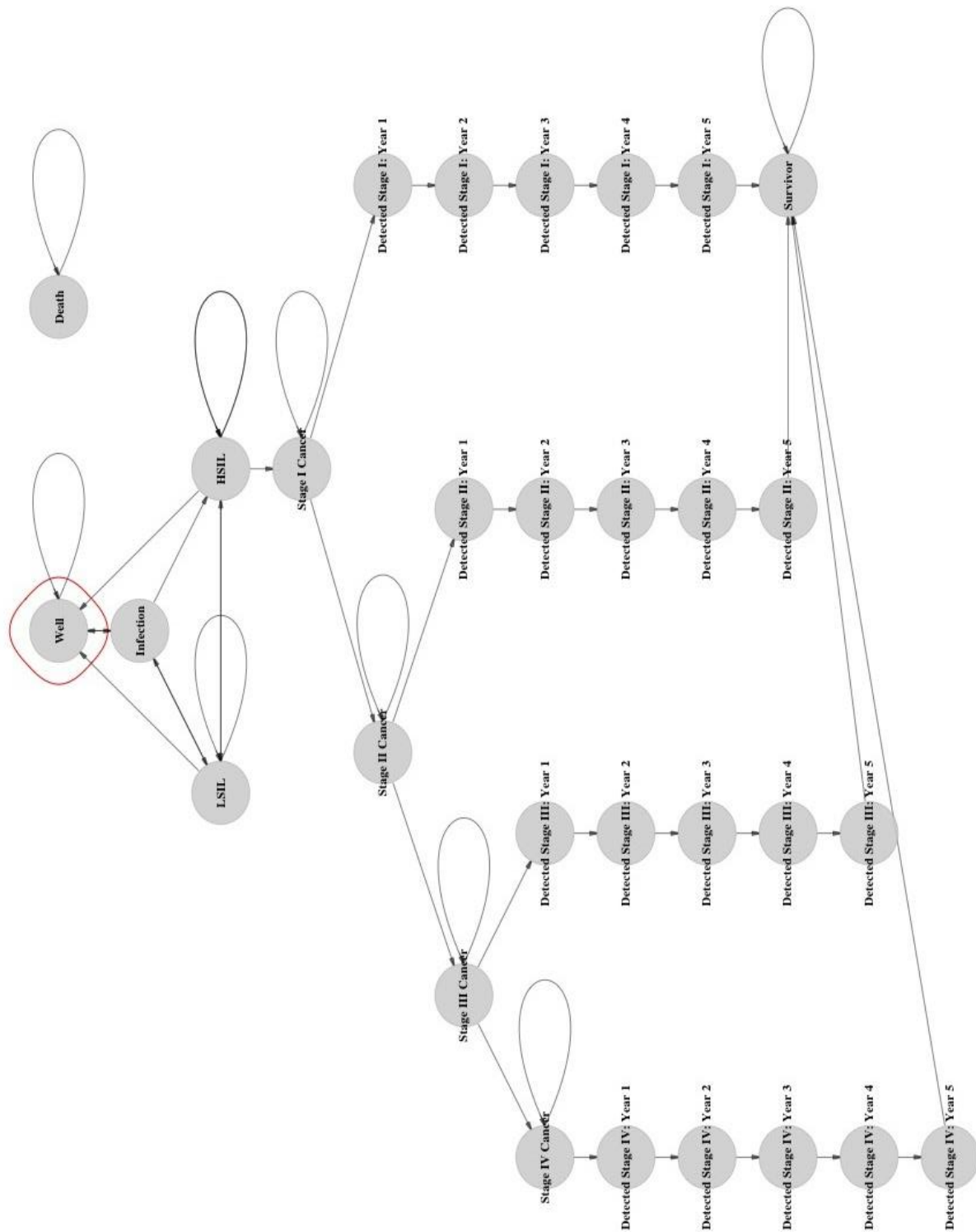


Figure 13. Markov Model structure. Note that the state of death is assumed reachable from all other states and that LSIL and HSIL are acronyms for low- and high-grade squamous intraepithelial lesion respectively.

4. Part D: Policy Brief

A Sensitivity Analysis Framework for Health Economic Evaluation in Middle Income Countries: Appropriately Incorporating a Comprehensive Approach

Joshua Soboil²

Introduction

The need for high-quality health economic decision-modelling techniques is becoming progressively apparent as Middle-Income Countries (MICs) move closer towards Universal Health Coverage (UHC).

- Fundamental to high-quality health economic decision-modelling is the use of robust sensitivity analysis.
 - However, the extent of information provided by a sensitivity analysis is *strongly* dependent on the type of sensitivity analysis that is employed. We summarise nuances concerns below:

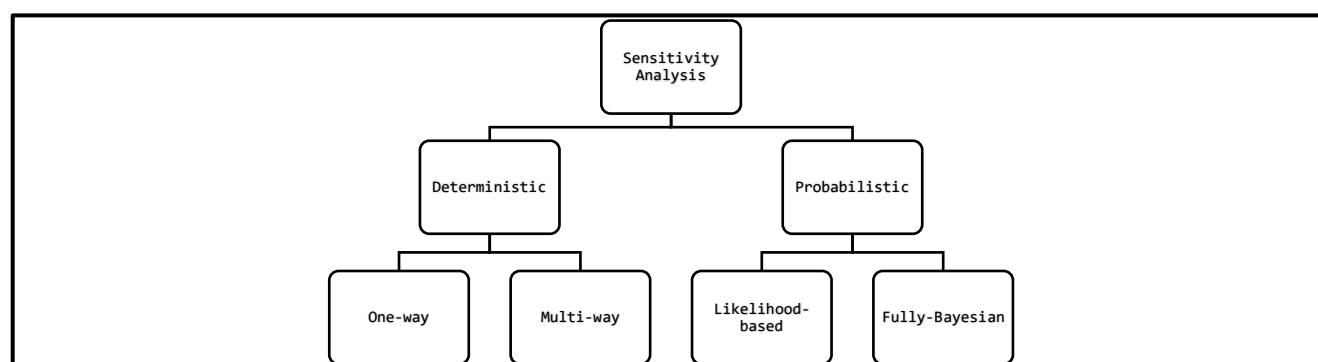


Figure 14. Tree-diagram of established sensitivity analysis methods.

- Deterministic approaches are:
 - Simple sensitivity analysis techniques.
 - Generally stratified into one- or multi-way sensitivity analysis, whereby an analyst manually varies selected input parameters of a model, either one-at-a-time or simultaneously. The simplest method is one-way.
 - Deterministic approaches provide a basic understanding of how changes in parameter values can affect the overall cost-effectiveness of a health care programme.
- Despite ease-of-implementation, deterministic techniques cannot inform decision-makers about how probable the decision is, in fact, the wrong decision and do not reflect problems of stochasticity ('randomness') which is a fundamental aspect of making decisions under uncertainty.
- They also desire use of empirical data for variation estimates.
 - Analysts working in MICs often have limited access to quality data and often resort to collection of empirical evidence, usually through observation of the setting related to the treatment under investigation, or evidence obtained from external jurisdictions.

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- However, using data from external jurisdictions has significant influence on uncertainty.
- **Probabilistic techniques** are:
 - dependent upon which approach to probabilistic sensitivity analysis technique is chosen.
 - generally achieved via use of **Monte Carlo simulation**, which is a method of randomly sampling from specific probability density distributions over many, many iterations.
 - **Monte Carlo** sensitivity analysis:
 - is typically performed in standard spreadsheet software, therefore incorporating important statistical relationships into the final health economic evaluation model can prove cumbersome and, can open up significant opportunity for error to enter into the overall decision-model.
 - can also be fragile in instances of scarce data.
 - also achieved with **Markov Chain Monte Carlo** (also called a comprehensive-modelling approach).
 - **The Markov Chain Monte Carlo** approach:
 - provides a probabilistic sensitivity analysis as a natural output of the simulation and implicitly induces statistical relationships between parameters - such as parameter correlation.
 - enables for a parsimonious means of incorporating complex statistical techniques - such meta-analysis – and disparate sources of data.
 - arguably demands more sophisticated software tools to be efficient - tools which are understandably unfamiliar to many decision-makers within MIC climates.
 - can be considerably demanding of an analyst's time.
 - Practical trade-offs of skills and time requirements are important to consider in relation to the benefits of an increased technical precision within MIC settings. MICs face frequent shortages of research capacity.

Approach

- Performing more sophisticated sensitivity analysis methods can be draining on already an already capacity strained context.
 - It is therefore important to develop a framework which will help analysts appropriately incorporate these sensitivity techniques within these climates.
- To develop an understanding of the likely trade-offs of using a comprehensive (probabilistic) approach to decision-modelling, we replicated a decision-model (originally deterministic) to determine whether using more a complex approach would have significantly changed the original study's conclusion.
 - The original model was used to inform the cost-effectiveness of adding a Human Papillomavirus (HPV) vaccine to South Africa's public cervical cancer screening programme.
 - The model encompassed 31 different health states using a Markov model to simulate the life-time probabilities of moving from one health state to another, year-on-year.

- The original study concluded adding an HPV vaccine to South Africa’s public cervical cancer prevention programme was potentially a “... cost-effective strategy.” [45] The authors suggested adding an HPV vaccine to treatment as usual would be “very cost effective” if a Gross Domestic Product (GDP) per capita approach was used as a yardstick threshold, with a value of US \$5724 (set at an exchange rate of US \$1 = R6.5) [45].
 - There was, however, still considerable uncertainty surrounding these estimates, cited due to the costs of the vaccine.
 - The original study utilised a deterministic approach to sensitivity analysis.

Results

The replicated model did not result in a change to the original model’s conclusion in a significant manner, which suggests that:

- implementing a comprehensive approach has not – hypothetically - lead to any real practical benefit in this case study despite the obvious increase in technical precision.
 - the difference in the precision of parameter estimation is nevertheless evident and, considering the technical advantages of a Markov Chain Monte Carlo sensitivity analysis approach, the result would likely be different given a decision space which faces acute shortages in data relating a treatment’s costs and effects.
 - Given these findings, the process of selecting a sensitivity analysis method is clearly nuanced and ought to be, as best as possible, grounded upon the constraints of the decision-context.
- We have therefore developed a framework (Table 1) which aims to help appropriately incorporate more resource demanding techniques within MIC contexts, which centres on a ‘bang-for-buck’ ideology that focuses on the needs of the decision-context rather than on the complexity of the decision-model.

Conclusion

- The first stage in the process of selecting an appropriate sensitivity analysis method should consider the preferences of the decision-maker [5, 15, 57, 58, 64].
 - First, understanding the power of the decision-maker and their ability to influence decision-making process is imperative. Second, is the idea of investment. The higher the investment, the higher the quality of sensitivity analysis should be desired. The final theme in this category relates to a decision-maker’s risk aversion. Higher the risk-aversion signals a desire for higher-quality methodology.
- The second category fundamental to influencing the choice of appropriate sensitivity analysis concerns the available resources given the decision context. These categories are specific to the contextual abilities of the analyst as well as the resources available.
 - Selecting an appropriate sensitivity analysis method must be carefully aligned with the resource constraints of the decision-context.
- Lastly, we encourage the analyst to consider the policy context. This is, perhaps, the most important category, as it emphasises the benefits of practical gains rather than purely technical.
 - The primary aim of any health economic evaluation should *always* be to provide tools that are interpretable for the decision-maker, regardless of technical precision.

Implications and Recommendations

- It is clear that more complex approaches to sensitivity analysis lead to improved technical precision for health economic evaluations. However, it is also evident that weighing up the technical and practical pros and cons associated with popular sensitivity analysis approaches is critical to help establish the sustainable use of scarce analytic resources.
- By using this framework, it aids the analyst in selecting an appropriate sensitivity analysis technique given their decision context.
 - More specifically, the framework helps to integrate the high-quality Markov Chain Monte Carlo sensitivity analysis technique into the general context of MICs more reasonably, as these contexts face a clear need to balance the technical benefits of a more demanding techniques with the practicality of their implementation.
- In addition to the above, we hope that this research will spur on further discussion regarding the use of more comprehensive modelling techniques.
 - As MICs edge closer towards UHC, and a continually rising demand in health care, using more precise methods, which help to avoid the opportunity-costs associated with making the wrong decision, will be critical. We therefore encourage the development of more specialised skills across MIC jurisdictions going forward.

Table 4. Sensitivity Analysis Framework for Health Economic Evaluation in Middle Income Countries

Decision-Maker Preferences:			Analytical Considerations				Policy Context	
			Available resources		Indirect Evidence			
Decision Power	Investment	Risk Aversion	Available Skills	Available Time	Costs	Effects	Knowledge of Topic	Technical Expertise

5. Part E: Appendix

5.1. Supplementary Appendix: A

5.1.1. Probability: a brief historical and technical supplement

The subject of probability has held long interest in human endeavours, being a point of known philosophical enquiry as far back as Plato and Aristotle [119, 132, 187, 188]. Of course, however, such ancient usage is unlike the term we associate with contemporary statistics [188]. More recently then, the subject is historically associated with gambling and games of chance [49, 111, 132, 189]. Thoroughly detailing how to act in such circumstances has naturally found interest in many notable figures throughout recent history. For example, letters between both famous physicist and mathematician B. Pascal (1623-1662) and lawyer P. de Fermat (1607-1665) in 1654 is one of the earliest known records explicitly attempting to create a rigorous concept of probability [132]. Interestingly, the motivation for this particular venture into probability is owed to a two-player game of chance which was interrupted for some undisclosed reason [132]. Following the disruption, one player (whom was a friend of Pascal's) wrote to Pascal wanting to know how to divide the winnings of the game fairly, as the players were unable to finish it, and simply wanted to know the most likely outcome [132]. But Pascal and Fermat never managed to set out a rigorous theory, and it took several more decades for the development of a more systematic definition, in the posthumous work of J. Bernoulli (1655-1705) in the early 18th century, titled *Ars Conjectandi*[‡] [17, 119, 132, 189, 190]. However, what *is* probability?

Roughly speaking, probability can be defined as a systematic and logical framework for quantifying uncertainty and randomness; often deemed the logic of uncertainty [49]. A 'naïve' definition of probability can be expressed as the total number of ways an event could happen divided by the total number of outcomes [49]. Note that an event is a subset of the total sample space, thus a partitioned set of outcomes [49]. Obviously, this view holds probabilities to be a simple *proportion* of outcomes [49, 132]. For example, if we let A be an event of an experiment with a *finite* sample space S , the *naïve* probability of A can be expressed as

$$P_{\text{naïve}}(A) = \frac{\text{the number of outcomes contained in } A}{\text{total number of outcomes in } S}$$

This is, however, a highly restrictive description of probability based on several weak assumptions[†] [110, 132]. Hence, the concept of probability can be more rigorously defined as a *probability space* that consists of a sample space S and a *probability function* $P(\cdot)$ which takes an event A_i from a sample space S as input, where $A_{i,\dots,n} \subseteq S^*$, and returns $P(A_i)$ as

[‡]Technically, the first known formal axiomatic system of probability was only developed later by A. Kolmogorov (1903-1987) in 1933.

[†]Most significantly, the naïve definition of probability assumes that all outcomes are equally likely and, moreover, it requires a finite sample space.

^{*}This can be read as 'event A with a set of possible outcomes $i, \dots, n$ is contained in the sample space S '. Thus, an event is a set of possible outcomes, a subset of the total sample space. For an obvious example, an arbitrary binary event may have a set of outcomes (1,0).

output, a real number between 0 and 1 [49, 119]. Importantly, a probability function must satisfy the following axioms in order to be logically consistent, i.e. *coherent** [49, 109, 117]. First is the rule of *convexity* [117]. The rule stipulates that any probability lies between the limits of 0 and 1, and that any event once observed is evidently true, i.e. it has a probability bounded at the upper limit of 1 [117]. Second, probabilities must be nonnegative, such that $P(A) \geq 0$ [49, 117]. Third, the sum probability for all *outcomes* $1, \dots, n$ within an *event (set)* A must sum to one, so $P(A_{1,\dots,n}) = 1$ [49, 117]. These axioms can be extended further in accordance with the nature of the event, i.e. whether the outcomes are *disjoint* or *jointed* [49, 117, 132]. Thus, if $A_1, A_2, \dots, A_n$ are *disjoint* (‘mutually exclusive’) outcomes, they are strictly added

$$P\left(\bigcup_{i=1}^{\infty} A_i\right) = \sum_{i=1}^{\infty} P(A_i)$$

Accordingly, the intersection of any two *disjoint* events or outcomes is null, as $A_i \cap A_{\infty} = \emptyset$, i.e. it is an empty set [49, 132]. This is also referred to as an ‘*additive*’ sequence of events [49]. Thus, the total probability of a sequence of *disjoint* events or outcomes is equal to the sum of its parts. In contrast, if a sequence of events or outcomes are *joint* events, i.e. they can occur simultaneously, the total probability is equal to the product of its parts [49, 117, 132]. This is referred to as a ‘*multiplicative*’ sequence of events, and in notational form can be, perhaps crudely, expressed as

$$P\left(\bigcap_{i=1}^{\infty} A_i\right) = \prod_{i=1}^{\infty} P(A_i)$$

Hence, the intersection of any two *joint* events is greater than null space, as $A_i \cap A_{\infty} \neq \emptyset$ [49, 119, 132]. Thus, joint probability can simply be thought of as a measure for two or more events occurring simultaneously [132].

5.1.1.1. Some Further Nuance

In a standard pack of 52 cards, there are several types of cards that cannot happen simultaneously and, thus, are ‘either-or’ type events. For example, one can either draw a card belonging to the suit of clubs or hearts, but not both. Therefore, the *disjoint* probability of picking a card that is either from the suit of clubs or hearts is

$$P(\text{clubs} \cup \text{hearts}) = \frac{13}{52} + \frac{13}{52}$$

$$P(\text{clubs} \cup \text{hearts}) = \frac{1}{2}$$

Because there are 13 cards in each of the 4 suits, the chance of getting ‘either-or’ is 50%. In contrast, there are certain characteristics in a deck of cards that can happen simultaneously. For example, the *joint* probability of picking a card that is simultaneously black and a Queen is

*The axioms of probability rest upon the formal foundations of Measure theory, though there is obvious nuance [12].

$$P(\text{black} \cap \text{Queen}) = \frac{26}{52} \times \frac{4}{52}$$

$$P(\text{black} \cap \text{Queen}) = \frac{2}{52} = \frac{1}{26}$$

Here half the cards are black, yet we are limited by the fact that there are only 2 Queens that can be black (either from the suit of clubs or spades). To move from this point, we can also pose the question of whether knowing the type of card, for example, could provide information on the probability of drawing other specific types of cards. Generally speaking, can information about one event provide information about another?

Whenever we observe new evidence, we may acquire information that can affect our uncertainties [117]. This process is known as *conditional* probability [49, 132]. The concept allows us to solve complex probability problems by using case-by-case reasoning and one can, in fact, think of all probabilities as being conditional (as there is arguably always some background information inherent in every probability) [37, 49]. A common illustration is to provide a story of uncertainty that we can all associate with: the weather [49, 117].

Take an event R , for example, which represents a rainy day. Let $P(R)$ be our assessment of the probability that it will rain, prior to looking outside [49, 117]. If, for example, we then look outside and see grey and gloomy clouds in the sky, we can safely assume that the probability of rain is higher than what we had previously thought [49, 117]; now, let C be the observed event of grey and gloomy clouds. Then, now that we have observed grey and gloomy clouds, which has changed our presumption about the chance of rain, and denote this as $P(R | C)$, which is read as “the probability of R given C ” [117]. As stated by Blitzstein and Hwang (2019), when we go from $P(R)$ to $P(R | C)$, we say that we are “conditioning on C ” [49].

We can also acknowledge that, as we go about our day, we may obtain more and more information about the condition of the weather. For example, if we observe that the events $B_1, \dots, B_n$ occurred we can then update our conditional probability of rain, given the new evidence, which is written as $P(R | B_1, \dots, B_n)$ [49]. Note that, in relation to the rule of convexity, if we eventually observe that it does indeed start to rain, our conditional probability becomes 1 (i.e. it is certainly ‘true’) [49, 117]. Using the notation above, the technical formula for calculating *conditional* probability can be written as

$$P(R | C) = P(R \cap C)$$

However, new evidence may not indeed result in any change to our uncertainty about some event [49]. In such cases, this is known as *independence*, and is equally an integral part of probability theory [49, 119]. Despite risk for some obvious tautology, we can then simply define independence as being a state where two events have no effect on each other, and hence are events that are *symmetric* in relation [49, 132]. In notational form, independence of two events can be expressed as $P(A \cap B) = P(A)P(B)$. This is equivalent to saying $P(A | B) = P(A)$, i.e. that is, conditioning on B gives no additional information on A [49]. As a corollary, this further enables us to know that, *vice versa*[†] [49],

[†]One must, however, be aware of invalid inversions.

$$P(A) = P(A \cap B) + P(A \cap \bar{B}) = P(B)P(A | B) + P(\bar{B})P(A | \bar{B})$$

Additionally, the contrast between independence and dependence can be intuitively thought as the difference between sampling *with replacement* and *without replacement*[†] [49, 132]. Let us again consider an example using a deck of cards. As mentioned earlier, an independent sequence of events is *symmetric*. Hence, if we were to draw two cards indiscriminately, *with replacement*, and shuffle the deck between each draw, we could express this as

$$P(B | A) = P(B \cap A)$$

$$= \frac{1}{52} \times \frac{1}{52} = \frac{1}{2704}$$

and

$$\therefore \sqrt{\frac{1}{2704}} = \left(\frac{1}{52}\right)^2$$

by the law of symmetry, it is obvious that these are equivalent as $P(B | A) = P(B)$. Now Suppose that we draw a Jack of some arbitrary suit first. What would the probability be for a Jack, of any suite, to appear on the second draw? Let A represent the first draw being a Jack of some arbitrary suit and let B represent the probability of obtaining a Jack on the second draw,

$$P(B | A) = P(B \cap A)$$

$$\therefore P(B | A) = \frac{3}{51} \times \frac{4}{52} = \frac{1}{221}$$

It is essential to take cognisance of the lack of symmetry here, as $P(B | A) \neq P(B)$ [‡].

5.1.2. What are Random Variables?

A random variable X is a function which assigns a value from the real number line $\mathbb{R}$ to every possible outcome in a sample space S , so that $X: S \rightarrow \mathbb{R}$ [49, 109]. From this, it is then possible to enquire about the probability of a specific outcome,

[†]Technical note: *independence* is distinct from *disjointness*. If $P(A \cap B) = 0$, this means that A and B are disjoint, and the events do not occur simultaneously – they are ‘either-or’. For instance, we cannot sample any card that is both a King *and* a Queen in any single draw from a standard deck of cards. Additionally, knowing one of two events has occurred, for example, could provide information that the other event has not occurred, such that if $P_1 \rightarrow \neg P_2$.

[‡]Which would demand the symmetric state $\sqrt{\frac{1}{289}} = \left(\frac{3}{51}\right)^2$.

via the *distribution* of the said outcomes [49, 109]. Although seemingly abstract, this intuitively means that if we were to have a set of binary outcomes for instance, a random variable function would sample from the sample space S , assigning real number values to each sample, such as $\{0,1\}$ indicating a binary relation between outcomes. After repetitive sampling of the sample space S , this could form a set of outcomes which conform to a random sequence of values, such as $X = \{0, 1, 0, 1, 0, 0, 1, 1, 1, 0, 0, 1\}$. From here we can ask what the probability of a random variable taking on the value of 1 is, or in the language of probability, $P(X | x = 1)$.

In the above example this is simply $\frac{6}{12}$, or 50%. Continuous variables, however, demand that we ask what the probability of random variable falling within a particular range is, e.g. $P(a \leq X \leq b)$, where a is the lower bound and b is the upper bound of a specified range[49]. Regardless, a random variable can be loosely thought to behave much like a ‘fair’ die [49, 109]. However, although the roll of a die can serve as an intuitive schema, it is necessary to understand that random variables still display certain parametric behaviours that relate to the distributional form of their outcomes [49, 109]. For instance, assuming a fair die would imply a discrete uniform distribution, so that $X \sim \text{uniform}(C)$ where the possible outcomes are $C = \{1, 2, 3, 4, 5, 6\}$. Or, for instance, if we wanted to model time-to-event data, we could make use of the Weibull distribution. Given $T = X^{1/\gamma}$, we can denote this type of distribution as $T \sim \text{Wei}(\lambda, \gamma)$ [49, 109].

5.1.3. Utility - a general background

Utility theory is a core concept embedded within health economic decision-modelling; roughly, it informs the praxis of quantifying an intervention’s health benefit in health economic evaluation models [1, 22]. When making decisions under uncertainty however, we must harness the more general idea of expected utility. The historical concept of expected utility was first popularised during the Age of Enlightenment (1685-1815) - a period where the notion of a ‘fair’ gamble began to be thought of as equivalent to the ‘expected’ payoff, i.e. the ‘average’ outcome, in a game of chance[‡] [17, 149, 150]. Thus, like probability theory, the concept of expected utility owes much of its genealogy to gambling [149].

A key contributor to the initial grounding of expected utility theory was D. Bernoulli (1700-1782), whom realised that the focus on the absolute mathematical quantity of an outcome was subtly different to the relative motivation for the choices people made [17, 149, 150]. Bernoulli’s formulation of utility, however, had a critical flaw in that it was only really applicable to long-run frequency events (rather than once-off gambles) [149, 150]. It took several more centuries for the first proper axiomatisation of utility and rational preferences, in the ground-breaking work of J. von Neumann (1903-1957) and O. Morgenstern (1902-1977) published in 1947* [17, 150, 191]. Though it assumed ‘fixed’ objective probabilities, the Neumann-Morgenstern framework readily enabled for the systematic elicitation of individual preferences, such as in the ‘standard gamble’ approach regularly used to inform quality-of-life measures in health economics [1, 17, 22]. The approach applies a discrete probability distribution $p(z)$ to a set of outcomes (i.e. a lottery) with a set of utilities associated with

[‡]C. Huygens (1629-1695) is known to have implemented a mathematical expectation framework prior to this, though it only considered the financial price of a lottery, i.e. a ‘certainty equivalent’, today commonly known as an insurance premium. Thus, his work still focused on the ‘price’ of an outcome, not an ‘intrinsic’ subjective value. However, D. Bernoulli did use Huygens’ work as a steppingstone for his own arguments.

*This is detailed in the book “Theory of Games and Economic Behaviour” [19].

each outcome $u(z)$ [17]. From this perspective, it is argued that the decision-maker must choose the action a which maximises the expected value [17]. If the utility preference for a pair of actions is $a_1 \succ a_2$, this implies

$$u_\theta(a_1) = \sum_z u(z) p(z) > u_\theta(a_2) = \sum_z u(z) p(z)$$

Nevertheless, having ‘fixed’ objective probabilities hindered Neumann-Morgenstern utility theory from fully establishing a proper formulation of decision-making under uncertainty [17]. Specifically, it did not expand on how to deal with the uncertainty of unknown future states of the world, and thus it principally concerned making decisions under risk (where a set of probable outcomes of an action are knowable to a decision-maker, e.g. in a game of roulette) [17, 150, 192].

It took the combined yet independent work of F. Ramsey (1903-1930), B. de Finetti (1906-1985), and L. Savage (1917-1971), with later notable contributions by D. Lindley (1923-2013), to provide a clear, tractable formulation of decision-making under uncertainty [17, 18, 116, 119, 124, 148, 149]. A novel attempt to axiomatize decisions under uncertainty was first by Ramsey in his article ‘*Truth and Probability*’, though the seminal work of Savage was most fundamental to the development of a more rigorous mathematical framework, incorporating continuous random variables and universal outcomes [49, 119, 124].

Regardless, Ramsey aptly characterised decision-making under uncertainty as “... the logic of partial belief...”, and argued that it ought to be considered a means of inferring how best to act given one’s present state of knowledge [124]. However, most significant for the reader to appreciate is that a formal axiomatisation of decision-making under uncertainty has enabled for the methodical incorporation of subjective judgement and real-world uncertainty into decision-making, enabling a systematic approach to decision making under uncertainty [17, 143].

5.1.3.1. Using subjective inputs

The formalisation of subjective probability can be largely attributed to the work of de Finetti. First and foremost, de Finetti explored the axioms of probability to be “conditions which characterize coherent opinions... and which distinguish them from others that are intrinsically contradictory.” [116] Finetti established this formally using mathematical logic, applying his argument to the concept of a Dutch Book bet [17]. Roughly, a Dutch Book is when a gambler bets on a system of incoherent probabilities, i.e. the probabilities do not conform to the formal axioms of probability [17]. Interestingly, such probability systems are often created by sports bookies to guarantee a profit [17]. Conversely, a gambler is guaranteed a loss. If the gambler hypothetically knew this information prior to placing the bet it would imply irrational behaviour, i.e. the person is apparently in discord with reason and logic, given that the bet is a sure loss [17, 116, 193, 194].

Although the concept of a Dutch Book predates the work of de Finetti, de Finetti used it to exquisitely develop a logical validation and probability calculus for the use of subjective probability judgements when making decisions (e.g. using expert opinion) [17, 116, 117]. Thus, according to de Finetti, when we assess a set of probabilistic outcomes of an uncertain event with limited information, we are obliged to embrace the formal axioms of probability to systematically communicate reasonable opinions [116, 119].

It is of course essential to use empirical data when possible [9, 195]. However, inputting subjective parameter values into a decision-model is often an unavoidable exercise when there is a clear scarcity of direct, empirical data sources [1, 9, 17, 22, 139, 143, 151, 195]. Hence, quantifying subjective judgements in a systematic and transparent way is obviously preferable to making *ad hoc* decisions [1, 9, 22, 139, 143, 151]. This is especially pertinent when making decisions on a population's behalf [151]. Moreover, it is important to realise that the consequence of failing to make a decision due to an absence of direct empirical data can, potentially, be more costly compared to making a decision informed largely by a model with more indirect, subjective parameter inputs [1, 22, 44, 139, 143, 151]. Nonetheless, the key take-away is that an absence of complete information is a characteristic feature of decision-making under uncertainty [17, 150]. Accordingly, it is almost always applicable to public policy decision-making and thus, de Finetti's proof provides a logical defence for the practical use of subjective inputs applied in a systematic way [1, 5, 22, 143].

5.1.4. A technical lemma on coherence: the Dutch Book bet

Related to the sections 4 and 5, we illustrate the significance of consistency in subjective judgements by providing a short lemma (i.e. an argument mapping) which closely follows references [17, 116, 117].

Consider a hypothetical event θ and its set of binary outcomes, where $\theta = 1$ indicates that the event occurred and $\theta = 0$ indicates it did not [17]. We can subsequently define a bet to be worth an associated stake S if θ does occur, and nothing if θ does not occur, i.e. we can either win a total pay-out of S or nothing [17]. The ratio $\pi_\theta : (1 - \pi_\theta)$ is a common format used to denote the betting odds in favour of an event θ [17]. Subsequently, Bookies are known to sell a bet at a price $\pi_\theta S$ [17]. If we let $a(\theta)$ denote the action of placing a bet on θ , it enables us to associate each action with a set of consequences [17]. For instance, if the outcome is $\theta = 1$ the purchaser of the bet will have a net gain of $(1 - \pi_\theta)S$, simply the stake S less the initial buy-in price $\pi_\theta S$; conversely, if $\theta = 0$ the net gain will be the loss of the initial buy-in price, which is obviously $-\pi_\theta S$ [17]. These rules for either positive or negative gains can be represented by the following function [17],

$$g\theta = \begin{cases} (1 - \pi_\theta)S, & \text{if } \theta = 1 \\ -\pi_\theta S, & \text{if } \theta = 0 \end{cases}$$

Accordingly, the above notation also allows us to systematically assign probability judgements π_θ to an event's θ possible outcomes [17, 116]. Earlier, this was suggested to be the 'price' of a bet. Irrespective of this point, and now that we have some familiarity with a notation that allows for precise language, we can develop a more complex series of decisions for 3, disjoint outcomes of an event, denoted θ_1 , θ_2 , and θ_3 respectively. As above, each decision has a corresponding stake S , thus conforming to the form of a vector $s = (S\theta_1, S\theta_2, S\theta_3)$. We can then consider the probability of each outcome - assuming this implies a probability > 0 and that every probability is a 'fair' judgement of each outcome - assigning the following probabilities for π_{θ_1} , π_{θ_2} , and π_{θ_3} [17, 116].

```
pi1 <- .1
pi2 <- .8
pi3 <- .2
```

We can conveniently construct our probabilities in an $n \times n$ square matrix R to track all possible outcomes therein [17, 116, 196]. Intuitively, this theoretically means that each set of outcomes in each column should meet the condition $\pi_{\theta_j} = \pi_{\theta_i} + \pi_i$, where π_{θ_j} here represents the outcome $\theta = 1$.

```
R <- matrix(
  c(1 - pi1, - pi2, - pi3,
    - pi1, 1 - pi2, - pi3,
    - pi1, - pi2, 1 - pi3
  ),
    ncol = 3, nrow = 3)
```

```
R =
      [,1] [,2] [,3]
[1,]  0.9 -0.1 -0.1
[2,] -0.8  0.2 -0.8
[3,] -0.2 -0.2  0.8
```

We can now place a stake on each outcome, so that a vector of stakes s multiplied by an $n \times n$ matrix R can solve for a vector of gains g_θ , so that $g_\theta = Rs$ [17, 116, 196]. Although this may initially seem logical, we must bring to attention the *incoherence* of these probability judgements. The initial probability judgements of the event is erroneous - it does not conform to the probability axiom for a set of disjoint outcomes, where $P(A_1 \cap \dots \cap A_n) = 1$ [17, 116]. The total probability of the event θ is

```
sum(pi1 + pi2 + pi3)
= 1.1
```

This implies that $\pi_{\theta_1} - \pi_{\theta_2} - \pi_{\theta_3} \neq 0$ [196]. Thus, the probability matrix R is invertible [17, 116, 196]. Technically speaking, and using a more commonly adopted notation, this means that there is a scalar x for a matrix A that solves the desired output b , such that $b = Ax$ [196]. Likewise, the determinant of the matrix $\det(R) \neq 0$, evidenced below.

```
det(R)
= -0.1
```

This indicates that the assigned probability judgements are linearly independent [116, 196]. Consequently, the probabilities logically do not correspond to a single set of disjoint outcomes (such as a set of probabilities for which horse might win the race), but rather imply an arbitrary set of outcomes for disparate events [17, 116].

This can intuitively be thought of as equivalent to hypothetically comparing the possible outcomes of cards to chess pieces, when one is logically required to compare cards to cards in order to be consistent [116]. It is thus important to prove whether the probability matrix R conforms to this condition, if $R^{-1}R = I$, to ensure that our probabilities are comparing objects of the same class [196]. For those unfamiliar, see the proceeding section for the primary characteristics of an identity matrix.

```
round(inv(R) %*% R, digits = 5)
=
      [,1] [,2] [,3]
[1,]    1    0    0
```

```
[2,]    0    1    0
[3,]    0    0    1
```

Applying $R^{-1}R$ unmistakably mirrors an $n \times n$ identity matrix. Consequently, we can solve for a vector of stakes s , now assumed to be a latent vector, and in turn can assign a vector of desirable gains g_θ which, therefore, can now be treated as known [17, 116, 196]. Note that we do follow the assumption that no individual would willingly accept a position that results in a negative gain. The assumption has been methodologically critiqued, though it is practically reasonable [17]. Now consider the following: if we assign the vector g_θ the following random positive desired gains,

```
g_theta <- sample(1:500, 3, replace = TRUE)
```

```
g_theta = 411, 430, 478
```

it is then possible to solve for a linear transformation of s , such that we are guaranteed the desired outcomes initially assigned to g_θ above [17, 116, 196]. First, multiply each side of the equation by R^{-1} , so that $R^{-1}Rs = R^{-1}g$, where $I \times s = s = R^{-1}g$, and thus, ultimately, $s = R^{-1}g$ [196].

```
s_solved <- inv(R)%*%g_theta
```

```
s_solved =
      [,1]
[1,]  -908
[2,] -10122
[3,] -2160
```

In turn, we are able to ensure a desired vector of gains g_θ with certainty,

```
R%*%s_solved
=
      [,1]
[1,]   411
[2,]   430
[3,]   478
```

To conclude in a concise yet technical fashion, it is therefore reasonable to assume that when R is an invertible matrix the solution to $Rs = g_\theta$ is simply $s = R^{-1}g$ [17, 116, 196]. Hence, ascertaining whether $R^{-1}R = I$ is a useful lemma for substantiating the coherency of our probability assessments [17, 116]. Critical, however, is to realise the significance of this. When R is an invertible matrix the gain of each outcome can be known with certainty – this is patently incompatible with the logic of decision-making under uncertainty; a context where the outcomes of an action are partly or completely unknown [116, 117]. This results because consistency is a key requirement for any formal system of logic, as its absence implies that the system can derive contradictory statements simultaneously [193, 194]. For instance, an inconsistent mathematical system may imply that that one can derive both P and $\neg P^\dagger$, notwithstanding that such outcomes form a necessary and sufficient ‘either-or’ (mutually exclusive) type event [193, 194]. Nevertheless, and in more plain language,

[†]Read as P and ‘not P ’. This is usually simply referred to as an outcome’s ‘complement’ in standard probability theory, denoted P^c or $(1 - p)$ for instance.

if we desire to make our probability assessments systematically interpretable, we have little incentive to make unintelligible conclusions that fail to conform to the rules of probability [17, 116].

5.1.4.1. The basic properties of an identity matrix

An identity matrix I has on its diagonals only 1's and the rest of the elements only 0's[196]. It is, broadly speaking, a convenient tool used for matrix manipulation. Likewise, it is a literal 'do nothing' matrix[196], formed by multiplying a matrix by its inverse, such that $A \times A^{-1} = I$. This can intuitively be thought of as when the matrix A is applied, A^{-1} undoes it[196]. This implies that $A^{-1}Ax = x$. To illustrate, we first, 1) present a typical $n \times n$ identity matrix I and second, 2) we show the 'do-nothingness' nature of this matrix (note that in this specific example the values of b are arbitrary).

1)
 $I =$

	[,1]	[,2]	[,3]
[1,]	1	0	0
[2,]	0	1	0
[3,]	0	0	1

2)
 $b \leftarrow c(1, 2, 3)$
 $I \%*\% b =$

	[,1]
[1,]	1
[2,]	2
[3,]	3

Hence, it is obvious to that the operation $I \times b$ does not change the initial values of b , such that $I \times b = b$ are equivalent[196].

5.1.5. A brief note on exchangeability

An additional influential contribution by de Finetti to systematic decision-modelling under uncertainty is the idea of *exchangeability* [116, 197]. The concept of exchangeability provides a strong rationale for modelling stochastic and informational uncertainty [37, 62, 63, 116, 197]. It can be roughly yet intuitively thought of as a applying a simple random sampling process to a *homogenous population*, given there is no prior information that can properly distinguish the set of random samples. Exchangeability is a 'representational' theorem, as it assumes a statistical model can reasonably reflect some real-world data generating process [62, 116]. A technical definition of this concept is as follows: "...the n number of values y_i may be regarded as *exchangeable*... [if] we can express uncertainty as a joint probability density $p(y_1, \dots, y_n)$ that is invariant to permutations of the indexes." [62] In more plain language however, this means that changes to the order of the sample does not change the expected population value, i.e. average.

Consider, for instance, a hypothetical scenario where there is no immediate information to empirically estimate a homogenous population's variance parameter ϕ [62, 197]. If, for instance $y_i \sim N(\theta, \phi)$, where θ and y_i are known, assuming exchangeability, there is a suitable prior distribution which is sufficiently 'representational' of the unknown information about ϕ , i.e. the distribution can model the parametric behaviour of ϕ [62, 198]. If this assumption is reasonable, a decision-theoretic model may adequately characterise this uncertainty by sampling from a '*hyper-*

distribution', for example $p(\psi)$, such that $p(\phi | \psi)$ [62, 197, 198]. Practically, this means that information about the parameter ϕ is sampled from a 'lower-level' distribution $p(\psi)$ – hence why such a style of modelling is referred to as 'hierarchical' or 'multi-level' modelling [62, 197].

5.1.6. References

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5.2. Supplementary Appendix: B

Appendix B provides the supplementary code for the case study presented in the manuscript section of this paper.

```
#####
## BEFORE RUNNING THE MODEL, PLEASE ENSURE THAT YOUR WORKING DIRECTORY IS SET ##
## TO THE DIRECTORY OF THE Rproj FOLDER SAVED ON YOUR COMPUTER. IN RSTUDIO ##
## THE EASIEST WAY TO DO THIS IS BY PRESSING Ctrl + Shift + H. #####
#####

libraries:
/(baseplot)
/(BCEA)
/(dampack)
/(readxl)
/(reshape2)
/(rjags)
/(R2jags)
/(tidyverse)

ialise start time counter:
time <- Sys.time()

we judged the advantages of using parallel processing to be negligible given the
of the model and run time, which is consistently < 60 secs on a relatively
powered MacBook pro 2018 13".

that the source code for this section sits on top of the code for the Markov Models for
at treatment found in the R folder (R/02_markov_model.R):
("R/02_markov_model.R")

=====
-Effectiveness Analysis -----
=====

is the code that runs the final Cost-Effectiveness Analysis script for the HPV model
loped by Sinanovic, E., et al. 2009): "The potential cost-effectiveness of adding a human
illomavirus vaccine to the cervical cancer screening programme in South Africa."

id_1 is the Status Quo (Screening only) treatment Markov model:
1_
id_2 is the New Treatment (Screening plus Vaccine) Markov model:
```

```
m_M_ad_2

# Health State utilities -----
u_Well <- 1 # utility of being in Well for one cycle
u_Infection <- 1 # utility of being in Infected for one cycle
u_LSL <- 0.91 # utility of being in LSL for one cycle
u_HSL <- 0.87 # utility of being in HSL for one cycle
u_StageI <- 0.65 # utility of being in Stage I Cancer for one cycle
u_StageII <- 0.56 # utility of being in Stage II Cancer for one cycle
u_StageIII <- 0.56 # utility of being in Stage III Cancer for one cycle
u_StageIV <- 0.49 # utility of being in state Stage IV Cancer for one cycle
u_CancerSurvivor <- 0.84 # utility of being in state Cancer Survivor for one cycle
u_Death <- 0 # utility of being in state of Death for one cycle

# Vector of state utilities for both treatments:
m_u_SQ <- m_u_NT <- matrix(c("Well" = u_Well,
"LSL" = u_LSL,
"HSL" = u_HSL,
"Stage-I Cancer" = u_StageI,
"Stage-II Cancer" = u_StageII,
"Stage-III Cancer" = u_StageIII,
"Stage-IV Cancer" = u_StageIV,
"Detected.Stage-I Year 1" = u_StageI,
"Detected.Stage-I Year 2" = u_StageI,
"Detected.Stage-I Year 3" = u_StageI,
"Detected.Stage-I Year 4" = u_StageI,
"Detected.Stage-I Year 5" = u_StageI,
"Detected.Stage-II Year 1" = u_StageII,
"Detected.Stage-II Year 2" = u_StageII,
"Detected.Stage-II Year 3" = u_StageII,
"Detected.Stage-II Year 4" = u_StageII,
"Detected.Stage-II Year 5" = u_StageII,
"Detected.Stage-III Year 1" = u_StageIII,
"Detected.Stage-III Year 2" = u_StageIII,
"Detected.Stage-III Year 3" = u_StageIII,
"Detected.Stage-III Year 4" = u_StageIII,
```

```

"Detected.Stage-I Year 4" = c_StageI,
"Detected.Stage-I Year 5" = c_StageI,
"Detected.Stage-II Year 1" = c_StageII,
"Detected.Stage-II Year 2" = c_StageII,
"Detected.Stage-II Year 3" = c_StageII,
"Detected.Stage-II Year 4" = c_StageII,
"Detected.Stage-II Year 5" = c_StageII,
"Detected.Stage-III Year 1" = c_StageIII,
"Detected.Stage-III Year 2" = c_StageIII,
"Detected.Stage-III Year 3" = c_StageIII,
"Detected.Stage-III Year 4" = c_StageIII,
"Detected.Stage-III Year 5" = c_StageIII,
"Detected.Stage-IV Year 1" = c_StageIV,
"Detected.Stage-IV Year 2" = c_StageIV,
"Detected.Stage-IV Year 3" = c_StageIV,
"Detected.Stage-IV Year 4" = c_StageIV,
"Detected.Stage-IV Year 5" = c_StageIV,
"Cancer Survivor" = u_CancerSurvivor,
"Death" = u_Death,
n_states, n_t + 1, dimnames = list(v_n, 0:(n_t)))

th costs from a health care perspective -----
costs in $US.
ine <- 570 # once off cost of vaccine from age 12.
ening <- 93 + 309 + 75 # cost of screening using HPV DNA, VIA, and cancer cytology tests.
<- 61 # cost of LSIL treatments*.
<- 764 # cost of HSIL treatments*.
: HPV 16/18 assumed asymptomatic in original mode and therefore not
ted.

t for treatment at each cancer stage:
eI <- 4615 # cost of treatment of Stage I Cancer for one cycle.
eII <- 6307 # cost of treatment of Stage II Cancer for one cycle.
eIII <- 6307 # cost of treatment of Stage III Cancer for one cycle.
eIV <- 8615 # cost of treatment of Stage IV Cancer for one cycle.

ix of state costs based on time interval t under Status Quo treatment:
<- matrix(c("Well" = 0,
"Infection" = 0,
"LSIL" = 0,
"HSIL" = 0,
"Stage-I Cancer" = 0,
"Stage-II Cancer" = 0,
"Stage-III Cancer" = 0,
"Stage-IV Cancer" = 0,
"Detected.Stage-I Year 1" = c_StageI,
"Detected.Stage-I Year 2" = c_StageI,
"Detected.Stage-I Year 3" = c_StageI,

```

```

"Detected.Stage-I Year 4" = c_StageI,
"Detected.Stage-I Year 5" = c_StageI,
"Detected.Stage-II Year 1" = c_StageII,
"Detected.Stage-II Year 2" = c_StageII,
"Detected.Stage-II Year 3" = c_StageII,
"Detected.Stage-II Year 4" = c_StageII,
"Detected.Stage-II Year 5" = c_StageII,
"Detected.Stage-III Year 1" = c_StageIII,
"Detected.Stage-III Year 2" = c_StageIII,
"Detected.Stage-III Year 3" = c_StageIII,
"Detected.Stage-III Year 4" = c_StageIII,
"Detected.Stage-III Year 5" = c_StageIII,
"Detected.Stage-IV Year 1" = c_StageIV,
"Detected.Stage-IV Year 2" = c_StageIV,
"Detected.Stage-IV Year 3" = c_StageIV,
"Detected.Stage-IV Year 4" = c_StageIV,
"Detected.Stage-IV Year 5" = c_StageIV,
"Cancer Survivor" = 0,
"Death" = 0),
n_states, n_t + 1, dimnames = list(v_n, 0:(n_t)))

# Screening costs for ages 30, 40, and 50:
m_c_SQ["Well", c(31, 41, 51)] <- (m_c_SQ["Well", c(31, 41, 51)] + c_Screening)
# LSIL costs for ages 30, 40, and 50:
# m_c_SQ["LSIL", c(31, 41, 51)] <- (m_c_SQ["LSIL", c(31, 41, 51)] + c_LSIL)
# HSIL costs for ages 30, 40, and 50:
# m_c_SQ["HSIL", c(31, 41, 51)] <- (m_c_SQ["HSIL", c(31, 41, 51)] + c_HSIL)
# Matrix of state costs based on time interval t under New Treatment:
m_c_NT <- m_c_SQ
# Vaccine cost at age 12:
m_c_NT["Well", c(13)] <- (m_c_NT["Well", c(13)] + c_Vaccine)
# Create cost and effects matrices:
m_utilities_NT <- m_costs_NT <- m_utilities_SQ <- m_costs_SQ <- matrix(0, n.sims, n_t + 1,
dimnames = list(
1:n.sims, 0:(n_t)
))

```

```

) costs over time interval t and n.sims i:
{
  in 1:n.sims {
    t in 0:n_t {
      For Status Quo (screening only)
      costs
      costs_SQ[i, t] <- (m_M_ad_1[t, i] * 0.5) ** m_c_SQ[t] # Note: half of cohort assumed screened
      ALVs
      utilities_SQ[i, t] <- m_M_ad_1[t, i] ** m_u_SQ[t]
      For New Treatment (screening and vaccine):
      costs
      costs_NT[i, t] <- (m_M_ad_2[t, i] * 0.5) ** m_c_NT[t] # Note: half of cohort assumed screened
      ALVs
      utilities_NT[i, t] <- m_M_ad_2[t, i] ** m_u_NT[t]
    }
  }
}

location -----
long-discounted costs and effects:
for Status Quo (screening only):
its
apply(m_costs_SQ, 1, sum)
}
apply(m_utilities_SQ, 1, sum)
for New Treatment (screening and vaccine):
its
apply(m_costs_NT, 1, sum)
}
apply(m_utilities_NT, 1, sum)

Discounted costs and effects
count rates:
- 0.03
- 0.03
count weights for costs
<- 1 / ((1 + d_c) ^ (0:n_t))
count weights for effects
<- 1 / ((1 + d_e) ^ (0:n_t))

```

```

counted costs and utilities matrices:
utilities_NTdisc <- m_costs_NTdisc <- m_utilities_SQdisc <- matrix(0, n.sims,
  n_t + 1,
  dimnames = list(
    1:n.sims, 0:n_t
  )
)

in 1:n.sims {
  t in 0:n_t {
    For Status Quo (screening only):
    costs
    costs_SQdisc[i, t] <- m_costs_SQ[i, t] * v_dwe[t]
    ALVs
    utilities_SQdisc[i, t] <- m_utilities_SQ[i, t] * v_dwe[t]
    For New Treatment (screening and vaccine):
    costs
    costs_NTdisc[i, t] <- m_costs_NT[i, t] * v_dwe[t]
    ALVs
    utilities_NTdisc[i, t] <- m_utilities_NT[i, t] * v_dwe[t]
  }
}

costs and effectiveness across all time points:
s <- Costs <- matrix(0, n.sims, 2)
for Status Quo (screening only):
its
[, 1] <- apply(m_costs_SQdisc, 1, sum)
}
s[, 1] <- apply(m_utilities_SQdisc, 1, sum)
for New Treatment (screening and vaccine):
its
[, 2] <- apply(m_costs_NTdisc, 1, sum)
}
s[, 2] <- apply(m_utilities_NTdisc, 1, sum)

itegy names:

```

```

is_str <- c("Status Quo: screening only", "New Treatment: screening & vaccine")

# A package summary:
i <- localEffects, Costs, ref = 2, interventions = v_names_str, kmax = 2000, plot = TRUE)
summary.bcea(df_cea, graph = "ggplot2", wtp = 1000)
ceef.plot(df_cea)
BCEA::multi.ce(he = df_cea)
ceef.plot(ce, graph = "ggplot2")
ceac.plot(df_cea, graph = "ggplot2")
the plot below, r represents the risk aversion parameter which is the square root of the
ance for the expected return on investment. Hence, simply speaking, the more averse,
more sure a decision-maker is wanting to be of the investment's return.
r <- 0Eriskal(he = df_cea, r = c(
000001, 0.00000001, 0.000001, 0.000001, 0.00001, 0.0001)

more risk averse the decision-maker, the greater the value of EVPI:
plot.0Eriskal(risklev)
in expected standard deviation of 0.0001, the the EVPI is virtually null and thus the
sion-maker should be theoretically willing to take on the expected variance (volatility)
the return on investment, given current information. Of course, this is only *theoretical* and
ultimately depends on the decision-maker's preferences and value judgement's.

ected Costs and Utility for both treatments across all simulations:
· apply(Costs, 2, mean)
· apply(Effects, 2, mean)
al ICER:
]) - E_c[1]) / (E_u[2] - E_u[1])

pack package summary:
summary <- dampack::calculate_icers(cost = E_c, effect = E_u, strategies = v_names_str)
summary

# run time -----
time counter:
me <- Sys.time()
# run time:
me - start_time

```

```

# =====
# Markov Model -----
# =====
# The following code runs a Markov Model script for the HPV model developed by Srinanovic, E.,
# et al. 2009): "The potential cost-effectiveness of adding a human papillomavirus vaccine to
# the cervical cancer screening programme in South Africa."

# Note that this code sits on top of the source code for the evidence synthesis model as well as
# the probability matrix (03_evidence_synthesis_and_probability_array.R).

source("R/03_evidence_synthesis_and_probability_array.R")

# m_M_ad_1 is the Status Quo treatment model; m_M_ad_2 is the vaccine treatment model.

# Initial state vector:
v_s_init <- c("Well" = 1, "Infection" = 0, "LSIL" = 0, "HSIL" = 0,
"Stage-I Cancer" = 0, "Stage-II Cancer" = 0,
"Stage-III Cancer" = 0, "Stage-IV Cancer" = 0,
"Detected.Stage-I Year 1" = 0, "Detected.Stage-I Year 2" = 0,
"Detected.Stage-I Year 3" = 0, "Detected.Stage-I Year 4" = 0,
"Detected.Stage-I Year 5" = 0, "Detected.Stage-II Year 1" = 0,
"Detected.Stage-II Year 2" = 0, "Detected.Stage-II Year 3" = 0,
"Detected.Stage-II Year 4" = 0, "Detected.Stage-II Year 5" = 0,
"Detected.Stage-III Year 1" = 0, "Detected.Stage-III Year 2" = 0,
"Detected.Stage-III Year 3" = 0, "Detected.Stage-III Year 4" = 0,
"Detected.Stage-III Year 5" = 0, "Detected.Stage-IV Year 1" = 0,
"Detected.Stage-IV Year 2" = 0, "Detected.Stage-IV Year 3" = 0,
"Detected.Stage-IV Year 4" = 0, "Detected.Stage-IV Year 5" = 0,
"Cancer Survivor" = 0, "Death" = 0)

# Initialize cohort trace for age-dependent cSTMs:
m_M_ad_1 <- array(matrix(0, nrow = n_t + 1, ncol = n_states),
dim = c(n_t + 1, n_states), n.sims),
dimnames = list(0:n_t, v_n, 1:n.sims))
m_M_ad_2 <- array(matrix(0, nrow = n_t + 1, ncol = n_states),
dim = c(n_t + 1, n_states), n.sims),
dimnames = list(0:n_t, v_n, 1:n.sims))

```

```

"Detected.Stage-II Year 3" = "#00C248",
"Detected.Stage-II Year 4" = "#007A04",
"Detected.Stage-II Year 5" = "#003035",
"Detected.Stage-III Year 1" = "#9800FA",
"Detected.Stage-III Year 2" = "#E700E0",
"Detected.Stage-III Year 3" = "#7400C2",
"Detected.Stage-III Year 4" = "#49007A",
"Detected.Stage-III Year 5" = "#25003D",
"Detected.Stage-IV Year 1" = "#F056B0",
"Detected.Stage-IV Year 2" = "#F051B3",
"Detected.Stage-IV Year 3" = "#D64941",
"Detected.Stage-IV Year 4" = "#B03033",
"Detected.Stage-IV Year 5" = "#702654",
"Cancer Survivor" = "#3EFA80",
"Death" = "#3BABA4")

ciates similar states with similar line types:
c("Well" = 1, "Infection" = 2, "LSII" = 3,
  "HSII" = 3, "Stage-I Cancer" = 4,
  "Stage-II Cancer" = 4, "Stage-III Cancer" = 4,
  "Stage-IV Cancer" = 4, "Detected.Stage-I Year 1" = 2,
  "Detected.Stage-I Year 2" = 2, "Detected.Stage-I Year 3" = 2,
  "Detected.Stage-I Year 4" = 2, "Detected.Stage-I Year 5" = 2,
  "Detected.Stage-II Year 1" = 3,
  "Detected.Stage-II Year 2" = 3,
  "Detected.Stage-II Year 3" = 3,
  "Detected.Stage-II Year 4" = 3,
  "Detected.Stage-II Year 5" = 3,
  "Detected.Stage-III Year 1" = 4,
  "Detected.Stage-III Year 2" = 4,
  "Detected.Stage-III Year 3" = 4,
  "Detected.Stage-III Year 4" = 4,
  "Detected.Stage-III Year 5" = 4,
  "Detected.Stage-IV Year 1" = 5,
  "Detected.Stage-IV Year 2" = 5,
  "Detected.Stage-IV Year 3" = 5,
  "Detected.Stage-IV Year 4" = 5,
  "Detected.Stage-IV Year 5" = 5,

a the initial state vector in the first row of the cohort trace
_1[, , ] <- v_s_init
_2[, , ] <- v_s_init

ative solution of age-dependent cSTM model 1:
in 1:n.t) {
  in 1:n.sims) {
    ll in cohort trace
    ad_1[t + 1, , i] <- m_M_ad_1[t, , i] %*% a_P_1[, , t, i]

ative solution of age-dependent cSTM model 2:
in 1:n.t) {
  in 1:n.sims) {
    ll in cohort trace
    ad_2[t + 1, , i] <- m_M_ad_2[t, , i] %*% a_P_2[, , t, i]

k for transition leakage (each cycle must sum to n.sims, otherwise there is something
g with the transitions probabilities):
m_M_ad_1, 1, sum)
m_M_ad_2, 1, sum)

=====
alisation of Markov Models -----
=====

ciates each state with a colour:
- c("Well" = "#D01800", "Infection" = "#FA7700", "LSII" = "#FA0343",
  "HSII" = "#FAF27F", "Stage-I Cancer" = "#9AFA65",
  "Stage-II Cancer" = "#80E06A", "Stage-III Cancer" = "#4B7A31",
  "Stage-IV Cancer" = "#243817", "Detected.Stage-I Year 1" = "#00C3FA",
  "Detected.Stage-I Year 2" = "#0084E0", "Detected.Stage-I Year 3" = "#0090C2",
  "Detected.Stage-I Year 4" = "#00627A", "Detected.Stage-I Year 5" = "#0013D0",
  "Detected.Stage-II Year 1" = "#00FA09",
  "Detected.Stage-II Year 2" = "#00E0C2",

```

```

e_y_continuous(labels = scales::percent) +
  ("Cycle") +
  ("Proportion of the cohort") +
  e_light(base_size = 14) +
  e_legend(position = "bottom",
    legend.background = element_rect(fill = NA),
    text = element_text(size = 15))
ival curve for Markov Model 2:
_2 <- rowSums(apply(m_M_ad_2[, -30, ], c(1, 2), mean)) # vector with survival curve
(data.frame(Cycle = 0:n.t, Survival = v_S_ad_2),
  aes(x = Cycle, y = Survival)) +
_line(size = 1.3) +
e_y_continuous(labels = scales::percent) +
  ("Cycle") +
  ("Proportion alive") +
  e_bw(base_size = 14) +
  e()

expectancy for average individual in Markov model 1 cohort:
1 <- sum(v_S_ad_1)
1
expectancy for average individual in Markov model cohort:
2 <- sum(v_S_ad_2)
2

absence of Infection in Model 1:
_infection_1 <- apply(m_M_ad_1[, "Infection", ], c(2, 1), mean)
_infection_1 <- apply(v_prev_infection_1, 2, mean) / v_S_ad_1
absence of Infection in Model 2:
_infection_2 <- apply(m_M_ad_2[, "Infection", ], c(2, 1), mean)
_infection_2 <- apply(v_prev_infection_2, 2, mean) / v_S_ad_2
() +
line(aes(x = 0:n.t, y = v_prev_infection_1), size = 1.3, colour = "skyblue", na.rm = TRUE) +
line(aes(x = 0:n.t, y = v_prev_infection_2), size = 1.3, colour = "darkred",
  alpha = 0.65, na.rm = TRUE) +
_y_continuous(labels = scales::percent) +
  ("Cycle") +
  "Cancer Survivor" = 6,
  "Death" = 1)

alisation of cohort proportions for Markov Model 1:
(melt(apply(m_M_ad_1, c(1, 2), mean)), aes(x = Var1, y = value,
  color = Var2, linetype = Var2)) +
_line(size = 0.5) +
_colour_manual(name = "Health state",
  values = cols) +
e_linetype_manual(name = "Health state",
  values = lty) +
e_y_continuous(labels = scales::percent) +
  ("Cycle") +
  ("Proportion of the cohort") +
  e_light(base_size = 14) +
  e_legend(position = "bottom",
    legend.background = element_rect(fill = NA),
    text = element_text(size = 15))
ival curve for Markov Model 1:
_1 <- rowSums(apply(m_M_ad_1[, -30, ], c(1, 2), mean)) # vector with survival curve
(data.frame(Cycle = 0:n.t, Survival = v_S_ad_1),
  aes(x = Cycle, y = Survival)) +
_line(size = 1.3) +
e_y_continuous(labels = scales::percent) +
  ("Cycle") +
  ("Proportion alive") +
  e_bw(base_size = 14) +
  e()

alisation of cohort proportions for Markov Model 2:
(melt(apply(m_M_ad_2, c(1, 2), mean)), aes(x = Var1, y = value,
  color = Var2, linetype = Var2)) +
_line(size = 0.5) +
_colour_manual(name = "Health state",
  values = cols) +
e_linetype_manual(name = "Health state",
  values = lty) +

```

```

=====
Hence Synthesis and Transition Probability Matrix -----
=====
e: this code below sits on top of the parameter Inputs.R file, which is the source code for
parameter data (04_parameter_inputs.R).

e(R/04_parameter_inputs.R")

eral distributions have had to be truncated at an upper bound of 1 – (max mortality prob).
found that the mortality rate when it included HIV/AIDS related mortality was extremely high
an the context of South Africa in 2009. In order to account for this, it would be
irable to incorporate a parameter which accounts for the conditional annual risk of dying
n HIV/AIDS. However, because this was purely a replication exercise, we did not
d it necessary and focused on the outcomes of the comparative models. The original model
the time horizon from 0–76 when HIV/AIDS mortality was included.

=====
Hence Synthesis Model -----
=====
_String <- "
{

JB-MODEL 1: AGE-SPECIFIC PREVALENCE
el parameters abbreviated by .age. Note: this is equivalent to Monte Carlo PSA,
it is technically sampling directly from a prior and is not propagated into a
terior using a likelihood model. However, a hyperprior is used for the population
iance to account for a greater uncertainty in each age-population.
(i in 1:86) {
omega.age[i] ~ dlnorm(mu.a.log[i], prec.age[i])

Note use of pow() function, using -2 is a shorthand inverse method equivalent
to (1 / x^2):
log(prec.age[i]) <- pow(sigma.age[i], -2)

Relatively wide prior on variance for each age group. See (Gelman, 2006) on
half-t for variance parameters in hierarchical models.
sigma.age[i] ~ dt(0, 1, 1)/t(0, )
file -----

```

```

"Prevalence (%): HPV Infection") +
15, 86) +
_bw(base_size = 14) +
()

ality in Model 1:
_1 <- rowSums(apply(m_M_ad_1[, "Death", ], c(1, 2), mean))
ality in Model 1:
_2 <- rowSums(apply(m_M_ad_2[, "Death", ], c(1, 2), mean))
() +
line(aes(x = 0:n.t, y = v_D_ad_1), size = 2, colour = "navyblue", na.rm = TRUE,
alpha = 1) +
point(aes(x = 0:n.t, y = v_D_ad_2), size = 1.5, colour = "red",
alpha = 0.96, na.rm = TRUE) +
_y_continuous(labels = scales::percent) +
"Cycle") +
"Comparative no. Deaths") +
15, 86) +
_bw(base_size = 14) +
()

alisation of cohort proportions for Markov Model 1:
t(apply(m_M_ad_1, c(2, 1), mean), space = 1,
ylab = "Proportion of patients in each state",
main = "Status Quo Treatment", col = cols, cex.names = 1, cex.main = 1.5)
("bottomright", legend = c("Well", "Infection", "Death"),
fill = c("Well" = "#BDB800", "Infection" = "#F77000", "Death" = "#3B8ABA"),
cex = .66, box.lwd = 1.85, x = 146.5, y = 1.02)
alisation of cohort proportions for Markov Model 2:
t(apply(m_M_ad_2, c(2, 1), mean), space = 1,
ylab = "Proportion of patients in each state",
main = "Vaccine Treatment", col = cols, cex.names = 1, cex.main = 1.5)
("bottomright", legend = c("Well", "Infection", "Death"),
fill = c("Well" = "#BDB800", "Infection" = "#F77000", "Death" = "#3B8ABA"),
cex = .66, box.lwd = 1.85, x = 146.5, y = 1.02)
file -----

```

```

inforamtions for SUB-MODEL 2:
invert LOR to OR
.vac <- exp(psi.vac)
invert OR to probability for vaccine efficacy
fficacy.vac <- 1 / (1 + OR.vac)

Predicted average
treatment effect:
delta.new ~ dnorm(psi.vac, prec.vac)

D OF SUB-MODEL 2.

B-MODEL 3: CANCER PROGRESSION AND 5-YEAR SURVIVAL STAGES I-IV.
1 parameters abbreviated by .canc. Note: this is equivalent to a standard
e Carlo PSA, as it is technically sampling directly from a prior and it is
* propagated into a posterior using a likelihood model. We have had to truncate
of these distributions in order for the ASSA mortality data to be properly combined
the state transition probabilities to be proper.

istribution according to Stage:
age.I.canc ~ dbeta(alpha.StageI, beta.StageI)T(0, 0.88)
age.II.canc ~ dbeta(alpha.StageII, beta.StageII)T(0, 0.88)
age.III.canc ~ dbeta(alpha.StageIII, beta.StageIII)T(0, 0.88)
ageIV.Detected ~ dbeta(alpha.StageIV, beta.StageIV)T(0, 0.88)

tage I Cervical Cancer detected 5-year Survival:
rv.StageI_year1 ~ dbeta(alpha.StageI_yearI, beta.StageI_yearI)
rv.StageI_year2 ~ dbeta(alpha.StageI_yearII, beta.StageI_yearII)
rv.StageI_year3 ~ dbeta(alpha.StageI_yearIII, beta.StageI_yearIII)
rv.StageI_year4 ~ dbeta(alpha.StageI_yearIV, beta.StageI_yearIV)
rv.StageI_year5 ~ dbeta(alpha.StageI_yearV, beta.StageI_yearV)

tage II Cervical Cancer detected 5-year Survival:
rv.StageII_year1 ~ dbeta(alpha.StageII_yearI, beta.StageII_yearI)
rv.StageII_year2 ~ dbeta(alpha.StageII_yearII, beta.StageII_yearII)
rv.StageII_year3 ~ dbeta(alpha.StageII_yearIII, beta.StageII_yearIII)
rv.StageII_year4 ~ dbeta(alpha.StageII_yearIV, beta.StageII_yearIV)

D OF SUB-MODEL 1.

B-MODEL 2: POP. LEVEL VACCINE-EFFICACY.
: this is a fully integrated Bayesian model, as it combines evidence directly via the
likelihood and a prior. Model parameters abbreviated by .vac.
(i in 1:Nstud.vac) {
Likelihood:
A.vac[i] ~ dbin(pA.vac[i], nA.vac[i])
B.vac[i] ~ dbin(pB.vac[i], nB.vac[i])

Logistic link function:
ogit(pA.vac[i]) <- mu.vac[i]
ogit(pB.vac[i]) <- mu.vac[i] + delta.vac[i]

Average effect prior for SUB-MODEL 2:
u.vac[i] ~ dnorm(0, 1e-4)
Prior for sub-model 2 (Random. pop. effect):
elta.vac[i] ~ dt(psi.vac, prec.vac, 1) # if desired can be ~ dnorm(psi.vac, prec.vac)

## Mixed predictive check for SUB-MODEL 2:
# Predictive likelihood:
rA.mvd[i] ~ dbin(pA.new[i], nA.vac[i])

# Predictive logit link function:
logit(pA.new[i]) <- mu.vac[i] + delta.new

# Mixed predictive p-value:
pA.mvd[i] <- step(rA.mvd[i] - rA.vac[i]) - 0.5 * equals(rA.mvd[i], rA.vac[i])

yperpriors for SUB-MODEL 2:
i.vac ~ dnorm(0, 1.0e-4)
ec.vac <- pow(tau.vac, -2)
u.vac ~ dt(0, 1, 1)T(0, )

```

```

I LSTL & HSTL to Normal or Infection across age groups:
I: because all other states except Death are assumed to be dependent and disjoint for
transition to normal or Infection from state of LSTL & HSTL, one can calculate all other
want states from the complement of the transitions that are obtained from the below:
15_34 ~ dbeta(alpha.LSTL_15to34, beta.LSTL_15to34)/(0, 0.88)
35_95 ~ dbeta(alpha.LSTL_35to85, beta.LSTL_35to85)/(0, 0.88)
n ~ dbeta(alpha.HSTL, beta.HSTL)/(0, 0.88)

IF SUB-MODEL 5.

I LSTL_year5 ~ dbeta(alpha.StageII_YearV, beta.StageII_YearV)
ge III Cervical Cancer detected 5-year Survival:
.StageII_year1 ~ dbeta(alpha.StageIII_YearI, beta.StageII_YearI)
.StageII_year2 ~ dbeta(alpha.StageIII_YearII, beta.StageIII_YearII)
.StageII_year3 ~ dbeta(alpha.StageIII_YearIII, beta.StageIII_YearIII)
.StageII_year4 ~ dbeta(alpha.StageIII_YearIV, beta.StageIII_YearIV)
.StageII_year5 ~ dbeta(alpha.StageIII_YearV, beta.StageIII_YearV)
ge IV Cervical Cancer detected 5-year Survival:
.StageIV_year1 ~ dbeta(alpha.StageIV_YearI, beta.StageIV_YearI)
.StageIV_year2 ~ dbeta(alpha.StageIV_YearII, beta.StageIV_YearII)
.StageIV_year3 ~ dbeta(alpha.StageIV_YearIII, beta.StageIV_YearIII)
.StageIV_year4 ~ dbeta(alpha.StageIV_YearIV, beta.StageIV_YearIV)
.StageIV_year5 ~ dbeta(alpha.StageIV_YearV, beta.StageIV_YearV)

OF SUB-MODEL 3.

MODEL 4: INFECTION PROGRESSION:
this is equivalent to a standard Monte Carlo PSA, as it is technically sampling
ly from a prior and it is *not* propagated into a posterior using a likelihood

n HPV to Normal across age groups:
e: because all other states except Death are assumed to be dependent and disjoint for
ression to normal from state of HPV/Infection, one can calculate all other relevant
tes from the complement of the transitions that are obtained from the below:
Well_15to24 ~ dbeta(alpha.HPVtoNormal_15to24, beta.HPVtoNormal_15to24)
Well_25to29 ~ dbeta(alpha.HPVtoNormal_25to29, beta.HPVtoNormal_25to29)
Well_30toend ~ dbeta(alpha.HPVtoNormal_30toPlus, beta.HPVtoNormal_30toPlus)

OF SUB-MODEL 4.

MODEL 5: LSTL & HSTL PROGRESSION:
this is equivalent to a standard Monte Carlo PSA, as it is technically sampling
ly from a prior and it is *not* propagated into a posterior using a likelihood
We have had to truncate these distributions in order for the ASSA mortality data
properly combined and for the state transition probabilities to be proper.

```

```

vac", "Efficacy.vac", "delta.vac", "psi.vac",
II to infection prevalence:
ga.age",
V Progression:
  _well_1st24", "HPV_well_25to29",
  _well_30to5end",
  IL and HSIL Progression:
    _15_34", "LSIL_35_85",
    _n",
  ancet Stage Progression:
    ge.I.canc", "Stage.II.canc",
    ge.III.canc", "StageIV.Detected",
  ncer Stage Survival progression:
    v.StageI_year1", "surv.StageI_year2", "surv.StageI_year3",
    v.StageI_year4", "surv.StageI_year5",
    v.StageII_year1", "surv.StageII_year2", "surv.StageII_year3",
    v.StageII_year4", "surv.StageII_year5",
    v.StageIII_year1", "surv.StageIII_year2", "surv.StageIII_year3",
    v.StageIII_year4", "surv.StageIII_year5",
    v.StageIV_year1", "surv.StageIV_year2", "surv.StageIV_year3",
    v.StageIV_year4", "surv.StageIV_year5",

xed predictive check. Provides a conservative p-value measure for
consistency of evidence across each study comparative to the rest:
mxd"

no. of iterations, burn-in period and thinned samples:
<- 35000
in <- 5000
<- floor((n.iter - n.burnin) / 250)

MCMC model:
US <- jags(data = data_JACS, parameters.to.save = params,
  model.file = "data/jags_model.txt", n.chains = 4,
  n.iter = n.iter, n.burnin = n.burnin, n.thin = n.thin)
s(max.print = 1500)

ncer Stage alpha's:
a.StageI = alpha.StageI, beta.StageI = beta.StageI_yearI,
a.StageII = alpha.StageII, beta.StageII = beta.StageI_yearII,
a.StageIII = alpha.StageIII, beta.StageIII = beta.StageI_yearIII,
a.StageIV = alpha.StageIV, beta.StageIV = beta.StageI_yearIV,

age I 5-year Survival:
a.StageI_yearI = alpha.StageI_yearI, beta.StageI_yearI = beta.StageI_yearI,
a.StageI_yearII = alpha.StageI_yearII, beta.StageI_yearII = beta.StageI_yearII,
a.StageI_yearIII = alpha.StageI_yearIII, beta.StageI_yearIII = beta.StageI_yearIII,
a.StageI_yearIV = alpha.StageI_yearIV, beta.StageI_yearIV = beta.StageI_yearIV,
a.StageI_yearV = alpha.StageI_yearV, beta.StageI_yearV = beta.StageI_yearV,

age II 5-year Survival:
a.StageII_yearI = alpha.StageII_yearI, beta.StageII_yearI = beta.StageII_yearI,
a.StageII_yearII = alpha.StageII_yearII, beta.StageII_yearII = beta.StageII_yearII,
a.StageII_yearIII = alpha.StageII_yearIII, beta.StageII_yearIII = beta.StageII_yearIII,
a.StageII_yearIV = alpha.StageII_yearIV, beta.StageII_yearIV = beta.StageII_yearIV,
a.StageII_yearV = alpha.StageII_yearV, beta.StageII_yearV = beta.StageII_yearV,

age III 5-year Survival:
a.StageIII_yearI = alpha.StageIII_yearI, beta.StageIII_yearI = beta.StageIII_yearI,
a.StageIII_yearII = alpha.StageIII_yearII, beta.StageIII_yearII = beta.StageIII_yearII,
a.StageIII_yearIII = alpha.StageIII_yearIII, beta.StageIII_yearIII = beta.StageIII_yearIII,
a.StageIII_yearIV = alpha.StageIII_yearIV, beta.StageIII_yearIV = beta.StageIII_yearIV,
a.StageIII_yearV = alpha.StageIII_yearV, beta.StageIII_yearV = beta.StageIII_yearV,

age IV 5-year Survival:
a.StageIV_yearI = alpha.StageIV_yearI, beta.StageIV_yearI = beta.StageIV_yearI,
a.StageIV_yearII = alpha.StageIV_yearII, beta.StageIV_yearII = beta.StageIV_yearII,
a.StageIV_yearIII = alpha.StageIV_yearIII, beta.StageIV_yearIII = beta.StageIV_yearIII,
a.StageIV_yearIV = alpha.StageIV_yearIV, beta.StageIV_yearIV = beta.StageIV_yearIV,
a.StageIV_yearV = alpha.StageIV_yearV, beta.StageIV_yearV = beta.StageIV_yearV

meters to monitor:
<- c()
ccine efficacy parameters:

```

```

"Detected.Stage-III Year 1", "Detected.Stage-III Year 2", "Detected.Stage-III Year 3",
"Detected.Stage-III Year 4", "Detected.Stage-III Year 5", "Detected.Stage-IV Year 1",
"Detected.Stage-IV Year 2", "Detected.Stage-IV Year 3", "Detected.Stage-IV Year 4",
"Detected.Stage-IV Year 5", "Cancer Survivor", "Death")
es <- length(v_n) # number of health states

sition array for each alternative:
<- array(0, dim = c(n_states, n_states, n_t + 1, n_sims),
dimnames = list(v_n, v_n, 0:(n_t), 1:n_sims))
<- array(0, dim = c(n_states, n_states, n_t + 1, n_sims),
dimnames = list(v_n, v_n, 0:(n_t), 1:n_sims))

: all progression probabilities are assumed dependent on the probability of regression. Moreover,
to the natural structure of the transition array, there is no need to fill in probabilities = 0,
as the transitions from Infection to LSIL for ages ≤ 14.

=====
us-Quo -----
=====
e are for all the state transitions with no vaccine treatment.

sitions from Well State -----

following enters all transition probabilities for ages 0-85 for each transition from
state Well, across the appropriate time horizon 1 and all probabilistic
lations j
  in 1:n.t {
    j in 1:n.sims {
      1["Well", "Death", i, j] <- v_p_mort_lessHPV[i]
      1["Well", "Infection", i, j] <- omega.age[j, i]
      1["Well", "Well", i, j] <- 1 - (v_p_mort_lessHPV[i] + omega.age[j, i])

sitions from Infection State -----

```

65

can automate convergence. However, the improvement is negligible, and it increased the run of the model from < 60secs to > 2 mins. However, if desired, uncomment the line of code `##` to add auto chain convergence:

```

JAGS <- autojags(mod_JAGS, Rhat = 1.01)

eror inspection:
eror <- as.array(mod_JAGS$BUGSoutput$sims.array)
anes(x = posterior)

r_scheme.set("mix-gray-brightblue")
_ompo$posterior, pars = c("pEfficacy.vac", "LSIL_15_34", "HSL_n", "Stage.III.canc"))

_dens_chaine_data(posterior, pars = c("pA.mxd[1]", "pA.mxd[2]", "pA.mxd[3]", "pA.mxd[4]",
"pA.mxd[5]", "pA.mxd[6]", "pA.mxd[7]", "pA.mxd[8]",
"pA.mxd[9]", "pA.mxd[10]", "pA.mxd[11]"))

ch JAGS model to envir.
-jags(mod_JAGS)

=====
ability Matrix -----
=====

following creates a transition array that is then used to simulate the Markov cohort for both
tents, Status Quo and New Treatment.

following sets up the structure of the transitions between Health States:
init <- 0 # age at baseline
max <- 85 # maximum age of follow up
n_age.max - n_age_init # time horizon, number of cycles

30 health states of the model:
c("Well", "Infection", "LSIL", "HSL", "Stage-I Cancer", "Stage-II Cancer",
"Stage-III Cancer", "Stage-IV Cancer", "Detected.Stage-I Year 1",
"Detected.Stage-I Year 2", "Detected.Stage-I Year 3", "Detected.Stage-I Year 4",
"Detected.Stage-I Year 5", "Detected.Stage-II Year 1", "Detected.Stage-II Year 2",
"Detected.Stage-II Year 3", "Detected.Stage-II Year 4", "Detected.Stage-II Year 5",

```

```

ulations j.
i in 31:36) {
or (j in 1:n.sims) {
a_p_1["Infection", "Well", i, j] <- HPV_Well_30toEnd[j]

a_p_1["Infection", "Death", i, j] <- v_p_mort_lessHPV(i)

a_p_1["Infection", "LSIL", i, j] <- (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 3))) * 0.9)

a_p_1["Infection", "HSL", i, j] <- (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 36))) * 0.1)

a_p_1["Infection", "Infection", i, j] <- 1 - (HPV_Well_30toEnd[j] + v_p_mort_lessHPV(i) + (((1 -
ell_30toEnd[j]) * (1 - exp(-2 * 3))) * 0.9) + (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 36))) * 0.1) * 0.1)

nsitions from LSIL State -----

Following enters all transition probabilities for ages 15-34 for each transition from
state LSIL, across the appropriate time horizon i and all probabilistic
ulations j.
i in 16:35) {
or (j in 1:n.sims) {
a_p_1["LSIL", "Well", i, j] <- (LSIL_15_34[j] * 0.9)

a_p_1["LSIL", "Death", i, j] <- v_p_mort_lessHPV(i)

a_p_1["LSIL", "Infection", i, j] <- (LSIL_15_34[j] * 0.1)

a_p_1["LSIL", "HSL", i, j] <- ((1 - (LSIL_15_34[j] + v_p_mort_lessHPV(i)) * (1 - exp(-0.1 * 6)))

a_p_1["LSIL", "LSIL", i, j] <- 1 - ((LSIL_15_34[j] * 0.9) + (LSIL_15_34[j] * 0.1) + v_p_mort_lessHPV(i)
(LSIL_15_34[j] + v_p_mort_lessHPV(i))) * (1 - exp(-0.1 * 6)))

Following enters all transition probabilities for ages ≥25 for each transition from
state Infection, across the appropriate time horizon i and all probabilistic
ulations j.
i in 16:25) {
or (j in 1:n.sims) {
a_p_1["Infection", "Well", i, j] <- HPV_Well_15to24[j]

a_p_1["Infection", "Death", i, j] <- v_p_mort_lessHPV(i)

a_p_1["Infection", "LSIL", i, j] <- (((1 - HPV_Well_15to24[j]) * (1 - exp(-2 * 3))) * 0.9)

a_p_1["Infection", "HSL", i, j] <- (((1 - HPV_Well_15to24[j]) * (1 - exp(-2 * 36))) * 0.1)

a_p_1["Infection", "Infection", i, j] <- 1 - (HPV_Well_15to24[j] + v_p_mort_lessHPV(i) + (((1 -
11_15to24[j]) * (1 - exp(-2 * 3))) * 0.9) + (((1 - HPV_Well_15to24[j]) * (1 - exp(-2 * 3))) * 0.1) * 0.1)

Following enters all transition probabilities for ages 25-29 for each transition from
state Infection, across the appropriate time horizon i and all probabilistic
ulations j.
i in 26:30) {
or (j in 1:n.sims) {
a_p_1["Infection", "Well", i, j] <- HPV_Well_25to29[j]

a_p_1["Infection", "Death", i, j] <- v_p_mort_lessHPV(i)

a_p_1["Infection", "LSIL", i, j] <- (((1 - HPV_Well_25to29[j]) * (1 - exp(-2 * 3))) * 0.9)

a_p_1["Infection", "HSL", i, j] <- (((1 - HPV_Well_25to29[j]) * (1 - exp(-2 * 3))) * 0.1)

a_p_1["Infection", "Infection", i, j] <- 1 - (HPV_Well_25to29[j] + v_p_mort_lessHPV(i) + (((1 -
11_25to29[j]) * (1 - exp(-2 * 3))) * 0.9) + (((1 - HPV_Well_25to29[j]) * (1 - exp(-2 * 3))) * 0.1) * 0.1)

Following enters all transition probabilities for ages 30-85 for each transition from
state Infection, across the appropriate time horizon i and all probabilistic
ulations j.
i in 31:85) {
or (j in 1:n.sims) {
a_p_1["Infection", "Well", i, j] <- HPV_Well_30toEnd[j]

a_p_1["Infection", "Death", i, j] <- v_p_mort_lessHPV(i)

a_p_1["Infection", "LSIL", i, j] <- (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 3))) * 0.9)

a_p_1["Infection", "HSL", i, j] <- (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 36))) * 0.1)

a_p_1["Infection", "Infection", i, j] <- 1 - (HPV_Well_30toEnd[j] + v_p_mort_lessHPV(i) + (((1 -
ell_30toEnd[j]) * (1 - exp(-2 * 3))) * 0.9) + (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 36))) * 0.1) * 0.1)

```

```

ions from Stage-I Cervix Cancer State -----
Following enters all transition probabilities for ages 15-85 for each transition from
the Stage-I Cancer, across the appropriate time horizon i and all probabilistic
ions j.
16:86) {
  j in 1:n.sims) {
    1["Stage-I Cancer", "Death", i, j] <- v_p_mort_lessHPV[i]
    1["Stage-I Cancer", "Stage-II Cancer", i, j] <- Stage.I.canc[j]
    1["Stage-I Cancer", "Detected.Stage-I Year 1", i, j] <- ((1 - Stage.I.canc[j]) * 0.15)
    1["Stage-I Cancer", "Stage-I Cancer", i, j] <- 1 - (v_p_mort_lessHPV[i] + Stage.I.canc[j] + ((1 -
    anc[j]) * 0.15))
  }
}

```

sitions from HSL State -----

```

ions from Stage-II Cervix Cancer State -----
Following enters all transition probabilities for ages 15-85 for each transition from
the Stage-II Cancer, across the appropriate time horizon i and all probabilistic
ions j.
16:86) {
  j in 1:n.sims) {
    1["Stage-II Cancer", "Death", i, j] <- v_p_mort_lessHPV[i]
    1["Stage-II Cancer", "Stage-III Cancer", i, j] <- Stage.II.canc[j]
    1["Stage-II Cancer", "Detected.Stage-II Year 1", i, j] <- ((1 - Stage.II.canc[j]) * 0.225)
    1["Stage-II Cancer", "Stage-II Cancer", i, j] <- 1 - (v_p_mort_lessHPV[i] + Stage.II.canc[j] + ((
    canc[j]) * 0.225))
  }
}

```

state LSL, across the appropriate time horizon i and all probabilistic
lations j.

```

16:86) {
  r (j in 1:n.sims) {
    _P_1["LSL", "Well", i, j] <- (LSL_35_85[j] * 0.9)
    _P_1["LSL", "Death", i, j] <- v_p_mort_lessHPV[i]
    _P_1["LSL", "Infection", i, j] <- (LSL_35_85[j] * 0.1)
    _P_1["LSL", "HSL", i, j] <- ((1 - LSL_35_85[j]) * (1 - exp(-0.35 * 6)))
    _P_1["LSL", "LSL", i, j] <- 1 - ((LSL_35_85[j] * 0.9) + (LSL_35_85[j] * 0.1) + v_p_mort_lessHPV[i]
    LSL_35_85[j]) * (1 - exp(-0.35 * 6)))
  }
}

```

sitions from HSL State -----

Following enters all transition probabilities for ages 15-85 for each transition from
state HSL, across the appropriate time horizon i and all probabilistic
lations j.

```

16:86) {
  r (j in 1:n.sims) {
    _P_1["HSL", "Well", i, j] <- (HSL_n[j] * 0.5)
    _P_1["HSL", "Death", i, j] <- v_p_mort_lessHPV[i]
    _P_1["HSL", "LSL", i, j] <- (HSL_n[j] * 0.5)
    _P_1["HSL", "Stage-I Cancer", i, j] <- ((1 - (HSL_n[j] * 0.5) + (HSL_n[j] * 0.5))) * (1 - exp(-0.4
    _P_1["HSL", "HSL", i, j] <- 1 - ((HSL_n[j] * 0.5) + (HSL_n[j] * 0.5) + v_p_mort_lessHPV[i] + ((1 -
    _n[j] * 0.5) + (HSL_n[j] * 0.5))) * (1 - exp(-0.4 * 10)))
  }
}

```

```

abilistic simulations j.
  in 16:86 {
    r (j in 1:n.sims) {
      _P_1["Detected.Stage-I Year 1", "Detected.Stage-I Year 2", i, j] <- surv.StageI_year1[j]

      _P_1["Detected.Stage-I Year 1", "Death", i, j] <- (1 - surv.StageI_year1[j])

      _P_1["Detected.Stage-I Year 2", "Detected.Stage-I Year 3", i, j] <- (surv.StageI_year1[j] *
tagel_year2[j])

      _P_1["Detected.Stage-I Year 2", "Death", i, j] <- (1 - (surv.StageI_year1[j] * surv.StageI_year2[j]))

      _P_1["Detected.Stage-I Year 3", "Detected.Stage-I Year 4", i, j] <- (surv.StageI_year1[j] *
tagel_year2[j] * surv.StageI_year3[j])

      _P_1["Detected.Stage-I Year 3", "Death", i, j] <- (1 - (surv.StageI_year1[j] * surv.StageI_year2[j] *
tagel_year3[j]))

      _P_1["Detected.Stage-I Year 4", "Detected.Stage-I Year 5", i, j] <- (surv.StageI_year1[j] *
tagel_year2[j] * surv.StageI_year3[j] * surv.StageI_year4[j])

      _P_1["Detected.Stage-I Year 4", "Death", i, j] <- (1 - (surv.StageI_year1[j] * surv.StageI_year2[j] *
tagel_year3[j] * surv.StageI_year4[j]))

      _P_1["Detected.Stage-I Year 5", "Cancer Survivor", i, j] <- (surv.StageI_year1[j] * surv.StageI_year2[j] *
tagel_year3[j] * surv.StageI_year4[j] * surv.StageI_year5[j])

      _P_1["Detected.Stage-I Year 5", "Death", i, j] <- (1 - (surv.StageI_year1[j] * surv.StageI_year2[j] *
tagel_year3[j] * surv.StageI_year4[j] * surv.StageI_year5[j]))

      sitions from All Stage-II Cancer Survivor/Detected States -----

      following enters all transition probabilities for ages 15-85 for each transition from
      states of Detected Stage-II Cancer, across the appropriate time horizon i and all
      abilistic simulations j.

      sitions from Stage-III Cervix Cancer State -----

      following enters all transition probabilities for ages 15-85 for each transition from
      state Stage-III Cancer, across the appropriate time horizon i and all probabilistic
      lations j.

      r (j in 1:n.sims) {
        _P_1["Stage-III Cancer", "Death", i, j] <- v_p_mort_lessHP[i]

        _P_1["Stage-III Cancer", "Stage-IV Cancer", i, j] <- Stage.III.canc[j]

        _P_1["Stage-III Cancer", "Detected.Stage-III Year 1", i, j] <- ((1 - Stage.III.canc[j]) * 0.6)

        _P_1["Stage-III Cancer", "Stage-III Cancer", i, j] <- 1 - (v_p_mort_lessHP[i] + Stage.III.canc[j] + ((
        III.canc[j]) * 0.6))

      sitions from Stage-IV Cervix Cancer State -----

      following enters all transition probabilities for ages 15-85 for each transition from
      state Stage-IV Cancer, across the appropriate time horizon i and all probabilistic
      lations j.

      in 16:86 {
        r (j in 1:n.sims) {
          _P_1["Stage-IV Cancer", "Death", i, j] <- v_p_mort_lessHP[i]

          _P_1["Stage-IV Cancer", "Detected.Stage-IV Year 1", i, j] <- Stage.IV.Detected[j]

          _P_1["Stage-IV Cancer", "Stage-IV Cancer", i, j] <- 1 - (v_p_mort_lessHP[i] + Stage.IV.Detected[j])

          sitions from All Stage-I Cancer Survivor/Detected States -----

          following enters all transition probabilities for ages 15-85 for each transition from
          states of Detected Stage-I Cancer, across the appropriate time horizon i and all
          abilistic simulations j.

```

```

r (j in 1:n.sims) {
  p_1["Detected.Stage-III Year 1", "Detected.Stage-III Year 2", i, j] <- surv.StageIII_year1[j]
  p_1["Detected.Stage-III Year 1", "Death", i, j] <- (1 - surv.StageIII_year1[j])
  p_1["Detected.Stage-III Year 2", "Detected.Stage-III Year 3", i, j] <- (surv.StageIII_year1[j] *
    tageIII_year2[j])
  p_1["Detected.Stage-III Year 2", "Death", i, j] <- (1 - (surv.StageIII_year1[j] * surv.StageIII_year2
    tageIII_year2[j]))
  p_1["Detected.Stage-III Year 3", "Detected.Stage-III Year 4", i, j] <- (surv.StageIII_year1[j] *
    tageIII_year2[j] * surv.StageIII_year3[j])
  p_1["Detected.Stage-III Year 3", "Death", i, j] <- (1 - (surv.StageIII_year1[j] * surv.StageIII_year2
    tageIII_year3[j]))
  p_1["Detected.Stage-III Year 4", "Detected.Stage-III Year 5", i, j] <- (surv.StageIII_year1[j] *
    tageIII_year2[j] * surv.StageIII_year3[j] * surv.StageIII_year4[j])
  p_1["Detected.Stage-III Year 4", "Death", i, j] <- (1 - (surv.StageIII_year1[j] * surv.StageIII_year2
    tageIII_year3[j] * surv.StageIII_year4[j]))
  p_1["Detected.Stage-III Year 5", "Cancer Survivor", i, j] <- (surv.StageIII_year1[j] *
    tageIII_year2[j] * surv.StageIII_year3[j] * surv.StageIII_year4[j] * surv.StageIII_year5[j])
  p_1["Detected.Stage-III Year 5", "Death", i, j] <- (1 - (surv.StageIII_year1[j] * surv.StageIII_year2
    tageIII_year3[j] * surv.StageIII_year4[j] * surv.StageIII_year5[j]))

  situations from All Stage-IV Cancer Survivor/Detected States -----

  following enters all transition probabilities for ages 15-85 for each transition from
  states of Detected Stage-IV Cancer, across the appropriate time horizon i and all
  abilistic simulations j.
  in 16:86) {
    r (j in 1:n.sims) {
      p_1["Detected.Stage-II Year 1", "Detected.Stage-II Year 2", i, j] <- surv.StageII_year1[j]
      p_1["Detected.Stage-II Year 1", "Death", i, j] <- (1 - surv.StageII_year1[j])
      p_1["Detected.Stage-II Year 2", "Detected.Stage-II Year 3", i, j] <- (surv.StageII_year1[j] *
        tageII_year2[j])
      p_1["Detected.Stage-II Year 2", "Death", i, j] <- (1 - (surv.StageII_year1[j] * surv.StageII_year2
        tageII_year2[j]))
      p_1["Detected.Stage-II Year 3", "Detected.Stage-II Year 4", i, j] <- (surv.StageII_year1[j] *
        tageII_year2[j] * surv.StageII_year3[j])
      p_1["Detected.Stage-II Year 3", "Death", i, j] <- (1 - (surv.StageII_year1[j] * surv.StageII_year2
        tageII_year3[j]))
      p_1["Detected.Stage-II Year 4", "Detected.Stage-II Year 5", i, j] <- (surv.StageII_year1[j] *
        tageII_year2[j] * surv.StageII_year3[j] * surv.StageII_year4[j])
      p_1["Detected.Stage-II Year 4", "Death", i, j] <- (1 - (surv.StageII_year1[j] * surv.StageII_year2
        tageII_year3[j] * surv.StageII_year4[j]))
      p_1["Detected.Stage-II Year 5", "Cancer Survivor", i, j] <- (surv.StageII_year1[j] * surv.StageII_yea
        tageII_year3[j] * surv.StageII_year4[j] * surv.StageII_year5[j])
      p_1["Detected.Stage-II Year 5", "Death", i, j] <- (1 - (surv.StageII_year1[j] * surv.StageII_year2
        tageII_year3[j] * surv.StageII_year4[j] * surv.StageII_year5[j]))

      situations from All Stage-III Cancer Survivor/Detected States -----

      following enters all transition probabilities for ages 15-85 for each transition from
      states of Detected Stage-III Cancer, across the appropriate time horizon i and all
      abilistic simulations j.
      in 16:86) {
        r (j in 1:n.sims) {
          p_1["Detected.Stage-III Year 1", "Detected.Stage-III Year 2", i, j] <- surv.StageIII_year1[j]
          p_1["Detected.Stage-III Year 1", "Death", i, j] <- (1 - surv.StageIII_year1[j])
          p_1["Detected.Stage-III Year 2", "Detected.Stage-III Year 3", i, j] <- (surv.StageIII_year1[j] *
            tageIII_year2[j])
          p_1["Detected.Stage-III Year 2", "Death", i, j] <- (1 - (surv.StageIII_year1[j] * surv.StageIII_year2
            tageIII_year2[j]))
          p_1["Detected.Stage-III Year 3", "Detected.Stage-III Year 4", i, j] <- (surv.StageIII_year1[j] *
            tageIII_year2[j] * surv.StageIII_year3[j])
          p_1["Detected.Stage-III Year 3", "Death", i, j] <- (1 - (surv.StageIII_year1[j] * surv.StageIII_year2
            tageIII_year3[j]))
          p_1["Detected.Stage-III Year 4", "Detected.Stage-III Year 5", i, j] <- (surv.StageIII_year1[j] *
            tageIII_year2[j] * surv.StageIII_year3[j] * surv.StageIII_year4[j])
          p_1["Detected.Stage-III Year 4", "Death", i, j] <- (1 - (surv.StageIII_year1[j] * surv.StageIII_year2
            tageIII_year3[j] * surv.StageIII_year4[j]))
          p_1["Detected.Stage-III Year 5", "Cancer Survivor", i, j] <- (surv.StageIII_year1[j] *
            tageIII_year2[j] * surv.StageIII_year3[j] * surv.StageIII_year4[j] * surv.StageIII_year5[j])
          p_1["Detected.Stage-III Year 5", "Death", i, j] <- (1 - (surv.StageIII_year1[j] * surv.StageIII_year2
            tageIII_year3[j] * surv.StageIII_year4[j] * surv.StageIII_year5[j]))

          situations from All Stage-IV Cancer Survivor/Detected States -----

          following enters all transition probabilities for ages 15-85 for each transition from
          states of Detected Stage-IV Cancer, across the appropriate time horizon i and all
          abilistic simulations j.
          in 16:86) {
            r (j in 1:n.sims) {

```

```

1["Cancer Survivor", "Death", i, j] <- v_p_mort_lessHP[i]

ions from Death State -----
Following enters all transition probabilities for ages 0-85 for each transition from
te of Death, across the appropriate time horizon i and all
listic simulations j.
0:n.t {
n 1:n.sims {
Death", "Death", i, j] <- 1
=====
atment -----
=====
re all the state transitions with added vaccine treatment. The following creates a
ion array that is then used to simulate the Markov cohort with treatment.

ions from Well State -----
Following enters all transition probabilities for ages 0-85 for each transition from
te Well, across the appropriate time horizon i and all probabilistic
ions j
0:n.t {
n 1:n.sims {
Well", "Death", i, j] <- v_p_mort_lessHP[i]

Well", "Infection", i, j] <- (1 - pEfficacy.vac[j]) * omega.age[j, i]

Well", "Well", i, j] <- 1 - (v_p_mort_lessHP[i] + ((1 - pEfficacy.vac[j]) * omega.age[j, i]))

```

```

_P_1["Detected.Stage-IV Year 1", "Detected.Stage-IV Year 2", i, j] <- surv.StageIV_year1[j]
_P_1["Detected.Stage-IV Year 1", "Death", i, j] <- (1 - surv.StageIV_year1[j])
_P_1["Detected.Stage-IV Year 2", "Detected.Stage-IV Year 3", i, j] <- (surv.StageIV_year1[j] *
tageIV_year2[j])
_P_1["Detected.Stage-IV Year 2", "Death", i, j] <- (1 - (surv.StageIV_year1[j] * surv.StageIV_year2[j])
_P_1["Detected.Stage-IV Year 3", "Detected.Stage-IV Year 4", i, j] <- (surv.StageIV_year1[j] *
tageIV_year2[j] * surv.StageIV_year3[j])
_P_1["Detected.Stage-IV Year 3", "Death", i, j] <- (1 - (surv.StageIV_year1[j] * surv.StageIV_year2[j]
tageIV_year3[j]))
_P_1["Detected.Stage-IV Year 4", "Detected.Stage-IV Year 5", i, j] <- (surv.StageIV_year1[j] *
tageIV_year2[j] * surv.StageIV_year3[j] * surv.StageIV_year4[j])
_P_1["Detected.Stage-IV Year 4", "Death", i, j] <- (1 - (surv.StageIV_year1[j] * surv.StageIV_year2[j]
tageIV_year3[j] * surv.StageIV_year4[j]))
_P_1["Detected.Stage-IV Year 5", "Cancer Survivor", i, j] <- (surv.StageIV_year1[j] * surv.StageIV_yea
.StageIV_year3[j] * surv.StageIV_year4[j] * surv.StageIV_year5[j])
_P_1["Detected.Stage-IV Year 5", "Death", i, j] <- (1 - (surv.StageIV_year1[j] * surv.StageIV_year2[j]
tageIV_year3[j] * surv.StageIV_year4[j] * surv.StageIV_year5[j]))

sitions from Cancer Survivor State -----

following enters all transition probabilities for ages 15-85 for each transition from
state of Cancer Survivor, across the appropriate time horizon i and all
abilistic simulations j.
in 16:86 {
r (j in 1:n.sims) {
_P_1["Cancer Survivor", "Cancer Survivor", i, j] <- (1 - v_p_mort_lessHP[i])

```

te Infection, across the appropriate time horizon i and all probabilistic
ions j.

```

31:86) {
  j in 1:n.sims) {
    2["Infection", "Well", i, j] <- HPV_Well_30toEnd[j]

    2["Infection", "Death", i, j] <- v_p_mort_lessHPV[i]

    2["Infection", "LSIL", i, j] <- (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 3))) * 0.9)

    2["Infection", "HSIL", i, j] <- (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 36))) * 0.1)

    2["Infection", "Infection", i, j] <- 1 - (HPV_Well_30toEnd[j] + v_p_mort_lessHPV[i] + (((1 -
30toEnd[j]) * (1 - exp(-2 * 3))) * 0.9) + (((1 - HPV_Well_30toEnd[j]) * (1 - exp(-2 * 36))) * 0.1 -

```

ions from LSIL State-----

lowing enters all transition probabilities for ages 15-34 for each transition from
te LSIL, across the appropriate time horizon i and all probabilistic
ions j.

```

16:35) {
  j in 1:n.sims) {
    2["LSIL", "Well", i, j] <- (LSIL_15_34[j] * 0.9)

    2["LSIL", "Death", i, j] <- v_p_mort_lessHPV[i]

    2["LSIL", "Infection", i, j] <- (LSIL_15_34[j] * 0.1)

    2["LSIL", "HSIL", i, j] <- ((1 - (LSIL_15_34[j] + v_p_mort_lessHPV[i])) * (1 - exp(-0.1 * 6)))

    2["LSIL", "LSIL", i, j] <- 1 - ((LSIL_15_34[j] * 0.9) + (LSIL_15_34[j] * 0.1) + v_p_mort_lessHPV[i]
    15_34[j] + v_p_mort_lessHPV[i])) * (1 - exp(-0.1 * 6)))

```

sitions from Infection State-----

following enters all transition probabilities for ages 15-24 for each transition from
state Infection, across the appropriate time horizon i and all probabilistic
lations j.

```

in 16:25) {
  r(j in 1:n.sims) {
    p_2["Infection", "Well", i, j] <- HPV_Well_15to24[j]

    p_2["Infection", "Death", i, j] <- v_p_mort_lessHPV[i]

    p_2["Infection", "LSIL", i, j] <- (((1 - HPV_Well_15to24[j]) * (1 - exp(-2 * 3))) * 0.9)

    p_2["Infection", "HSIL", i, j] <- (((1 - HPV_Well_15to24[j]) * (1 - exp(-2 * 3))) * 0.1)

    p_2["Infection", "Infection", i, j] <- 1 - (HPV_Well_15to24[j] + v_p_mort_lessHPV[i] + (((1 -
15to24[j]) * (1 - exp(-2 * 3))) * 0.9) + (((1 - HPV_Well_15to24[j]) * (1 - exp(-2 * 3))) * 0.1))

```

following enters all transition probabilities for ages 25-29 for each transition from
state Infection, across the appropriate time horizon i and all probabilistic
lations j.

```

in 26:30) {
  r(j in 1:n.sims) {
    p_2["Infection", "Well", i, j] <- HPV_Well_25to29[j]

    p_2["Infection", "Death", i, j] <- v_p_mort_lessHPV[i]

    p_2["Infection", "LSIL", i, j] <- (((1 - HPV_Well_25to29[j]) * (1 - exp(-2 * 3))) * 0.9)

    p_2["Infection", "HSIL", i, j] <- (((1 - HPV_Well_25to29[j]) * (1 - exp(-2 * 3))) * 0.1)

    p_2["Infection", "Infection", i, j] <- 1 - (HPV_Well_25to29[j] + v_p_mort_lessHPV[i] + (((1 -
15_25to29[j]) * (1 - exp(-2 * 3))) * 0.9) + (((1 - HPV_Well_25to29[j]) * (1 - exp(-2 * 3))) * 0.1))

```

following enters all transition probabilities for ages 30-85 for each transition from

```

sitions from Stage-I Cervix Cancer State -----
following enters all transition probabilities for ages 15-85 for each transition from
state Stage-I Cancer, across the appropriate time horizon i and all probabilistic
lations j.
in 16:86) {
  r(j in 1:n.sims) {
    p_2["Stage-I Cancer", "Death", i, j] <- v_p_mort_lessHPV[i]
    p_2["Stage-I Cancer", "Death", i, j] <- v_p_mort_lessHPV[i]
    p_2["Stage-I Cancer", "Infection", i, j] <- (LSL_35_85[j] * 0.1)
    p_2["Stage-I Cancer", "HSL", i, j] <- ((1 - LSL_35_85[j]) * (1 - exp(-0.35 * 6)))
    p_2["Stage-I Cancer", "HSL", i, j] <- 1 - ((LSL_35_85[j] * 0.9) + (LSL_35_85[j] * 0.1) + v_p_mort_lessHPV[i]
    LSL_35_85[j]) * (1 - exp(-0.35 * 6)))

sitions from HSL State -----
following enters all transition probabilities for ages 15-85 for each transition from
state HSL, across the appropriate time horizon i and all probabilistic
lations j.
in 16:86) {
  r(j in 1:n.sims) {
    p_2["HSL", "Well", i, j] <- (HSL_n[j] * 0.5)
    p_2["HSL", "Death", i, j] <- v_p_mort_lessHPV[i]
    p_2["HSL", "LSL", i, j] <- (HSL_n[j] * 0.5)
    p_2["HSL", "Stage-I Cancer", i, j] <- ((1 - (HSL_n[j] * 0.5) + (HSL_n[j] * 0.5))) * (1 - exp(-0.4
    p_2["HSL", "HSL", i, j] <- 1 - ((HSL_n[j] * 0.5) + (HSL_n[j] * 0.5) + v_p_mort_lessHPV[i] + (1 -
    n[j] * 0.5) + (HSL_n[j] * 0.5)) * (1 - exp(-0.4 * 10)))

sitions from Stage-II Cervix Cancer State -----
following enters all transition probabilities for ages 15-85 for each transition from
state Stage-II Cancer, across the appropriate time horizon i and all probabilistic
lations j.
in 16:86) {
  r(j in 1:n.sims) {
    p_2["Stage-II Cancer", "Death", i, j] <- v_p_mort_lessHPV[i]
    p_2["Stage-II Cancer", "Stage-II Cancer", i, j] <- Stage.II.canc[j]
    p_2["Stage-II Cancer", "Detected.Stage-I Year 1", i, j] <- ((1 - Stage.II.canc[j]) * 0.16)
    p_2["Stage-II Cancer", "Stage-I Cancer", i, j] <- 1 - (v_p_mort_lessHPV[i] + Stage.II.canc[j] + ((1 -
    I.canc[j]) * 0.16))

sitions from Stage-II Cervix Cancer State -----
following enters all transition probabilities for ages 15-85 for each transition from
state Stage-II Cancer, across the appropriate time horizon i and all probabilistic
lations j.
in 16:86) {
  r(j in 1:n.sims) {
    p_2["Stage-II Cancer", "Death", i, j] <- v_p_mort_lessHPV[i]
    p_2["Stage-II Cancer", "Stage-III Cancer", i, j] <- Stage.II.canc[j]
    p_2["Stage-II Cancer", "Detected.Stage-II Year 1", i, j] <- ((1 - Stage.II.canc[j]) * 0.225)
    p_2["Stage-II Cancer", "Stage-II Cancer", i, j] <- 1 - (v_p_mort_lessHPV[i] + Stage.II.canc[j] + ((1 -
    II.canc[j]) * 0.225))

```

```

states of Detected Stage-I Cancer, across the appropriate time horizon i and all
abilistic simulations j.
in 16:86) {
r (j in 1:n.sims) {
_P_2["Detected.Stage-I Year 1", "Detected.Stage-I Year 2", i, j] <- surv.StageI_year1[j]
_P_2["Detected.Stage-I Year 1", "Death", i, j] <- (1 - surv.StageI_year1[j])
_P_2["Detected.Stage-I Year 2", "Detected.Stage-I Year 3", i, j] <- (surv.StageI_year1[j] *
tageI_year2[j])
_P_2["Detected.Stage-I Year 2", "Death", i, j] <- (1 - (surv.StageI_year1[j] * surv.StageI_year2[j]))
_P_2["Detected.Stage-I Year 3", "Detected.Stage-I Year 4", i, j] <- (surv.StageI_year1[j] *
tageI_year2[j] * surv.StageI_year3[j])
_P_2["Detected.Stage-I Year 3", "Death", i, j] <- (1 - (surv.StageI_year1[j] * surv.StageI_year2[j] *
tageI_year3[j]))
_P_2["Detected.Stage-I Year 4", "Detected.Stage-I Year 5", i, j] <- (surv.StageI_year1[j] *
tageI_year2[j] * surv.StageI_year3[j] * surv.StageI_year4[j])
_P_2["Detected.Stage-I Year 4", "Death", i, j] <- (1 - (surv.StageI_year1[j] * surv.StageI_year2[j] *
tageI_year3[j] * surv.StageI_year4[j]))
_P_2["Detected.Stage-I Year 5", "Cancer Survivor", i, j] <- (surv.StageI_year1[j] * surv.StageI_year2[
tageI_year3[j] * surv.StageI_year4[j] * surv.StageI_year5[j])
_P_2["Detected.Stage-I Year 5", "Death", i, j] <- (1 - (surv.StageI_year1[j] * surv.StageI_year2[j] *
tageI_year3[j] * surv.StageI_year4[j] * surv.StageI_year5[j]))
itions from All Stage-II Cancer Survivor/Detected States -----
following enters all transition probabilities for ages 15-86 for each transition from
states of Detected Stage-II Cancer, across the appropriate time horizon i and all

```

```

i in 16:86) {
  pr (j in 1:n.sims) {
    a_P_2["Detected.Stage-III Year 1", "Detected.Stage-III Year 2", i, j] <- surv.StageIII_year1[j]
    a_P_2["Detected.Stage-III Year 1", "Detected.Stage-III Year 2", i, j] <- surv.StageIII_year1[j]
    a_P_2["Detected.Stage-III Year 1", "Detected.Stage-III Year 2", i, j] <- (1 - surv.StageIII_year1[j])
    a_P_2["Detected.Stage-III Year 2", "Detected.Stage-III Year 3", i, j] <- (surv.StageIII_year1[j] *
      StageIII_year2[j])
    a_P_2["Detected.Stage-III Year 2", "Detected.Stage-III Year 3", i, j] <- (1 - (surv.StageIII_year1[j] *
      surv.StageIII_year2[j]))
    a_P_2["Detected.Stage-III Year 3", "Detected.Stage-III Year 4", i, j] <- (surv.StageIII_year1[j] *
      StageIII_year2[j] * surv.StageIII_year3[j])
    a_P_2["Detected.Stage-III Year 3", "Detected.Stage-III Year 4", i, j] <- (1 - (surv.StageIII_year1[j] *
      surv.StageIII_year2[j] * surv.StageIII_year3[j]))
    a_P_2["Detected.Stage-III Year 4", "Detected.Stage-III Year 5", i, j] <- (surv.StageIII_year1[j] *
      StageIII_year2[j] * surv.StageIII_year3[j] * surv.StageIII_year4[j])
    a_P_2["Detected.Stage-III Year 4", "Detected.Stage-III Year 5", i, j] <- (1 - (surv.StageIII_year1[j] *
      surv.StageIII_year2[j] * surv.StageIII_year3[j] * surv.StageIII_year4[j]))
    a_P_2["Detected.Stage-III Year 5", "Cancer Survivor", i, j] <- (surv.StageIII_year1[j] *
      StageIII_year2[j] * surv.StageIII_year3[j] * surv.StageIII_year4[j] * surv.StageIII_year5[j])
    a_P_2["Detected.Stage-III Year 5", "Cancer Survivor", i, j] <- (1 - (surv.StageIII_year1[j] *
      surv.StageIII_year2[j] * surv.StageIII_year3[j] * surv.StageIII_year4[j] * surv.StageIII_year5[j]))
  }
}

```

nsitions from All Stage-IV Cancer Survivor/Detected States -----

following enters all transition probabilities for ages 15-85 for each transition from
states of Detected Stage-IV Cancer, across the appropriate time horizon i and all
pabilistic simulations j.

```

i in 16:86) {

```

```

  abilistic simulations j.
  in 16:86) {
    r (j in 1:n.sims) {
      p_2["Detected.Stage-II Year 1", "Detected.Stage-II Year 2", i, j] <- surv.StageII_year1[j]
      p_2["Detected.Stage-II Year 1", "Detected.Stage-II Year 2", i, j] <- (1 - surv.StageII_year1[j])
      p_2["Detected.Stage-II Year 2", "Detected.Stage-II Year 3", i, j] <- (surv.StageII_year1[j] *
        tageII_year2[j])
      p_2["Detected.Stage-II Year 2", "Detected.Stage-II Year 3", i, j] <- (1 - (surv.StageII_year1[j] *
        surv.StageII_year2[j]))
      p_2["Detected.Stage-II Year 3", "Detected.Stage-II Year 4", i, j] <- (surv.StageII_year1[j] *
        tageII_year2[j] * surv.StageII_year3[j])
      p_2["Detected.Stage-II Year 3", "Detected.Stage-II Year 4", i, j] <- (1 - (surv.StageII_year1[j] *
        surv.StageII_year2[j] * surv.StageII_year3[j]))
      p_2["Detected.Stage-II Year 4", "Detected.Stage-II Year 5", i, j] <- (surv.StageII_year1[j] *
        tageII_year2[j] * surv.StageII_year3[j] * surv.StageII_year4[j])
      p_2["Detected.Stage-II Year 4", "Detected.Stage-II Year 5", i, j] <- (1 - (surv.StageII_year1[j] *
        surv.StageII_year2[j] * surv.StageII_year3[j] * surv.StageII_year4[j]))
      p_2["Detected.Stage-II Year 5", "Cancer Survivor", i, j] <- (surv.StageII_year1[j] *
        StageII_year2[j] * surv.StageII_year3[j] * surv.StageII_year4[j] * surv.StageII_year5[j])
      p_2["Detected.Stage-II Year 5", "Cancer Survivor", i, j] <- (1 - (surv.StageII_year1[j] *
        surv.StageII_year2[j] * surv.StageII_year3[j] * surv.StageII_year4[j] * surv.StageII_year5[j]))
    }
  }

```

sitions from All Stage-III Cancer Survivor/Detected States -----

following enters all transition probabilities for ages 15-85 for each transition from
states of Detected Stage-III Cancer, across the appropriate time horizon i and all
abilistic simulations j.

```

=====
parameter Input Values -----
=====

#-----
# the following script is the source code for all model input parameter values.
#-----

data are derived from (Sisanovic, E., et al. 2009): "The potential cost-effectiveness of
ing a human papillomavirus vaccine to the cervical cancer screening programme in South
ca." Most parameters are simulated using an empirical Bayes' approach, bar vaccine
cacy.

#-----
# : across all empirical bayes estimates, we assume a 5% standard error.
#-----

ability Dying less HPV for all States -----
=====

rt ASSA mortality table:
data <- read_excel("data-raw/mortality tables.xls", sheet = "final tables", range = "D1:D87")
rt_lessHPV <- as.matrix(mort_data[1])

#-----

the original study, the replication study is hugely sensitive to the HIV caused mortality
South Africa in 2009. The mortality table below excludes HIV/AIDS related mortality.

ment the two lines of code below and comment the code above to exclude HIV/AIDS related
ality.
data <- read_excel("data-raw/mortality tables.xls", sheet = "final tables", range = "F1:F87")
mort_lessHPV <- as.matrix(mort_data[1])

#-----

ial/Well State Progression -----
=====

ial to HPV -----
groups:
oup <- c("15-16", "17", "18", "19", "20", "<21", "22-23",
"24-29", "30-49", "55+")

ated Prevalence:
ence <- c(rep(0, length(0:14)), rep(0.00516258, length(15:16)),
rep(0.1130796, length(17:17)),

```

```

ers for this regression:
/normal_15to24 <- beta_params(mean = HPV_Normal_15, sigma = 0.05)$alpha
:normal_15to24 <- beta_params(mean = HPV_Normal_15, sigma = 0.05)$beta

/normal_25to29 <- beta_params(mean = HPV_Normal_25, sigma = 0.05)$alpha
:normal_25to29 <- beta_params(mean = HPV_Normal_25, sigma = 0.05)$beta

/normal_30toPlus <- beta_params(mean = HPV_Normal_30plus, sigma = 0.05)$alpha
:normal_30toPlus <- beta_params(mean = HPV_Normal_30plus, sigma = 0.05)$beta

=====
tel for progressions from LSIL -----
=====
ction or Normal -----
tion distribution parameter values Ages 15-34:

important to place an upper bound on this distribution in order to make the probabilities
le due to the South African mortality context.
x34 <- (1 - exp(-0.65 * 6))

[.L_15to34 <- beta_params(mean = LSIL_15to34, sigma = 0.05)$alpha
_.15to34 <- beta_params(mean = LSIL_15to34, sigma = 0.05)$beta

tion distribution parameter values Ages 25-50:
x85 <- (1 - exp(-0.4 * 6))

[.L_35to85 <- beta_params(mean = LSIL_35to85, sigma = 0.05)$alpha
_.35to85 <- beta_params(mean = LSIL_35to85, sigma = 0.05)$beta

=====
tel for progressions from HSIL -----
=====
(1 - exp(-.35 * 6))

[.L <- beta_params(mean = HSIL, sigma = 0.05)$alpha
.<- beta_params(mean = HSIL, sigma = 0.05)$beta

rep(0.139292, length(18:18)), rep(0.156352, length(19:19)),
rep(0.1392920, length(20:20)),
rep(0.113076, length(21:21)), rep(0.09516258, length(22:23)),
rep(0.04877068, length(24:29)),
rep(0.009950166, length(30:49)), rep(0.004987521, length(50:86)))
information for input to JAGS:
<- log(Prevalence)

=====
> efficacy data -----
=====
) (A) AND VACCINE(B).
of studies:
> <- 10
re participants in Control group:
- c(435, 41, 28, 219, 15, 10, 21, 56, 20, 17)
number of participants in control group:
- c(5375, 355, 277, 2924, 392, 175, 7838, 7312, 372, 2502)
re participants in Trial group:
- c(32, 12, 1, 61, 0, 0, 2, 4, 0, 1)
- c(5406, 366, 310, 2910, 387, 193, 7788, 7344, 401, 2497)

=====
fection State Progression -----
=====
ire the equations for relationships between all states from HPV/infection:
>24:
il_15 <- (1 - exp(-0.7 * 1.5))
>29:
il_25 <- (1 - exp(-.5 * 1.5))
j0:
il_30plus <- (1 - exp(-.15 * 1.5))

Normal -----
ite progressions are conditional on not regressing to Normal. Therefore, can model
er parameters using one input distribution.

```

```

=====
al probability of symptoms from Stage III to Treatment:
V.Detect.mu <- 0.9
=====

ribution parameters
StageIV <- beta_params(mean = StageIV.Detect.mu, sigma = 0.05)$alpha
tageI <- beta_params(mean = StageIV.Detect.mu, sigma = 0.05)$beta
=====

e I 5-year Survival -----
=====
1:
ive = 0.9688
= 1 - (0.9688 + mortality_lessHPV) .. etc.
StageI_YearI <- beta_params(mean = 0.9688, sigma = 0.05)$alpha
tageI_YearI <- beta_params(mean = 0.9688, sigma = 0.05)$beta
=====
2
ive = 0.9525
= 1 - (0.9525+ mortality_lessHPV)
StageI_YearII <- beta_params(mean = 0.9525, sigma = 0.05)$alpha
tageI_YearII <- beta_params(mean = 0.9525, sigma = 0.05)$beta
=====
3
ive = 0.9544
= 1 - (0.9544 + mortality_lessHPV)
StageI_YearIII <- beta_params(mean = 0.9544, sigma = 0.05)$alpha
tageI_YearIII <- beta_params(mean = 0.9544, sigma = 0.05)$beta
=====
4
ive = 0.9760
= 1 - 0.9760
StageI_YearIV <- beta_params(mean = 0.9760, sigma = 0.05)$alpha
tageI_YearIV <- beta_params(mean = 0.9760, sigma = 0.05)$beta
=====
5
ive = 0.9761
= 1 - 0.9761
=====

=====
Cancer States Progression -----
=====

: I -----
: I to Stage II probability:
.mu <- (1 - exp(-0.9 * 4))
=====

ribution parameters
StageI <- beta_params(mean = StageI.mu, sigma = 0.05)$alpha
tageI <- beta_params(mean = StageI.mu, sigma = 0.05)$beta
=====

al probability of symptoms from Stage I to Treatment:
.Detect.mu <- 0.15
=====

: II -----
: II to Stage III probability:
I.mu <- (1 - exp(-0.9 * 3))
=====

ribution parameters
StageII <- beta_params(mean = StageII.mu, sigma = 0.05)$alpha
tageII <- beta_params(mean = StageII.mu, sigma = 0.05)$beta
=====

al probability of symptoms from Stage II to Treatment:
I.Detect.mu <- 0.225
=====

: III -----
: III to Stage IV probability:
II.mu <- (1 - exp(-0.9 * 2))
=====

ribution parameters
StageIII <- beta_params(mean = StageIII.mu, sigma = 0.05)$alpha
tageIII <- beta_params(mean = StageIII.mu, sigma = 0.05)$beta
=====

al probability of symptoms from Stage III to Treatment:
II.Detect.mu <- 0.6
=====

: IV -----

```

```
StageII_YearI <- beta_params(mean = 0.9604, sigma = 0.05)$beta
tageI_YearI <- beta_params(mean = 0.9761, sigma = 0.05)$beta

ar survival:
88) * (0.9525) * (0.9544) * (0.9768) * (0.9761) * (0.9761))

=====
e II 5-year Survival -----
=====
1:
ive = 0.9066
= 1 - 0.9066
StageII_YearI <- beta_params(mean = 0.9066, sigma = 0.05)$alpha
tageII_YearI <- beta_params(mean = 0.9066, sigma = 0.05)$beta

2
ive = 0.8760
= 1 - 0.8760
StageII_YearII <- beta_params(mean = 0.8760, sigma = 0.05)$alpha
tageII_YearII <- beta_params(mean = 0.8760, sigma = 0.05)$beta

3
ive = 0.9225
= 1 - 0.9225
StageII_YearIII <- beta_params(mean = 0.9225, sigma = 0.05)$alpha
tageII_YearIII <- beta_params(mean = 0.9225, sigma = 0.05)$beta

4
ive = 0.9332
= 1 - 0.9332
StageII_YearIV <- beta_params(mean = 0.9332, sigma = 0.05)$alpha
tageII_YearIV <- beta_params(mean = 0.9332, sigma = 0.05)$beta

5
ive = 0.9604
= 1 - 0.9604
StageII_YearV <- beta_params(mean = 0.9604, sigma = 0.05)$alpha

StageII_YearI <- beta_params(mean = 0.9604, sigma = 0.05)$beta
tageII_YearI <- beta_params(mean = 0.9761, sigma = 0.05)$beta

ar survival:
66) * (0.8760) * (0.9225) * (0.9332) * (0.9604))

=====
e III 5-year Survival -----
=====
1:
ive = 0.7064
= 1 - 0.7064
StageIII_YearI <- beta_params(mean = 0.7064, sigma = 0.05)$alpha
tageIII_YearI <- beta_params(mean = 0.7064, sigma = 0.05)$beta

2
ive = 0.7378
= 1 - 0.7378
StageIII_YearII <- beta_params(mean = 0.7378, sigma = 0.05)$alpha
tageIII_YearII <- beta_params(mean = 0.7378, sigma = 0.05)$beta

3
ive = 0.8610
= 1 - 0.8610
StageIII_YearIII <- beta_params(mean = 0.8610, sigma = 0.05)$alpha
tageIII_YearIII <- beta_params(mean = 0.8610, sigma = 0.05)$beta

4
ive = 0.9231
= 1 - 0.9231
StageIII_YearIV <- beta_params(mean = 0.9231, sigma = 0.05)$alpha
tageIII_YearIV <- beta_params(mean = 0.9231, sigma = 0.05)$beta

5
ive = 0.9142
= 1 - 0.9142
StageIII_YearV <- beta_params(mean = 0.9142, sigma = 0.05)$alpha
tageIII_YearV <- beta_params(mean = 0.9142, sigma = 0.05)$beta
```

```

-----
survival:
* (0.7378) * (0.8610) * (0.9231) * (0.9142))

=====
V 5-year Survival -----
=====

i = 0.3986
.- 0.3986
geIV_YearI <- beta_params(mean = 0.3986, sigma = 0.05)$alpha
jeIV_YearI <- beta_params(mean = 0.3986, sigma = 0.05)$beta

i = 0.4982
.- 0.4982
geIV_YearII <- beta_params(mean = 0.4982, sigma = 0.05)$alpha
jeIV_YearII <- beta_params(mean = 0.4982, sigma = 0.05)$beta

i = 0.7638
.- 0.7638
geIV_YearIII <- beta_params(mean = 0.7638, sigma = 0.05)$alpha
jeIV_YearIII <- beta_params(mean = 0.7638, sigma = 0.05)$beta

i = 0.8652
.- 0.8652
geIV_YearIV <- beta_params(mean = 0.8652, sigma = 0.05)$alpha
jeIV_YearIV <- beta_params(mean = 0.8652, sigma = 0.05)$beta

i = 0.8592
.- 0.8592
geIV_YearV <- beta_params(mean = 0.8592, sigma = 0.05)$alpha
jeIV_YearV <- beta_params(mean = 0.8592, sigma = 0.05)$beta

```