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Bayesian probabilistic sensitivity analysis of Markov models for natural history of a disease: an application for cervical cancer

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ABSTRACT

BACKGROUND: parameter uncertainty in the Markov model's description of a disease course was addressed. Probabilistic sensitivity analysis (PSA) is now considered the only tool that properly permits parameter uncertainty's examination. This consists in sampling values from the parameter's probability distributions.

METHODS: Markov models fitted with microsimulation were considered and methods for carrying out a PSA on transition probabilities were studied. Two Bayesian solutions were developed: for each row of the modeled transition matrix the prior distribution was assumed as a product of Beta or a Dirichlet. The two solutions differ in the source of information: several different sources for each transition in the Beta approach and a single source for each transition from a given health state in the Dirichlet. The two methods were applied to a simple cervical cancer's model.

RESULTS: differences between posterior estimates from the two methods were negligible. Results showed that the prior variability highly influence the posterior distribution.

CONCLUSIONS: the novelty of this work is the Bayesian approach that integrates the two distributions with a product of Binomial distributions likelihood. Such methods could be also applied to cohort data and their application to more complex models could be useful and unique in the cervical cancer context, as well as in other disease modeling.

Key words: Markov model; Probabilistic sensitivity analysis; Bayesian methods; Cervical cancer

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INTRODUCTION

Quantifying uncertainty is relevant in medical decision making in order to properly acknowledge confidence in health impact estimates, to identify critical assumptions and to compare the impact of alternatives (1). In this paper, we address Markov models to describe the natural history of a disease. The components of uncertainty in these kinds of models are: population variability, heterogeneity, structural uncertainty, parameters uncertainty. These uncertainties are reflected in decision

uncertainty by specifying a distribution for the cost-effectiveness outcomes (2).

Individual variability consists of differences among patients that occur by chance and cannot be reduced by additional information. Heterogeneity, on the contrary, relates to differences between patients that can be in part explained. By simulating different life histories within a Markov model according to given transition probabilities, which can eventually be a function of subject-specific covariates like age, heterogeneity can be reproduced. Structural uncertainty is related to the assumptions we are making about the phenomenon being studied and the specification of the mathematical model. Structural uncertainty can be addressed with Bayesian model averaging methods as demonstrated in (3).

Parameters uncertainty is usually understated. In the context of Markov models, life histories of a cohort of patients are generated one at time by microsimulation. In each Markov cycle, each transition made is sampled in accordance with the corresponding probability (age, sex, race, etc.). Information about these probabilities is usually limited, because scientific literature about age-, type- and population-specific natural history and transmission is scarce. Moreover, for some parameters, such as progression rates for cancer, empirical studies cannot be carried out for ethical reasons.

The most common method for dealing with uncertainty in transition probabilities consists in carrying out the microsimulations under extreme different values of the given model parameters - one-way or multi-way if parameters are varied one or more at a time respectively (4). This "deterministic" method is in opposition to probabilistic sensitivity analysis (PSA) in which parameters values are sampled from appropriate theoretical or empirical distributions. While a deterministic approach still has a role in specific contexts, as in scenario analysis, probabilistic methods are considered the only tool that properly allows for the examination of parameter uncertainty in the current literature (5, 6). PSA is now largely diffused in health technology assessment and in screening policy simulations (6).

Bayesian methods are widely studied in the context of medical decision making (7). One advantage of using Bayesian methods in the context of PSA for Markov models is in overcoming the problem of estimating transition probabilities when zero counts are observed for the event of interest. If in the specification of distributions for transition probabilities the parameters are estimated uniquely from observed event counts, zero probability will be associated to those transitions that have never been observed. With a Bayesian approach, it is natural to combine data with prior information and, as a result, a non null probability, even if small, will be associated with the unobserved transitions (8).

The Bayesian approach is also useful for integrating information when several datasets or expert opinions are available (9).

In the present paper, we developed two Bayesian methods for carrying out a PSA on transition probabilities. We also applied these methods to a very simple model for natural history of cervical cancer.

METHODS

Using a PSA within a decision making problem allows to take directly into account uncertainty on the parameters involved in the model by treating them as random quantities with a specific probability distribution.

In carrying out a Bayesian PSA for transition probabilities, a joint posterior density function is associated with each element of the transition matrix related to the Markov model under study. Obtaining the joint posterior density function requires the definition of an appropriate Bayesian model for transition probabilities and therefore the selection of suitable distributions for prior information and data.

We developed two Bayesian models for PSA on transition probabilities based on different prior specification (Table 1). In particular we assumed that transition probabilities are a priori distributed as independent Beta random variables or follow a Dirichlet distribution.

Likelihood

Usually information on transition probabilities between health states is from independent epidemiological studies. In such a case the suitable approach is to define a model based on a series of independent random likelihoods. Data relative to each transition probability consists of the number of successes in a sequence of independent Binomial experiments. When the whole transition matrix is considered, data for each row $\{x_1, \ldots, x_k\}$ are the product of independent Binomial distributions (10):

$$f(x_1,\ldots,x_k;\pi_1,\ldots,\pi_k;n_1,\ldots,n_k)=\prod_i \binom{n_i}{x_i}\pi_i^{x_i}(1-\pi_i)^{n_i-x_i},$$

TABLE 1

BAYESIAN MODELS FOR BAYESIAN PSA ON ROW *h* OF THE TRANSITION MATRIX

TRANSITION	BETA MODEL	DIRICHLET MODEL
Likelihood	$\{x_1,\ldots,x_k\} \sim \prod_i Binomial(\pi_i, n_i)$	
Prior	$\pi_i \overset{indep}{\sim} Beta(a_i,b_i), i=1,\ldots,k; i \neq h$ $\pi_h = 1 - \sum_{i=1,i\neq h}^{k} \pi_i$	$\{\pi_1,\ldots,\pi_k\} \sim Dirichlet(\alpha_1,\ldots,\alpha_k)$
Posterior	$\pi_i \overset{indep}{\sim} Beta(x_i + a_i, b_i + n_i - x_i), i=1,\ldots,k; i \neq h$ $\pi_h = 1 - \sum_{i=1,i\neq h}^{k} \pi_i$	Approximated by MCMC

where x_i is the observed number of transitions to the i^{th} state, n^i represents the related sample size and πi the probability of making a transition to state i.

The vector of probabilities $\{\pi_1, \ldots, \pi_k\}$ must satisfy the constraint of the row sum to one that derives from the assumption in the Markov model of health states that are mutually exclusive. Since data for the probability of remaining in the same health state at time t+1 is usually not available, we model progression and regression data with Binomial independent distributions and impose the constraint of row elements summing up to one by fixing the probability to not change status as the difference between one and the sum of all other transition proportions. For example, if we are modeling the h^{th} row of the transition matrix, the constrain is the following

$$\pi_h = 1 - \sum_{i=1,i\neq h}^{k} \pi_i$$

In the case the transitions to different states are observed in the same study, the distribution for the number of success can be assumed Multinomial:

where n is the study sample size.

$$f(x_1,\ldots,x_k;\pi_1,\ldots,\pi_k;n) = \frac{n!}{x_1!\ldots x_k!}\pi_1^{x_1}\ldots\pi_k^{x_k}$$

Prior distributions

The prior distribution summarizes current knowledge on each transition probability. Prior distributions can be of clinical relevance or non-informative (11). Clinical priors represent the combined prior belief of informed experts. This will include the subjective prior opinions of the trial investigators and/or other experts, as well as the results of previous similar studies. Informative priors can be skeptical or enthusiastic depending on the grade of confidence experts put on the transition (11). In principle a non-informative prior would correspond to the situation when none or very little prior information is available.

In this work, we will use Beta or Dirichlet prior distributions to model transition probabilities.

Beta priors

The Beta distribution is a natural choice for representing uncertainty on the probability parameter π when a Binomial distribution is assumed on the number of success on a sequence of independent dichotomous experiments (2, 12, 13). In fact, the Beta and the Binomial distributions are conjugated (14). The Beta distribution is continuous, constrained by the interval (0, 1), and characterized by two parameters a and b, which are strictly positive:

$$f(\pi;a,b) = \frac{\pi^{a-1}(1-\pi)^{b-1}}{B(a,b)},$$

where $B(a,b)$ is the Beta function. Beta parameters are related to the mean and the

variance of π: mean and variance of π are respectively

$$E[\pi] = \frac{a}{a+b},$$

$$Var[\pi] = \frac{ab}{(a+b)^2(a+b+1)}.$$

The Beta distribution has the property of being very versatile and can be used to model random variables with quite different shapes. Beta priors can be tuned by multiplying Beta parameters by an inflation factor c. The result is that while the mean remains constant the variance will be modified approximately inversely to c.

We assumed that, given the hth row of the transition matrix, probabilities $\pi_1, \ldots, \pi_k$ have independent Beta distributions. For each π_i we defined the Beta parameters a_i and b_i. The specification of these parameters permits the generation of a distribution consistent with available information on transition, i.e. knowledge about the phenomenon from expert opinion, literature revision or new empirical data.

Dirichlet priors

The Dirichlet distribution is conjugated with the Multinomial distribution, and then it is a natural choice for representing uncertainty on the probability vector $\{\pi_1, \ldots, \pi_k\}$ even for different sampling designs, as the Product Binomial model discussed above (8).

The Dirichlet distribution is an extension of the Beta generally used in the case of several mutually exclusive events. Each row of the transition matrix can then be modeled by the multivariate Dirichlet distribution to deal with uncertainty in transition probabilities. The constraint of row elements summing up to one is implicitly fulfilled. The distribution is parameterized by a vector of positive real numbers $\{\alpha_1, \ldots, \alpha_k\}$. These parameters code prior information on event probabilities. The density function of a Dirichlet variable $\{\pi_1, \ldots, \pi_k\}$ is

$$f(\pi_1,\ldots,\pi_k;\alpha_1,\ldots,\alpha_k) = \frac{\Gamma(\alpha_1+\ldots+\alpha_k)}{\Gamma(\alpha_1)\cdot\ldots\cdot\Gamma(\alpha_k)}\prod_{i=1}^{k}\pi_i^{\alpha_i-1},$$

with $\alpha_i \geq 0$, for all $i = 1, \ldots, k$ and $\sum_{i=1}^{k}\pi_i = 1$.

Setting, $\alpha_0 = \sum_{i=1}^{k}\alpha_i$ mean and variance of each π_i are respectively

$$E[\pi_i] = \frac{\alpha_i}{\alpha_0},$$

$$Var[\pi_i] = \frac{\alpha_i(\alpha_0-\alpha_i)}{\alpha_0^2(\alpha_0+1)}.$$

Note that Dirichlet distribution parameters are related to the mean and the variance of the transition probabilities. Likewise, multiplying such parameters by an inflation factor c, we obtain a series of Dirichlet distributions, $\pi'_i \sim \text{Dir}(c \cdot \alpha_1, \ldots, c \cdot \alpha_k)$, with the same expected value, but different variability:

$$\alpha'_i = c\alpha_i, \quad \alpha'_0 = c\alpha_0$$

$$E[\pi'_i] = \frac{\alpha'_i}{\alpha'_0} = E[\pi_i]$$

$$Var[\pi'_i] = \frac{\alpha'_i(\alpha'_0-\alpha'_i)}{\alpha'^2_0(\alpha'_0+1)} = \frac{c^2\alpha_i(\alpha_0-\alpha_i)}{c^2\alpha_0^2(c\alpha_0+1)} = Var[\pi_i]\frac{\alpha_0+\alpha_1}{c\alpha_0+1}.$$

Given the inflation factor *c*, the variance of the row transition probabilities will be jointly modified inversely to *c*: the larger the value of *c* the smaller is the variance. The coefficient *c* can be thought of as the dimension of a hypothetical sample from which information about parameters is obtained and represents the degree of prior confidence.

Posterior distributions

Given a row of the transition matrix, if we assume Binomial likelihoods and independent Beta prior distributions on each transition probability $\pi_1, \ldots, \pi_k$, the resulting posterior distribution can be simply obtained in closed form relying on conjugacy. A posteriori each parameter πi has a Beta distribution with parameters $x_i + a_i$, $b_i + n_i - x_i$. The joint posterior is then computed in closed form as product of these Betas. Under this approach, we can introduce expert opinions through parameters ai and bi for all *i=1,…,k* to develop priors on $\pi_1, \ldots, \pi_k$.

If we assume Binomial likelihoods and Dirichlet prior distribution on $\{\pi_1, \ldots, \pi_k\}$, a simple analytical form for the joint posterior density does not exist due to the non conjugacy of the prior (Dirichlet) and the likelihood (product of Binomial). The marginal posterior of each parameter can be approximated by Markov Chain Monte Carlo (MCMC) method to draw repeatedly from the joint posterior distribution.

It should be noticed that in the case in which prior belief is obtained by the same expert(s) for all the transitions from a given health state (a row in the transition matrix), the variance is fixed for all the parameters and a Dirichlet prior is

FIG. 1

SIX HEALTH STATE MODELS FOR HPV NATURAL HISTORY AND CARCINOGENESIS

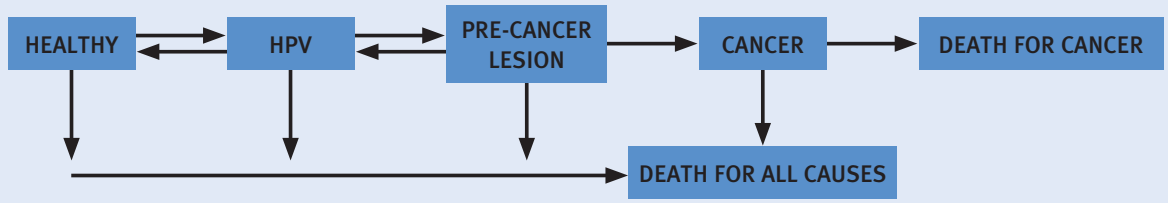


TABLE 2

DATA USED IN THE HPV AND CARCINOGENESIS NATURAL HISTORY MODEL WITH THEIR REFERENCES

TRANSITION	X	N	SE	TIME	REFERENCE
Healthy → HPV	122	608	0.016	12	(22)
HPV → Healthy	115	288	0.029	12	(23)
HPV → SIL	6	83	0.028	12	(22)
SIL → Healthy	52	376	0.018	72	(24)
SIL → HPV	6	376	0.0065	72	(24)
SIL → Cancer	4	481	0.0041	72	(24)

x: cases, n: sample dimension, se: standard error for proportions, time: period in which data is relative (months), SIL: pre-cancer lesions

particularly appropriate to model each row of the transition matrix.

Example

As an example of the two approaches we considered a very simple model for natural history of cervical cancer (Figure 1). In cervical cancer modeling the natural history considers the Human Papillomavirus (HPV) infection, that is considered a necessary cause for cervical cancer (15). The health states are the following: Healthy, HPV infected, Pre-cancer lesion, Cancer, Death by cancer, Death by other causes (16).

Microsimulation with Bayesian PSA was then carried out as follows. We fixed a number of iterations and, for each iteration, we defined different transition matrices sampling from the joint posterior distribution of the transition probabilities obtained under the two approaches. In simulating life histories, a cohort of women of a fixed dimension is considered. For each woman and for each iteration a life history is simulated by sampling transitions from the corresponding posterior matrix. Repeating for all women and for all iterations, a set of life histories is generated.

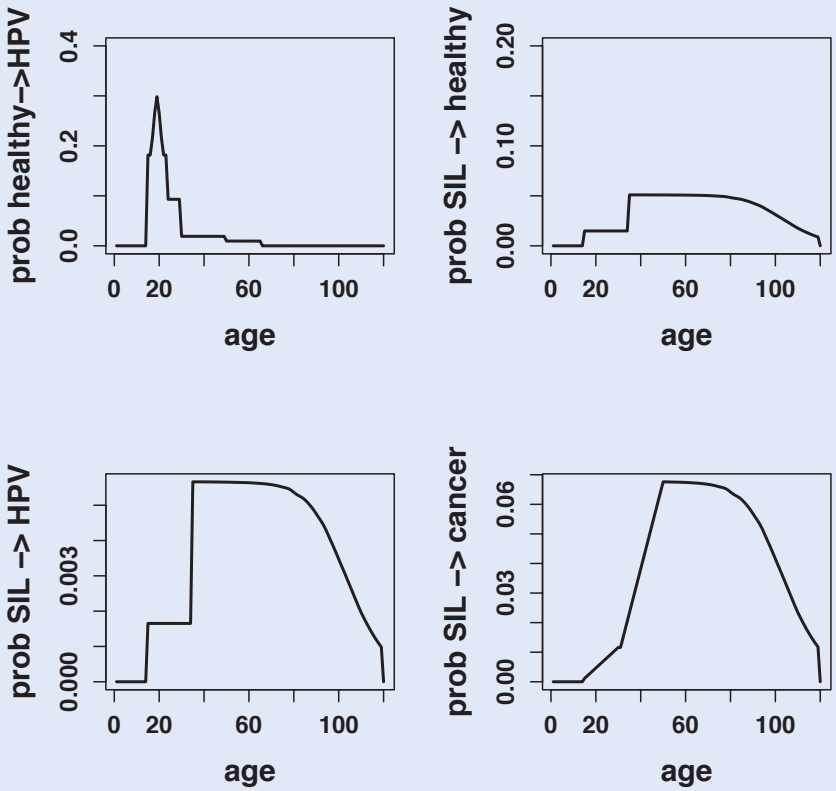
Clinical age-specific prior distributions were developed for each transition probability as explained in a recent work (16). Age-specific values of the Beta and Dirichlet parameters used to specify the prior distributions for some transition probabilities are reported in Figure 2.

Data for transitions was extracted from published studies (Table 2). Transition data relative to periods different than 12 months was converted in accord with (17). Using this method we are implicitly assuming that only a transition is possible from each state; in the case of partially observed data a matrix decomposition approach (18) or a method that estimates the underlying rate matrix using Kolmogorov's forward equations (19) are surely more appropriate. However we are here considering a simplified example of cervical cancer disease and not interested at real parameter estimates.

The microsimulation was implemented using the software R 2.8.0 (20). WinBugs (21) was used for approximating the joint posterior distribution with the Dirichlet method, with burn-in 1 000 and 2 000 iterations.

FIG. 2

AGE-SPECIFIC MEAN VALUES FOR SOME TRANSITION PROBABILITIES, USED TO SPECIFY THE PRIOR DISTRIBUTIONS. SIL: PRE-CANCER LESIONS



RESULTS

We applied the Bayesian PSA with the Beta and the Dirichlet priors to the simple model for cervical cancer natural history. Data in (22) is from a study on 608 female students from a state University in New Brunswick, New Jersey. Their mean (± SD) age was 20 ± 3 years. Data in (23) is from a cohort of 688 young women 13 to 22 years old positive for HPV recruited in two clinic sites in San Francisco and visited every 4 months. Data in (24) is from a study of 528 women with a mean age of 29 included in a prospective follow-up study conducted at the University Hospital in Kuopio, Finland (Table 2).

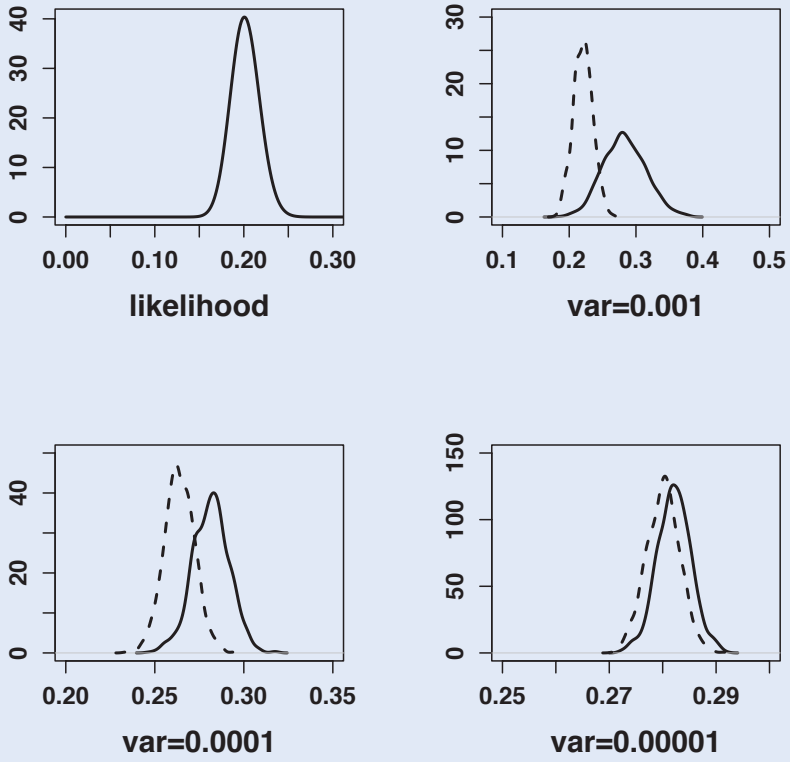
It should be noticed that age-specific transition data was not available and we assumed the same likelihood for all classes of age. Prior specifications were then highly informative and higher weight was given to prior respect to data.

We sampled 100 values from the joint posterior distribution for the elements of the transition matrix under the two approaches and generated 1 000 life histories. When independent Beta prior distributions were assumed on the row transition probabilities, uncertainty on each row parameter was treated separately. When a Dirichlet prior was assumed, the row variance was modified by applying an inflation factor c to the distribution hyperparameters. The larger c is the smaller is the marginal variance of each row parameter. In general we found that the posterior distributions are highly sensitive to the prior variances.

As an example, we report some transition probabilities for a given age (25 years). For each transition, we used three different Beta priors (with variance respectively 0.001, 0.0001 and 0.00001) and we plotted them with the corresponding posterior distributions (Figure 3). Results for the Bayesian model with Dirichlet prior are reported in Figure 4. In all cases, the marginal variance on each prior distribution was varied by applying different inflation factors (c=100, 1 000, 10 000).

FIG. 3

LIKELIHOOD FUNCTION, PRIOR (SOLID LINE) AND POSTERIOR (DASHED LINE) DISTRIBUTIONS FOR THE TRANSITION FROM HEALTHY TO HPV INFECTED STATE WITH THE BETA MODEL WITH PRIOR VARIANCE 0.001, 0.0001 AND 0.00001



DISCUSSION

We proposed a Bayesian approach with two different prior specifications to carry out a PSA on transition probabilities in Markov models for disease natural history. PSA using Dirichlet or Beta distributions to model probabilities is not new in the context of Markov models (2, 8). The novelty of our work is the Bayesian approach that integrates these two distributions with a likelihood which is the product of Binomial distributions.

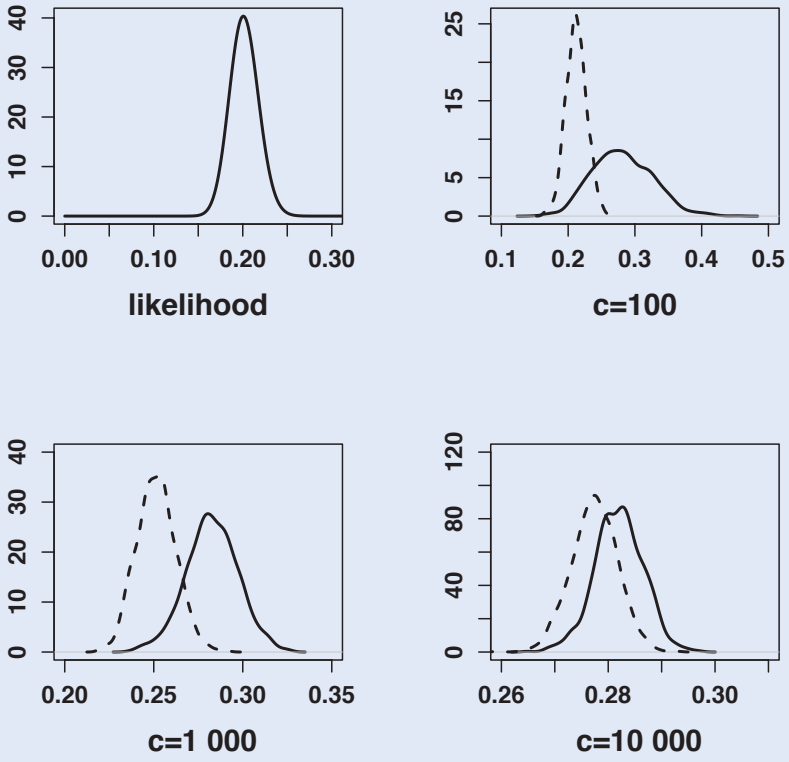
Boshuiozen et al. (12) handled Bayesian methods for Binomial proportions by considering non informative priors (uniform or Jeffrey priors). However, in case of sparse empirical data on transitions between health states, informative priors are useful. In addition, if studies with large sample size are available, the results will be less sensitive to prior specification (7).

A novelty in our approaches is the use of independent Binomial data. In many works on transition probabilities, a Multinomial likelihood is specified for data (8, 19, 23, 24). This choice models state transitions as the number of success in a sampling experiment with fixed sample size. A Multinomial likelihood could be appropriate if transitions from a given health state to k possible other states are observed in the same cohort of individuals. However, since transition data is typically from different and independent studies, it is more appropriate to model transition data using independent Binomial data. By using an improper prior distribution Beta(0,0), i.e. assuming a priori ignorance on transition probabilities, than the Beta approach results in the standard non Bayesian PSA practice. In this case, the non Bayesian PSA approach implicitly corresponds to the use of independent Binomial likelihoods. However, the use improper prior is controversial and a priori ignorance may by assumed by using other uninformative priors, i.e. Beta(1,1).

There is a main difference between using Beta prior and Dirichlet prior for modeling transition probabilities. Under the Beta approach, we assume that prior information on transitions comes from independent experts. Under the Dirichlet

FIG. 4

LIKELIHOOD FUNCTION, PRIOR (SOLID LINE) AND POSTERIOR (DASHED LINE) DISTRIBUTIONS FOR THE TRANSITION FROM HEALTHY TO HPV INFECTED STATE WITH THE DIRICHLET MODEL WITH INFLATION FACTORS 100, 1000, 10 000



approach, we assume that prior information on all transition probabilities from a given health state comes from a single expert. This involves that given a health state, all transitions from that state are modeled with a joint prior distribution and the same degree of uncertainty is assumed for all transitions from that health state. In this case, the parameter's variance could be jointly modified by applying an inflation factor c. This factor is inversely proportional to the distribution variance and can therefore be interpreted as the sample size of a hypothetical experiment. The larger c is the smaller is the marginal variance of each row parameter. Under the Dirichlet approach, also a certain correlation among parameters was assumed. Differing from the Boshuizen et al. (12) study, in this case uncertainty on different parameters (transition from a given health state) is not assumed independent, but correlation between the uncertainty is taken into account.

We didn't take here in consideration the elicitation problem, i.e. it is not investigated the appropriate distribution in the case where different expert beliefs give correlated probabilities, neither the case of different levels of uncertainty about each probability from a single expert, even if in this case the Beta approach could be used. Both in the data and prior specification, it is assumed that information is previously selected by meta-analytical techniques with the aim of making the standard assumption that the different studies informing data and prior probabilities (that often have differences in population, clinical context, design, and so on) represent the same underlying population. Therefore possible conflicts between the informing studies could be weighted by relevance.

The models here presented are applicable to transitions with very low probabilities. In the likelihood specification the probability to not change health state is fixed as the difference between one and the sum of other transition proportions. This is possible only in the case of very small probabilities, otherwise a negative likelihood to not change state, as well as a negative posterior probability, could result.

We applied our methods to a very simple

model for cervical cancer natural history. As an example of the two model application, the prior variance was varied to examine the resulting effect on posterior distribution. In the application to a complex problem prior variance should be fixed.

Results show that decreasing the variance of the prior Beta distributions as well as increasing the value of the inflation factor c for the Dirichlet prior, the posterior distributions are closer to the priors and the likelihoods become negligible. As shown in Figures 3-4, the posterior distribution moves toward the prior as the variability decreases. When prior and likelihood are centered on the same value, decreasing the prior variability, the posterior distribution becomes narrower. In our application, prior information was age-specific, while data was not. This implied that prior was strongly informative in particular for extreme classes of age. Further studies should be planned to obtain age-dependent data in order to improve likelihood for the most critical transitions.

In cervical cancer modeling, screening and recent vaccination strategies are evaluated on the basis of natural history models for HPV. Large uncertainty is present in various parameter values, such as screening efficacy, HPV progression and regression rates, transmission probabilities. In most of the proposed models for cervical screening evaluation (16, 25) sensitivity analysis was conducted on parameters concerning diagnostics and follow-up protocol, because the emphasis was on studying cost and benefits of different screening strategies. PSA methods in cervical cancer modeling were used for economic parameters (26). Uncertainty about transition probabilities was taken into account with calibration methods where a posterior set of parameters was selected that generates model outcomes in accord with epidemiological data (27). Bayesian PSA methods on transition probabilities have not yet been developed in cervical cancer modeling. The application of our methods to more complex models could therefore be very useful and unique in the cervical cancer context. With our approach, uncertainty about transition probability is treated with PSA methods that are now considered to be the only tool that properly allows for the examination of parameter uncertainty. In addition, the Bayesian approach allows to use information coming from different sources at the same time to update the transition probability distribution. This is important in the cervical cancer field where a large number of sources of information and studies are present.

This work is a step forward in developing a Bayesian comprehensive decision analytic model that could be applied to the evaluation of cervical cancer screening and vaccination interventions while taking into account all components of uncertainty and combining multiple sources of information and empirical data. These methods could be applied in Markov models that generate cohort data besides microsimulation and also in modeling diseases different than cervical cancer.

DISCLAIMERS: *the authors declare that they have no competing interests.*

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