International Journal of Technology Assessment in Health Care, 15:3 (1999), 563–572.

PROBABILISTIC SENSITIVITY ANALYSIS IN COST-EFFECTIVENESS

An Application from a Study of Vaccination Against Pneumococcal Bacteremia in the Elderly

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Abstract

Objectives: We explore the policy implications of probabilistic sensitivity analysis in cost-effectiveness analysis by applying simulation methods to a decision model.
Methods: We present the multiway sensitivity analysis results of a study of the cost-effectiveness of vaccination against pneumococcal bacteremia in the elderly. We then execute a probabilistic sensitivity analysis of the cost-effectiveness ratio by specifying posterior distributions for the uncertain parameters in our decision analysis model. In order to estimate probability intervals, we rank the numerical values of the simulated incremental cost-effectiveness ratios (ICERs) to take into account preferences along the cost-effectiveness plane.
Results: The 95% probability intervals for the ICER were generally much narrower than the difference between the best case and worst case results from a multiway sensitivity analysis. Although the multiway sensitivity analysis had indicated that, in the worst case, vaccination in the 85 and older age group was not acceptable from a policy standpoint, probabilistic methods indicated that the cost-effectiveness of vaccination was below $50,000 per quality-adjusted life-year in greater than 92% of the simulations and below $100,000 in greater than 95% of the simulations.
Conclusions: Probabilistic methods can supplement multiway sensitivity analyses to provide a more comprehensive picture of the uncertainty associated with cost-effectiveness ratios and thereby inform policy decisions.

Keywords: Cost-effectiveness analysis, Decision analysis, Simulation, Pneumococcal disease

The incremental cost-effectiveness ratio (ICER) measures the incremental price of obtaining a unit health effect from an intervention in comparison to an alternative.

Financial support for this study was provided in part by unrestricted contributions from Pasteur Merieux MSD, Lyon, France, and Merck Vaccine Division, West Point, PA, by a cooperative agreement with the U.S. Public Health Service (The REMATCH Trial, HL-53968), and by a grant from the Columbia-Presbyterian Medical Center Office of Clinical Trials.

The U.S. Panel on Cost-Effectiveness in Health and Medicine has recommended that analysts who perform model-based cost-effectiveness studies conduct univariate and multiway sensitivity analyses, and where possible, estimate a confidence interval through statistical or simulation methods (12). Univariate and multiway sensitivity analyses explore the effects of uncertainty in single or multiple parameters on the results of a cost-effectiveness study by systematically varying the parameters in the model and re-analyzing the outcome. Because combinations of extreme parameters are very unlikely to occur, global best and worst case studies are helpful primarily in the pragmatic sense when they demonstrate results that are not substantially different from those of the reference case.

Probabilistic sensitivity analysis attempts to quantify the uncertainty in the ICER, by placing a probability distribution over parameter values. Several studies have examined different methods of estimating uncertainty in ICERs, including the delta method, Fieller's method, Bonferroni methods, Bayesian estimation techniques, and nonparametric bootstrapping (2;4;10;11;14;15;16;19). A number of investigators have applied these techniques to cost-effectiveness analyses of health care interventions (2;3;4;5;7;9;10;11;12;15;17;19;20), which have been based both on clinical trials and on decision models that use secondary data sources.

An important issue in the estimation of distributions for ICERs arises from the treatment of negative values in the numerator, the denominator, or both. Chaudhary and Stearns (4) have characterized negative ratios as reflective of one of the following:

- Cost savings where treatment costs are less and health is improved by an intervention; or
- A bad investment where treatment costs are greater and health is worse due to the intervention.

These two situations represent very different meanings for a decision maker who is interested in maximizing health benefits for resources spent. Therein lies a problem with certain methods for estimating confidence intervals of ratios, such as Fieller's method and the delta method; they treat the confidence interval as if it were continuous with respect to preference and as such do not distinguish between the different kinds of negative ratios. Unless one explicitly qualifies the source of the negative values, the interval is ambiguous. Even if the different types of negative ratios are distinguished from each other, others postulate that they do not present useful quantitative information for decision making (2;18). Given that ICERs with negative lower confidence limits are making their way into the clinical literature (4;11), the issue of differentiating among different types of negative ratios becomes more important.

A second issue, unique to the estimation of uncertainty in decision models, is the fact that they are usually not the result of primary data collection in a randomized setting, and therefore cannot be used to estimate confidence intervals in the frequentist sense. A frequentist 95% confidence interval is a realization of a random interval that will cover the true value of a parameter in 95% of a hypothetical set of replications (10); clearly, "confidence intervals" based on decision trees that use multiple data sources may not be able to make this claim.

In light of the above limitations to interpreting uncertainty in the ICER, we discuss the use of sensitivity analysis in a Markov model that analyzes the cost-effectiveness of vaccination against pneumococcal bacteremia in the elderly. We present a multiway sensitivity analysis as one method of reflecting parameter uncertainty. Then, under two different methods of assigning probability densities to

Table 1. Parameter Distributions in Probabilistic Sensitivity Analysis

Parameter	Method 1	Method 2
Vaccination		
Serotype coverage	Uniform	Logistic normal
Effectiveness	Logistic normal	Logistic normal
Bacteremia		
Incidence	Uniform	Logistic normal
Case fatality rate	Uniform	Logistic normal
Costs		
Vaccination	Uniform	Uniform
Inpatient bacteremia	Uniform	Uniform
Future medical costs	Normal	Normal
Discount rate	Uniform	Uniform

uncertain parameters, we execute a Bayesian probabilistic sensitivity analysis of the ICER. We incorporate a reordering of simulation results conditioned on the cost-effectiveness (C/E) plane that overcomes the difficulties posed by negative values for the ICER and demonstrate how Bayesian probability intervals are informative for decision makers.

METHODS

The analysis employs a variety of secondary sources of data that were discussed in our previous C/E analysis of vaccination against pneumococcal bacteremia in elderly people (17). A Markov model, created using the computer software DATA (6), compares bacteremia in vaccinated and unvaccinated cohorts. Outcomes are measured in U.S. dollars (costs) and quality-adjusted life-years (QALY) (health effects). Separate analyses were performed using two models, one that included the future medical costs of survivors, and one in which such costs were excluded. We did not include costs that were separate from the health sector, such as consumption and changes in production, in our analyses. We thereby followed the recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine on costs to include in the reference case, which takes the societal perspective. At the same time, conducting one analysis including the future medical costs of survivors and another analysis without those costs takes into account the controversy surrounding their inclusion and the difficulty of clearly separating future medical costs that are and are not related to pneumococcal bacteremia. The uncertain parameters in the decision-tree model included the following (Table 1): percentage of bacteremia-causing pneumococci that the vaccine would cover; effectiveness of vaccination against covered vaccine serotypes; incidence and case fatality rates from pneumococcal bacteremia; cost of vaccination; cost of hospitalization for bacteremia; future medical costs for survivors; and the discount rate.

Prior to the estimation of ICERs, best and worst case values were determined for each parameter. Global best and worst case values for the ICER in each age group were calculated by setting all the individual parameters in the model to their best or worst case values, respectively, in a multiway sensitivity analysis.

Because the data that we entered into our model were based on different secondary data sources as well as expert opinion, we incorporated uncertainty in parameter values by means of a Bayesian probabilistic sensitivity analysis (1;10;15). In Bayesian analysis, one summarizes uncertainty with a probability distribution

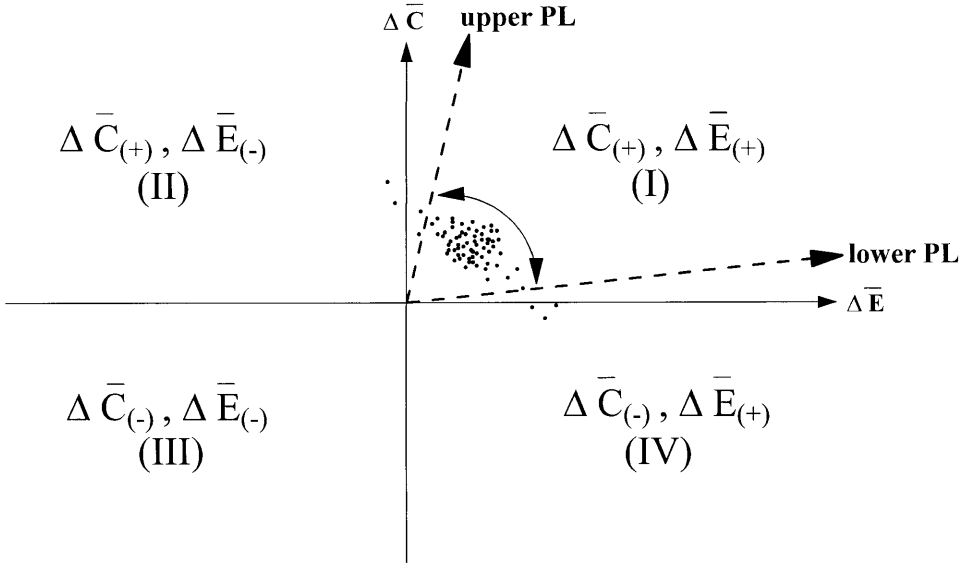

Figure 1. Approach to probability interval estimation. Quadrants are represented by roman numerals and by $\Delta\bar{C}$ and $\Delta\bar{E}$ for net costs and net health effects, respectively. PL denotes probability limit.

over the parameter values, the posterior distribution, that one modifies in the light of accumulating data. By comparison, frequentists fix parameter values and consider the randomness that arises in hypothetical replications of the current study. Thus, a Bayesian is 95% sure, given the data, that the parameter lies within his or her 95% probability interval after having seen the data; by comparison, a frequentist is 95% sure that his or her 95% confidence interval will cover the true value of the parameter, whatever it may be, and this degree of confidence is unchanged by looking at the data. In this study, we assumed that posterior distributions had been estimated, and used these to summarize uncertainty about parameters in our decision model. Heitjan et al. (10) and Parmagiani et al. (15) provide further discussion of Bayesian estimation of ICERs.

We defined probability intervals and the probability that the ratio fell within meaningful limits in the cost-effectiveness plane by sampling from probability distributions on model parameters.

We sampled from two separate sets of posterior distributions on parameters (Table 1). In method 1, we assumed uniform distributions for those parameters where the best and worst case values were estimated by expert judgment. High and low bounds of the uniform distributions were the same as the best and worst case values used in the multiway analysis. In method 2, we developed logistic normal approximations to the posterior from random effects meta-analyses for incidence, case fatality rate, and serotype coverage of the vaccine (8). The distributions for the other parameters under this method were the same as under method 1. One thousand simulations were performed in each age group and for each method. All told, we executed 12 sets of 1,000 simulations.

Each simulation resulted in a single estimate for the ICER. In order to incorporate the meaning of different values for the ICER in our probabilistic sensitivity analysis, we categorized the simulation results according to the cost-effectiveness plane (Figure 1):

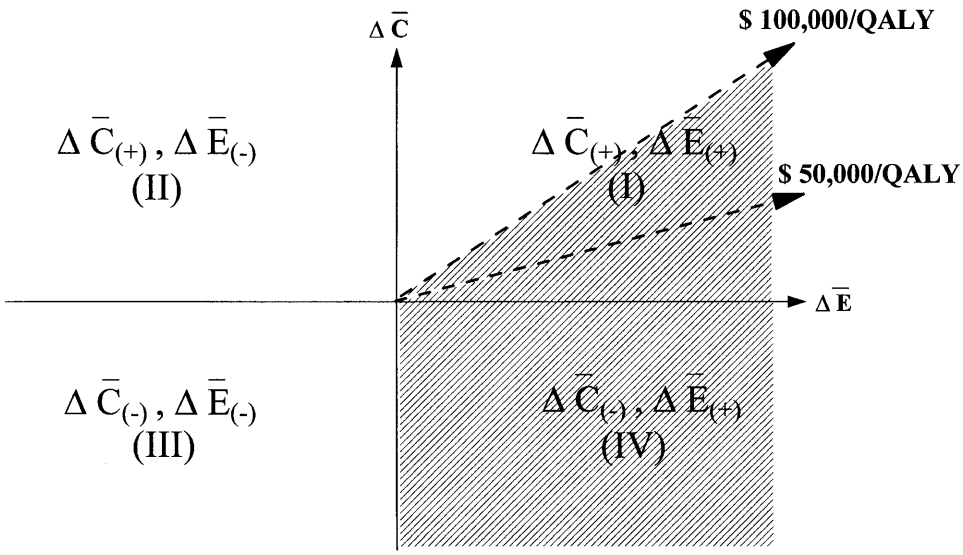

Figure 2. Areas (*shaded*) in the cost-effectiveness plane representing incremental cost-effectiveness ratios with negative costs and positive health effects or values less than $50,000 per QALY and $100,000 per QALY.

- The lower right quadrant (IV), negative costs and positive health effects, designated as $\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$;
- The upper right quadrant (I), positive costs and positive health effects, designated as $\Delta\overline{C}_{(+)}$, $\Delta\overline{E}_{(+)}$;
- The lower left quadrant (III), negative costs and negative health effects, designated as $\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(-)}$;
- The upper left quadrant (II), positive costs and negative health effects, designated as $\Delta\overline{C}_{(+)}$, $\Delta\overline{E}_{(-)}$.

If a ratio was from quadrant II we labeled it according to the symbol $\Delta\overline{C}_{(+)}$, $\Delta\overline{E}_{(-)}$ and ranked it at the high (less favorable) end of the distribution of estimates for the ICER. If a ratio was from quadrant IV we labeled it according to the symbol $\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$ and ranked it at the low end of the distribution. We constructed two-sided $100(1-\alpha)\%$ probability intervals in each age group and for each method by excluding the top and bottom $[100(\alpha/2)\%]$ of the estimates in each instance. To avoid the illusion of perfectly ordered intervals, we used symbols ($\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$ and $\Delta\overline{C}_{(+)}$, $\Delta\overline{E}_{(-)}$) for probability limits in quadrants IV and II, respectively. We also calculated the probability that the ratio represented negative costs and positive health effects or was less than $50,000 per QALY and $100,000 per QALY, respectively (Figure 2).

RESULTS

Reference case results and the global best case–worst case sensitivity analyses for three age groups (65–74, 75–84, $\geqslant$ 85 years) are presented in Table 2 (17). In the reference case, vaccination against pneumococcal bacteremia actually resulted in cost savings and health benefits in models that excluded survivors' future medical costs and was cost-effective by current standards in models that included survivors'

Table 2. Multiway Sensitivity Analysis Results per Person Vaccinated: Best and Worst Cases

Age	Incremental cost ($)	Incremental effectiveness (quality-adjusted days gained)	Cost/effectiveness (incremental cost/ incremental quality-adjusted life-years)
Excluding future medical costs of survivors			
65–74			
Reference case	−6.68	+1.48	Cost-saving[a]
Best case	−20.50	+3.03	Cost-saving[a]
Worst case	+18.21	+0.26	$26,116
75–84			
Reference case	−10.91	+0.97	Cost-saving[a]
Best case	−37.45	+2.87	Cost-saving[a]
Worst case	+20.99	+0.09	$87,572
⩾85			
Reference case	−8.58	+0.58	Cost-saving[a]
Best case	−52.55	+2.12	Cost-saving[a]
Worst case	+23.48	+0.01	$579,065
Including future medical costs of survivors			
65–74			
Reference case	+36.84	+1.48	$9,090
Best case	+70.12	+3.03	$8,446
Worst case	+24.98	+0.26	$35,822
75–84			
Reference case	+30.82	+0.97	$11,597
Best case	+89.73	+2.87	$11,394
Worst case	+24.32	+0.09	$101,470
⩾85			
Reference case	+22.68	+0.58	$14,263
Worst case	+62.93	+2.12	$10,809
Worst case	+24.27	+0.01	$598,487

Source: Sisk et al. (17)

[a] "Cost-saving" denotes negative net costs and positive net health effects ($\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$).

future medical costs. In the global worst case analysis, for 65–74-year-olds, our results suggested that the ICER was acceptable by current standards, regardless of whether we included the cost of care for future survival. This was not so clearly the case for the other age groups. In particular, when the future medical costs of survivors were included, the worst case ICER for those aged 85 and older was about $600,000 per QALY.

Tables 3 and 4 present the results of the simulations for each age group. Table 3 shows the probability of the ICER being in various quadrants or regions of interest of the C/E plane. In all cases, there was zero probability that the intervention saved costs at the expense of health effects (i.e., that the ratio extended into quadrant III). The probability that the intervention offered an incremental benefit at either a cost savings or at a rate of less than $50,000 per QALY was 0.92 or 0.95 for a rate less than $100,000 per QALY. The probability of positive costs and negative health effects (i.e., $\Delta\overline{C}_{(+)}$, $\Delta\overline{E}_{(-)}$) was generally 0.01 or less; this was due to the small probability of anaphylactic reaction to the vaccine.

Table 4 compares the results of the multiway sensitivity analysis with the probability intervals derived from the simulations. In each age group, the range of the probability interval for the ICER was much narrower than the range established

Table 3. Probability of ICER Being in Different Regions of the C/E Plane[a]

	Quadrant IV $\Delta\bar{C}_{(-)}$, $\Delta\bar{E}_{(+)}$	Quadrant IV $\Delta\bar{C}_{(-)}$, $\Delta\bar{E}_{(+)}$ or under \$50,000/ QALY	Quadrant IV $\Delta\bar{C}_{(-)}$, $\Delta\bar{E}_{(+)}$ or under \$100,000/ QALY	Quadrant II $\Delta\bar{C}_{(+)}$, $\Delta\bar{E}_{(-)}$
Excluding future medical costs of survivors				
65–74				
Method 1	0.551	1.000	1.000	0.000
Method 2	0.544	1.000	1.000	0.000
75–84				
Method 1	0.725	0.999	1.000	0.000
Method 2	0.675	1.000	1.000	0.000
85 and over				
Method 1	0.650	0.958	0.975	0.008
Method 2	0.608	0.954	0.974	0.008
Including future medical costs of survivors				
65–74				
Method 1	0.000	1.000	1.000	0.000
Method 2	0.000	1.000	1.000	0.000
75–84				
Method 1	0.000	0.999	1.000	0.000
Method 2	0.000	0.999	1.000	0.000
85 and over				
Method 1	0.000	0.924	0.955	0.010
Method 2	0.000	0.921	0.954	0.010

[a] $\Delta\bar{C}$ and $\Delta\bar{E}$ denote net costs and net health effects, respectively. Methods 1 and 2 refer to the different approaches to specifying probability distributions on the decision model parameters.

by a best and worst case analysis. For the group aged 85 and older, in particular, the upper limit of the 95% probability intervals for the ICER was less than the worst case value by almost \$400.00 per QALY. The conservative nature of the probabilistic analysis is evident from the median ICERs for the simulation approaches, which were uniformly higher than the reference case ICERs from the multiway analysis (Table 4). This was the case regardless of whether method 1 or 2 was used to specify the parameter distributions in the model.

DISCUSSION

This probabilistic sensitivity analysis contributes fundamental insight to better inform the decision about whether to vaccinate groups over age 74. It is easy to misinterpret the importance of a global worst case and best case sensitivity analysis, but relatively straightforward to interpret a confidence interval or probability interval derived using probabilistic methods. In this analysis, we found that, excluding future medical costs of survivors, pneumococcal vaccination would save lives as well as cost, under reference case and best case circumstances for all three age groups. In our global worst case analysis, models with and without future medical costs of survivors suggested that the ICER associated with vaccination against pneumococcal bacteremia was acceptable by current standards for 65–74-year-olds, but was less clear for other age groups. In particular, the \$579,065–\$598,487 worst case range for 85-year-olds was clearly unacceptable to many decision makers. However, when one examined the 95% probability interval, the strong likelihood

Table 4. Multiway and Probabilistic Sensitivity Analyses, Results per Person Vaccinated ($/QALY)[a]

	Multiway sensitivity analysis		Simulations, method 1	Simulations, method 2
Excluding future medical costs of survivors				
65–74				
Reference case	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	Median	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$
Best case	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	Lower 95% prob. limit	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$
Worst case	26,116	Upper 95% prob. limit	3,597	3,658
75–84				
Reference case	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	Median	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$
Best case	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	Lower 95% prob. limit	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$
Worst case	87,572	Upper 95% prob. limit	6,464	7,409
85 and over				
Reference case	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	Median	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$
Best case	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	Lower 95% prob. limit	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$	$\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$
Worst case	579,065	Upper 95% prob. limit	100,742	102,379
		Upper 90%, prob. limit	38,981	41,244
Including future medical costs of survivors				
65–74				
Reference case	9,090	Median	10,306	10,138
Best case	8,466	Lower 95% prob. limit	7,241	6,974
Worst case	35,822	Upper 95% prob. limit	14,257	14,400
75–84				
Reference case	11,597	Median	13,718	13,901
Best case	11,394	Lower 95% prob. limit	9,507	9,386
Worst case	101,470	Upper 95% prob. limit	21,792	23,344
85 and over				
Reference case	14,263	Median	17,208	17,921
Best case	10,809	Lower 95% prob. limit	10,322	10,604
Worst case	598,487	Upper 95% prob. limit	250,688	271,626
		Upper 90% prob. limit	86,879	96,125

[a] $\Delta\overline{C}$ and $\Delta\overline{E}$ denote net costs and net health effects, respectively.

was that vaccination would be cost-effective in all three age groups. From a policy standpoint, the probabilistic analysis provided an added insight about the implications of vaccination that was important for an informed resource allocation decision.

Current computer software packages make probabilistic sensitivity analysis much more accessible than it has been in the past; however, there is also the potential for researchers to misinterpret the results of such analyses because equivalently valued ICERs may represent very different trade-offs. It is critically important to keep in mind the quadrant in the cost-effectiveness plane that a ratio lies in, so that probability intervals can be ordered in a meaningful manner. The respective medians and lower 95% probability limits of the cost-effectiveness ratio were cost-saving and health-producing ($\Delta\overline{C}_{(-)}$, $\Delta\overline{E}_{(+)}$) for all three age groups when the additional nonbacteremia costs of future survival were ignored. Thus, the negative ratios here fell into quadrant IV in the cost-effectiveness plane and were important to distinguish from similarly valued ratios from quadrant II, which represent a loss of health at a dollar premium.

Our presentation of probability intervals on the ICER was considerably more straightforward than it would have been had data from our simulations extended into quadrant III. We are not aware of any cost-effectiveness analyses that focus

on interventions where there are negative costs and negative health effects. This may well become an important issue, however, as increased emphasis is placed on conserving financial resources in the health sector. It is notable that when we included the future medical costs of survivors in our analysis, best case estimates of the ICER exceeded the calculated lower 95% probability limit of that ratio. This paradoxical finding, a consequence of the parameter estimates selected for our multiway sensitivity analysis, illustrates a potential pitfall in the multiway sensitivity analysis process that probabilistic methods address. In particular, clinical experts must specify the bounds for parameter values for sensitivity analysis ex-ante, when the ultimate effect of their estimates on the outcome of the decision model cannot always be predicted.

This is particularly true when the outcome measure is a ratio such as cost/effectiveness. This was the case for our estimates of the fatality rate from bacteremia. When our model did not include future medical costs of survivors, a higher case fatality rate produced more "potential" health benefits from vaccination, and thus a more favorable cost-effectiveness ratio. However, when the future medical costs of survivors are included, the same "best case" fatality rate produces results with higher costs as well as increased survival for vaccinees. The result is a less favorable cost-effectiveness ratio. Thus, the multiway sensitivity analysis did not produce a "best case" that was actually the lowest possible value for the cost-effectiveness ratio. Under such circumstances, probabilistic sensitivity analysis helped to uncover the unanticipated variability in the cost-effectiveness ratio, and was certainly more expeditious and tractable than the multiple analyses that would have been necessary to achieve the same insight from traditional multiway sensitivity analysis.

An issue in the use of Bayesian probability distributions in cost-effectiveness is the use of posteriors. In this analysis we used two different methods, one based on expert judgment and another based to a greater extent on our data sources, to define posterior distributions for our model parameters. In this case there was not a large difference in the size of the probability intervals despite differences in the shapes of the posteriors used, and our policy conclusions would not have changed. However, it may well be that under other circumstances the posteriors used will have more of an effect on the results. With advances in simulation methods, it has become much easier to compare the use of different posteriors based on different sets of prior information and different likelihoods.

Cost-effectiveness increasingly influences the discussion of the appropriateness of health care. Probabilistic sensitivity analysis represents a methodological advance in reflecting parameter uncertainty in cost-effectiveness analysis. With the additional information produced by this method, together with a meaningful way of interpreting the results, policy makers may more accurately utilize the results of cost-effectiveness analysis in health to evaluate technologies and allocate resources.

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