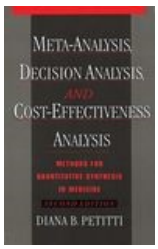

Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis (2nd edn)

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CHAPTER

2 Overview of the Methods

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Abstract

This chapter describes the steps used in a systematic review and meta-analysis, a simple decision analysis, and a straightforward cost-effectiveness analysis. It makes liberal use of examples to illustrate the usefulness of the information derived from the three methods for clinical decision-making and policy. It emphasizes the importance of being systematic and carefully documenting what is done when using the methods.

Keywords: systematic review, meta-analysis, decision analysis, cost-effectiveness analysis, guidelines, policy, decision-making

Subject: Public Health, Epidemiology

Collection: Oxford Scholarship Online

Doing a study that involves meta-analysis, decision analysis, or cost-effectiveness analysis is complex for most real-life applications, reflecting the complexity of the problems that the methods are used to address. However, each method involves a limited number of discrete, fairly simple steps.

The three sections of this chapter give an overview of meta-analysis, decision analysis, and cost-effectiveness analysis and describe the steps in applying the methods in their simplest form. In later chapters, advanced issues in application of the three methods are discussed in depth.

2.1 META-ANALYSIS

2.1.1 Overall Goals, Main Uses, and Description of Steps

The overall goal of meta-analysis is to combine the results of previous studies to arrive at summary conclusions about a body of research. It is used to calculate a summary estimate of effect size, to explore the reasons for differences in effects between and among studies, and to identify heterogeneity in the effects of the intervention (or differences in the risk) in different subgroups.

Meta-analysis has historically been useful in summarizing prior research based on randomized trials when individual studies are too small to yield a valid conclusion.

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> *EXAMPLE:* In 1982, use of thrombolytic agents after acute myocardial infarction was controversial. At that time, eight randomized clinical trials examining ↳ the effect of a loading dose of at least 250,000 international units of intravenous streptokinase on mortality given a short time after an acute myocardial infarction had occurred (Stampfer et al. 1982). As shown in Table 2-1, two of the trials found a higher risk of mortality in treated patients, five found a lower risk, and one found essentially identical mortality in the treated and the control patients. The trials were all fairly small, and the difference in mortality between treated and control patients was statistically significant in only one trial. These studies were interpreted as inconclusive about the benefit of early treatment with intravenous streptokinase.
>
> In a meta-analysis based on these trials, Stampfer et al. (1982) estimated the relative risk of mortality in patients treated with intravenous streptokinase to be 0.80 with 95% confidence limits of 0.68 and 0.95. A subsequent study of intravenous streptokinase after acute myocardial infarction involving thousands of patients (GISSI 1986) confirmed the conclusion based on the meta-analysis of early studies—that intravenous treatment with streptokinase reduces mortality following acute myocardial infarction.

Table 2-1 Results of randomized trials of effect on mortality of intravenous streptokinase following acute myocardial infarction published before 1982

Reference	*N* Deaths/Total		Mortality (%)		Estimated Relative Risk	95% Confidence Interval
	Treated	Control	Treated	Control		
Avery et al. (1969)	20/83	15/84	24.1	17.9	1.35	0.74–2.45
European Working Party (1971)	69/373	94/357	18.5	26.3	0.70	0.53–0.92[a]
Heikinheimo et al. (1971)	22/219	17/207	10.0	8.2	1.22	0.67–2.24
Dioguardia et al. (1971)	19/164	18/157	11.6	11.5	1.01	0.55–1.85
Breddin et al. (1973)	13/102	29/104	12.7	27.9	0.46	0.26–0.81
Bett et al. (1973)	21/264	23/253	8.0	9.1	0.88	0.50–1.54
Aber et al. (1976)	43/302	44/293	14.2	15.0	0.95	0.64–1.40
European Cooperative Study Group for Streptokinase in Acute Myocardial Infarction (1979)	18/156	30/159	11.5	18.9	0.61	0.36–1.04
			Summary	relative risk	0.80	0.68–0.95

a $p < 0.01$.

Source: Stampfer et al. (1982); table references cited there.

Because randomized trials reduce the effects of confounding on study results and because randomized trials are more homogeneous in their design, meta-analysis is applied most appropriately to randomized trials. However, there are many topics for which randomized trials are impossible. For example, smoking, alcohol use, use of contraceptive methods, and family history cannot be assigned at random. Meta-analysis of observational studies of such topics is useful to explore dose-response relationships, to understand the reasons
p. 15 for discrepancies among the results ↳ of different studies, and to assess the possibility of differences in the effects of the exposure in subgroups by taking advantage of the larger number of subjects upon which such the meta-analysis is based.

There are four steps in a meta-analysis. First, studies with relevant data are identified. Second, eligibility criteria for inclusion and exclusion of the studies are denned. Third, data are abstracted. Fourth, the abstracted data are analyzed statistically. This analysis includes formal statistical tests of heterogeneity and exploration of the reasons for heterogeneity.

2.1.2 Identifying Studies for the Meta-Analysis

A critical feature of the proper application of the method of meta-analysis is development of systematic, explicit procedures for identifying studies with relevant data. The systematic, explicit nature of the procedures for study identification distinguishes meta-analysis from qualitative literature review. In being systematic, the procedures reduce bias. In being explicit, the procedures help to ensure reproducibility. No matter how sophisticated the statistical techniques used to aggregate data from studies, a review does not qualify as meta-analysis unless the procedures to identify studies are both systematic and explicit.

Identification of published studies usually begins with a search of personal reference files and is followed by a computerized search of MEDLINE and of other computerized literature databases. The title and abstract of studies identified in the computerized search are scanned to exclude any that are clearly irrelevant. The full text of the remaining articles is retrieved, and each paper is read to determine whether it contains information on the topic of interest. The reference lists of articles with information on the topic of interest are reviewed to identify citations to other studies of the same topic, and publications that were not identified in the computerized literature search are retrieved and reviewed for presence of relevant information. Reference lists of review articles are also reviewed to check for completeness of the assembled list of relevant publications. In many cases, the list of studies identified by computer literature search and reference checks is submitted for review to a knowledgeable expert, who is asked to identify studies of the topic that were not been included in the list.

> *EXAMPLE:* Dupont and Page (1991) set out to identify publications that presented information on menopausal estrogen replacement therapy and breast cancer. They used MEDLINE to identify 556 articles indexed with a MeSH heading of "breast neoplasms" and either "estrogens" or "estrogens, synthetic" and were also classified under the MeSH category "occurrence," "etiology," "epidemiology," or "chemically induced" and in the MeSH category "human" and "female." Thirty-five publications identified in the MEDLINE search provided an estimate of breast cancer risk in women who took estrogen replacement therapy. The reference lists of these 35 publications and those in a review article led to identification of 15 more publications with information on breast cancer risk in women using estrogen replacement therapy.

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Details of procedures for identifying studies for a meta-analysis are discussed in Chapter 4.

2.1.3 Defining Eligibility Criteria for the Meta-Analysis

After studies with relevant information have been identified, the next step in the meta-analysis is to define eligibility criteria for the meta-analysis. Just as not all people are eligible for a randomized trial, not all studies can or should be included in the meta-analysis. For example, nonexperimental studies usually are not eligible for a meta-analysis of randomized trials; studies of stroke should not be eligible for a meta-analysis of coronary heart disease; and studies of a nontherapeutic dose of a drug should not be included in a meta-analysis of the efficacy of the drug.

> *EXAMPLE:* The meta-analysis of intravenous streptokinase and mortality after acute myocardial infarction by Stampfer et al. (1982) excluded four studies because a careful reading of the methods sections for these four studies showed that allocation to the treatment and control groups was not strictly random.

The goals of defining eligibility criteria are to ensure reproducibility of the meta-analysis and to minimize bias in selection of studies for the meta-analysis. Another analyst faced with the same body of literature applying the same eligibility criteria should choose the same set of studies. The studies chosen for the meta-analysis should be unbiased with respect to their results and their conclusions.

> *EXAMPLE:* Early studies of intravenous streptokinase used loading doses that ranged from several thousand to over 1 million international units. If dose is an important determinant of the effect of streptokinase on mortality, inclusion of studies with very low doses might bias the meta-analysis toward finding no effect of the drug. Recognizing this, Stampfer et al. (1982) restricted their meta-analysis to studies that used a loading dose at least 250,000 international units of streptokinase.

Additional detail on defining the eligibility criteria for a meta-analysis appears in Chapter 6.

2.1.4 Abstracting Data

In a meta-analysis, there are usually two levels of data abstraction. First, data that document whether or not identified studies are eligible for the meta-analysis study need to be abstracted for all of the studies identified. Next, for all eligible studies, data on the relevant outcomes of the study and the characteristics of the study, such as number of patients, are abstracted. The procedures for abstracting data in a meta-analysis should be similar to procedures to abstract data from a medical record or other administrative document. That is, data should be abstracted onto structured forms that have been pretested, and an explicit plan to ensure reliability of abstraction should be in place.

p. 17 Greater detail on development of forms and on ensuring reliability of data abstraction appears in Chapter 5.

2.1.5 Analyzing the Data

The last step in a meta-analysis is to analyze the data. Analysis appropriately includes tests of homogeneity of the effect sizes. If the results are homogeneous, a summary estimate of effect size can be appropriately estimated. The meta-analysis should also explore heterogeneity. The exploration of heterogeneity should attempt to determine whether there are features of the study or the study population that are related to effect size. Exploration of heterogeneity also includes examination of subgroup results in the aggregate of studies.

When it is appropriate to present a summary estimate of effect size, this estimate should include a measure of its variance and its 95% confidence interval.

Models of dose-response may also be developed, and the predictors of effect size may be explored in multivariate models.

Chapters 7 and 8 describe the statistical methods to derive summary estimates of effects based on both fixed-effects and random-effects models. Chapter 14 discusses the exploration of heterogeneity.

2.2 DECISION ANALYSIS

2.2.1 Overall Goals, Main Uses, and Description of Steps

Decision analysis is a systematic quantitative approach for assessing the relative value of one or more different decision options. Historically, it was developed as a method to help clinicians make decisions on how to manage individual patients (Weinstein and Fineberg 1980; Sox et al. 1988). It is increasingly used to help develop policies about the management of groups of patients by providing information on which of two or more strategies for approaching a medical problem has the “best” outcome or the most value. Decision analysis often is the conceptual model used for cost-effectiveness analysis, and it is used increasingly for this purpose.

Decision analysis is useful when the clinical or policy decision is complex and information is uncertain.

> *EXAMPLE:* Gallstones are often detected in persons who have no symptoms of gallstone disease. In such persons, a decision must be made on whether to do a "prophylactic" cholecystectomy or to wait until symptoms develop to operate. Ransohoff et al. (1983) did a decision analysis to compare the effect on life expectancy of prophylactic cholecystectomy and expectant waiting.
>
> If a person has a prophylactic cholecystectomy, an immediate consequence is the possibility of operative death. If a person does not have a prophylactic cholecystectomy, possible consequences are death from other causes before the gallstones cause symptoms or development of pain or another ↳ complication of biliary disease before death from another cause, events that would require a cholecystectomy. Operative mortality after cholecystectomy is influenced by the age of the patient and by the presence during the operation of complications of gallstone disease, such as acute cholecystitis. The decision about whether to do a prophylactic cholecystectomy or to wait is complex at least in part because the consequences of waiting are far removed in time from the decision about whether or not to operate.
>
> The analysis by Ransohoff et al. (1983) showed that a decision to do prophylactic cholecystectomy would result in an average loss of 4 days of life for a 30-year-old man and 18 days for a 50-year-old man. The analysis supports whether to forgo prophylactic cholecystectomy.

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There are five steps in a decision analysis (Weinstein and Fineberg 1980). First, the problem is identified and bounded. Second, the problem is structured, a process that usually includes construction of a decision tree. Third, information necessary to fill in the decision tree is gathered. Fourth, the decision tree is analyzed. Last, a sensitivity analysis is done.

2.2.2 Identified and Bounding the Problem

The first step in a decision analysis is to identify and bound the problem (Weinstein and Fineberg 1980). Problem identification consists of stating the main issue concisely. Identifying and bounding the problem consists of breaking the problem down into its components. The first component of a problem is always identification of the alternative courses of action.

> *EXAMPLE:* Fifteen new cases of measles are reported in a small urban area. This is the first report of measles in the area in several years. All of the cases are in children age 8 through 15 who previously received only one measles vaccination. This schedule was recommended at the time these children were infants, but it is now known not to confer complete and lifelong immunity to measles in all persons who are vaccinated. The problem is deciding whether to recommend that children who were vaccinated only once be revaccinated. The first component of the problem is identification of the alternative courses of action. One course of action is to recommend revaccination for all children 8 through 15; the alternative is not to recommend revaccination.

Other components of the problem are then identified. These are usually events that follow the first course of action and its alternative. The final component of the decision problem is identification of the outcome.

> *EXAMPLE:* The relevant event that follows revaccinating or not revaccinating children is exposure to an infectious case of measles. Upon exposure to an infectious case, children either contract or do not contract measles. If they contract measles, the outcome of interest (for the purpose of this example) is death from measles.

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2.2.3 Structuring the Problem

To structure the problem in a decision analysis, a decision tree is constructed. The decision tree depicts graphically the components of the decision problems and relates actions to consequences (Schwartz et al. 1973).

The building of a decision tree is guided by a number of conventions. Thus, by convention, a decision tree is built from left to right. When time is an issue, earlier events and choices are depicted on the left and later ones on the right.

A decision tree consists of nodes, branches, and outcomes. There are two kinds of nodes—decision nodes and chance nodes. Decision nodes are, by convention, depicted as squares. Chance nodes are depicted as circles. Outcomes are depicted as large rectangles. Branches are conventionally drawn at right angles to nodes; they connect nodes with nodes and nodes with outcome.

> *EXAMPLE:* Figure 2-1 is the skeleton of a decision tree with nodes, branches, and Outcomes labeled

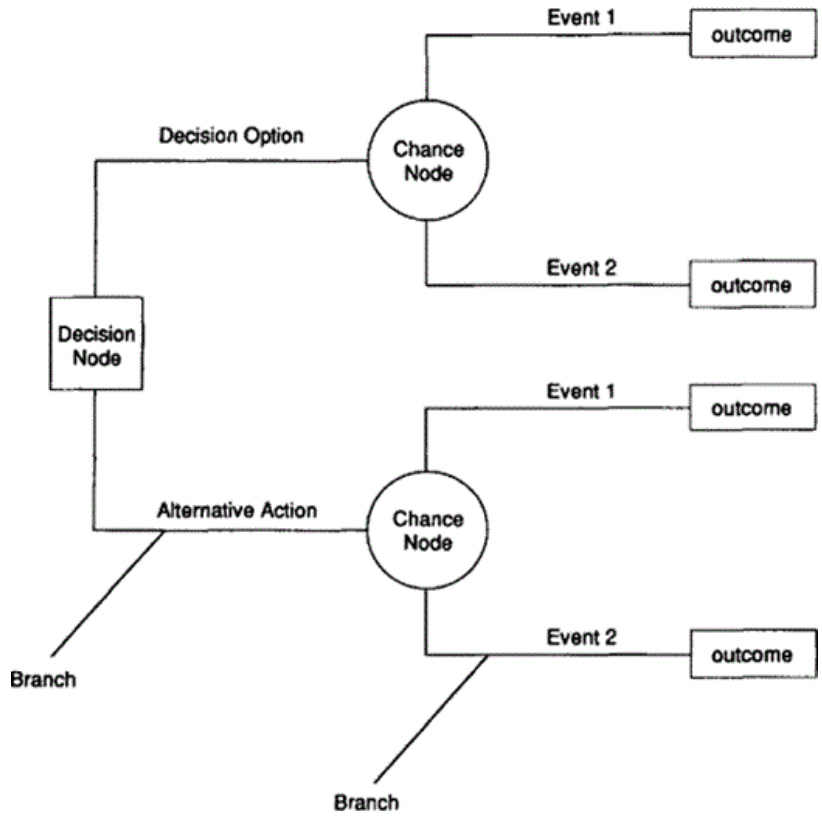

Figure 2-1 Hypothetical decision tree. The decision node is represented with a square. Chance nodes are represented with circles. Outcomes are represented with rectangles. Branches are drawn at right angles to the decision and chance nodes.

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Decision nodes identify points where there are alternative actions that are under the control of the decision maker. In the simplest problem, the decision node describes the problem.

> *EXAMPLE:* Figure 2-2 shows the beginning of a decision tree for the problem of whether or not to recommend measles revaccination of children 8 to 15. The square decision node at the left of the diagram represents the decision; the alternative courses of action—to recommend revaccination or not to recommend revaccination—are labeled on the horizontal portions of the branches.

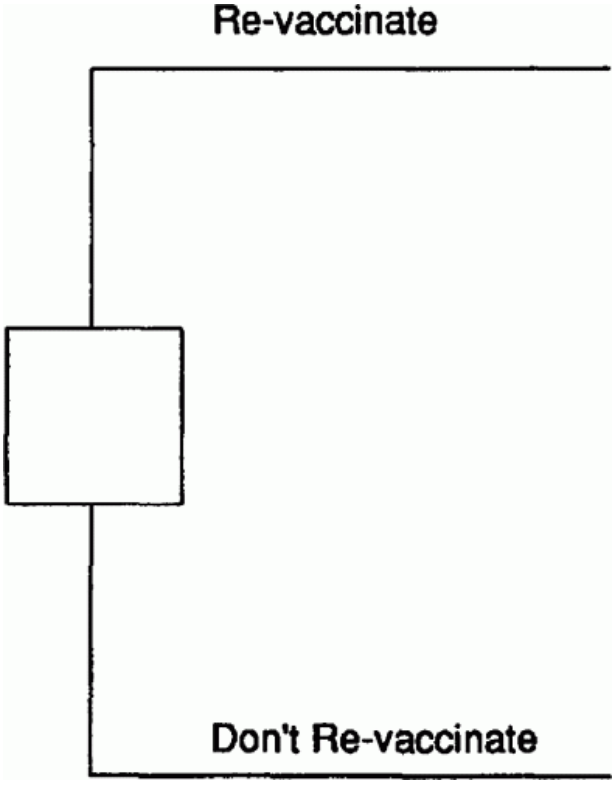

Figure 2-2 The first step in construction of a decision tree for the measles revaccination problem. The decision node is drawn as a square. The two alternatives—revaccinate and do not revaccinate—are represented as branches.

Chance nodes identify points where one or more of several possible events that are beyond the control of the decision maker may occur. Chance nodes for the same events should line up horizontally in the decision tree.

Probabilities are associated with the events depicted at chance nodes. At any given chance node, the sum of the probabilities of the events must be equal to 1. That is, the chance node defines events that are mutually exclusive and jointly exhaustive.

> *EXAMPLE:* Figure 2-3 is a decision tree for the measles revaccination problem. The circular chance nodes identify the first event that follows the decision to revaccinate—either children are exposed to measles or they are not exposed to measles. This event is out of the control of the decision maker. The sum of the probabilities of being exposed or not being exposed to measles is 1.

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> ↳ *EXAMPLE:* Figure 2-4 is a decision tree for the measles problem with circular chance nodes to also identify events that follow the exposure to measles. Children exposed to measles either get measles or they do not get measles. Again, this is an event that is out of the control of the decision maker, and it is depicted by a chance node. The sum of the probabilities of getting or not getting measles is 1.

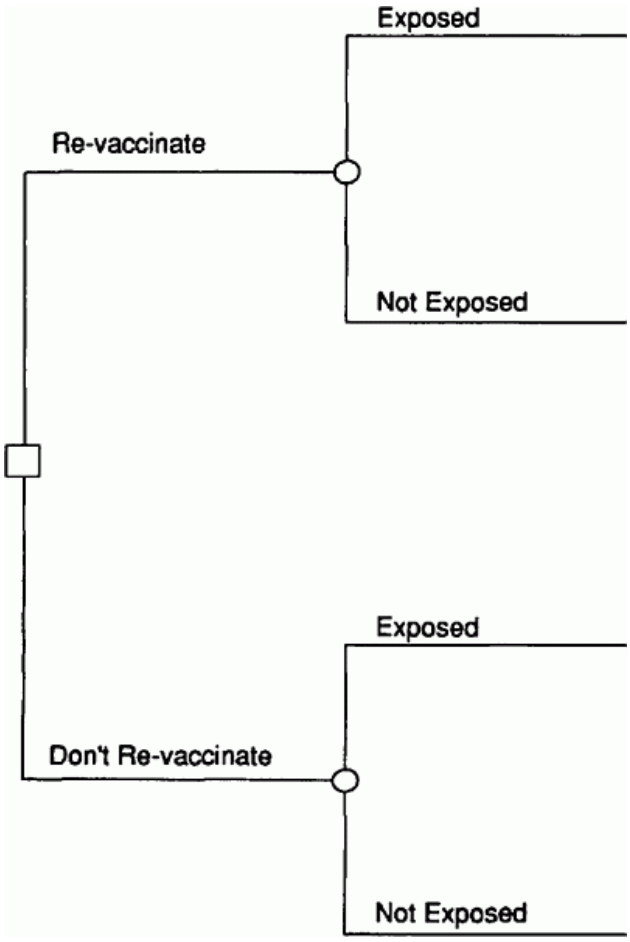

Figure 2-3 The second step in construction of a decision tree for the measles revaccination problem. Chance nodes that represent the likelihood of being exposed to measles are drawn.

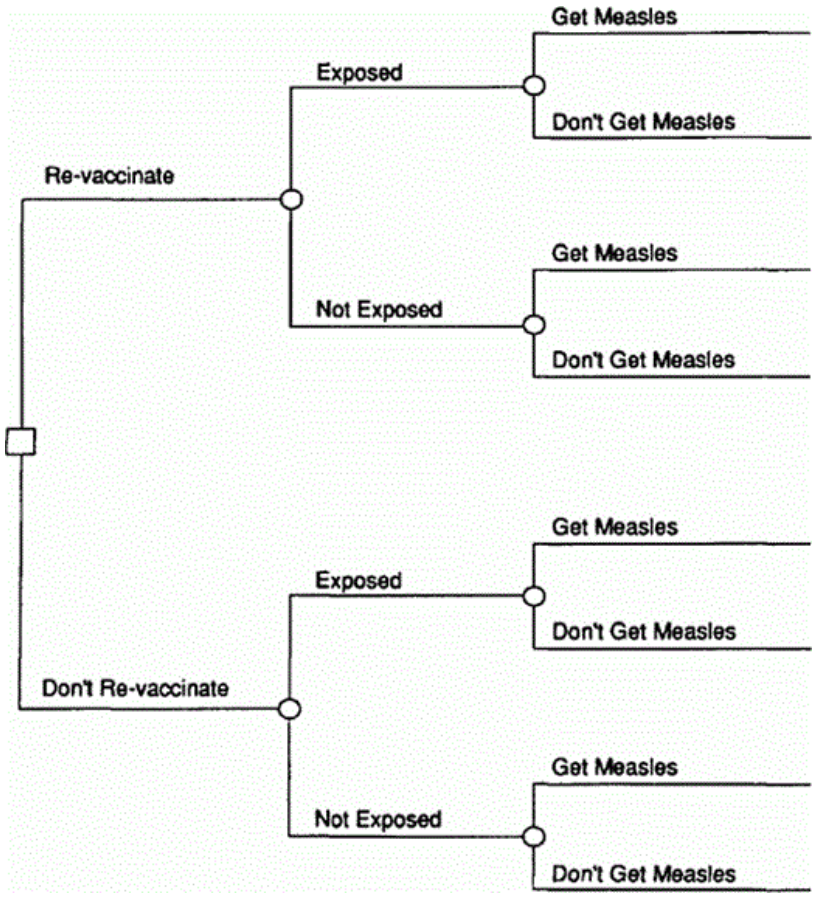

Figure 2-4 The third step in construction of a decision tree for the measles revaccination problem. For each branch of the exposed/not exposed dichotomy represented in the prior step, the chance of getting or not getting measles is represented with a chance node.

In the decision tree, outcomes are the consequences of the final events depicted in the tree. Outcomes may include life or death; disability or health; or any of a variety of other risks or benefits of the treatment.

> *EXAMPLE:* The rectangular boxes in Figure 2-5 identify the outcome of getting and of not getting measles. For this example, the outcomes of interest are death or nondeath from measles.

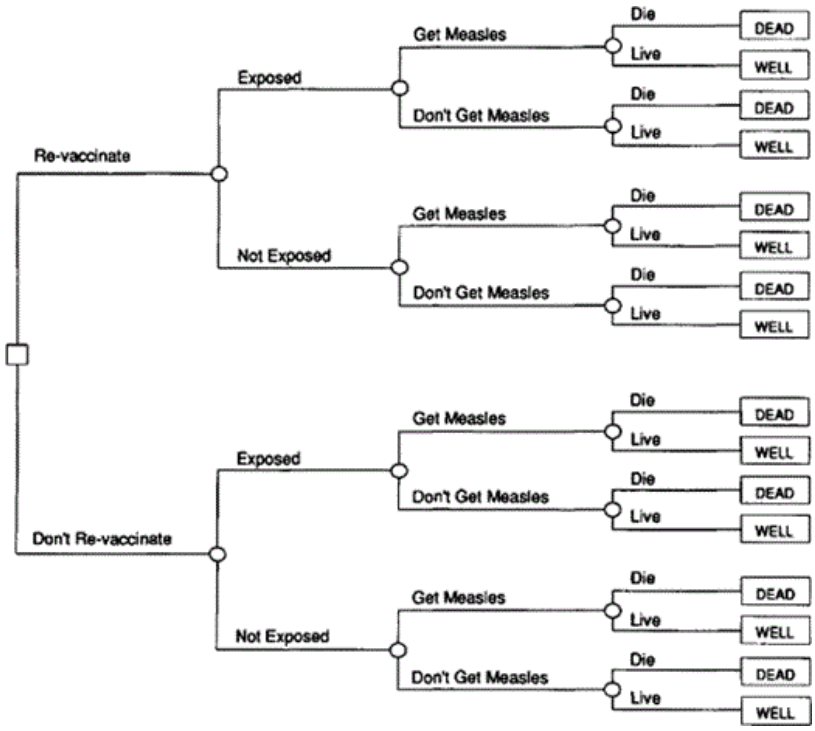

Figure 2-5 Final decision tree for the measles revaccination problem. The chances of dying or remaining alive after getting or not getting measles are represented with chance nodes, and the outcome is represented as a rectangle. In this problem, the outcome is death or remaining well, which is the same as the final event.

Most current decision analyses do not focus simply on the comparison of decision options in terms of their
p. 22 effect on life and death. They focus on the amount of ↳ extension in life and on measures of the quality of life. This focus recognizes the use of medical care to do things other than prevent death. Moreover, everyone dies, and analyses of medical interventions can reasonably expect only to delay death, not to prevent it. The outcome measures used in many current decision analyses is life expectancy or quality adjusted life expectancy. Estimation of quality adjusted life expectancy involves the measurement of utilities. A utility is a measure of the preference for the outcome to society or to an individual. Chapter 11 is devoted to a description of the concept of utilities and the methods for measuring utilities. Chapter 13 discusses incorporation of measures of utility into decision analysis and cost-effectiveness analysis.

2.2.4 Gathering Information to Fill in the Decision Tree

The next step in the decision analysis is to gather information on the probabilities of each chance event.
p. 23 Information gathering for decision analysis almost always ↳ uses one or more of the following: literature review, including meta-analysis; primary data collection; consultation with experts. After the information on the probabilities and the outcome is obtained, it is recorded on the decision tree.

> *EXAMPLE:* In the context of an epidemic of measles in an inner-city population, experts estimate that 20 out of every 100 children age 8 through 15 will come in contact with an infectious case of measles each year. Literature review reveals that the probability of getting measles if exposed to an infectious case is 0.33 in a child who has had only one measles vaccination and 0.05 in a child who is revaccinated (Mast et al. 1990). The probability of getting measles in children who are not exposed to measles is, of course, zero. During the current epidemic, the probability of dying from measles if a child gets measles is 23 per 10,000 cases, or 0.0023 (Centers for Disease Control 1990). It is assumed
> p. 24 that the probability of dying from measles in ↳ children who don't get measles is zero. Figure 2-6 shows the decision tree on which these probability estimates are shown.

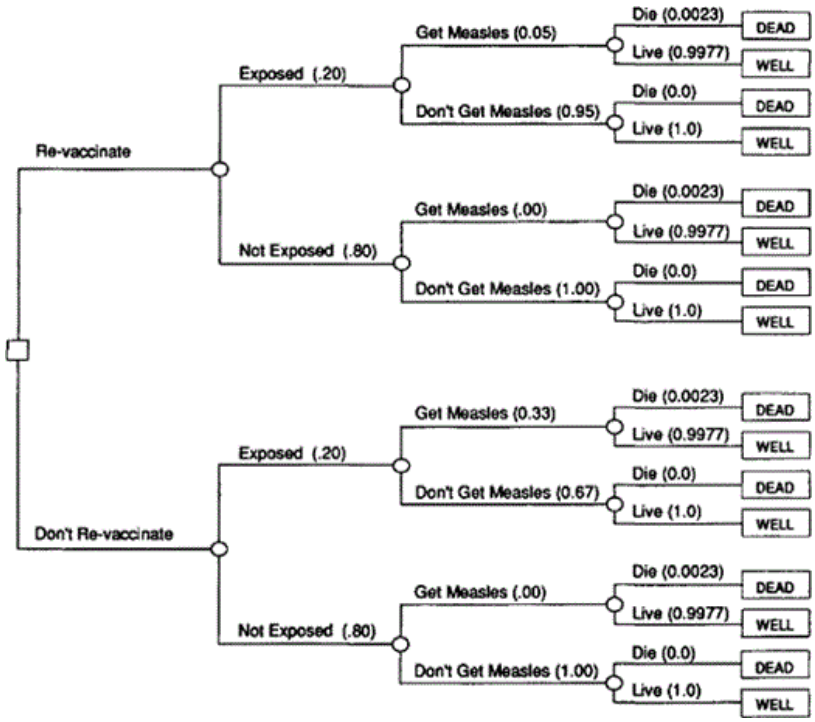

Figure 2-6 Measles decision tree showing all of the probabilities used in the analysis.

2.2.5 Analyzing the Decision Tree

The decision tree is analyzed by a process called folding back and averaging. The final result is an estimate of the probability of the expected outcome of each of the decision alternatives.

Specialized computer software for analyzing decision trees is available. However, the computations necessary to analyze decision trees are simple arithmetic operations that can be done with widely available spreadsheet programs. Here, the mechanics of the process of folding back and averaging are illustrated by analyzing the decision tree as if it were two spreadsheets. Showing these computations as spreadsheet computations facilitates an understanding of the mechanics of decision analysis.

The decision tree is considered to consist of spreadsheets, one for each of the decision alternatives. The number of rows in each spreadsheet is equal to the number of outcome boxes in the decision tree. The spreadsheet has a
p. 25 column for ↳ each probability estimate and a column for the estimated probability of the outcome.

> *EXAMPLE:* Table 2-2 recasts the measles problem as two blank spreadsheets—one for the revaccination decision option and one for the no-revaccination option. For each spreadsheet, there are eight rows, because there are eight outcome boxes in the decision tree. There are three columns, one for each probability estimate and one for the outcome.

Table 2-2 Measles decision analysis as a spreadsheet

Revaccination			
Probability of Exposure	**Probability of Getting Measles**	**Probability of Outcome**	
			die
			don’t die
			die
			don’t die
			die
			don’t die
			die
			don’t die
No Revaccination			
Probability of Exposure	**Probability of Getting Measles**	**Probability of Outcome**	
			die
			don’t die
			die
			don’t die

	die
	don’t die
	die
	don’t die

After the spreadsheets are set up, the probabilities are filled in.

> *EXAMPLE:* Table 2-3 shows the spreadsheet for the revaccination arm of the decision tree with the relevant probabilities in their proper columns.

Table 2-3 Measles decision analysis as a spreadsheet

	Revaccination		
Probability of Exposure	**Probability of Getting Measles**	**Probability of Outcome**	
0.2	0.05	0.0023	die
0.2	0.05	0.9977	don't die
0.2	0.95	0.0000	die
0.2	0.95	1.0000	don't die
0.8	0	0.0023	die
0.8	0	0.9977	don't die
0.8	1	0.0000	die
0.8	1	1.0000	don't die
	No Revaccination		
Probability of Exposure	**Probability of Getting Measles**	**Probability of Outcome**	
0.2	0.33	0.0023	die
0.2	0.33	0.9977	don't die
0.2	0.67	0.0000	die
0.2	0.67	1.0000	don't die

0.8	0	0.0023	die
0.8	0	0.9977	don’t die
0.8	1	0.0000	die
0.8	1	1.0000	don’t die

The next step is to carry out the process of folding back and averaging. For each row, all of the probabilities in the row are multiplied together. This is folding back the decision tree. The products of the rows that represent
p. 26 the same outcome (die or don't die) are summed for each decision option. This is averaging. The sum ↳ of the products is the expected value of that outcome for the specified decision option.

> *EXAMPLE:* Table 2-4 shows the measles problem with a column labeled "product" for each row. The number in the column labeled "product" is the product of the probabilities for the corresponding row. For example, the value in the first row of the column labeled "product" is 0.000023, which is
>
> $0.2 \times 0.05 \times 0.0023$
>
> The expected probability of death from measles in the example is equal to the sum of the values in the product column for the rows that correspond to the outcome "die." For the revaccination option, this is
>
> $0.000023 + 0.000000 + 0.000000 + 0.000000 = 0.000023$
>
> For the no-revaccination option, it is
>
> $0.000152 + 0.000000 + 0.000000 + 0.000000 = 0.000152$

Table 2-4 Measles decision analysis as a spreadsheet

Product	**Revaccination**			
	Probability of Exposure	**Probability of Getting Measles**	**Probability of Outcome**	
0.000023	0.2	0.05	0.0023	die
0.009977	0.2	0.05	0.9977	don't die
0.000000	0.2	0.95	0.0000	die
0.190000	0.2	0.95	1.0000	don't die
0.000000	0.8	0	0.0023	die
0.000000	0.8	0	0.9977	don't die
0.000000	0.8	1	0.0000	die
0.800000	0.8	1	1.0000	don't die
Sum for death				
0.000023				

Product	**No Revaccination**			
	Probability of Exposure	**Probability of Getting Measles**	**Probability of Outcome**	
0.000152	0.2	0.33	0.0023	die
0.065848	0.2	0.33	0.9977	don't die
0.000000	0.2	0.67	0.0000	die
0.134000	0.2	0.67	1.0000	don't die
0.000000	0.8	0	0.0023	die
0.000000	0.8	0	0.9977	don't die
0.000000	0.8	1	0.0000	die
0.800000	0.8	1	1.0000	don't die
Sum for death				
0.00152				
Difference between Revaccination and No Revaccination				
Death 0.000129				
Difference Expressed as Events per 100,000				
Death 12.9				

p. 27 The final step is to compare the two strategies by subtracting the results of the preceding calculations for the revaccination arm from the result for the alternative arm.

EXAMPLE: The difference in the expected probability of death from measles between a strategy of revaccination and a strategy of no-revaccination is

0.000152 − 0.000023 = 0.000129

p. 28 ↳ This is interpreted to mean that 12.9 deaths from measles are prevented per 100,000 children revaccinated.

2.2.6 Sensitivity Analysis

Analysis of a decision tree virtually always includes sensitivity analysis. Sensitivity analysis is described in detail in Chapter 13. The overall goal of sensitivity analysis is to assess the stability of the conclusion of the analysis to assumptions made in the analysis. Sensitivity analysis also may identify crucial areas of information deficiency and may guide further research.

Assumptions about the probabilities used in the analysis are among the most important assumptions made in the analysis. A sensitivity analysis varying these probabilities one at a time while holding all of the other variables in the analysis constant is almost always done.

EXAMPLE: The probability of being exposed to an infectious case of measles varies according to the area of the county. It is 1 per 100 in the suburban areas, whereas it is 45 per 100 in one inner-city area where an epidemic is in progress. The results of a sensitivity analysis varying the probability of exposure to an infectious case of measles between 0.01 and 0.45 is shown in Table 2-5. The number of deaths from measles prevented per 100,000 children revaccinated is highly dependent on the assumption about the probability of being exposed to an infectious case. Revaccination is estimated to prevent less than 1 death from measles per 100,000 children revaccinated in the low-risk area and 29 in the highest risk area.

Table 2-5 Results of sensitivity analysis varying probability of exposure to measles

Assumed Probability of Exposure	Net Number of Lives Saved per 100,000 Children Revaccinated
0.01	0.6
0.05	3.2
0.10	6.4
0.15	9.7
0.20[a]	12.9
0.25	16.1
0.30	19.3
0.35	22.5
0.40	25.8
0.45	29.0

a Probability in baseline analysis.

2.3 COST-EFFECTIVENESS ANALYSIS

2.3.1 Overall Goals, Main Uses, and Description of Steps

Cost-effectiveness analysis compares the outcome of decision options in terms of their monetary cost per unit of effectiveness. It is used to help in the setting of priorities for the allocation of resources and to decide among one or more treatments or interventions based on their value, as expressed in monetary terms.

> *EXAMPLE:* Patients with nonvalvular atrial fibrillation are at high risk of ischemic stroke. Ischemic stroke can be prevented using either warfarin or aspirin. The efficacy of warfarin in preventing ischemic stroke is higher than that of aspirin, but warfarin is more likely than aspirin to cause bleeding, sometimes fatal, and it is more expensive, especially when the cost of monitoring prothrombin time is considered.
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> Gage et al. (1995) did a cost-effectiveness analysis comparing warfarin and aspirin for stroke prophylaxis in patients with nonvalvular atrial fibrillation. They showed that warfarin was preferred to aspirin in patients at high risk for stroke but that aspirin was preferred to warfarin in patients at low risk for stroke. In this example, the question posed is not whether to treat patients with nonvalvular atrial fibrillation, but how to treat them.

Table 2-6 describes the steps in a cost-effectiveness analysis.

Table 2-6 Steps in a cost-effectiveness analysis

State the probabilities
Describe the conceptual model
Define the perspective
Identify costs and gather data to value costs
Identify outcomes and gather data to value outcomes
Estimate cost-effectiveness
Do sensitivity analysis

The first step is the same as in a decision analysis. The problem is identified and the intervention and its alternatives are defined.

The second step in a cost-effectiveness analysis is to describe the conceptual model for the analysis. The conceptual model for a cost-effectiveness analysis outlines the full range of events stemming from the intervention and guides the analysis. Decision analytic models are used most often as the conceptual framework for cost-effectiveness analysis. Decision analysis has become so closely linked with cost-effectiveness as to be an almost integral part of it. This book describes decision analysis as the cornerstone of cost-effectiveness analysis and discusses conduct of cost-effectiveness analysis solely within the decision analytic framework. Thus, in the second step in the cost-effectiveness analysis, a decision tree is constructed and information to estimate the probabilities in the decision tree is gathered.

p. 30 Next, the perspective of the analysis is defined. Based on this perspective, costs ↳ are identified and valued. The outcomes are identified and data are gathered to value the outcomes. The data are analyzed to estimate net cost of each decision option per unit of the outcome measure, and the decision options are compared in relation to net cost per unit of outcome. Finally, a sensitivity analysis is done.

2.3.2 Defining the Perspective

Costs are seen differently from different points of view. For example, the cost of hospitalization from the perspective of an insurance company is the amount of money that the company pays the hospital for that illness under the coverage plan for the individual who is hospitalized. The cost from the perspective of the hospital is the true cost of providing the service, which includes the labor costs, the costs of the building in which the services are provided, and other overhead costs.

It is important to state explicitly the perspective of a cost-effectiveness analysis, since the perspective determines which costs should be included in the analysis and what economic outcomes are considered as benefits. Usual perspectives in cost-effectiveness analysis are the societal perspective and the program perspective.

> *EXAMPLE:* The decision about whether to revaccinate children against measles could be made based on considerations of cost. A county health department might decide to undertake a cost-effectiveness analysis of revaccinating versus not revaccinating taking the program perspective, since the question addressed is how many deaths from measles an investment in revaccination might prevent. Taking the program perspective, the costs that will be considered are the costs that are born directly by the program.

2.3.3 Identifying Cost and Gathering Data to Value Costs

The contributors to the cost of the intervention must first be identified. Contributors to cost include direct health care cost, such as the cost of vaccine or drug, as well as costs to people to partake of the intervention, such as the cost of travel and the cost of lost wages. Induced costs, such as the cost to take care of side effects of the intervention, and averted costs, due, for example, to averted future illness, are also direct health care costs that should be counted as contributors to cost. Chapter 12 discusses the identification of costs in detail.

Once the contributors to cost have been identified, data on these costs must be gathered. Cost data can be obtained by primary data collection (i.e., in a special study) or from secondary sources. In practice, cost data are most often gathered either from administrative sources, such as Medicare fee schedules or insurance company payments.

> *EXAMPLE:* The costs of vaccination from the perspective of the program consist of the cost of purchasing the vaccine and the cost of administering it.
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> By doing a survey of pharmaceutical suppliers, the county determines that the measles vaccine can be purchased in bulk quantities for $4.44 per dose (Mast et al. 1990). An expert estimates that it will take
> p. 31 15 minutes for ↳ a nurse to vaccinate each child. Based on a nurse's salary of $36,000 per year and considering the cost of space for the waiting room, the nurses' office, and the room in which the vaccine will be administered of $2.00 per child revaccinated, it is estimated that the total cost of revaccination is $9.44 per child.

2.3.4 Gathering Data to Value Outcomes

The next step in a cost-effectiveness analysis is to identify the relevant outcomes and to value the outcomes.

In the measles example, the outcome of interest to the health department is prevention of death due to measles. It is assumed that prevention of death due to measles has value to society.

2.3.5 Estimating Cost-Effectiveness

In the simplest case, the decision analysis proceeds as described in the section on decision analysis, yielding an estimate of the net benefit of one decision option compared with the other. The net cost of the intervention in relation to its alternative is calculated by subtracting of the total costs of the alternative from the cost of the intervention. The cost-effectiveness of the intervention relative to its alternative is the ratio of the net cost to the net benefit.

> *EXAMPLE:* Based on the estimate that it will cost $9.44 to revaccinate each child, the cost to the county of a program revaccinating 100,000 children is $944,000; the cost to the county of not revaccinating 100,000 children is $0. The net cost of a program of revaccination compared with no program of revaccination is $944,000. The net number of deaths from measles prevented per 100,000 children revaccinated, estimated in the decision analysis, is 12.9. Thus, compared with a strategy of no-revaccination, a school-based program of measles revaccination costs $73,178 per death prevented, or ($944,000–$0)/12.9.

When costs and monetary benefits of an intervention are spread over time, it is necessary to discount costs and benefits and to consider inflation. These issues are discussed in detail in Chapter 12.

2.3.6 Sensitivity Analysis

As in decision analysis, sensitivity analysis is almost always done in a cost-effectiveness analysis. It has the same goal in cost-effectiveness analysis as it does in decision analysis—to assess the effect of the various assumptions made in the analysis on the conclusion.

> *EXAMPLE:* The sensitivity analysis from the decision analysis in which the probability of being exposed to measles was varied is used to do a sensitivity analysis for the cost-effectiveness analysis. The number of deaths prevented ↳ by a program, compared with no program, was estimated in Section 2.2.6 for several estimates of the probability of being exposed to measles. The net cost of the program compared with no program is divided by each of these estimates to estimate the cost per death prevented for several estimates of the probability of exposure to measles. These results are shown in Table 2-7 . The estimated cost per death prevented is highly variable, depending on the assumption about the probability of exposure to measles. In low-risk areas, the analysis shows that the cost of the program is over $1.5 million per death prevented; in the highest risk area, it is $32,552 per death prevented.

Table 2-7 Results of sensitivity analysis varying probability of exposure to measles

Assumed Probability of Exposure	Cost per Life Saved
0.01	$1,573,333
0.05	295,000
0.10	147,500
0.15	97,320
0.20[a]	73,178
0.25	58,634
0.30	48,912
0.35	41,956
0.40	36,589
0.45	32,552

a Probability in baseline analysis.