New Vaccine Development: Establishing Priorities: Volume I, Diseases of Importance in the United States

Committee on Issues and Priorities for New Vaccine Development, Division of Health Promotion and Disease Prevention

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New Vaccine Development

Establishing Priorities

VOLUME I

Diseases of Importance in the United States

Part One of a Two-Part Study by the Committee on
Issues and Priorities for New Vaccine Development

Division of Health Promotion and Disease Prevention
INSTITUTE OF MEDICINE

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Committee on Issues and Priorities for New Vaccine Development

SAMUEL L.KATZ *(chair)*, Department of Pediatrics, Duke University Medical Center
A.JOHN BEALE, Wellcome Research Laboratories, United Kingdom
MARSHALL H.BECKER, Department of Health Behavior, University of Michigan, Ann Arbor
JAMES CHIN, Department of Health Services, State of California Health and Welfare Agency, Berkeley
PURNELL W.CHOPPIN, Professor of Virology, Rockefeller University
THEODORE C.EICKHOFF, Department of Internal Medicine, Presbyterian/St. Luke's Medical Center, Denver
FRANCIS A.ENNIS, Department of Medicine and Molecular Genetics, University of Massachusetts Medical Center, Worcester
HARVEY V.FINEBERG, Institute for Health Research, Harvard School of Public Health
MAURICE R.HILLEMAN, Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories
GERALD T.KEUSCH, Division of Geographic Medicine, Tufts University
RICHARD F.KINGHAM, Covington and Burling, Washington, D.C.
BERNARD ROIZMAN, Department of Microbiology and Biophysics, University of Chicago
HENRY R.SHINEFIELD, Department of Pediatrics, Kaiser Permanente Medical Group, San Francisco
JANE E.SISK, Office of Technology Assessment, United States Congress
CLADD E.STEVENS, Laboratory of Epidemiology, The New York Blood Center
LEROY WALTERS, Kennedy Institute of Ethics, Georgetown University
MILTON C.WEINSTEIN, Institute for Health Research, Harvard School of Public Health

See Appendix S for further information on committee members.

Consultants

GENEVIVE A.LOSONSKY, Department of Pediatrics, Johns Hopkins University Hospital
ARNOLD S.MONTO, School of Public Health, University of Michigan
B.FRANK POLK, School of Hygiene and Public Health, Johns Hopkins University
JOHN B.ROBBINS, National Institute of Child Health and Human Development, National Institutes of Health
DONALD S.SHEPARD, Institute for Health Research, Harvard School of Public Health
DAVID H.SMITH, Department of Pediatrics, University of Rochester

Institute of Medicine Staff

ROY WIDDUS, Study Director
ENRIQUETA C.BOND, Director, Division of Health Promotion and Disease Prevention
BARBARA S.BROWN, Research Associate
STEPHANIE BRUGLER, Research Assistant
ELAINE MCGARRAUGH, Staff Associate
EVE K.NICHOLS, Editor
JUDE C.PAYNE, Research Assistant
GAIL E.SPEARS, Committee Secretary

National Institute of Allergy and Infectious Diseases Steering Committee

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JOHN E.NUTTER, Chief, Office of Program Planning and Evaluation
BERNARD TALBOT, Deputy Director, National Institute of Allergy and Infectious Diseases
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JEFFREY KOPLAN, Assistant Director for Public Health Practice, Centers for Disease Control
PHILIP K.RUSSELL, Commander General, Fitzsimmons Army Medical Center, Aurora, Colorado

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Preface

Resource constraints in both the public and the private sector limit investment in vaccine research and development. The choice of options is complicated by large variations in the severity and duration of disease-related conditions, the existing knowledge base for new vaccine development, the time and resources required to bring the vaccine to licensure and the expected utilization. This report presents a comprehensive model designed to help government decision makers set priorities for vaccine development. It can be used to assess new vaccine candidates or to reassess current contenders as additional information becomes available.

The history of this study extends back to the fall of 1980, when the Secretary of the Department of Health and Human Services (DHHS) accepted a recommendation by the DHHS Steering Committee for Development of a Health Research Strategy to establish a program of accelerated development for new vaccines. The purpose of the initiative, proposed by the National Institute of Allergy and Infectious Diseases (NIAID), was to develop within DHHS a coordinated approach to the further conquest of vaccine-preventable diseases.

The first step toward implementation of the program was a three-day meeting in the fall of 1981 of the staff of NIAID's Microbiology and Infectious Diseases Program. Participants reviewed the status of NIAID's vaccine development effort, which included studies on more than 50 vaccine antigens for more than 30 bacterial, viral, fungal, and parasitic diseases. A tentative list of priorities was developed.

One year later, NIAID contracted with the National Academy of Sciences for assistance in developing a more comprehensive approach to setting priorities for accelerated vaccine development. The Committee on Issues and Priorities for New Vaccine Development was established in the Institute of Medicine's Division of Health Promotion and Disease Prevention. Careful selection of members produced a committee with the collective expertise necessary to conduct a study of this scope; research virologists, bacteriologists, physicians, economists, epidemiologists, sociologists, public health experts, and industry leaders all have made significant contributions to the final product.

The committee was asked to develop a decision-making framework for selecting among vaccine candidates of importance to the U.S. population, and to use it to rank such candidates. It also was charged with evaluating the usefulness of the model in setting priorities for vaccines needed by technologically less developed nations, and with modifying the model as necessary to rank potential vaccines for international use. (The committee's findings relative to the international aspects of vaccine development will appear in a second volume of this report.)

Among the factors that NIAID requested be considered in developing the priority setting approach were:

- scientific and technical readiness
- opportunities for safety and efficacy testing

- socioeconomic impact, including the incidence, prevalence, severity, and cost of the target condition; and where feasible, the cost-effectiveness of potential vaccines
- social impact, including legal and ethical problems, patient and provider acceptance, special problems with certain populations (e.g., immunization of pregnant females or young infants), policy considerations (e.g., whether a program should be comprehensive and mandatory or selective and voluntary), and the respective roles of government and industry.

The importance of industry-government relations in assuring a stable supply of existing vaccines and continued development of new ones has become increasingly clear over the past decade. There has been a decrease in the willingness of pharmaceutical companies to become involved in vaccine research, development, and manufacturing. There is, therefore, cause for concern that the supply of existing vaccines may be endangered and that technically feasible vaccines will not be manufactured and made available to the public.

The reasons for these problems are complex and include economic, legal liability, and sociopolitical factors. An analysis of impediments and disincentives to vaccine innovation is being undertaken by the Institute of Medicine's Committee on Public-Private Sector Relations in Vaccine Innovation. The current report touches on these issues only briefly as they relate to the controversy surrounding the existing pertussis vaccine (Chapter 8).

The Committee on Issues and Priorities for New Vaccine Development would like to take particular note of the excellent support provided by the Institute of Medicine staff headed by Roy Widdus. The assistance of NIAID project officer C.David Wise is also gratefully acknowledged.

Samuel L.Katz
Chairman

Abstract

This report describes a method designed to aid the National Institute of Allergy and Infectious Diseases (NIAID) in establishing priorities for accelerated vaccine development. The method is based on a quantitative model in which vaccine candidates are ranked according to two principal characteristics: expected health benefits (reduction of morbidity and mortality) and expected net savings of health resources. One vaccine automatically ranks higher on the priority list than another if it produces both greater health benefits and greater savings. If a vaccine produces greater benefits but costs more (or produces a smaller savings) then a policy judgment is required to decide whether the additional benefit justifies the extra expenditure.

The approach uses the same (incomplete) information that could theoretically be used in other methods of decision making. Because the information is incomplete and because the method entails, in some instances, predicting the future, lacunae must be filled by estimates or judgments by experts. Commentary is included in Chapter 1 to explain the advantages of the system and to forestall misinterpretation of the power and precision of the method.

The committee believes that final selection of priorities should be made after decision makers have evaluated certain non-quantifiable considerations discussed in the report, but not incorporated into the model. These include the goals of the agency and its schedule for achieving them; considerations of equity in the distribution of benefits; the opportunity and need for the agency to exert influence on development; the balance of the desired portfolio of vaccine development projects; and the arguments that can be made for treating certain vaccines as unique because of their potential for restoration of public confidence in immunization programs, (The committee believes an improved pertussis vaccine merits such treatment.) Because the method does not address the number of projects that are worth pursuing, no list of favored choices is presented in this summary. Readers are referred to the main report for an array of the rankings.

The method was applied to 14 diseases of importance in the United States and for which new or improved vaccines were judged technically feasible within the next decade. (A separate assessment will consider vaccines of importance to less technologically developed countries.) Costs and benefits are viewed from an aggregate societal perspective. The committee did not address the issues of balance between basic scientific research and vaccine development and it expressly refrained from placing a monetary value on health benefits.

An important early step in the evaluation of a potential vaccine is the selection of an appropriate target population. The committee developed a technique for estimating vaccine utilization within a target population. It should be recognized, however, that utilization can be modified by factors such as legal requirements, education programs, or combination with existing vaccines; the committee did not attempt to predict the likelihood of these interventions. A new technique also was designed to compare

quantitatively the health impacts of diseases and vaccines using units of "mortality equivalents."

Elements incorporated into the calculation of a vaccine's expected health benefit include data (and estimates) on the disease burden resulting from each pathogen; value judgments on the undesirability of conditions arising from the disease; the proportion of the disease falling in the target population; various predictions on the vaccine's development (e.g., probability of success) and its characteristics (e.g., efficacy and potential for adverse effects); the likely utilization of the vaccine; and the time before benefits would be achieved. The way in which value judgments on the undesirability of conditions resulting from disease (e.g., levels of acute and chronic morbidity, infertility, or death) are incorporated into the system allows quantitative expression of any perspective and an examination of its effects on the ranking. Two perspectives are used to illustrate application of the method—the median of committee members' viewpoints and an "age-neutral" perspective. (The committee, however, does not endorse either perspective for policy formulation in this area.)

Elements used in the calculation of net costs (often savings) for each vaccine candidate include the cost of vaccine development, the likely cost of the vaccination program, and the expected cost savings from treatment averted. No "indirect" economic measures of health outcome were used.

Implementing the method requires substantial amounts of information about diseases and vaccine characteristics. Data of the desired degree of reliability is not always available, however. When data are unavailable, expert judgments are required to quantify factors that are incorporated into the calculations. Scientific opinions differ on some of these judgments (e.g., the probability of success) and uncertainty surrounds much of the data (e.g., disease incidence and efficacy). The method requires the user to identify and be explicit about such factors, which the committee believes is preferable to leaving them unspecified, amorphous or unquantified. The attempt to be explicit about certain estimates should not, however, be interpreted as an indication that a high degree of precision, unanimity, or certainty in comparisons is currently possible.

The final format is flexible, can be updated as necessary to assess new vaccine candidates or to reassess current contenders, and allows users to vary estimates or predictions across a range of plausible values to determine their effects on the final result. The performance of several sensitivity analyses indicates that the rank order of candidates remains fairly stable for the issues tested; additional analyses are suggested to provide additional information on the key elements that affect decisions and to indicate where new information is most necessary.

Lack of data in some areas and the variable quality of data in other areas are serious impediments to the implementation of any priority selection scheme. Hence, the NIAID and other agencies should consider means of improving the epidemiologic information on which disease comparisons can be based.

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Summary

Establishing priorities for vaccine development is complicated by large variations in the morbidity and mortality arising from diseases, the extent of knowledge about relevant pathogens and host responses, the resources and time required for vaccine development, and anticipated vaccine utilization. This report presents a comprehensive model designed at the request of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, to help government decision makers set priorities for accelerated development of vaccines. It can be used to assess new vaccine candidates or to reassess current contenders as additional information becomes available.

The approach suggested uses the same (incomplete) information that could theoretically be used in other methods of decision making. Because the information is incomplete and because the method entails, in some instances, predicting the future, lacunae must be filled by estimates or judgments by experts.

The act of providing a structural framework within which information and judgments are used and combined does not of itself improve the quality of currently available information (although further research to generate new data might be guided by a framework). Nor does it reduce the range of opinion likely to be expressed in predictions, judgments, or estimates (except as issues are more precisely defined).

The committee believes that the system it proposes is the most appropriate for the desired purpose and has implemented it with the best data and estimates that it could develop. It believes that the system would improve the quality of the decision-making process by making it more accessible to evaluation/reconstruction by other decision makers and by facilitating examination of the effect of adopting different assumptions or estimates. However, some cautions and comments are needed to forestall misinterpretation of the power and precision of the method.

In setting out to identify the components on which quantitative information is desirable (but not necessarily available) the system (more than others) exposes areas of ignorance and uncertainty in which expert judgment, by necessity, must be used. Within the proposed approach the use of equations defines the way in which information or estimates are combined (something not always specified in other approaches); this does not imply that the components or the results

have the accuracy sometimes associated with formal mathematical calculations. The results are simply the consequence of combining both factual and uncertain quantities, both objective and subjective elements, that are an inescapable part of reaching conclusions about the preferred investments in new vaccines.

A quantitative structured model facilitates examination of the effect of uncertainty (in data and estimates) in a fashion that intuitive integration of such components does not. This is expressed in the sensitivity analysis reported in the study.

Value judgments on disease conditions are involved in all processes in which the importance of different diseases is ranked; incorporation of value judgments may be explicit, implicit, or unrecognized. These judgments are more subjective than those of a scientific nature. Providing a specific point at which the required value judgments are described and incorporated furnishes one means of isolating these differences of opinion (which are often incorporated into decision making in an ill-defined fashion) and determining if they affect the ultimate priorities.

The committee resolved many internal differences of opinion over these problems and others it as sought agreement on the approach it would follow in this complex area. Where information was incomplete or where quantitative prediction was complicated by many as yet unresolved issues, it chose to lay out what it felt was the most rational approach to selecting priorities, recognizing that exact data on all components required by the system would not be available before decisions had to be taken. Because of the many uncertainties involved in data and estimates used in the calculation of health benefits and costs, the usefulness of the numbers used in the final rankings lies in their relation to each other rather than their absolute precision, i.e., the system facilitates comparison of vaccine projects in a fashion that is open to revision if different estimates or assumptions seem appropriate and as new data becomes available.

The model is based on comparisons of expected health benefits and expected net costs (or savings) calculated for candidate vaccines. This approach combines elements of decision analysis and cost-effectiveness analysis. It was developed by the committee because it identifies each logical component contributing to vaccine benefits and costs but does not require placement of a monetary value on human life or suffering, in addition, it requires substantial amounts of information about diseases and vaccine characteristics. Committee members believe that the activity of gathering this information is beneficial in itself; it strengthens the decision-making process and highlights areas in which more research is needed. Chapter 2 describes four other approaches to establishing priorities that were considered but judged less satisfactory.

It should be emphasized that the proposed system is designed as an aid to decision making and not as a definitive answer to the selection process. Rather than provide a single list of priorities, the committee intends to demonstrate how different rankings could result from the adoption of different viewpoints on the undesirability of illness or death in specific age groups, or from assumptions about utilization and

other factors that cannot be predicted with certainty. Several other nonquantifiable issues, all of which fall into the realm of the policymaker, also must be incorporated into the final judgment on vaccine priorities. These include:

- the goals of the responsible agency and its schedule for achieving them
- the ethical questions that must be considered in the distribution of benefits
- the most appropriate points at which the agency can exert influence and the opportunity and need for such influence
- the desired balance of the development portfolio
- the argument that can be made for treating certain vaccine development projects as unique because of their potential impact on immunization in general.

The committee sought to develop a flexible system that could be updated as necessary. This required an effort to explicitly identify all assumptions, estimates, and predictions incorporated in each calculation. Values incorporated into the calculations represent the committee's best efforts to develop the necessary information. It is recognized that scientific opinion differs on some of the judgments and uncertainty surrounds other factors, e.g., disease incidence and efficacy data. The final format allows users of the system to perform sensitivity analyses, in which an estimate or prediction in a specific area, such as the probability of success, can be varied systematically across its plausible range to examine its impact on the final result. Some sensitivity analyses are discussed in Chapter 9.

Chapter 3 presents an overview of the approach used in this report. It also identifies certain basic assumptions that are maintained throughout the study. For example, in assessing the economic impact of vaccines, the report considers only direct costs—the cost of treatment for illness resulting from a disease, the cost of vaccine development, and the cost of vaccination programs. Effects of morbidity and mortality are expressed in non-monetary terms.

Selection of Candidates

The committee defined vaccine candidates for accelerated development as those for which success was reasonably foreseeable within the next decade. The criterion for inclusion was whether a reasonable consensus could be identified on the nature of potential vaccine components (protective antigens). A more detailed description of the selection process appears in Appendix B.

The diseases and vaccine candidates chosen for the ranking process are shown in Table 1.1. Detailed information about individual candidates is presented in appendixes C through P. Some marginal candidates were excluded because the committee decided that it would be more appropriate to consider them in its deliberations on vaccine candidates for technologically less developed countries or because of resource

TABLE 1.1 Candidates for Accelerated Vaccine Development: Domestic Diseases

Pathogen	Vaccine Envisaged	Target Population
Bordetella pertussis	Acellular	Infants
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas
Cytomegalovirus	Attenuated live virus	High-risk individuals, i.e., seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas
		Nonpregnant adolescent females
	Glycoprotein produced by recombinant DNA technology	All children
Hemophilus influenzae type b	Conjugated polysaccharide	Infants
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)
	Subunit	Susceptibles of all ages (routine for children)
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles
	Attenuated live virus	Children up to age 12 and older susceptibles

Herpesvirus varicellae	Attenuated live virus	High-risk individuals, i.e., recipients of bone marrow and organ transplants and persons under age 25 with leukemias and lymphomas
		Normal susceptibles, routine for children (booster for adults)
Influenza viruses A and B	Subunit vaccine (purified hemagglutinin/neuraminidase proteins)	High-risk population as currently defined (see Appendix K)
	Attenuated live virus	High-risk population as currently defined (see Appendix K)
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants
	Attenuated live virus	Infants
Rotavirus	Attenuated live bovine virus	Infants
	Attenuated live human or reassortment virus	Infants
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates

constraints. Pathogens for which accelerated vaccine development did not seem appropriate at this time and the reasons for their exclusion are described briefly in the latter portion of Appendix B, which also contains suggestions for marginal candidates that should be included in future applications of the method or kept under regular review (e.g., an improved vaccine for Streptococcus pneumoniae).

This report does not make a judgment about the number of vaccines that are worthy of development. It also does not attempt to compare the benefits of basic research with those of vaccine development.

Determination of Health Benefits

To compare diseases and vaccines, it was necessary to develop a system that would allow expression of the total morbidity and mortality associated with each disease as a single number.* The system that evolved, described in Chapter 4, consolidates information on the annual numbers of episodes of illness and their durations with additional data on related complications, sequelae, and deaths. It also incorporates value judgments on the undesirability (disutility) of various conditions occurring in different age groups.

Disease Burden Estimates

Whenever possible, disease burden estimates were based on data from the Centers for Disease Control or other knowledgeable sources. For many conditions, however, information needed to estimate disease burdens was not available or was not of the desired quality; in these cases, calculations were based on judgments and assumptions made by committee members and staff with the aid of consultants. Table 1.2 presents an example of the format used to consolidate disease burden information.

Infant Mortality Equivalence Values

An important feature of the system is that it allows the user to change the perspective on disutility to any level desired and to observe the effect of this change on rankings. The undesirability of conditions for morbidity category/age group combinations are expressed as infant mortality equivalence (IME) values, i.e., the number of acute morbidity days or chronic cases considered to be equal in undesirability to the death of an infant. Two perspectives are used as examples throughout this report: one reflects the median of committee member perspectives (elicited by means of a questionnaire [see Appendix Q]) and the other is an age-neutral perspective (Table 1.3). The

*See Appendix R for information on the computer software used in this analysis.

committee, however, does not endorse either perspective for policy formulation in this area.

For most diseases considered in this report, the two perspectives produce very similar results. An exception is gonorrhea, for which the position in the rank order using the age-neutral perspective is considerably higher than the position using the committee median perspective. The difference between the two arises from the use in the age-neutral perspective of an IME value that equates first-trimester fetal deaths (resulting from ectopic pregnancies) with all other deaths. This case provides an excellent example of how different rankings result from the adoption of different viewpoints on the undesirability of illness and death at different stages of life.

Total Disease Burden Values

The system that has been developed provides a means for comparing diseases, as well as a method for comparing vaccines. The total disease burden value (TDBV) indicates the relative importance of each disease expressed in units equivalent to the undesirability of the death of an infant (infant mortality equivalents). It is calculated in a stepwise fashion from subtotals for each morbidity category/age group combination. It incorporates the number and duration (for acute episodes) of cases and the infant mortality equivalence values. A similar process is used to calculate vaccine preventable illness values, described below.

Vaccine Characteristics

Predictions of Vaccine Development

Committee discussions supplemented by consultations with outside experts led to the development of specific predictions or estimates for each vaccine in the following areas:

- probability of successful vaccine development
- time to licensure
- future cost of development up to licensure
- protective efficacy
- incidence of adverse side effects
- route of administration
- number of doses
- cost per dose
- delivery requirements
- technical difficulty of production.

All of these factors have been incorporated into the calculations of expected health benefits and expected net costs. Chapter 5 presents specific information on each of the vaccine candidates.

TABLE 1.2 An Example of the Format Used to Compile Information on the Burden of Illness Arising from Infectious Diseases

			Patient Age	
			Under 1 Year	
Morbidity Category	Description	Condition	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Urethritis, discharge		
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Pelvic inflammatory disease (initial and recurrent, all in women)		
C	Requiring hospitalization	Severe pelvic inflammatory disease (PID), ectopic pregnancy (all in women)		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)			n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)			n.a.
F	Total impairment			n.a.
G	Reproductive impairment resulting in infertility	Infertility following PID		n.a.
H	Death	Adult deaths from PID; fetal deaths from ectopic pregnancy	13,600	n.a.

Notes: n.a.=not applicable. This table shows the disease burden estimates for Neisseria gonorrhoeae (see Appendix L).

1–4 Years		5–14 Years		15–24 Years		25–59 Years		60 Years and Over	
Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
		14,225	3	902,815	3	577,960	3		
		8,000	5	294,400	5	97,600	5		
		2,400	6	91,720	6	39,480	6		
	n.a.		n.a.		n.a.		n.a.		n.a.
	n.a.		n.a.		n.a.		n.a.		n.a.
	n.a.		n.a.		n.a.		n.a.		n.a.
	n.a.		n.a.	15,000	n.a.	45,000	n.a.		n.a.
	n.a.	1	n.a.	36	n.a.	12	n.a.		n.a.

TABLE 1.3 Infant Mortality Equivalence Values

Infant Mortality Equivalence Values: A Median of Committee Members' Perspectives

Morbidity Category[a]	Age Group (years)					
	Under 1	1-4	5-14	15-24	25-59	60 and Over
A	1,000,000	800,000	500,000	500,000	500,000	2,000,000
B	100,000	50,000	50,000	50,000	40,000	100,000
C	10,000	5,000	5,000	5,000	4,000	8,000
D	200	100	100	125	125	2,000
E	5	5	7.2	5	10	16
F	0.5	0.5	0.5	0.5	0.5	2
G	1,000	500	250	250	2,000	--[c]
H	1(100)[b]	1	0.7	0.5	0.7	3

Infant Mortality Equivalence Values: An Age-Neutral Perspective

Morbidity Category[a]	Age Group (years)					
	Under 1	1-4	5-14	15-24	25-59	60 and Over
A	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000
B	100,000	100,000	100,000	100,000	100,000	100,000
C	10,000	10,000	10,000	10,000	10,000	10,000
D	200	200	200	200	200	200
E	5	5	5	5	5	5
F	0.5	0.5	0.5	0.5	0.5	0.5
G	1,000	1,000	1,000	1,000	1,000	1,000
H	1(1)[b]	1	1	1	1	1

Note: The number of acute morbidity days or chronic cases in each morbidity category/age group combination that are considered to be equal in undesirability to the death of an infant.

[a]Morbidity Categories are defined in Table 1.2.
[b]The value for first trimester fetal deaths is shown in parentheses.
[c]Generally considered not applicable.

Definition of Probable Vaccine Target Population

The determination of a probable vaccine target population for each vaccine was based on the age distribution of the relevant disease and the relative risk of illness.

Estimation of Vaccine Utilization

To estimate the probable utilization of each vaccine candidate, a technique was developed to combine scores assigned to reflect lay (target population) and provider perceptions of risk of illness, severity of disease, vaccine benefits, and barriers to vaccination. Use of the technique is described in Chapter 6.

Estimation of Time to Licensure, Time to vaccine Adoption, and Delay of Vaccination Benefits: Discounting

For different vaccines, the length of time required for development to licensure and that required after licensure to achieve estimated utilization levels (i.e., to be adopted) varies. In addition, the health benefits produced by vaccines are realized at different times after vaccination.

These factors affect the time interval before cost outlays, savings, and health benefits associated with a vaccine will reach a steady state, and are used to determine the annualized "present value" of results that will be achieved in the future.

The process by which benefits and costs that are delayed for some years are converted to their equivalent value now is termed "discounting." This procedure enhances the relative importance of effects realized after a short as compared to a long delay. In the central analysis the discount rate used is 0.05. The effect of discounting at different rates is examined in Chapter 9.

Estimation of vaccine Preventable Illness

Vaccine preventable illness (VPI) is defined as that part of the disease burden that is preventable by delivery to the entire target population of a hypothetical vaccine that is 100 percent effective.

Calculation of Expected Health Benefits for Each Vaccine

Chapter 7 describes the integration of the components outlined above to derive the annualized present value of the health benefits expected from each vaccine candidate. Figure 1.1 summarizes the basic steps used in the analysis.

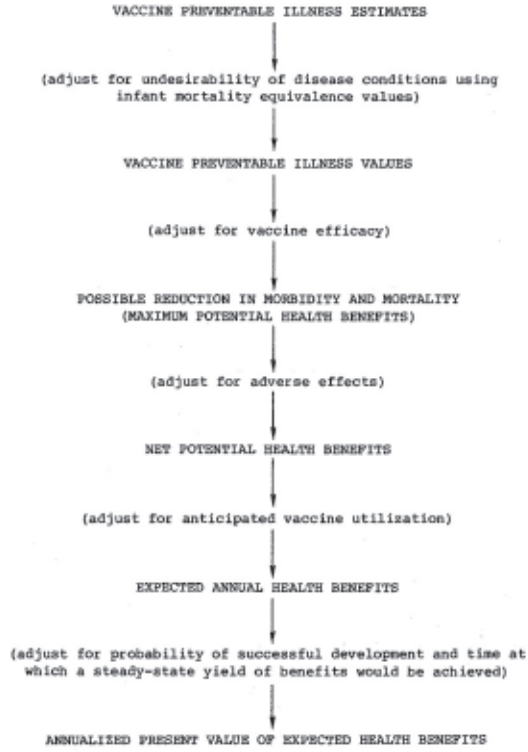

FIGURE 1.1 Calculation of expected health benefits.

Cost Calculations

Calculation of Morbidity Costs Averted by the Vaccine

Cost calculations for both overall disease and that portion of the disease that is vaccine preventable begin with the development of a "typical treatment profile" for each major condition included in the disease burden. For acute cases, the cost reflects the proportion of cases involving physician visits, diagnostic techniques, medications, etc. For hospitalizations, the level of care also is included; and for chronic conditions, the profile incorporates costs resulting from the expected duration of the condition.

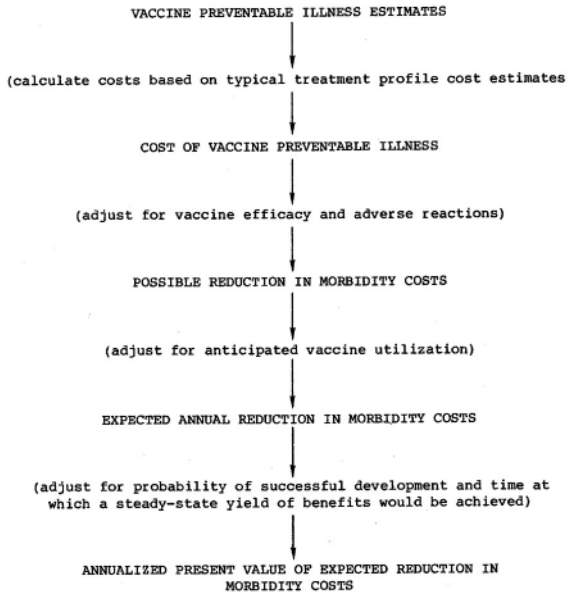

FIGURE 1.2 Calculation of expected reduction in morbidity costs.

Provision is made in the system for calculating and adjusting for the cost of adverse side effects of a vaccine. The procedure is similar to that described above for morbidity averted. Figure 1.2 shows how the various elements that affect expected savings in morbidity costs are integrated for each vaccine candidate.

Vaccination Program Costs

The probable cost of each vaccination program is calculated as shown in Figure 1.3. It reflects the cost of the vaccine and delivery costs adjusted for number of doses and size of target population.

Integration of Costs

Chapters 3 and 7 describe how the various cost components are integrated. These include the cost of development, the cost of adverse

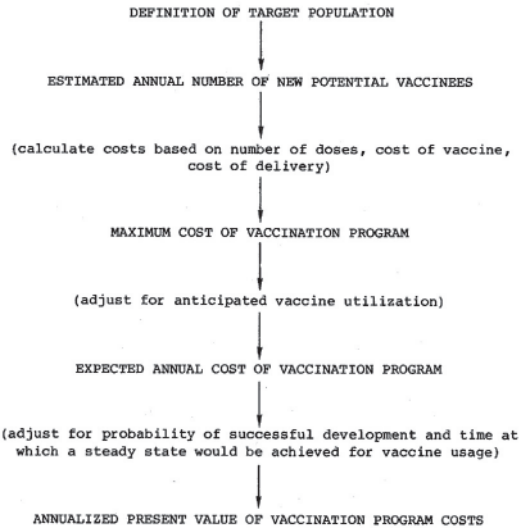

FIGURE 1.3 Calculation of vaccination program costs.

effects (if any), the cost of the vaccination program, and the costs averted by prevention of morbidity. If the total cost associated with a vaccine is negative, then it is potentially cost saving; if positive, there is a cost involved in reducing morbidity and mortality.

Interpretation of Health Benefit and Net Cost Rankings

The process of ranking vaccines in order of desirability using the expected health benefit and cost information developed with this method depends on the ultimate goals of the exercise and the constraints that limit the number of candidates that may be selected. Chapter 3 provides a detailed description of the procedures used to establish priority rankings. These are based on the concept of dominance: if a vaccine candidate is more desirable than another on one dimension (either health benefits or net costs) and at least as good on the second dimension, then it dominates the other candidate. Thus, the method ranks highest those vaccine candidates that would result in both the greatest expected health benefit (reduction of morbidity and mortality) and the greatest expected net cost savings of health resources. The relative ranking of vaccines that produce greater

health benefits than others, but at a higher cost (or a smaller savings), is a matter of policy judgment as to whether the incremental expenditure is justified for the vaccine that yields the additional benefit.

Chapter 8 identifies some additional issues that should be considered in the selection of priorities for accelerated vaccine development. These include the distribution of benefits from new vaccines among population subgroups; the significance of the public perception of adverse reactions to the current pertussis vaccine; and the role of the private sector in vaccine development.

Findings, Conclusions, Recommendations

Chapter 9 presents the committee's findings on the benefits and costs associated with the development of specific vaccines and the implications of a number of sensitivity analyses. The resulting priority list (interpreted for a hypothetical situation in which five vaccines are to be selected) is not meant to dictate the actions of government decision makers, however. The principal focus of this report is the method developed by the committee to provide a flexible, reproducible technique for the assessment of vaccine projects.*

The analyses indicate that vaccines for hepatitis B, RSV (the attenuated live virus vaccine), H. influenzae type b, influenza (probably the attenuated live virus vaccine), and Herpesvirus varicellae (for high-risk individuals; see Table 1.1) rank at or near the top of priority lists for accelerated development under a wide range of assumptions, although streptococcal group B vaccine and N. gonorrhoeae would move up considerably if utilization predictions were more optimistic. The slate of top choices among the vaccine candidates remains stable when alternative but plausible assumptions are adopted regarding discount rates and perspectives on morbidity and mortality.

The top choices also remain stable for a wide range of willingness-to-pay values per IME, i.e., between $125,000 per IME and several million dollars per IME. White (1983) has reported that most estimates of how much individuals would be willing to pay to save a life lie well within this range.

Many vaccines fail to enter the top five under even the most extreme assumptions.

Final decisions on the number of vaccines to be selected for accelerated development and on the ultimate choices should be addressed in a broader political/public policy forum, after consideration of the issues identified above and discussed fully in Chapter 8. In this con-

*Every effort has been made to ensure that all calculations in the report are correct; however, it is possible in a document of this length and complexity that a typographical error or other minor mistake may have escaped detection. It is hoped that this type of error would not detract from the reader's disposition towards the basic method.

text the committee reiterates its conclusion that an improved pertussis vaccine merits unique treatment because of its potential for restoration of public confidence in immunization programs.

Scientific opinion differs on some of the judgments incorporated into the proposed method and uncertainty surrounds much of the data, e.g., disease incidence and efficacy. When data are unavailable, expert judgments are required. The attempt to be explicit about certain estimates should not be interpreted as indicating that a high degree of precision, unanimity, or certainty in comparisons is possible in this situation. Hence, additional sensitivity analyses are suggested (see Chapter 9) to provide further information on key elements which may alter decisions. These include study of alternative IME profiles and variation in other factors for individual vaccines such as the number of required vaccine doses or the probability of success. Assessments involving alternative assumptions on the choice of target population are also desirable; these would entail more extensive recalculation including reestimation of vaccine preventable illness.

Recommendation

Lack of data on some diseases and the variable quality of data for others are serious impediments to the development of a comprehensive priority selection scheme. The National Institute of Allergy and Infectious Diseases and other agencies should consider means of improving the epidemiologic data on which disease comparisons can be made.

Reference

White, L.J. 1983. Public decision-making with respect to atmospheric PAH sources and emissions. Pp. D1–D26 in Polycyclic Aromatic Hydrocarbons. National Academy of Sciences. Washington, D.C.: National Academy Press.

2

Priority Setting for Health Related Investments: A Review of Methods

One of the first tasks in ranking and choosing among health related investments is selection of an appropriate method. Several methods have been applied successfully to problems conceptually similar to that of setting priorities for accelerated development of vaccines. Examples of these problems include setting priorities for resource allocation to medical technologies; setting priorities in medical research; selecting chemicals for toxicity testing; and selecting hazardous waste sites for clean-up. The methods themselves draw from techniques in systems analysis, decision analysis, and cost-benefit analysis. (Selected applications are described in Appendix A.)

Methods for Project Ranking and Selection

The five methods considered for use in ranking vaccine candidates are described below. They are (1) multiattribute accounting; (2) multiattribute scoring; (3) decision analysis with multiple objectives; (4) cost-effectiveness and cost-utility analysis; and (5) benefit-cost analysis. They differ from one another in several ways, most notably the extent of quantification demanded and the extent to which the ranking procedure is fashioned to reflect particular normative rules. The last part of this chapter considers some general issues in implementing any ranking methodology, including sources of estimates, appropriate use of sequential or "lexicographic" methods, problems of interdependence among projects, and the "portfolio" question.

Multiattribute Accounting

The ranking method requiring the least quantification and demanding the fewest normative assumptions is multiattribute accounting. This approach arrays the performance of each alternative on each valued objective, without attempting to produce an explicit overall score for each alternative. In deferring the final ranking to decision makers or consensus panels, multiattribute accounting differs from the other

methods considered. In other respects, however, many of the steps in this process are identical to those required for the other techniques.

As in all the methods, the first step in multiattribute accounting is to specify the menu of alternatives from which the projects will be selected. The second step is to define a set of valued objectives or criteria for the program (i.e., costs and benefits of various kinds). The result of the first two steps is to define the rows and columns of a matrix; a simplified example is shown in Table 2.1.

The third step is to fill in the cells in the matrix. Since multiattribute accounting requires no quantitative aggregation of scores across criteria (objectives), the entries in the matrix may be either quantitative or qualitative (e.g., high/medium/low). Table 2.1 contains both quantitative and qualitative information.

The fourth step is to determine if some candidates clearly dominate others, i.e., perform equally well or better on all objectives. In Table 2.1, vaccine C is dominated by vaccine B and, therefore, should be ranked below vaccine B in the final rankings.

The fifth step—the ranking itself—is left to the judgment of the decision makers or panels and is not an inherent part of the methodology. The only constraint imposed by the methodology is that dominance between pairs be preserved in the final rankings. The rest is left to intuitive judgment, which may be viewed either as an advantage or a limitation of the method.

Multiattribute Scoring

The method of multiattribute scoring goes beyond multiattribute accounting by generating a composite score for each candidate project. This requires three additional steps: (1) entry of a quantitative score (x_{ij}) in each cell in the matrix corresponding to the j^{th} criterion (objective) and the i^{th} project (vaccine candidate); (2) specifying a set of weights, w_j, which the individual factor scores will be combined; and (3) computing the weighted scores (s_i),

$$s_i = \sum_j w_j x_{ij}$$

Projects are ranked according to these scores. As an intermediate step, scores for groups of criteria are often combined into subscores (e.g., a "Disease Impact" subscore composed of the first three criteria in Table 2.1), and then the subscores are combined. Also, the individual scores are often "normalized" to a 0–100 scale before weighting for computational convenience. Sometimes, multiplicative rather than additive aggregation rules are used.

A hypothetical example of the process of multiattribute scoring is shown in Table 2.2. The end result is that vaccine candidate A is ranked highest, followed by vaccines B, D, and C. If desired, a sensitivity analysis can be performed, in which the weights are varied to see whether the rankings change. If only one of the four vaccine candidates in Table 2.2 could be developed, a sensitivity analysis would be desirable because the scores of A and B are so close. How-

TABLE 2.1 A Hypothetical Example of Multiattribute Accounting

	Criteria								
Vaccine Candidates	Potential Lives Saved per Year	Potential Direct Economic Cost Saved per Year (dollars)	Potential Morbidity Averted	Vaccine Efficacy[a] (percent)	Cost of Development ($ millions)	Time to Development (years)	Likelihood of Successful Development	Ease of Implementation	Cost of Production and Implementation
A	10,000	500,000	High	75	10	2-3	Good	Excellent	Moderate
B	15,000	1,500,000	Moderate	60	20	1-2	Fair to Good	Good	Moderate
C	3,000	1,000,000	Low	50	30	2-3	Fair	Good	High
D	0	500,000	Very High	40	5	3-4	Excellent	Poor	Low

[a]Reduction in expected frequency of disease among vaccinees.

TABLE 2.2 A Hypothetical Example of Multiattribute Scoring

	Criterion (weighting factor)												
	Disease Impact (0.4)				Vaccine Costs and Efficacy (0.4)				Characteristics of Development (0.2)				
Vaccine Candidate	Potential Lives Saved per Year (0.6)	Potential Direct Economic Cost Saved per Year (0.1)	Potential Morbidity Averted (0.3)	Subscore	Vaccine Efficacy (0.7)[a]	Ease of Implementation (0.2)	Cost of Production and Implementation (0.1)	Subscore	Cost of Development (0.2)	Time to Development (0.2)	Likelihood of Success (0.6)	Subscore	Total Score
A	67	33	60	61	75	100	50	77	80	60	80	76	70
B	100	100	30	79	60	60	50	59	40	100	65	67	68
C	20	67	10	22	50	60	0	47	0	60	50	42	36
D	0	33	100	33	40	30	100	44	100	20	90	78	46

Note: Scores and subscores are normalized to 100.

[a]Reduction in expected frequency of disease among vaccinees.

ever, if two vaccines could be developed, vaccines A and B probably would come out on top for most plausible sets of weights.

Decision Analysis With Multiple Objectives

One obvious limitation of the multiattribute scoring method just described is that the weights are arbitrary. This is especially disconcerting, considering that one is adding such disparate items as likelihood of success and disease mortality.

Decision analysis avoids this problem by distinguishing between probabilities and consequences of project alternatives. These are then combined in logical fashion to obtain, for each candidate project, an expected effectiveness or expected utility score. For the examples presented in Table 2.1, for instance, one may estimate the expected number of lives saved per year with the following equation:

Expected # of lives saved	=	Potential # of lives saved	x	Vaccine Efficacy	x	Vaccine Coverage	x	Probability of Development

For vaccine A (Table 2.1), for example, the efficacy score is 75. Vaccine coverage combines information on ease of implementation and cost, which for vaccine A are "excellent" and "moderate," respectively. Expert judgment would probably translate this into a score of 0.80 for vaccine coverage. The 0.70 estimate for the probability of successful development makes more explicit the entry "good" in Table 2.1. Thus:

Expected # of lives saved	=	(10,000)	x	(.75)	x	(.80)	x	(.70)
	=	4,200 per year.						

A similar calculation of expected values could be made for other valued consequences, such as days of morbidity averted, medical costs saved, and costs of development. These expected values for each consequence could be combined into a composite score using the methods illustrated in Table 2.2, though with expected values of valued consequences as the weighted items rather than a mixture of consequences and probabilities.

More rigorous application of decision analysis would entail combining the valued consequences into a utility score for each possible scenario, prior to averaging out by the probabilities, rather than averaging out each valued consequence separately and then combining the averaged-out values. The two ways of performing these steps will give the same result as long as the rule for combining consequence scores (utilities) is linear and additive. If the combination rule were multiplicative, for example, the answers generally would differ.

Cost-Effectiveness and Cost-Utility Analysis

Cost-effectiveness analysis is a formal method for selecting projects under a resource constraint. It requires that the constrained resource be identified (e.g., NIAID budget for new vaccine development or national expenditures on vaccinations) and that the resource burden of each candidate project be estimated, it also requires that a measure of effectiveness or expected value be defined for each candidate project. If the resource cost for the i^{th} candidate is C_i, and the expected effectivness is E_i, then the resources will be optimized if the candidate projects are ranked in increasing order by the cost-effectiveness ratio, C_i/E_i, and selected in that rank order as far down the list as resources permit.

There are at least two ways of applying cost-effectiveness analysis to the vaccine development problem. The first would treat the NIAID budget as the constrained resource, so the cost C_i would be the burden of developing the i^{th} vaccine on that budget. The effectiveness, then, would be the net effectiveness, considering all other benefits and costs (excluding the cost of development). One possible effectiveness measure would be the score, or expected utility, resulting from the multiattribute scoring method or the decision-analytic method described above. For example, U_i might be the expected utility for the i^{th} vaccine, as estimated by the procedure described in the preceding section. Then the cost-utility ratio, C_i/U_i, would become the basis for ranking. This is illustrated in Table 2.3. In the example, the ranking based on C/U would be as follows: candidates A and D (tied at $200,000); B ($500,000); and C ($1,500,000). Note that the lower the ratio, the higher the priority. Note also that vaccine D is given a high priority because of its low cost of development, even though its expected utility score is not as high as A or B.

Alternatively, the constrained resource might be all health-related expenditures. In that case, the numerator of the cost-effectiveness ratio would include three terms: the cost of development (C_i), plus the present value of future expected costs of production and administration (PC_i), less the present value of expected savings in morbidity costs from the disease (MC_i). The method of present value (the inverse of compound interest) is required to ensure that all costs and benefits are expressed in terms consistent with the same point in time.

The denominator of the cost-effectiveness ratio would be a measure of the expected health (non-economic) benefits from the vaccine. It is also calculated as a present value. One measure used by several researchers is the expected number of quality-adjusted years of life saved (Weinstein and Stason, 1977). This quantity, E_i, may be derived using the decision-analytic approach described above. Finally, the ratio, $(C_i+PC_i \bullet MC_i)/E_i$, is calculated for each candidate project, and the ranking is based on the ratios. For example, in Table 2.3, vaccine A ($5,000 per quality-adjusted year of life) would be given the highest priority, followed by D, B, and C.

TABLE 2.3 A Hypothetical Application of Cost-Effectiveness Analysis

Vaccine Candidate	Cost of Development (C_i) ($ million)	Total Expected Resource Costs[a] ($C_i+PC_i-MC_i$) ($ million)	Net Expected Utility (U_i)	Net Effectiveness[b] (E_i)	C_i/U_i (dollars)	$(C_i+PC_i-MC_i)/E_i$ (dollars)
A	10	25	50	5,000	200,000	5,000
B	20	35	40	4,000	500,000	8,750
C	30	50	20	2,500	1,500,000	20,000
D	5	12	25	2,000	200,000	6,000

Note: See text for definitions.

[a]Present value.
[b]Exclusive of resource costs, expressed in quality-adjusted years of life.

Benefit-Cost Analysis

In benefit-cost analysis, all consequences are reduced to a single, monetary quantity: the net expected economic benefit of a project. This requires that a monetary value be placed on health outcomes such as lives saved, as well as on non-health outcomes. Measures of economic productivity, such as earnings, often are used to monetize health improvements, but any such method has serious problems. (In fact, multiattribute scoring and decision analysis with multiple objectives often use this kind of judgment implicitly.) After all valued consequences have been monetized, the calculation of expected values proceeds as in multiattribute decision analysis: probabilities of various scenarios are multiplied by the corresponding utility values (or, in benefit-cost analysis, dollar values) and then summed.

Benefit-cost analysis is deeply rooted in the economic theory of social welfare. A society that wishes to maximize its welfare, according to theory, is supposed to adopt programs whose aggregate benefits exceed aggregate costs, to whomever those benefits and costs accrue. In recent years, the normative rationale for benefit-cost analysis has been challenged, though its value as a prescriptive tool is recognized even by some critics of its ethical standing (Swartzman et al., 1982; Office of Technology Assessment, 1980).

Selection of an Approach

The committee found that initial efforts to define its own goals and to identify the kinds of information necessary to choose among vaccine candidates simplified the task of selecting an appropriate methodology.

Neither the multiattribute accounting method nor the multiattribute scoring method satisfied the committee's intention to make full use of available data. In addition, they did not permit identification of all subjective elements included in the analysis.

The benefit-cost approach also had two major drawbacks from the committee's perspective. First, it required that a monetary value be assigned to health benefits such as avoidance of death, pain, and suffering. This is a very difficult and controversial task. The second problem was that the benefit-cost approach seemed to go beyond the committee's goal of comparing ways to reduce morbidity and mortality.

An approach that combines the essential features of cost-effectiveness analysis and decision analysis was selected after lengthy consideration as the most appropriate for the committee's purpose. It provides insights on both the expected health benefits from a vaccine (i.e., the morbidity and mortality it could avert) and the costs of achieving those benefits.

Every method has limitations and drawbacks and the cost-effectiveness approach is no exception. It is important to note that some factors cannot be quantified and incorporated into a cost-effectiveness analysis. Chapter 8 deals with issues of this type that should be

considered in the ultimate selection of vaccines for accelerated development.

Issues in Project Ranking Methodologies

Sources of Estimates

Data from case reports, published studies, government statistics, and other sources, as well as the subjective judgments of experts, are required for all of the methods described above. Expert judgments may be elicited either informally or by formal procedures such as the Delphi method (Dalkey, 1969). In the Delphi method, a panel of experts is assembled for each item. Each panel member gives an anonymous estimate of the quantity in question. The assembled responses are then fed back to panel members (without matching estimates to estimators), and the process is repeated until some prespecified level of convergence is reached or a prespecified number of rounds have been completed. An alternative to the Delphi method is to ask each expert panel member for a weight (1–10) describing his or her self-judged expertise on each particular question, and then to weight each response accordingly (National Academy of Sciences, 1975).

Sequential or "Lexicographic" Methods

Sometimes ranking schemes are based on sequential rather than simultaneous consideration of objectives. One variation of this approach is often called "lexicographic" because, like the ordering of words in a dictionary, it first groups the candidates according to their performances on a selected attribute (e.g., number of deaths due to the disease), then according to a second attribute, and so forth, until all ties are broken. Obviously, the order in which the attributes are considered is important. The assumption inherent in such methods is that one does not need to look at any but the first attribute, except in the case of ties. Most decision analysts discredit the use of lexicographic methods (Keeney and Raiffa, 1976), although sequential screening methods are sometimes necessary if the number of candidates on the menu is very large. The latter consideration, while important in the case of selecting from among 70,000 potentially toxic chemicals, is less germane to the selection of priorities among candidates for accelerated vaccine development, which at the outside probably number less than 50.

Interdependence Among Projects

The methods described above assume, in general, that the consequences of implementing one project on the menu are independent of which other projects also are selected. This may not be a valid assumption if, for example, costs of administration can be shared (e.g., the

combination diphtheria, pertussis, tetanus vaccine), or if immunologic responses are related, either synergistically or antagonistically. If the assumption of independence does not hold, then the affected vaccines must be assessed separately under each possible menu before the optimal menu is selected.

The "Portfolio" Question

Aside from determining interdependence among vaccines with respect to costs and effectiveness, NIAID may wish to consider certain goals with respect to specific target populations or diseases. For example, the individual rankings might reveal that vaccines K, L, and M are all higher priority than vaccine N. However, if K, L, and M all benefit urban whites, while N benefits rural blacks, then a portfolio of three vaccines might reasonably include vaccine N along with K and L. In other words, a pairwise comparison might reveal that M is preferred to N, yet the portfolio (K, L, N) is preferred to the portfolio (K, L, M). This kind of effect may be examined as a second-order iteration after the initial rankings are in hand, or it may be built into the process by examining each possible combination of vaccines separately. However, if there were 20 candidates, and the objective was to pick the top 5, for example, then the latter approach would involve examining

$$\frac{20!}{15!5!} = 15{,}504$$

combinations of 5, rather than just 20 individual candidates.

Appendix A contains examples of the application of the methods described above to problems of setting priorities in various areas of health resource allocation.

Summary

The selection of an appropriate method is the first step in setting priorities for accelerated vaccine development. This chapter reviews five methods that have been used successfully in other efforts to choose among health related investments: (1) multiattribute accounting; (2) multiattribute scoring; (3) decision analysis with multiple objectives; (4) cost-effectiveness and cost-utility analysis; and (5) benefit-cost analysis.

All of the methods require a mixture of factual information, carefully defined estimates, and subjective judgments. They differ in the extent to which they specify how the various elements should be combined. Multiattribute accounting, which requires the fewest normative assumptions, depends heavily on the intuitive judgment of decision makers. In contrast, benefit-cost analysis reduces all consequences to a single, monetary quantity: the net expected economic benefit of a project.

The committee decided that an approach that combines essential features of cost-effectiveness analysis and decision analysis would be

the most appropriate for ranking vaccines for accelerated development. Such an approach generates substantial information on both the expected health benefits from a vaccine and the costs of achieving those benefits. Unlike the benefit-cost approach, it does not require that a monetary value be placed on health benefits. Information on how to interpret the results of a cost-effectiveness analysis is presented in Chapter 3.

The final portion of this chapter considers some general issues in implementing any ranking methodology. These include how to elicit and weigh estimates, use of the sequential or "lexicographic" method, problems of interdependence among projects, and the "portfolio" problem.

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3

Overview of the Analytic Approach

This chapter presents an overview of the combined cost-effectiveness/decision analysis approach taken by the committee. Although reasonably straightforward in principle, the necessary calculations* demand a substantial amount of quantitative information, expose areas of ignorance, and require value judgments as well as facts. The committee sought the best available data from published sources and experts as a foundation for its calculations. Although concerned about the probabilistic and subjective aspects of its estimates, the committee recognized these elements as unavoidable in a priority-setting exercise such as this one. When factual information was not available, the choice was whether needed probabilities should be made explicit or left implicit. The committee chose to identify and quantify pertinent probabilities rather than to leave them vague or unspecified.

The report strives to identify the sources and reasons for all assumptions and estimates. One purpose is to make it easier to adjust assumptions and assess their effects on the implied rank order. The explicit, quantitative approach also facilitates the performance of sensitivity analyses, in which selected estimates are varied systematically across their plausible ranges to examine their impact on the cost-effectiveness calculations.

Several assumptions underlie the analysis. Some of these are considered further in Chapter 8.

1. Only specified vaccines and diseases are assessed. The preliminary selection of candidates for new or improved vaccine development was based on expert views of the current state of knowledge about each disease pathogen and the corresponding host response. Appendix B summarizes the committee's conclusions about some disease problems for which vaccine prospects are unclear or for which more basic research is required before targeted vaccine development will be realistic. If a candidate vaccine is omitted from the full analysis, it obviously will

*See Appendix R for information on the computer software used for this analysis.

not appear in the rank order, and no conclusions should be drawn regarding its position relative to the assessed contenders.

2. The committee's method can produce a priority ranking of candidate vaccines, but it is silent on the question of how many of the vaccines are worthy of development. The committee expressly refrained from equating dollars with the value of any health benefits.
3. The analysis has no bearing on basic scientific research. It does not compare the value of further investment in basic scientific research with the benefits or costs of vaccine development.
4. The analysis views costs and benefits from a societal perspective: it does not anticipate the source of funds for vaccine development, trials, or utilization, or the identity of those who will benefit from potential cost savings. Once the ranking of vaccine candidates has been completed, decision makers at the National Institute of Allergy and Infectious Diseases (NIAID) can determine the most effective distribution of the Institute's funds among those candidates selected for accelerated development.
5. The analysis recognizes only primary and secondary economic impacts of new vaccines on the medical care system. The primary impacts include costs of vaccine development, production, and administration; the secondary impacts deal with changes in the costs of care for patients who avoid having the disease in question or who develop side effects requiring treatment. (These impacts are sometimes called "induced costs and savings.") The tertiary impacts, which are not considered in this analysis, involve changes in the costs of care for other diseases that the patient will get (eventually) or already has (for example, in immunocompromised patients) because the vaccine has prevented death due to the target disease.
6. This analysis covers vaccine priorities for the population of the United States as a whole. (A separate assessment considers priorities for diseases of importance to less technologically developed countries.) The analysis regards vaccine benefits and costs irrespective of the population subgroups affected by particular diseases.
7. The analysis treats each potential vaccine as an independent investment decision. Possible second-order dependencies among vaccines are not considered. For example, the analysis does not take account of the possible effect of an improved pertussis vaccine on the long-term acceptance of other childhood vaccines (see Chapter 8).

Method

The basic strategy of the approach adopted by the committee is reductionist: each logical component of expected benefits and of expected costs is assessed separately, then the components are aggregated in a stepwise fashion for each disease-vaccine contender. The analysis distinguishes valued consequences, i.e., benefits and costs, from the probabilistic events that contribute to the likelihood of their occurrence. All component estimates are spelled out so they may be examined, questioned, and altered, if necessary.

The net expected health system costs and the net expected health benefits are annualized and discounted to their present values. "Annualized" means that all benefits and costs are expressed as steady-state (constant) streams, beginning immediately and extending indefinitely into the future. The procedure of discounting converts any benefit and cost streams that are delayed for some years to their equivalent annualized values starting now. Fixed expenditures (e.g., for vaccine development) are "amortized" to produce a constant annual equivalent value.

Discounting enhances the relative importance of effects realized after a short as compared to a long delay. The discount rate (r) used in the committee's calculations reflects the preference for present over future consumption of resources. In the central analysis, the discount rate is set at 0.05. The effect of discounting is evaluated in the sensitivity analyses described in Chapter 9.

The present value of the annualized equivalent of the net expected health system costs associated with a candidate vaccine includes the cost of development, the cost of the vaccination program, and the cost of adverse side effects, less the cost of medical treatment averted. It may be expressed as

$$rC_{Dev} + \frac{P_{Dev}C_{VP}}{(1+r)^{T_{Use}}} - \frac{P_{Dev}C_{Tr}}{(1+r)^{T_{Use}+T_{Lag}}} + \frac{P_{Dev}C_{SE}}{(1+r)^{T_{Use}}}$$

where:

- r = Discount rate
- C_{Dev} = Cost of vaccine development
- P_{Dev} = Probability of vaccine development
- C_{VP} = Annual cost of the vaccination program
- T_{Use} = Time until steady-state vaccine use, i.e., the time to licensure plus the time to adoption at the predicted use rate
- C_{Tr} = Annual cost of medical treatment averted
- T_{Lag} = Lag between administration of vaccine and realization of health benefits, i.e., the delay of vaccination benefits
- C_{SE} = Annual medical costs from side effects

Net expected health benefits, expressed as the annualized equivalent of the present value, consist of clinical benefits adjusted for adverse side effects of the vaccine, it may be expressed as

$$\frac{P_{Dev}B}{(1+r)^{T_{Use}+T_{Lag}}} - \frac{P_{Dev}SE}{(1+r)^{T_{Use}}}$$

where symbols are defined as above and;

B = Expected annual steady-state benefits from vaccine, adjusted for efficacy (E) and utilization (U)

SE = Expected annual incidence of vaccine side effects

Figure 3.1 summarizes the hierarchy of components that make up expected benefits and expected costs for each prospective vaccine. Each element of benefit and of cost rests upon estimates related to the target disease or estimates related to the subject vaccine. For expository convenience, these elements are grouped into three logical categories: (1) the morbidity, mortality, and direct costs associated with the disease and with vaccine side effects (Chapter 4 and appendixes); (2) the anticipated characteristics of the vaccine, including its efficacy and the incidence of adverse side effects, and the likelihood and timing of vaccine development (Chapter 5); and (3) the expected utilization of available vaccine (Chapter 6). Chapter 7 integrates the components of benefit and separately integrates the components of cost, adjusts each for the probability that they will occur and the expected delay until realization, and presents the conclusions of the baseline analysis.

Interpretation of Results

After all assumptions and estimates have been made and all calculations performed, the analysis yields the annualized net expected costs and the annualized net expected health benefits for each candidate vaccine. These could be arrayed in a table like that shown in Table 3.1. The entries in the table are meant to illustrate the interpretation of conceivable results and do not represent actual results.

Table 3.1 summarizes results for ten vaccine candidates, A through J. Each vaccine is associated with a net expected cost and a net expected benefit, both adjusted to their present values to make results with different time horizons comparable to one another, and converted to annualized equivalents. The "expected net" figures take account of all uncertainties that apply to the development, use, and consequences of each vaccine. Built into the interpretation of these results is an assumption that society is risk neutral with respect to alternative vaccine investments. This means, for example, that the benefits from a vaccine investment that has a 50 percent chance of ultimately saving 2,000 lives per year are valued the same as the benefits from an alternative vaccine investment that has a 25 percent chance of ultimately saving 4,000 lives per year, because the expected number of lives saved per year is equal to 1,000 lives in both cases.

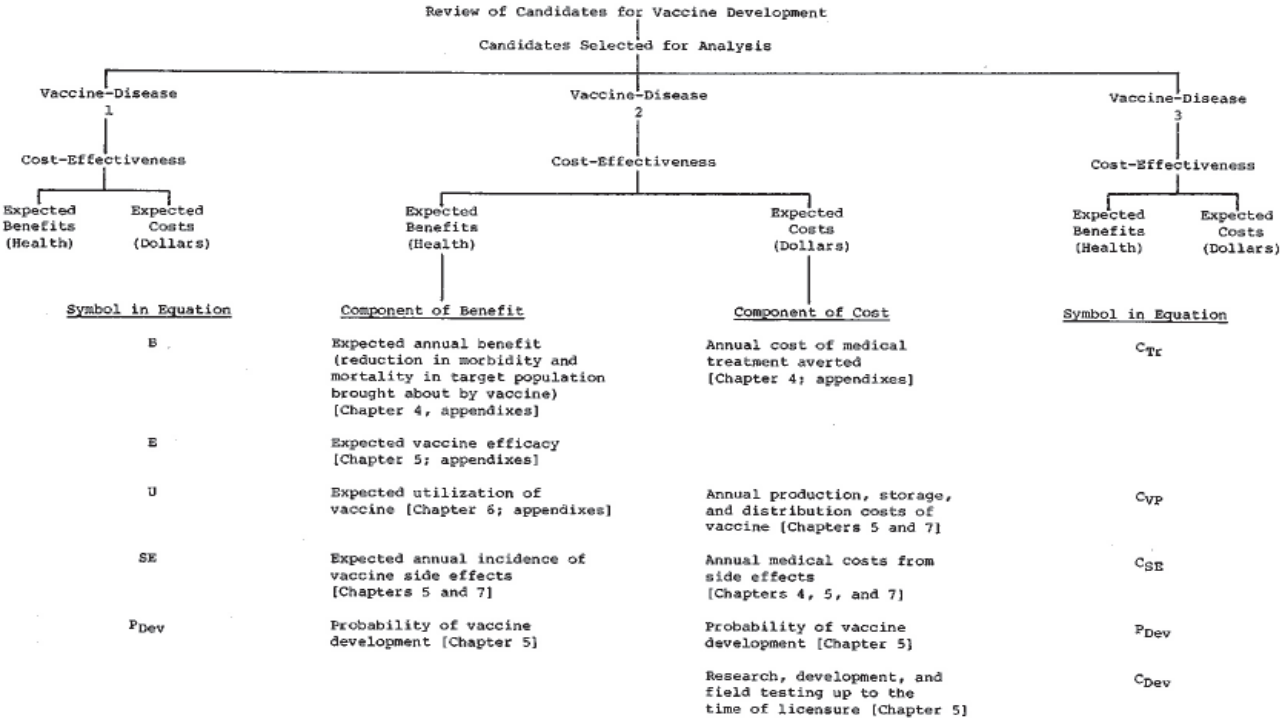

FIGURE 3.1 Summary of Analytical Strategy

TABLE 3.1 Sample Array of Hypothetical Vaccine Costs and Benefits

Vaccine	Annualized Present Value of Expected Net Costs ($ million)	Annualized Present Value of Expected Health Benefits
A	-1,000	250
B	- 800	200
C	- 500	200
D	- 400	100
E	- 200	150
F	- 50	100
G	10	125
H	20	105
I	40	150
J	80	80

The annualized expected net costs are negative for vaccines A through F. Negative net costs mean that an investment in the vaccine is expected to produce net savings. In other words, the health resources saved from reduction in disease more than outweigh the investments required for vaccine development, production, and administration.

If a vaccine is expected to produce both net savings (negative costs) and positive benefits, it qualifies automatically as a socially advantageous investment. Some vaccines with calculated positive costs may have other substantial savings in indirect costs, such as time lost from work or expenditures for certain public health measures (e.g., contact tracing for sexually transmitted diseases). Methods described in this report do not deal specifically with such indirect costs for reasons discussed in Chapter 4.

The net cost figures attempt to take account of the total needed investment, from both public and private sources, to develop and administer a vaccine. Decisions of a single agency like the NIAID should take account of the expected investment by others. Also, the NIAID may not have sufficient resources at this time to invest in each of the vaccines that are expected to be both cost saving and beneficial. This type of analysis can help the NIAID set necessary priorities among vaccines that are gainful in both economic savings and health benefits. The analysis may support the wisdom of additional allocations of public funds to the development of new vaccines, though this is not its primary purpose.

When the net expected costs are positive, as in vaccines G through J, a vaccine may still be an excellent investment. Most investments in health interventions produce a net consumption of resources. The desirability of different expenditures then depends on the extent to which alternative investments produce health benefits. Conceivably, if the benefits are sufficiently great relative to what we would be willing to pay for a unit of health benefit, some of these vaccines could be better investments than one or more of vaccines A through F.

In Table 3.1, the vaccines are listed in order of increasing cost, and this is the preliminary step in interpreting results of the analysis. Costs generally parallel the benefits because a decline in disease reduces treatment expenditures, but no strict relationship exists because vaccination program costs also markedly affect net costs.

The process for ranking vaccines in order of desirability depends on the type of constraint that limits the number of candidate vaccines that may be selected. One constraint for NIAID, for example, could be the total funds available to the agency for investment in new vaccines. In this case the ranking process would need to take account of the anticipated investment required from NIAID for each candidate vaccine. The following section demonstrates how to select a particular number of top-ranked vaccine candidates based on the net expected costs and net expected benefits from each vaccine.

Guidelines

The initial phase of establishing a priority ranking for social investment in the candidate vaccines is based on the concept of dominance of one investment over another.

Definition of Dominance

If vaccine x is better on one dimension (either costs or benefits) than vaccine y, and if x is as good as or better than y on the second dimension, then the choice of vaccine x dominates vaccine y.

Applying this rule to the candidate vaccines produces the results shown in Table 3.2 and summarized below:

- vaccine A dominates all others
- vaccine B dominates all except A
- vaccine C dominates all except A and B
- vaccine D dominates F and J
- vaccine E dominates F, G, H, I, and J
- vaccine F dominates J
- vaccine G dominates H and J
- vaccine H dominates J
- vaccine I dominates J.

By the rule of dominance, the top three social investments are vaccines A, B, and C, and the least attractive of the listed vaccines

TABLE 3.2 Vaccine Dominance (column dominates row)

	A	B	C	D	E	F	G	H	I	J	Total
A	-										0
B	X	-									1
C	X	X	-								2
D	X	X	X	-							3
E	X	X	X		-						3
F	X	X	X	X	X	-					5
G	X	X	X		X		-				4
H	X	X	X		X		X	-			5
I	X	X	X		X				-		4
J	X	X	X	X	X	X	X	X	X	-	9
Total	9	8	7	2	5	1	2	1	1	0	

is J. The need to proceed further depends on the number of alternatives to be selected for development: if only one, two, or three were desired, we could identify the priorities as vaccines A, A and B, or A and B and C, respectively.

Step 1

If S vaccines are to be selected from among N vaccine contenders, select any candidate vaccine that dominates at least the number (N"S) other vaccines.

In the example, there are ten vaccine candidates (N=10). To select four candidates for investment (S=4), begin by choosing any that dominate as many as six (10•4) other vaccines. From the bottom row of Table 3.2, it is apparent that vaccines A, B, and C satisfy this condition, and so would be selected. This would leave one more to be selected.

Step 2

Eliminate any candidate vaccines that are dominated by the number of vaccines that will be selected for investment.

If, for example, we want to invest only in four vaccines, we should eliminate F, G, H, I, and J because, from the rightmost column of Table 3.2, these are each dominated by at least four other vaccines.

TABLE 3.3 Contenders for Fourth vaccine

Vaccine	Annualized Present Value of Expected Net Costs ($ million)	Annualized Present Value of Expected Health Benefits	Incremental C/E (dollars)
D	-400	100,000	
E	-200	150,000	
E-D	200	50,000	4,000

This leaves two remaining candidates for the fourth vaccine, D and E. The choice between vaccines D and E requires a value judgment about society's willingness to forgo resource savings (or to incur costs) in order to realize health benefits.

Step 3

From the contenders for the remaining slot(s), calculate the incremental cost: effectiveness (C/E) ratio for each vaccine relative to the least costly contender. The incremental C/E ratio is the difference in costs divided by the difference in benefits for two vaccine candidates.

Table 3.3 shows the incremental C/E ratio for vaccine E vs. vaccine D. The rightmost column indicates that each additional unit of benefit from vaccine E (compared to vaccine D) costs $4,000. Now comes the value judgment.

Step 4

Two remaining contenders Decide whether the incremental costs are worth paying to gain the incremental benefits. If they are, choose the more beneficial (and more costly) vaccine (in this case, vaccine E). If the costs are not worth paying, choose the less costly vaccine (vaccine D). In this case, if we were willing to pay as much as $4,000 per unit of health benefit, we should choose vaccine E over vaccine D (Table 3.3).

More than two remaining contenders If Step 3 involves a comparison of more than two remaining contenders, Step 4 is similar in principle, though slightly more work. If, for example, five vaccines were to be chosen, then three vaccines would be left for the selection of a fifth after Step 2: D, G, and I. (Vaccine E already would be included as the fourth choice according to Step 1 because it dominates five other vaccines and N•S=10–5=5.) Table 3.4 shows the incremental C/E ratios for vaccines G and I, each relative to vaccine D.

TABLE 3.4 Contenders for Fifth Vaccine

Vaccine	Annualized Present Value of Expected Net Costs ($ million)	Annualized Present Value of Expected Health Benefits	Incremental C/E (dollars)
D	-400	100,000	
G	10	125,000	
I	40	150,000	
G-D	410	25,000	16,400
I-D	440	50,000	8,800

The decision required is whether the incremental costs for the most beneficial vaccine are worth paying. If so, select the most beneficial. (In this example, vaccine I would be selected if the decision maker were willing to pay $8,800 per unit of benefit.) If the incremental C/E ratio for the most beneficial vaccine is unacceptable, consider the next most beneficial candidate. If none is acceptable, choose the least costly contender (in this case, vaccine D).

In this example, the second most beneficial vaccine, G, has an incremental C/E ratio that is even higher than the C/E ratio for the most beneficial vaccine, I, so if we are unwilling to select vaccine I, we are surely unwilling to select vaccine G. This so-called incremental dominance of a more beneficial vaccine (I) over a less beneficial vaccine (G) will not always hold; in some cases a vaccine G could have an incremental C/E ratio that would be lower than that for the more costly vaccine I, and, conceivably, could be selected for the fifth priority. As the figures in the example stand in Table 3.4, the rational choice for the fifth vaccine is either vaccine D or, if the decision maker is willing to pay as much as $8,800 per unit of benefit, vaccine I.

Summary

The approach described in this report is recommended by the committee for selection of priorities for accelerated development because it separately identifies each logical component of expected benefits and expected costs associated with individual vaccine contenders. The analysis distinguishes quantifiable consequences from the probability that they will occur, and also incorporates information on when they are likely to occur. The result is a ranking of prospective candidates according to the expected return in health benefit per dollar of health resources invested.

The committee does not attempt to place a monetary value on health benefits, to suggest how many vaccines are worthy of development, to

compare investment in basic scientific research with investment in accelerated vaccine development, or to anticipate the source of funds for any vaccine-related programs. In addition, the approach requires that an effort be made to state the sources and reasons for all assumptions and estimates.

The selection of candidates for accelerated vaccine development should be an ongoing process. One of the benefits of the model is that it provides a structured format in which to incorporate new research findings. This is especially important given the rapid development of new techniques in biotechnology.

After the annualized net expected costs and the annualized net expected health benefits have been determined for each vaccine, the results must be interpreted based on the type of constraints that limit the number of candidates that may be selected. Specific procedures exist to establish the dominance of one investment over another. If dominance considerations alone do not provide a complete slate of candidates, decision makers must make judgments to determine whether incremental costs are worth paying to gain incremental benefits in specific cases.

4

Comparison of Disease Burdens and Costs

The objective of any vaccine development program is to reduce morbidity, mortality, and costs resulting from disease. Unfortunately, time and resource limitations make it impossible to pursue intensive development programs for all vaccines simultaneously. Priorities must be set in a manner that is consistent both with the needs of the population and the capabilities of current technologies. The committee sought a methodology that would allow quantitative comparison of the burdens of morbidity and mortality resulting from disease candidates for accelerated vaccine development.

In the proposed system, information on morbidity and mortality are combined into a single numerical score for each disease.* The same principles have been used to calculate the expected health benefits from individual vaccine candidates in Chapter 7. Application of the system to diseases that are candidates for long-term rather than accelerated development is discussed in Appendix B.

The methods used to calculate and compare the costs associated with the diseases are described in the latter portion of this chapter, and the cost savings that may be achieved from the vaccines are presented in Chapter 7.

Elements of the System for Comparing Morbidity and Mortality Burdens Arising From various Diseases

The system described below was designed not only to incorporate information relating to a disease (i.e., incidence, severity, complications, sequelae, duration, and distribution), but also to allow expression of individual value judgments on the undesirability (disutility) of different consequences resulting from that disease. Such value judgments are an inevitable part of the ranking process, whether they are explicit or implicit. The committee chose to make them explicit.

*See Appendix R for information on the computer software used in this analysis.

A format was devised with generic categories for estimates of the number of cases, complications, sequelae, and deaths associated with each disease. Three levels of severity were established for both acute and chronic morbidity and provision was made for recording the duration of an acute illness. The scheme also was designed to allow distribution of cases, complications, sequelae, and deaths among six age groups. An example of the matrix used to compile these estimates is shown in Table 4.1; the methods used to determine the entries are described below. Data on individual diseases are presented in Appendixes C through P.

Trade-Off Values

Individual value judgments (trade-off values)* on the disutility of particular disease states were elicited through a questionnaire (see Appendix Q) completed by individual committee members. Respondents to the questionnaire were first asked to judge the undesirability of one unit of each acute and chronic morbidity category against death within a specific age group. The units were specified as one day for each state of acute illness and one case for each type of chronic illness (assumed to last a lifetime). Respondents then were asked to evaluate the undesirability of deaths across age groups. An example is shown in Table 4.2. The morbidity/mortality and age categories used in the questionnaire were those described above. The scheme was designed to cover all major conditions that result from infectious diseases.

With these trade-offs, a set of values was derived for each respondent that represented on a single numeric scale the individual's feelings about various disease consequences. The unit of comparison was designated as the "infant mortality equivalence" (IME) value. The IME value of a morbidity category/age group combination was calculated by multiplying the trade-off value for that combination by the trade-off value assigned to a death in that age group compared to the death of an infant under one year of age (for an example derived from Table 4.2, see Table 4.3).

Expression of Morbidity and Mortality Burdens

Specific infant mortality equivalence values can be combined with disease burden estimates such as those given in Appendixes C through P to generate scores that express the seriousness of a disease relative to others as viewed by the individual making the trade-off decisions.

* A trade-off value expresses an individual's perception of the undesirability or disutility of a morbidity state compared to a death in the same age group.

The procedure begins with the calculation of a subtotal for each morbidity category/age group combination, as shown:

$$\text{Disease Burden Subtotal}_{\text{Category}}^{\text{Age Group}} = \frac{\text{Cases} \times \text{Duration}}{\text{Infant-Mortality Equivalence}_{\text{Age Group Category}}}, \text{ for acute episodes}$$

$$\text{or} \quad \frac{\text{Cases}}{\text{Infant-Mortality Equivalence}_{\text{Age Group Category}}}, \text{ for chronic disability or death}$$

The total score or total disease burden value (TDBV) is then a summation of the subtotals. A sample calculation sheet (from Appendix L) is shown in Table 4.4.

The views of different individuals on the relative importance of diseases can be compared by ranking diseases based on their TDBVs or by normalizing values so that the highest value represents some arbitrary common number, such as 100.

Prior to presentation of the results of the disease burden comparison performed by this committee, some discussion of the implementation of the method is desirable.

Procedures Used in Deriving Disease Estimates

Individuals knowledgeable about particular diseases were solicited for information that would enable estimates to be made in the format shown in Table 4.1. If the disease was not one for which the Centers for Disease Control collects information, other sources were contacted. Committee staff integrated information from various sources with the assistance of consultants. Reviews of preliminary estimates were obtained from initial sources and other individuals. Revised estimates were generated on the basis of reviews, with committee members arbitrating if reviewers made conflicting recommendations for modification of preliminary efforts.

Estimates of disease burden for the diseases that are candidates for accelerated vaccine development are included in Appendixes C through P.

Certain general procedures and assumptions were adopted to promote consistency in the derivation of estimates:

- Cases were included under chronic categories (D through G) only if the condition would persist for the remainder of the individual's life; protracted illness or convalescence from which the individual eventually would recover was not considered chronic disability.
- To simplify implementation of the scheme, acute episodes of illness usually were assigned wholly to the morbidity category representing the most severe signs and symptoms present (see below for

TABLE 4.1 An Example of the Format Used to Compile Information on the Burden of Illness Arising from Infectious Diseases

			Patient Age	
			Under 1 Year	
Morbidity Category	Description	Condition	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Urethritis, discharge		
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Pelvic inflammatory disease (initial and recurrent, all in women)		
C	Requiring hospitalization	Severe pelvic inflammatory disease (PID), ectopic pregnancy (all in women)		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)			n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)			n.a.
F	Total impairment			n.a.
G	Reproductive impairment resulting in infertility	Infertility following PID		n.a.
H	Death	Adult deaths from PID; fetal deaths from ectopic pregnancy	13,600	n.a.

Notes: n.a.=not applicable. This table shows the disease burden estimates for Neisseria gonorrhoeae (see Appendix L).

1–4 Years		5–14 Years		15–24 Years		25–59 Years		60 Years and Over	
Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
		14,225	3	902,815	3	577,960	3		
		8,000	5	294,400	5	97,600	5		
		2,400	6	91,720	6	39,480	6		
	n.a.		n.a.		n.a.		n.a.		n.a.
	n.a.		n.a.		n.a.		n.a.		n.a.
	n.a.		n.a.		n.a.		n.a.		n.a.
	n.a.		n.a.	15,000	n.a.	45,000	n.a.		n.a.
	n.a.	1	n.a.	36	n.a.	12	n.a.		n.a.

TABLE 4.2 Example of an Individual Scheme of Trade-off Values

Morbidity Category	Description	Unit	Trade-off Value					
			Under 1 Year	1-4 Years	5-14 Years	15-24 Years	25-59 Years	60 Years and Over
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Days	1,000,000	1,000,000	1,000,000	500,000	500,000	500,000
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Days	100,000	150,000	150,000	100,000	500,000	50,000
C	Requiring hospitalization	Days	10,000	15,000	15,000	15,000	10,000	10,000
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Cases	30	30	50	50	50	100
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Cases	5	5	5	5	10	15
F	Total impairment	Cases	0.5	0.75	0.8	0.85	0.9	1
G	Reproductive impairment resulting in infertility	Cases	10	10	5	5	20	
H	Death	Cases	1	1	1	1	1	1
		Deaths adjusted for age group	1[a]	0.8	0.9	1	2.5	5

[a] First trimester fetal death=100.

TABLE 4.3 Example of an Individual Scheme of Infant Mortality Equivalence Values

Morbidity Category	Description	Unit	Trade-off Value					
			Under 1 Year	1-4 Years	5-14 Years	15-24 Years	25-59 Years	60 Years and Over
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Days	1,000,000	800,000	900,000	500,000	1,250,000	2,500,000
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Days	100,000	120,000	135,000	100,000	1,250,000	250,000
C	Requiring hospitalization	Days	10,000	12,000	13,500	15,000	25,000	50,000
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Cases	30	24	45	50	125	500
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Cases	5	4	4.5	5	25	75
F	Total impairment	Cases	0.5	0.6	0.72	0.85	2.25	5
G	Reproductive impairment resulting in infertility	Cases	10	8	4.5	5	50	
H	Death	Cases	1[a]	0.8	0.9	1	2.5	5

[a] First trimester fetal death=100.

TABLE 4.4 An Example of the Calculation of a Total Disease Burden Value

Morbidity Category	Description	Condition	Under 1 Year				5–14 Years			
			Number of Cases	Duration	Infant Mortality Equivalence Value	Disease Burden Subtotal	Number of Cases	Duration	Infant Mortality Equivalence Value	Disease Burden Subtotal
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Urethritis, discharge					14,225	3	500,000	0.09
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Pelvic inflammatory disease (initial and recurrent, all in women)					8,000	5	50,000	0.8
C	Requiring hospitalization	Severe pelvic inflammatory disease (PID), ectopic pregnancy (all in women)					2,400	6	5,000	3
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)									
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)									
F	Total impairment									
G	Reproductive impairment resulting in infertility	Infertility following PID								
H	Death	Fetal deaths from ectopic pregnancy; adult deaths from PID	13,600	n.a.	100	136	1	n.a.	0.7	1
Total						136				5

Note: This table shows the total disease burden value calculated for Neisseria gonorrhoeae, using infant mortality equivalence (IME) values representing the median of committee members' IME perspectives (see Table 4.5).

Morbidity Category	Description	Condition	15–24 Years				25–59 Years				60 Years and Over	Total
			Number of Cases	Duration	Infant Mortality Equivalence Value	Disease Burden Subtotal	Number of Cases	Duration	Infant Mortality Equivalence Value	Disease Burden Subtotal	Number of Cases	
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Urethritis, discharge	902,815	3	500,000	5.4	577,960	3	500,000	3	None	9
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Pelvic inflammatory disease (initial and recurrent, all in women)	294,400	5	50,000	29	97,600	5	40,000	12		42
C	Requiring hospitalization	Severe pelvic inflammatory disease (PID), ectopic pregnancy (all in women)	91,720	6	5,000	110	39,480	6	4,000	59		173
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)											
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)											
F	Total impairment											
G	Reproductive impairment resulting in infertility	Infertility following PID	15,000	n.a.	250	60	45,000	n.a.	2,000	23		83
H	Death	Fetal deaths from ectopic pregnancy; adult deaths from PID	36	n.a.	0.5	72	12	n.a.	0.7	17		277
Total						277				115		584

exceptions), despite the fact that the episode might include periods of recovery at less severe levels.

- Category C was interpreted as requiring hospitalization (to minimize subjectivity on severity of pain).
- If it was thought that convalescence from hospitalization would include a period of impairment at least as severe and as long as that associated with unhospitalized cases, the numbers of such cases were added to the unhospitalized estimates with an appropriate duration (examples include hepatitis A and B; see Appendixes G and H).
- For diseases in which the pathogen produces a broad spectrum of illness severity rather than a set of reasonably discrete conditions, estimates of the portions falling into different morbidity categories were obtained from individuals familiar with the disease's clinical symptoms and epidemiology; in some cases, estimates were made from the most recent annual reports of disease; in other cases previously reported incidence rates were applied to 1984 population projections (Bureau of the Census, 1984). Estimates derived by both methods were assumed to be reasonable reflections of the 1984 disease burden.
- It was judged that trends in the patterns of diseases under consideration (see Appendixes C through P) were not of sufficient magnitude to obscure differences among diseases. This is amenable to verification. The effect of trends in population numbers and disease incidence on future vaccine benefits is discussed in Chapter 7.

Limitations of the Current Estimates

Limitations on the accuracy of estimates included in Appendixes C through P need to be identified clearly. The extent to which the estimates represent true disease patterns varies among diseases because:

- the quality and availability of data on specific diseases varies
- the types of data from which estimates were made varied (For some diseases, infection rates for certain populations could be coupled to estimates of the proportion of clinically symptomatic infections to yield numbers of cases producing symptoms. For other diseases, estimates were based on health interview recall data, on prospective or retrospective studies in certain populations, or on reported disease incidence.)
- the extent of underreporting was known for some diseases but not for others (Although the distribution of reported cases may have been suspected of being biased, for example, towards more severe cases, the extent of the bias was not known.)
- for certain conditions the estimates (both absolute numbers and distributions) were based on the clinical and epidemiological experience and judgment of individuals, for which no means of verification existed
- the resources and time available to generate estimates were limited.

The committee cautions, therefore, that while the current estimates have been judged sufficient for the purposes of this report, additional efforts to develop new data on relative disease burdens and to refine estimates from available data would be highly desirable. Discussions of uncertainty in the estimates for each disease appear in Appendixes C through P.

Value Judgments in Quantifying Morbidity and Mortality

The use of infant mortality equivalence (IME) values in quantifying disease burdens (as in Table 4.4) intentionally introduces into the system for comparing diseases a component that reflects variations among individuals on the relative undesirability of disease consequences within and among age groups. Each individual's perspective is equally valid, hence, there can be no single, correct set of IME or trade-off values.

Several composite or hypothetical perspectives are worth considering, however, because they illustrate how differences in perspectives are reflected in the ultimate rankings of disease burdens and benefits to be expected from vaccines.

The intent of selecting priorities for accelerated vaccine development is to benefit the public health; hence, the perspectives of individuals with expertise in medicine or public health are of interest. Those of the public, the intended beneficiaries and ultimate sponsors of the enterprise, also are important.

If a representative sample from each group (health practitioners or the public) were polled, the range of trade-offs or IMEs probably would be extensive. It would be possible to calculate a median perspective for the range, but other clusters also might exist. To illustrate, consider the way individuals rate mortality at different ages: while most members of a group might consider an adult death (25–59 years) more undesirable than an infant death, a fairly large minority might believe just the opposite. Aggregation of preferences is a complex issue both methodologically and ethically and needs careful consideration.

The ultimate total disease burden value used for ranking diseases is a function of IME values and the number of cases (times days for acute episodes). A preliminary effort was made to determine which of these factors would be dominant in deciding the order of candidates for accelerated vaccine development on the basis of disease burden magnitude. The results were inconclusive: while the general rankings that resulted from use of individual committee member IME values were reasonably consistent, differences in placement on a normalized scale were considerable.

The committee recognized that perspectives represented by committee members probably did not encompass the full range of perspectives that should be included in an analysis of this type, but time and resource limitations prevented acquisition of additional judgments. The perspectives described below were adopted to illustrate application of the system and to describe the qualitative effects of using different perspectives.

IME Perspectives used in This Study

One of the sets of values used in the study's calculations employs a median of committee member IME perspectives, although trade-offs elicited from the committee were distributed over a considerable range. The other set reflects an age-neutral IME perspective constructed from the median trade-offs for the under-1-year age group. The latter set of values represent the view that specific levels of morbidity and numbers of deaths are equally undesirable across all age groups.

The median of committee member perspectives and the age-neutral perspective IME values (shown in Tables 4.5 and 4.6) are used here and in Chapter 7 solely to illustrate the operation of the system. Their use should not be taken as a judgment that either is the most appropriate or correct. The issue of which IME values should be chosen to guide policy formulation is discussed at the end of this chapter.

The Effect of Adopting Other IME Perspectives

Other sets of IME values might reflect the view that morbidity and mortality in young age groups, chronic disability inflicted on adults, hospitalizations (at any age), or infertility is relatively more undesirable than expressed by the committee median and age-neutral perspectives. The effect of adopting such a perspective would be that diseases inflicting or vaccines preventing a particularly disfavored morbidity or mortality would rise in the rankings of disease importance and vaccine priority. The extent of the rise would depend on the numbers of disfavored cases and the extent to which the relevant IME values differed from the median.

Adopting certain IME perspectives is comparable in some ways to ranking diseases or vaccines within groups. Grouping of vaccine candidates is discussed further in Chapter 8.

Comparison of Direct Costs Resulting from Diseases

One way to compare candidates for accelerated vaccine development is to determine the extent to which they will render unnecessary expenditures for treating disease and their cost-effectiveness in doing so. To make these comparisons, it is necessary to know the costs associated with each disease and vaccine, and the extent to which a vaccine will actually reduce disease. This section deals with the method adopted by the committee to estimate the costs associated with treatment of disease. Chapter 7 describes calculation of the costs of vaccination programs and adverse effects, and the cost savings associated with the reduction of morbidity by vaccines.

TABLE 4.5 Infant Mortality Equivalence Values: A Median of Committee Member Perspectives

Category	Under 1 Year	1-4 Years	5-14 Years	15-24 Years	25-59 Years	60 Years and Over
A	1,000,000	800,000	500,000	500,000	500,000	2,000,000
B	100,000	50,000	50,000	50,000	40,000	100,000
C	10,000	5,000	5,000	5,000	4,000	80,000
D	200	100	100	125	125	20,000
E	5	5	7.2	5	10	16
F	0.5	0.5	0.5	0.5	0.5	2
G	1,000	500	250	250	2,000	b
H	1[a]	1	0.7	0.5	0.7	3

[a] First trimester fetal death=100.
[b] Generally considered not applicable.

TABLE 4.6 Infant Mortality Equivalence Values: An Age-Neutral Perspective

Category	Under 1 Year	1-4 Years	5-14 Years	15-24 Years	25-59 Years	60 Years and Over
A	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000
B	100,000	100,000	100,000	100,000	100,000	100,000
C	10,000	10,000	10,000	10,000	10,000	10,000
D	200	200	200	200	200	200
E	5	5	5	5	5	5
F	0.5	0.5	0.5	0.5	0.5	0.5
G	1,000	1,000	1,000	1,000	1,000	1,000
H	1[a]	1	1	1	1	1

[a] First trimester fetal death=1.

Scope of Cost Calculations

Excluded from these calculations are costs resulting from loss of work, loss of future earnings, and public health measures instituted to prevent further spread (e.g., contact tracing for sexually transmitted diseases).

Calculation of indirect costs associated with disease, such as loss of work time or loss of future earnings, is the subject of considerable controversy. The committee did not feel that it had the time or resources to address this question adequately, nor did it feel that monetization of health benefits was either necessary or appropriate. Reduction of the overall economic burden imposed by certain diseases is definitely an important health goal; however, if these indirect economic aspects of disease burden were included among the costs, then interpretation of the disease burden figures would have to be modified to ensure that health benefits were not double counted (because IME and trade-off values already incorporate some psycho-social considerations). In contrast, costs associated with contact tracing, quarantine, etc., are not currently reflected in the disease burden figures and should be addressed in future applications of this model.

Calculation of the precise costs arising from each disease would require accurate data on the number of cases of each condition that result from the disease, exactly how each is treated, and the costs of all such treatments. For this study, differentiating between diseases with this degree of precision was judged neither practicable nor necessary. The information required to calculate precise costs is not available for many diseases because of the diversity of conditions they produce and because of the variation in treatment regimens among health care settings and even among health professionals working in the same setting. More important for valid comparisons than absolute precision is the ability to treat each disease in a uniform fashion, in sufficient depth that no important cost elements are overlooked.

Procedures

To estimate the approximate direct costs associated with the diseases that are candidates for accelerated vaccine development, the committee adopted the following procedures.

1. For each major condition identified in the disease burden estimates (Appendixes C through P), a "typical treatment profile" was developed. These profiles have been judged by committee members and consultants to be reasonably representative of the way in which each condition is treated, taking into account the fact that treatments vary among providers and settings. The profiles are not intended to prescribe or endorse standards of practice.
2. The costs associated with the typical treatment profiles were estimated by those members of the committee with experience in clinical practice, after consultation with others with similar experience. Given the lack of uniform national sources of cost information for the

conditions under consideration, the committee could identify no alternative but to resort to such judgments. As described below, uniform unit costs for various types of medical services were applied to all diseases.

3. The costs associated with the typical treatment profile for each condition were applied to the number of cases of that condition (drawn from the disease burden estimates). Total costs calculated for each disease are included in Appendixes C through P.

An outline of the components of the typical treatment profiles for acute and chronic cases follows.

1. Categories A and B (acute)
   a. Percentage of cases that involve physician visits
   b. Number of physician visits
   c. Percentage of cases getting diagnostic procedures
   d. Cost of disease-specific diagnostic procedures
   e. Percentage of cases getting medication or treatment
   f. Cost of disease-specific medication/treatment
2. Category C (acute)
   a. Percentage of patients in various types of hospital care, i.e., normal hospitalization vs. intensive care vs, neonatal intensive care
   b. Length of stay in each setting
   c. Percentage of patients receiving additional treatment
   d. The average total cost of treatment (diagnostic procedures, drugs, etc.)
   e. Surgical costs or other "heroic" procedures where appropriate and the percentage of patients who receive them
3. Categories D, E, F, and G (chronic)
   a. A per-case cost estimate that includes, as appropriate:
      (1) cost of physician visits necessitated by condition
      (2) cost of diagnostic/testing procedures
      (3) cost of drugs, services (nurses), and other remedial treatment
      (4) cost of special training or special education
      (5) cost of institutionalization (if necessary)
      (6) cost of remedial surgery (if necessary)
   b. The length of time that these costs would be incurred. This is required so that for conditions in which a stream of costs result from the occurrence of an event within any one year (e.g., central nervous system damage), the present value (see Chapter 3) of future payments can be calculated and included as part of the costs associated with that event.

      The duration of such costs depends on the condition. For a handicap such as blindness, the costs are incurred from the time of onset to the time of death, based on a normal life expectancy. In contrast, a severe neurological handicap may shorten life expectancy, and this fact is reflected in relevant cost determinations. Costs

associated with specific services are adjusted according to the length of time service is rendered (e.g., special schooling for individuals with mild mental retardation may last only until the beginning of adult life).

Many elements in the cost calculations are common to all or most diseases, so certain simplifying assumptions could be adopted:

- the cost of any physician visit is assumed to be $30.00 (Health Care Financing Administration, 1982)
- the per diem charge for normal hospitalization, including admission, discharge room fees, and routine medical attention is estimated to be $400 because the reported national average bed fee alone is about $200 (Health Insurance Association of America, 1983); intensive care (including routine medical attention, etc.) is assumed to cost $600 per day, and neonatal intensive care $800 per day
- institutionalization (Morbidity Category F) necessitated by very severe central nervous system damage is assumed to cost an average of $20,000 per annum (Koplan and White, 1982); the costs of disability associated with less severe central nervous system damage have been established by comparison with this figure (namely, Category D, $2,000; Category E, $5,000)
- no costs beyond those associated with illness are incurred by cases resulting in death
- costs are expressed in 1984 dollars
- calculation of present values employs a 5 percent per annum discount rate.

Findings

Application of the procedures described above to the disease candidates for accelerated vaccine development is illustrated in Appendixes C through P. Table 4.7 shows the total disease burden values calculated for each disease (using the two IME perspectives) and the direct costs associated with disease treatment. Use of these total disease burden values and cost figures in ranking the diseases is demonstrated in Table 4.8.

It should be noted that the costs presented here are those associated with the total disease burden rather than those potentially avertable by vaccine usage. Chapter 7 describes application of the disease comparison system to calculation of the benefits and the estimated cost savings expected from candidate vaccines.

Limitations of the Proposed System

The aggregate nature of the total disease burden value for each disease may be regarded by some individuals as obscuring important differences among disease consequences. Even though assigned to the same generic morbidity category, cases of some diseases may be regarded

TABLE 4.7 Morbidity and Mortality Burdens and Direct Costs Resulting from Various Diseases

	Infant Mortality Equivalence Perspective					
	Committee Median		Age-Neutral		Direct Costs Associated with Disease Treatment ($ millions)	Normalized (percent)
Pathogen	Total Disease Burden Value	Normalized[a] (percent)	Total Disease Burden Value	Normalized (percent)		
Bordetella pertussis	b	b	b	b	19	0.4
Coccidioides immitis	343	2	268	1	51	1
Cytomegalovirus	3,018	13	2,682	7	1,001	22
Hemophilus influenzae type b	1,986	9	1,919	5	425	9
Hepatitis A virus	181	1	176	0.5	105	2
Hepatitis B virus	5,866	26	5,665	16	285	6
Herpes simplex viruses 1 & 2	2,684	12	1,857	5	413	9
Herpesvirus varicellae	1,949	9	1,332	4	272	6
Influenza viruses A & B	22,373	100	36,410	100	4,633	100
Neisseria gonorrhoeae[c]	534	2	13,814	38	937	20
Parainfluenza viruses	1,167	5	1,104	3	347	7
Respiratory syncytial virus	4,759	21	4,707	13	343	7
Rotavirus	281	1	227	1	117	3
Streptococcus group B	3,957	18	3,915	11	727	16

[a] Calculated with the highest disease burden value equal to 100.
[b] See Appendix C for discussion of pertussis.
[c] The age-neutral TDBV for *N. gonorrhoeae* becomes 350 if an IME value of 100 is adopted for first trimester fetal deaths (as in the committee median perspective).

TABLE 4.8 Ranking of Diseases by Total Disease Burden Value and by Treatment Costs

IME Perspective

Committee Median		Age-Neutral		Direct Costs Associated with Disease Treatment	
Disease	TDBV	Disease	TDBV	Disease	Costs ($ millions)
Influenza viruses A & B	22,373	Influenza viruses A & B	36,410	Influenza viruses A & B	4,633
		(Neisseria gonorrhoeae)	(13,184)[b]	Cytomegalovirus	1,001
Hepatitis B virus	5,866	Hepatitis B virus	5,665	Neisseria gonorrhoeae	937
Respiratory syncytial virus	4,759	Respiratory syncytial virus	4,707	Streptococcus group B	727
Streptococcus group B	3,957	Streptococcus group B	3,915	Hemophilus influenzae type b	425
Cytomegalovirus	3,018	Cytomegalovirus	2,682	Herpes simplex virus 1 & 2	413
Herpes simplex viruses 1 & 2	2,684	Hemophilus influenzae type b	1,920	Parainfluenzae viruses	347
Hemophilus influenzae type b	1,986	Herpes simplex virus 1 & 2	1,857	Respiratory syncytial virus	343
Herpesvirus varicellae	1,949	Herpesvirus varicellae	1,332	Hepatitis B virus	285
Parainfluenza viruses	1,167	Parainfluenza viruses	1,104	Herpesvirus varicellae	272
Neisseria gonorrhoeae	534	(Neisseria gonorrhoeae)	(350)	Rotavirus	117
Coccidioides immitis	343	Cocciodioides immitis	268	Hepatitis A virus	105
Rotavirus	281	Rotavirus	227	Coccidioides immitis	51
Hepatitis A virus	181	Hepatitis A virus	176	Bordetella pertussis	a
Bordetella pertussis	a	Bordetella pertussis	a		

a See Appendix C for discussion of pertussis.

b The age-neutral TDBV for N. gonorrhoeae becomes 350 if an IME value of 100 is adopted for first trimester fetal deaths (as in the committee median perspective).

as more severe (more undesirable) than those of another disease. This problem would exist with any system of categories; a system involving assignment of trade-off (or IME) values to the spectrum of cases arising from each disease would be unmanageably complex to implement.

Perhaps more important is the fact that the system does not, as presently conceived, permit differentiation of diseases on the basis of duration of episodes, i.e., whether hospitalization of 100 individuals for 2 days each is more or less desirable than 1 individual for 200 days or 10 individuals for 20 days.

Problems in obtaining accurate estimates of disease incidence, lack of nationwide data on the costs of disease treatment, and difficulties in deciding which IME perspectives to adopt also limit the usefulness of the system. Even with these difficulties, the system has the potential to be a useful tool for selecting priorities for accelerated vaccine development. Recommendations that might remedy some of the problems are made below.

Summary and Conclusions

The system described in this chapter allows quantitative comparison of the morbidity and mortality caused by various diseases. It takes into account specific information about each disease (number of cases, complications, sequelae, deaths) and can accommodate various perspectives on the disutility (undesirability) of different disease consequences.

To illustrate use of the proposed system, candidates for accelerated vaccine development have been ranked according to both a median of committee member perspectives and a perspective that reflects the assumption that morbidity of similar severity or death is equally undesirable at any age. The effects of adopting alternative perspectives also have been explored.

The total direct costs arising from the diseases have been compared based on estimates of numbers of cases and sequelae, and on assumptions about types of treatment typically received and the costs of such services.

Recommendations

The National Institute of Allergy and Infectious Diseases and other agencies should consider means of improving the data on which disease burden comparisons are based. Lack of data in some areas and the variable quality of data in other areas are serious impediments to the development of a comprehensive priority selection scheme.

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5
Predictions on Vaccine Development

The Need for Predictions

Predictions about specific vaccines and the processes used to develop them are an integral part of the selection scheme outlined in Chapter 3. These predictions are required to calculate the expected health benefits that would be derived from each new vaccine and the costs associated with achieving those benefits. The characteristics of a vaccine (e.g., live attenuated virus vs. subunit) may affect its efficacy and often have an impact on acceptance and utilization patterns (Chapter 6). The complexity of the development process affects the costs associated with producing health benefits and the time at which they would be achieved.

This chapter outlines the types of predictions included in the analysis. Predictions were developed separately for each vaccine/ disease combination, based on the available literature and a variety of other sources. The final predictions were made after extensive discussions within the committee and consultations with almost 100 individuals in academic institutions, government, and industry.

Selection of Candidates

The committee defined candidates for accelerated development as those diseases for which vaccine development was foreseeable within the next decade. The criterion for inclusion was whether a reasonable consensus could be identified on the nature of potential vaccine components (protective antigens). (The selection process is described further in Appendix B).

The diseases and vaccine candidates chosen for the ranking process are shown in Table 5.1 and described in detail in Appendixes C through P. Some marginal candidates were excluded because the committee decided that it would be more appropriate to consider them in its deliberations on vaccine candidates for less technologically developed countries. The latter portion of Appendix B consists of pathogens considered by the committee to be unsuitable for accelerated vaccine development at this time.

TABLE 5.1 Predictions for New Vaccine Development

Pathogen	Vaccine Envisaged	Target Population	Development to Licensure: Probability of Success (p)	Development to Licensure: Estimated Future Costs ($ millions)	Development to Licensure: Time to Licensure (years)	Comments
Bordetella pertussis	Acellular	Infants	0.90	10	3-5	
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	0.50	10	6-7	
Cytomegalovirus	Attenuated live virus	Seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas	0.50	10	3	
		Nonpregnant adolescent females	0.50	10	7	Further development of above vaccine. Safety trials difficult.
	Glycoprotein produced by recombinant DNA technology	All children	0.50	45	7-10	
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	0.90	30	3	
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	0.95	15	4	
	Subunit	Susceptibles of all ages (routine for children)	0.95	25	5	
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	0.95	10	1-2	
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	0.90	30	5	
	Attenuated live virus	Children up to age 12 and older susceptibles	0.50	30	8	

Herpesvirus varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias and lymphomas	0.99	5	2	
		Normal susceptibles, routine for children (booster for adults)	0.95	5	4	
Influenza viruses A & B	Purified hemagglutinin/ neuraminidase proteins	High-risk population as currently defined (see Appendix K)	0.90	20	4	
	Attenuated live virus	High-risk population as currently defined (see Appendix K)	0.70	20	6	
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	0.50	50	10	Time to success could be shortened by a greater effort but probably not below 8 years; certainly not below 6 years
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	0.80	25	5	
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	0.80	25	5	
	Attenuated live virus	Infants	0.80	25	5	
Rotavirus	Attenuated live bovine virus	Infants	0.95	10	2-3	
	Attenuated live human or reassortment virus	Infants	0.90	20	2-4	
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	0.65	40	7	Shorter time unlikely because basic research needed on immunology and methods of conjugation

TABLE 5.1 (Continued)

			Vaccine Characteristics						
Pathogen	Vaccine Envisaged	Target Population	Protective Efficacy (percent)	Adverse Reactions/Dose	Administration	Doses	Cost/Dose ($)	Probable Delivery Requirements	Production Difficulty
Bordetella pertussis	Acellular	Infants	80	5-10% mild local; 0.1% moderate systemtic	IM	5 (3 initial + 2 boosters in early childhood)	10	Refrigeration	Moderate
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	70 (maximum)	50% moderate local	IM	3	10	Refrigeration	Not unusual
Cytomegalovirus	Attenuated live virus	Seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas	70	100% local; 50% moderate systemic; concerns about severity of reactivated virus in transplant patients	IM	1	25	Nothing unusual	Moderate because virus labile
		Nonpregnant adolescent females	80		IM	1	25	Nothing unusual	Moderate because virus labile
	Glycoprotein produced by recombinant DNA technology	*All children*	80	*None*	IM	3	25	*Nothing unusual*	*Moderate*
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	80	5% local	IM	4 (3 initial + 1 booster if given to young infants)	20	Freezing	Minor, some problems scaling up conjugation
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	90	Minimal	Parenteral SC/IM	1	15	Refrigeration of lyophilized preparation	Minor
	Subunit	Susceptibles of all ages (routine for children)	90	Minimal	SC/IM	3	20	Refrigeration	Minor
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	90	None	IM/SC	3	30	Refrigeration	Not unusual
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	*Children up to age 12 and older susceptibles*	45% effective in achieving a 50% reduction in the number of primary cases, a 75% reduction in the number of recurrences, and a 60% reduction in severity	None	IM	3 + boosters	20	Nothing unusual	Complex
	Attenuated live virus	Children up to age 12 and older susceptibles	65% effective in achieving a 50% reduction in the number of primary cases, a 75% reduction in the number of recurrences, and a 60% reduction in severity	None	IM	1	20	Nothing unusual	Complex

Herpesvirus varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias and lymphomas	90	5–10% local; 35–40% mild rash; unpredictable number of probably mild H. zoster infections possible	SC	2	25	Freezing of lyophilized preparation until in distribution chain	Minor
		Normal susceptibles, routine for children (booster for adults)	90% (duration unknown)	5–10% local; unpredictable number of probably mild H. zoster infections possible	SC	2 (1 for children plus boosters for adults)	25	Freezing of lyophilized preparation until in distribution chain	Minor
Influenza viruses A & B	Purified hemagglutinin/ neuraminidase proteins	High-risk population as currently defined (see Appendix K)	85% for correct match of vaccine and prevalent strain	Essentially none	SC	Primary + booster annually	15	Nothing unusual	Not unusual
	Attenuated live virus	High-risk population as currently defined (see Appendix K)	85% for correct match of vaccine and prevalent strain	Essentially none	Intranasal	1 (possibly 2)	10	Freezing	Minor
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	85% for pelvic inflammatory disease; 70% for mucosal	None	Local and parenteral	3 + boosters	20	Nothing unusual	Not unusual
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	80% (against severe disease in young children)	None	SC	2 + boosters	15	Nothing unusual	Not unusual
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	80% (against severe disease in young children)	None	SC	2 + booster	15	Nothing unusual	Not unusual
	Attenuated live virus	Infants	80% (against severe disease in young children)	None	Intranasal	1 (possibly 2)	15	Nothing unusual	Not unusual
Rotavirus	Attenuated live bovine virus	Infants	90	Minimal	Oral	1–2	Less than 10	Nothing unusual	Not unusual
	Attenuated live human or reassortment virus	Infants	90	Probably none	Oral plus parenteral May need to combine oral and parenteral immunization for effective response	1–2	Less than 10	Nothing unusual	Not unusual
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	80	5% local; safety trial difficult	IM	1	20–25	Freezing	Not unusual

Vaccine Candidates and Target Populations

One or more vaccine candidates have been identified for each disease included in the slate of candidates for accelerated development, vaccine descriptions usually are based on current research approaches. For some pathogens, including cytomegalovirus, hepatitis A virus, and herpes simplex, several possible vaccines have been evaluated. The number of vaccine possibilities for gonorrhea led the committee to handle it somewhat differently: predictions are based on a combination of specific research findings and general knowledge about probable requirements for licensure.

To identify an appropriate vaccine target population, the committee considered the age distribution of a disease (particularly of those conditions considered most desirable to avoid); the relative risk of illness in various population subgroups; and accessibility to the health care system.

Predictions on Vaccine Development

Predictions on vaccine development reflect an attempt to foresee events between the present (mid-1984) and the time at which vaccine licensure might occur. Predictions are based solely on technical feasibility and not on judgments about the desirability of particular courses of action; no distinction has been made between public and private sector resources used in development.

Probability of Successful Development

The likelihood of bringing a specific vaccine to licensure within the time allotted, and with the predicted efficacy and other characteristics, is described as the probability of successful development. This probability is based on the state of current research, the complexity of the problem (e.g., the number of known serologic types), and characteristics of the natural immune response.

Cost of Development

The estimate given for the cost of development includes all future costs needed to bring the vaccine to licensure, irrespective of the source of funds. Factors considered in estimating this amount were the current state of vaccine development, the complexity of the problem (e.g., difficulties encountered in culturing the pathogen), the availability of animal models, the number of alternatives to be tested in human clinical trials (e.g., in the instance of gonorrhea), and possible difficulties in conducting clinical trials or establishing efficacy in subsets of the target population.

Time to Licensure

The time to licensure is defined as the earliest time that a vaccine could be licensed if all developmental stages are completed without major delays. Factors considered in determining this time were similar to those used to estimate the cost of development.

Comments

The committee also considered interrelationships between the probability of success, the cost of development, and the time to licensure, for example, the extent to which extra funding could significantly reduce the time to licensure for a particular vaccine.

Predictions on Vaccine Characteristics

The committee based predictions on the characteristics of individual vaccines primarily on known characteristics of existing vaccines of similar type, e.g., live attenuated virus, polysaccharide, or subunit vaccine. These predictions also incorporate assumptions about likely licensure requirements.

Efficacy

The prediction of a vaccine's efficacy represents a population-based measure of protection* rather than a measure of antibody production in an individual. Factors considered in estimating the efficacy were the type of pathogen and number of serotypes involved in the disease, the nature of the vaccine candidate, and the extent of immunity from natural infection.

Adverse Reactions

Adverse side effects of a vaccine, especially those likely to occur at very low frequency, are extremely difficult to predict but can seriously affect acceptance. Predictions about side effects are based on the nature of the vaccine envisaged and its purity, and observations of similar existing vaccines. Predictions concerning the incidence of adverse reactions are expressed "per dose" rather than "per vaccinee."

$$\text{Efficacy} = \frac{\text{Rate of Illness in Unvaccinated Population} - \text{Rate of Illness in Vaccinated Population}}{\text{Rate of Illness in Unvaccinated Population}}$$

Production Technology, Delivery Requirements, and Cost/Dose

The technical difficulty of producing a vaccine and delivery (storage) requirements both affect vaccine cost. The committee based predictions in these areas on the nature of each vaccine candidate and on requirements for existing similar vaccines. Production technology and delivery requirements also affect the cost per dose, which, in turn, may affect vaccine acceptance.

Number of Doses and Route of Administration

The number of doses necessary to achieve the predicted protective efficacy of a vaccine and the route of administration also may affect vaccine acceptance. Predictions on these characteristics are based largely on the nature (including the probable antigenicity) of each vaccine candidate.

Conclusions

The predictions in Table 5.1 resulted from extensive deliberations by the full committee on estimates made by a subgroup, with suggested revisions from a broad spectrum of outside consultants. They were designed to reflect relative differences in the prospects of development of vaccine candidates; they are not expected to be precise descriptions of future events. Efforts to make predictions about vaccine development are complicated by many factors, including the rapid pace of new advances in biotechnology.

Although the outcome of scientific investigations cannot be predicted, the committee believes that the estimates and probabilities presented in Table 5.1 are reasonable, because the investigations on which they are based lie more in the realm of development than basic research. The factors considered in arriving at each prediction have been stated in as much detail as possible, in the belief that regular reappraisal of these factors is essential. The flexible nature of the model described in this report makes it easy to substitute alternative or updated predictions as they become available.

6

Assessing the Likely Utilization of New Vaccines

The expected health benefits to be derived from the development of a particular vaccine depend not only on the number of potential recipients of the vaccine (i.e., the target population), but also on the proportion of the target population who will actually receive it. This chapter describes the method used to arrive at an estimate of this proportion for each vaccine candidate.

To predict in advance the extent to which a vaccine candidate would be utilized is a difficult task, because vaccine utilization depends on many interrelated and complex factors. These factors include the following:

- vaccine availability
- the effects of statutory interventions such as school or day-care immunization requirements
- characteristics of the target population, including its access to health care providers and the ease with which its members can be identified by the health care system (in turn, dependent on size, composition, age, and socioeconomic status of the target population)
- characteristics of the vaccine affecting provider utilization (route of administration, storage conditions, shelf-life, cost of delivery, and special procedures required prior to or during vaccination)
- characteristics of the vaccine affecting patient acceptance (number of doses, route of administration, and cost)
- provider attitudes toward the vaccine, which are affected by perceptions of efficacy, safety, liability, ease of administration, profitability, professional consensus, and patient need or demand
- target population attitudes toward the vaccine, which are influenced by perceptions of the likelihood of contracting the disease, its severity if contracted, and the vaccine's efficacy and safety.

These factors affect each other in ways that are not fully understood or quantifiable. To develop a method of predicting the likely utilization of new vaccines, the committee chose to consider three distinct groups of factors, namely, those influencing vaccine availability, lay attitudes, and provider attitudes.

Vaccine Availability

Utilization of a licensed vaccine depends on the willingness of a pharmaceutical company or other entity to undertake its manufacture and on the company's ability to produce the vaccine in sufficient quantities to meet the demand. Factors influencing a pharmaceutical company's willingness to manufacture a vaccine include:

- profitability in public or private sale, which is affected by market size and composition, public health initiatives, patentability or status as sole supplier, and provider and lay acceptance
- legal concerns, particularly costs associated with vaccine injury compensation liability
- technical difficulty of production
- humanitarian/public relations issues.

The committee felt that it did not have sufficient information to include these factors in calculations of the expected benefits of new vaccines,* so it was decided to assume that any licensed vaccine would be available in quantities sufficient to meet the demand.

Statutory Interventions

The high levels of immunization achieved in the U.S. for the seven major pediatric vaccines currently available (measles, mumps, rubella, diphtheria, pertussis, tetanus, and polio) are due in large part to the existence of state laws requiring evidence of immunization for school entry.

The process of predicting possible changes in such laws and the effects such changes might have on utilization of new vaccines is complicated because:

- many different legislative bodies are involved
- it is not possible to predict how state legislatures will respond (with or without federal pressure) to encouragement to incorporate requirements for new vaccines into existing legislation
- requirements for new vaccines probably will not gain acceptance until a medical consensus has developed on the desirability of such action
- the speed with which such a consensus could develop might be affected by federal promotional campaigns, the likelihood of which would depend on characteristics of the licensed vaccine and on unpredictable political and funding considerations

* The Committee on Public-Private Sector Relations in Vaccine Innovation, Institute of Medicine, will soon make recommendations aimed at encouraging public-private sector collaboration in development and manufacture of vaccines, particularly those of low commercial potential.

- the attitude of legislatures toward requirements for additional vaccinations for school entry will be affected by efforts to improve current vaccines, particularly to eliminate the side effects of the pertussis vaccine.

The committee recognized that considerable uncertainty would be associated with the majority of these topics and therefore chose to address only the question of voluntary acceptance of the new vaccines, except in the case of an improved pertussis vaccine. The committee believes that use of the pertussis vaccine would continue to be mandated, and that the use rate of the new vaccine would be as high as that observed for the current vaccine. The general benefits that would result from the availability of such a vaccine are discussed further in Chapter 8.

Determinants of Lay and Provider Attitudes Toward New Vaccines

To develop a theoretical basis for predicting vaccine utilization, the committee adapted basic concepts from the "health belief model" (HBM), a social-psychological model of health-related decision making developed by psychologists working at the U.S. Public Health Service in the early 1950s (Becker, 1974). Questions abound concerning the validity of the HBM as a predictive tool, but it offers an appropriate conceptual framework for studying public immunization behavior. A description of the methods used by the committee to predict vaccine utilization follows a brief review of the health belief model.

The Health Belief Model

As it was originally conceived, the health belief model hypothesized that persons generally will not take preventive health actions unless they possess minimal levels of related health motivation and knowledge, view themselves as potentially vulnerable to the disease, view the condition as threatening, are convinced of the efficacy of intervention, and see few difficulties in taking the recommended actions.

More specifically, the HBM contains the following major elements (see Figure 6.1): (1) the individual's subjective state of readiness to take action, which is determined by both perceptions of the likelihood of susceptibility to the particular illness and perceptions of the probable severity of the consequences (organic and social) of contracting the disease; (2) the individual's evaluation of the feasibility and efficacy of the advocated health behavior (i.e., an estimate of the action's potential benefits in reducing susceptibility, severity, or both), weighed against perceptions of physical, psychological, financial, and other barriers involved in the proposed action; and (3) the occurrence of one or more cues to action to stimulate conscious or semiconscious feelings about the disease threat or about the recommended action.

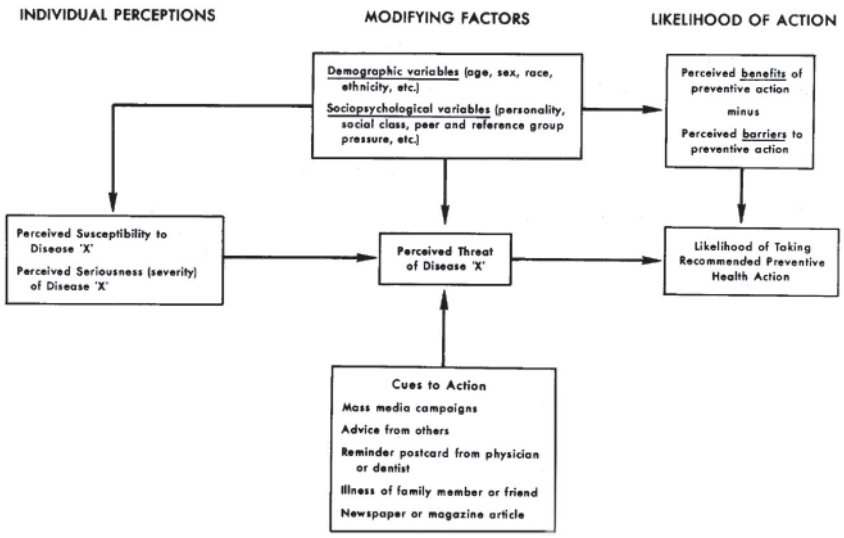

FIGURE 6.1 Variables and relationships in the health belief model.
Source: Reprinted, with permission, from Becker et al. (1977a), Selected psychosocial models and correlates of individual health-related behaviors, Medical Care (supplement), 15(5):27–46.

Cues to action may be either internal (e.g., symptoms) or external (e.g., mass media or interpersonal communications). Although it is assumed that diverse demographic and sociopsychological variables may, in any given instance, influence an individual's health-related attitudes and beliefs, these variables are not thought to be directcauses of health action (Becker and Maiman, 1980).

Table 6.1 summarizes findings from several studies that have examined one or more of the HBM elements as determinants of vaccine-acceptance behavior. These findings indicate that factors included in the HBM play a significant role in decisions about vaccination. They suggest that efforts to maximize public participation in immunization programs should begin with a survey of the intended vaccine recipients to obtain information about their HBM-related perceptions. If a problem is noted, those promoting the vaccine can develop and implement a campaign that addresses and modifies the perceptions most likely to act as obstacles.

In some cases, lay perception of a vaccine's safety may be the most important obstacle to its acceptance (e.g., concern about the occurrence of Guillain-Barré syndrome interfered with the swine influenza vaccine program). In other instances, the difficulty may be a low perception of the severity of the disease should it be contracted.

TABLE 6.1 Summary of Studies Using One or More Health Belief Model Variables to Explain Degree of public Acceptance of Recommendations to Obtain Vaccination

Investigators	Recommended Vaccination	Susceptibility	Severity	Benefits	Barriers
Rosenstock et al. (1959)	Polio	+	+	+	+
Leventhal et al. (1960)	Influenza	+	+	n.m.[a]	n.m.
Becker et al. (1977c)	Well-child clinic visits (immunizations)	+	+	+	+
Opinion Research Corporation (1978)	7-13 diseases (vaccines)	+	+	+	+
Aho (1979)	Swine flu	?[b]	?	+	+
Rundall and Wheeler (1979)	Swine flu	+	+	+	+
Cummings et al. (1979)	Swine flu	+	+	+	n.s.[c]
Larson et al. (1982)	Influenza	+	+	+	+

an.m.=not measured.
bAssessment unclear.
cn.s.=not significant.

This has occurred with measles and influenza. There is also evidence supporting the important role played by the provider's recommendation (Cummings et al., 1979).

King (1982) has discussed two difficulties in HBM research: (1) many HBM studies have employed retrospective designs, thus limiting their predictive value; and (2) few data exist concerning the origins or determinants of the beliefs themselves. However, a recent review of HBM research has identified 19 prospective studies with generally favorable results (Janz and Becker, in press). The paucity of information regarding the belief-formation process is a problem more relevant to the planning of educational interventions than to the use of the HBM to predict public acceptance of vaccines. Although other models of health-related behavior are available (Cummings et al., 1980), the HBM has received by far the greatest empirical attention and support (both in general and with particular reference to vaccine acceptance).

Provider Acceptance

The question of whether or not a provider will "accept" a new vaccine fits logically within the framework provided by literature on the adoption and diffusion of medical innovations in the health profession (Greer, 1977). Researchers in this area generally have

posited that three classes of variables are important: (1) characteristics of the adopters (in this case, both the providers and their patients); (2) characteristics of the innovation (the vaccine); and (3) characteristics of the "setting" into which the innovation is introduced (e.g., the norms and values of a population or population subgroup or the norms and policies of a health care delivery organization [Becker, 1970a]).

Investigations show that the diffusion of many new medical technologies depends on their successful adoption by "opinion leaders" in the relevant medical community. Compared with their colleagues, opinion leaders tend to be younger, to hold more advanced degrees, to be more active in national health and medical organizations, to be more interested in publishing in scientific journals, to be more likely to read and be influenced by research reports in scientific journals (they rate them as their primary source of reliable information), and to be more aware of the latest advances in their areas of specialization. These opinion leaders influence their colleagues, who use them as a primary source of credible information and advice—this process then continues as a multi-tiered flow of influence.

These findings suggest that if one wishes to increase the likelihood or rate of acceptance of a new vaccine by health care providers, efforts at persuasion should be concentrated on those physicians and other providers who exercise the relevant opinion leadership. Scarce influence resources should not be spread evenly across all providers (Becker, 1970a).

Innovations themselves possess characteristics that have been shown to influence their potential for adoption by providers (Becker, 1970b). These include:

- relative advantage: the degree to which the innovation is perceived as being better than the idea it supersedes (Is the new vaccine superior to what was previously available to prevent or treat the disease in terms of efficaciousness, safety, costs, ease of administration, and other factors?)
- compatibility: the degree to which the innovation "fits in" with existing values, procedures, past experiences, etc. (Does the vaccine require new techniques of administration, new personnel, or interactions with groups of clients not familiar with vaccination processes?)
- complexity: the degree to which the innovation is seen as relatively difficult to understand and use (Is the new vaccine's mode of operation, mode of administration, or follow-up schedule simple or complex?)
- suitability for pilot studies: the degree to which the innovation can be implemented and assessed on a limited basis (Does the new vaccine require large commitments of resources?)
- observability: the degree to which the results of adopting the innovation are visible to others (How much time must elapse before the provider is able to estimate the benefits and adverse effects associated with prescription of the new vaccine in a group of patients?)

- risk: the degree to which adopting the innovation poses danger to the adopter (Can the new vaccine cause serious injury to some recipients? Is the provider who prescribes the vaccine earlier than his peers likely to be admired or scorned? Will the provider be protected against possible litigation?)

Riddiough et al. (1981, p. 534) list several factors that may influence physicians' vaccine-prescribing behavior and that seem to fit within one or more of the innovation characteristics described above:

- attitudes and knowledge about the targeted disease
- attitudes and knowledge about the safety and efficacy of vaccines
- perceptions about a patient's need for vaccination
- consideration of revenue generated by administering vaccines
- consideration of the potential liability for vaccine-related injury.

The authors suggest that concern about possible adverse reactions and concomitant legal action are the greatest obstacles to physician acceptance. They add that

> in assessing a patient's need for a particular vaccine, physicians may consider (a) the likelihood of the patient's being exposed to a given disease-producing organism; (b) the patient's vulnerability to the disease after being exposed to the organism; and (c) the extent to which contracting the disease will disrupt the patient's life. (Riddiough et al., 1981:534)

In other words, it is possible to describe a health belief model for physicians with dimensions parallel to those of the patient (although the physician's perceptions may be quite different from those of the patient).

When attempting to influence the adoption and diffusion of a new vaccine, it is extremely important to obtain information from the potential adopters about how they rate the innovation (Becker, 1970b). If these ratings indicate that one or more of the vaccine's characteristics present obstacles, at least two courses of action are possible: (1) attempt to persuade the potential adopters that their perceptions about those characteristics are wrong; or (2) attempt to alter the real (or perceived) characteristics of the vaccine to overcome the adopters' objections (Becker, 1970a).

Provider prescribing behavior is influenced by the setting in which the behavior takes place (e.g., the structure of the health care delivery organization, group versus solo practice [Becker et al., 1972]). Some communities or population subgroups hold beliefs, attitudes, and norms that oppose vaccination in general, or that oppose a particular vaccine. Any campaign to introduce a new vaccine should be based on a prior assessment of the relevant setting, taking into account important sources of opposition.

Predicting Utilization of New Vaccines

Committee efforts to develop a method of predicting likely lay and provider attitudes toward new vaccines were focused on two criteria. The technique had to allow conversion of attitudes into anticipated use rates by the target population, as well as permit ranking of vaccines relative to each other. The first requirement was imposed by the need for such an estimate in the calculation of relative benefits to be expected from the new vaccines.

The method proposed for predicting the likely acceptance of new vaccines is based conceptually on the health belief model. This approach structures the process of assessing attitudes in a fashion that, compared with other methods discussed below, more explicitly defines the factors considered and the judgments made on them. It also permits identification of the major determinants of behavior for each vaccine.

In some situations, attitudes toward new vaccines might be modified by educational programs designed to alter mistaken provider or lay perceptions. The committee decided, however, to adopt the assumption that no major educational campaigns would be initiated for these new products. This assumption was made solely to simplify the process of making predictions and should not be taken as an indication that such campaigns would not benefit public health. Moreover, the analytical model permits assessment of the likely effects of such campaigns on vaccine utilization, conditional on their success at altering the critical barriers.

Polling a relevant new vaccine target population and the providers who serve it probably would be the most accurate method of ascertaining likely attitudes. Although time and budgetary constraints precluded this option for the present study, the committee suggests that the National Institute of Allergy and infectious Diseases (NIAID), in collaboration with the Centers for Disease Control, consider methods for evaluating likely provider and lay attitudes based on polls in target populations.

If opinions are solicited from lay populations on likely vaccine acceptance, care should be taken to elicit information in a fashion comprehensible to responders, without informing them to an extent that would make them atypical of the group they are supposed to represent. For example, lay attitudes toward a vaccine for cytomegalovirus infection could be sought by describing it as a vaccine against a virus that is thought to be a major cause of congenital mental retardation.

Scoring of Determinants of Acceptance by Patients and Providers

To provide some indication of likely acceptance, the committee chose to act as surrogates for the various vaccine target populations and provider groups. Each candidate for accelerated development was scored twice—once from the assumed perspective of the appropriate lay group, and once from the assumed perspective of the appropriate provider group—on each of the four criteria shown to be of major importance in the health belief model:

- perception of risk of illness: a combination of the risk of exposure and the risk, if exposed, of experiencing clinical illness
- perception of disease severity: an aggregate of the severity of the typical disease, its complications and sequelae, and its medical, social, and personal economic effects
- perception of vaccination benefits: vaccine efficacy (for the lay perspective this encompasses willingness to accept provider recommendations)
- perception of barriers (disincentives) to vaccination: a combination of cost considerations, if applicable; safety, both in terms of mild, local adverse reactions and more severe consequences; and convenience of vaccination (number of doses and route of administration).

Issues considered in assigning scores in these categories differed depending on whether the lay or the provider perspective was being adopted. For example, larger potential profit from an expensive vaccine might be an ancillary benefit of vaccination from a provider perspective, but vaccine cost might act as a barrier to recipients.

It is possible that new vaccines might be combined with each other or with existing vaccines. If a new vaccine were combined with an existing vaccine that had a high utilization rate, the utilization rate of the new vaccine might be favorably affected. The likelihood of such an event is difficult to predict, however, so the assignment of utilization scores was made with the assumption that delivery of new vaccines would not be as part of a combination. (The importance of this assumption in determining the final rankings can be tested by performing a sensitivity analysis with respect to utilization rate; see Chapter 9.)

For each vaccine, four lay scores and four provider scores were assigned, one each for risk, severity, benefits, and barriers. Scores ran from zero to ten, where ten represented the highest perceived risk, severity, benefits, or barriers, and zero represented the absence of each of these determinants. A subcommittee consisting of persons with experience in providing primary health care or knowledge about the factors affecting lay or provider behavior supplied these scores, following extensive briefings from those knowledgeable about the characteristics of the prospective vaccine and the target disease. Scores were subjected to a number of rounds of review and compared in an effort to achieve consistency.

Admittedly, this process is subjective, relying on the informed judgment of experts. The committee knows of no objective basis for predicting utilization without recourse to expert opinion; this approach is the best available under the circumstances. The alternative—to ignore differences among vaccines with regard to their likely utilization by assuming equal utilization—would be less responsible because it would ignore important issues that should be considered in setting priorities for vaccine development.

Scores assigned in the various HBM categories are shown in Tables 6.2 and 6.3 for lay and provider attitudes, respectively. Discussion of factors that influenced these scores on specific pathogens are in the "Anticipated Vaccine Acceptance" sections of Appendixes C through P.

TABLE 6.2 Lay Acceptance Scores for New Vaccines

Pathogen	Vaccine Envisaged	Target Population	Risk	Severity	Benefits	Barriers	(10-Barriers)	Total Score: Weighted Additive	Total Score: Weighted Multiplicative
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	2	2	2	8	2	-14	256
Cytomegalovirus	Attenuated live virus	Seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas	9	9	9	2	8	39	30,233,088
		Nonpregnant adolescent females	1	9	9	7	3	16	177,147
	Glycoprotein produced by recombinant DNA technology	All children	1	6	7	5	5	12	220,500
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	2	9	8	4	6	24	2,239,488
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	1	5	8	4	6	15	345,600
	Subunit	Susceptibles of all ages (routine for children)	1	5	8	6	4	9	102,400
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	8	7	9	4	6	28	6,858,432
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and other susceptibles	4	7	7	6	4	14	614,656
	Attenuated live virus	Children up to age 12 and other susceptibles	4	7	7	6	4	14	614,656

Herpesvirus varicellae	Attenuated live virus	Recipients of organ and bone marrow transplants and persons under age 25 with leukemias and lymphomas	6	10	9	1	9	41	35,429,400
		Normal susceptibles, routine for children (booster for adults)	9	3	9	3	7	24	2,250,423
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	7	5	4	5	5	10	350,000
	Attenuated live virus	High-risk population as currently defined (see Appendix K)	7	5	4	4	6	13	604,800
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	3	3	7	6	4	5	84,672
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	1	8	7	4	6	19	677,376
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	4	8	5	6	4	12	409,600
	Attenuated live virus	Infants	4	8	5	4	6	18	1,382,400
Rotavirus	Attenuated live bovine virus	Infants	3	5	5	3	7	14	643,125
	Attenuated live human or reassortment virus	Infants	3	5	5	3	7	14	643,125
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	4	4	9	8	2	6	41,472

TABLE 6.3 Provider Acceptance Scores for New Vaccines

Pathogen	Vaccine Envisaged	Target Population	Risk	Severity	Benefits	Barriers	(10-Barriers)	Total Score: Weighted Additive	Total Score: Weighted Multiplicative
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	5	5	7	5	5	14	765,625
Cytomegalovirus	Attenuated live virus	Seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas	10	10	7	3	7	35	16,807,000
		Nonpregnant adolescent females	2	8	7	8	2	8	50,176
	Glycoprotein produced by recombinant DNA technology	All children	8	8	7	3	7	29	8,605,184
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	5	9	8	3	7	30	8,890,560
Hepatitis A virus	Attenuated live virus	Susceptibles of all age (routine for children)	2	2	9	3	7	15	222,264
	Subunit	Susceptibles of all age (routine for children)	2	2	9	5	5	9	81,000
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	8	8	9	3	7	33	14,224,896
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and other susceptibles	5	5	6	3	7	18	1,543,500
	Attenuated live virus	Children up to age 12 and other susceptibles	5	5	6	5	5	12	562,500

Herpesvirus varicellae	Attenuated live virus	Recipients of organ and bone marrow transplants and persons under age 25 with leukemias and lymphomas	8	8	6	1	9	33	13,436,928
		Normal susceptibles, routine for children (booster for adults)	8	2	9	4	6	18	559,872
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	5	5	5	3	7	16	1,071,875
	Attenuated live virus	High-risk population as currently defined (see Appendix K)	5	5	5	3	7	16	1,071,875
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	3	4	8	4	6	15	663,552
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	6	8	6	3	7	25	4,741,632
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	6	8	6	5	5	19	1,728,000
	Attenuated live virus	Infants	6	8	7	5	5	21	2,352,000
Rotavirus	Attenuated live bovine virus	Infants	3	3	7	2	8	17	677,376
	Attenuated live human or reassortment virus	Infants	3	3	7	2	8	17	677,376
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	6	8	8	6	4	20	1,572,864

Aggregation of Component Scores into an Overall Score

Research on how individuals formulate overall opinions on health protection measures indicates that the various components of the HBM differ in their degree of influence on final attitudes. Thus, the four component scores must be weighted according to their expected leverage on provider or lay behavior. The weights used in this analysis were as follows: risk (1); severity (2); benefits (2); barriers (“3). The negative sign for the barriers weight reflects the fact that a high score is less conducive to acceptance (Becker, 1974; Becker et al., 1977a,b,c).

Given these weights, both weighted additive and weighted multiplicative methods of combining scores are plausible. A weighted additive method would treat each factor as independent; a weighted multiplicative method might allow for the fact that two or more factors have an interactive effect on the overall likelihood of acceptance. The two methods considered for combining categories within the lay or provider domain were:

Weighted Additive Method

```
Total Score = (Risk Score) + (2 x Severity Score) +
              (2 x Benefits Score) - (3 x Barriers Score)
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Weighted Multiplicative Method

Weighted Multiplicative Method

$$\text{Total Score} = (\text{Risk Score})(\text{Severity Score})^2(\text{Benefits Score})^2(10-\text{Barriers Score})^3$$

As shown in Tables 6.2 and 6.3, the two methods give similar results, at least in terms of the ranking of the vaccines with respect to utilization. However, two theoretical considerations favor the multiplicative combination. First, the various HBM dimensions are actually subjective estimates or probabilities of some occurrence or outcome (e.g., the perceived likelihood of contracting a condition), and therefore the overall HBM estimate is appropriately the product of the individual-component probabilities. Second, it would not make conceptual sense to construct an HBM formula that would yield some predictive probability for a situation in which the estimate for any given component was zero (e.g., in the case of an individual who felt there was no possibility at all of contracting the condition). An additive model would still yield an overall HBM estimate by summing the values for the remaining model components; however, a multiplicative model would yield an overall estimate of zero. (The multiplicative approach is illustrated in Haefner and Kirscht, 1970.) Both methods have been carried forward to illustrate that they ultimately yield similar results.

Aggregation of Lay and Provider Weighted Scores

The additive and multiplicative combination of total lay and provider scores (from Tables 6.2 and 6.3) is shown in Table 6.4. Again, theoretical considerations favor the multiplicative score

Table 6.4 Combination of Scores for Factors Affecting Voluntary Vaccine Acceptance

			Total Scores				Combined Scores			
			Lay		Provider		Weighted Additive Scores		Weighted Multiplicative Scores	
Pathogen	Vaccine Envisaged	Target Population	Weighted Additive	Weighted Multiplicative ($\times 10^{-6}$)	Weighted Additive	Weighted Multiplicative ($\times 10^{-6}$)	Additive	Multiplicative	Additive ($\times 10^{-6}$)	Multiplicative ($\times 10^{-12}$)
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	-14	0.0003	14	0.77	0	-196	0.7703	0.000231
Cytomegalovirus	Attenuated live virus	Seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas	39	30.23	35	16.8	74	1365	47.03	507.864
		Nonpregnant adolescent females	16	0.18	8	0.05	24	128	0.23	0.009
	Glycoprotein produced by recombinant DNA technology	All children	12	0.22	29	8.6	41	348	8.82	1.892
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	24	2.23	30	8.9	54	720	11.13	19.847
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	15	0.34	15	0.22	30	225	0.56	0.0748
	Subunit	Susceptibles of all ages (routine for children)	9	0.1	9	0.081	18	81	0.181	0.0081
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	28	6.9	33	14.22	61	924	21.12	98.118

TABLE 6.4 (Continued)

Pathogen	Vaccine Envisaged	Target Population	Total Scores: Lay: Weighted Additive	Total Scores: Lay: Weighted Multiplicative ($\times 10^{-6}$)	Total Scores: Provider: Weighted Additive	Total Scores: Provider: Weighted Multiplicative ($\times 10^{-6}$)	Combined Scores: Weighted Additive Scores: Additive	Combined Scores: Weighted Additive Scores: Multiplicative	Combined Scores: Weighted Multiplicative Scores: Additive ($\times 10^{-6}$)	Combined Scores: Weighted Multiplicative Scores: Multiplicative ($\times 10^{-12}$)
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and other susceptibles	14	0.61	18	1.54	32	252	2.15	0.9394
	Attenuated live virus	Children up to age 12 and other susceptibles	14	0.61	12	0.56	26	168	1.17	0.3416
Herpesvirus varicellae	Attenuated live virus	Recipients of organ and bone marrow transplants and persons under age 25 with leukemias and lymphomas	41	35.42	33	13.43	74	1353	48.85	475.6906
		Normal susceptibles, routine for children (booster for adults)	24	2.25	18	0.56	42	432	2.81	1.26
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	10	0.35	16	1.07	26	160	1.42	0.3745
	Attenuated live virus	High-risk population as currently defined (see Appendix K)	13	0.6	16	1.07	29	208	1.67	0.642
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	5	0.085	15	0.66	20	75	0.745	0.0561
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	19	0.68	25	4.74	44	475	5.42	3.2232
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	12	0.41	19	1.7	31	228	2.11	0.697
	Attenuated live virus	Infants	18	1.38	21	2.3	39	378	3.68	3.174
Rotavirus	Attenuated live bovine virus	Infants	14	0.64	17	0.68	31	238	1.32	0.4352
	Attenuated live human or reassortment virus	Infants	14	0.64	17	0.68	31	238	1.32	0.4352
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	6	0.041	20	1.57	26	120	1.611	0.06437

because a vaccine must be accepted by both provider and patient to be utilized. Thus, even the highest degree of acceptance by the patient is cancelled by near zero acceptance by the provider, and vice versa. This logic supports the multiplicative form of aggregation of provider and lay scores. All methods of aggregation have been carried forward, however, to illustrate that they ultimately give similar results. Data shown in Table 6.4 could be used to generate a ranking of vaccine candidates on the basis of acceptance scores.

Translation of Acceptance Scores into Anticipated Use Rates

To calculate benefits that might accrue from developing each vaccine candidate, it is necessary to calculate an anticipated use rate, it is not obvious, however, how the acceptance "scores" (Table 6.4) map onto the range of utilization "rates" from 0 to 100 percent. Two steps were followed to derive such a mapping.

First, to relate acceptance scores to likely actual use rates, the HBM scoring system was applied "retrospectively" to the introduction of certain vaccines now in use: the influenza, pneumococcal,* and pertussis vaccines. Relatively reliable information was available on voluntary use rates for these vaccines. Pertussis had a utilization rate of approximately 85 percent prior to the legal requirement of vaccination for school entry; influenza, 20 percent; and pneumococcal, 10 percent within the high-risk target populations (Orenstein, personal communication, 1983). HBM scores were estimated retrospectively for these vaccines, adopting what were thought to be the perspectives of appropriate lay and provider groups at a time prior to the introduction of the vaccines. These scores are shown in Tables 6.5 and 6.6.

Next, a logistic regression was performed to define the mathematical relationship between the "retrospective" acceptance scores in our HBM model and the observed use rates. The data points were the use rate-combined score combinations for pertussis, influenza, and pneumococcal vaccines shown in Table 6.6.

The regression equations were as follows, where P=use rate, and S=acceptance score:

$$\ln\left(\frac{p}{1-p}\right) = a + bS + \text{error}$$ (Case A: lay and provider weighted additive scores combined in additive fashion)

$$\ln\left(\frac{p}{1-p}\right) = a + b\sqrt{S} + \text{error}$$ (Case B: lay and provider weighted additive scores combined in multiplicative fashion)

$$\ln\left(\frac{p}{1-p}\right) = a + b(\ln S) + \text{error}$$ (Cases C&D: weighted multiplicative scores combined in either additive or multiplicative fashion)

*Streptococcus pneumoniae.

TABLE 6.5 Retrospective Estimation of Lay and Physician Attitudes Prevailing Prior to the Introduction of Three Vaccines

Pathogen	Risk Score	Severity Score	Benefits Score	Barriers Score	10-Barriers Score	Total Score	
						Weighted Additive	Weighted Multiplicative
Lay Attitudes							
Bordetella pertussis	6	7	9	4	6	26	5.14×10^6
Influenza viruses	7	5	3	5	5	8	0.20×10^6
Streptococcus pneumoniae	2	4	4	3	7	9	0.18×10^6
Provider Attitudes							
Bordetella pertussis	6	8	9	3	7	31	10.67×10^6
Influenza viruses	5	5	4	3	7	14	0.69×10^6
Streptococcus pneumoniae	2	7	3	2	8	16	0.45×10^6

TABLE 6.6 Combination of Scores for Factors Affecting Voluntary Acceptance of Vaccines From Retrospective Estimation for Three Vaccines Now in Use

		Total Scores				Combined Scores			
		Lay		Provider		Weighted Additive Scores		Weighted Multiplicative Scores	
Pathogen	Observed Vaccine Use Rate (percent)	Weighted Additive	Weighted Multiplicative ($\times 10^{-6}$)	Weighted Additive	Weighted Multiplicative ($\times 10^{-6}$)	Additive	Multiplicative	Additive ($\times 10^{-6}$)	Multiplicative ($\times 10^{-12}$)
Bordetella pertussis	85	26	5.14	31	10.67	57	806	15.81	54.84
Influenza viruses	20	8	0.20	14	0.69	22	112	0.89	0.14
Streptococcus pneumoniae	10	9	0.18	16	0.45	25	144	0.63	0.08

The logistic formulation ensures that the use rate will fall between 0.0 and 1.0 (i.e., between 0 and 100 percent).

The scores for pneumococcal, influenza, and pertussis vaccines and their voluntary use rates were used to obtain the following regression equations:

Case A (additive/additive combination)	$\ln\left(\frac{p}{1-p}\right) = -4.1876 + 0.1030(S)$
Case B (additive/multiplicative combination)	$\ln\left(\frac{p}{1-p}\right) = -4.0527 + 0.2022\sqrt{S}$
Case C (multiplicative/additive combination)	$\ln\left(\frac{p}{1-p}\right) = -1.4656 + 1.1676(\ln S)$
Case D (multiplicative/multiplicative combination)	$\ln\left(\frac{p}{1-p}\right) = -0.5283 + 0.5695(\ln S)$

The anticipated use rate for each new vaccine was obtained by substituting its score (Table 6.4) into the appropriate regression equation, and solving for the use rate, p. The results are shown in Table 6.7.

Alternatives to the HBM Approach for Predicting Anticipated Use Rates for New Vaccines

The possibility of deriving anticipated use rates for new vaccines by adjusting the observed use rate of an existing comparable vaccine was evaluated. For example, the current use rate for MMR or DPT could be adjusted and applied to new pediatric vaccines. This approach was considered less satisfactory than the HBM for several reasons. Factors considered in adjusting the observed rate and their weights would be identified less explicitly, making assessment of changes in them more difficult. In addition, for certain new vaccines appropriate comparable vaccines do not exist. Although this approach was not adopted, it could be used to double check the calculated HBM anticipated use rates of selected new vaccines that do resemble existing vaccines.

Limitations of the Approach

Application of the system to recently developed vaccines, such as the mumps vaccine, may reveal possible limitations of the model as a predictive tool. For example, unexpected controversy may depress use rates, while unforeseeable events (e.g., the opportunity to combine the mumps vaccine with measles/rubella vaccine) may increase them.

TABLE 6.7 Predictions of Anticipated Voluntary Vaccine Use Rates

Pathogen	Vaccine Envisaged	Target Population	Score Combination Method			
			Additive: Additive	Additive: Multiplicative	Multiplicative: Additive	Multiplicative: Multiplicative
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	0.01	0.001	0.14	0.005
Cytomegalovirus	Attenuated live virus	Seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas	0.96	0.97	0.95	0.95
		Nonpregnant adolescent females	0.15	0.15	0.04	0.04
	Glycoprotein produced by recombinant DNA technology	All children	0.51	0.43	0.74	0.46
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	0.80	0.80	0.79	0.76
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	0.25	0.27	0.1	0.12
	Subunit	Susceptibles of all ages (routine for children)	0.08	0.10	0.03	0.04
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	0.89	0.89	0.89	0.89
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	0.29	0.30	0.36	0.36
	Attenuated live virus	Children up to age 12 and older susceptibles	0.18	0.19	0.21	0.24

TABLE 6.7 (Continued)

Pathogen	Vaccine Envisaged	Target Population	Score Combination Method: Additive: Additive	Additive: Multiplicative	Multiplicative: Additive	Multiplicative: Multiplicative
Herpesvirus varicellae	Attenuated live virus	Recipients of organ and bone marrow transplants and persons under age 25 with leukemias and lymphomas	0.97	0.98	0.95	0.95
		Normal susceptibles, routine for children (booster for adults)	0.53	0.54	0.43	0.4
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	0.18	0.18	0.25	0.25[a]
	Attenuated live virus	High-risk population as currently defined (see Appendix K)	0.23	0.24	0.29	0.31[a]
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	0.11	0.09	0.14	0.1
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	0.59	0.59	0.62	0.53
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	0.27	0.27	0.35	0.32
	Attenuated live virus	Infants	0.46	0.47	0.51	0.53
Rotavirus	Attenuated live bovine virus	Infants	0.27	0.28	0.24	0.27
	Attenuated live human or reassortment virus	Infants	0.27	0.28	0.24	0.27
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	0.18	0.14	0.28	0.11

Note: Anticipated use rates are proportion of target population receiving vaccine.

[a] The score for the current influenza vaccine would translate into a use rate of 0.16 using the regression equation. Thus, the incremental change in vaccine use would be 0.09 for the subunit vaccine and 0.15 for the attenuated live virus vaccine.

Conclusions and Recommendations

Utilization of vaccines is dependent on availability, acceptance among lay and provider groups, and statutory interventions.

The committee believed that it did not have sufficient information to assess factors affecting manufacturers' willingness to produce licensed vaccines, the probability of legislative intervention, or the likelihood of federal promotional campaigns on behalf of a specific vaccine. Thus, the method developed to predict vaccine utilization assumes that licensed vaccines would be made in sufficient quantities to meet the demand, that use of these vaccines would not be mandated, and that no special campaigns would be launched to promote them. The technique also assumes that none of the new vaccines would be distributed as part of a vaccine combination.

The health belief model can be utilized to assess the likelihood that an individual (potential vaccine recipient or provider) will undertake preventive health actions. Retrospective application of the model to existing vaccines for which use rates have been recorded enables anticipated use rates to be predicted.

In addition, application of the model to new vaccines permits identification of the major determinants of behavior for each vaccine. This information can be used to begin alteration of mistaken provider or lay perceptions through campaigns designed to promote immunization, or to guide attempts to develop vaccine variants with more acceptable character istics.

Ideally, assessments of likely attitudes toward new vaccines employing the health belief model should use data from polls of the relevant vaccine target population and the health care providers serving it.

By acting as surrogates for specific vaccine target populations and provider groups, the committee assessed attitudes toward the vaccines that are candidates for accelerated development. Several combinations of lay and provider scores incorporating components of the health belief model are theoretically possible and plausible. In the committee's judgment, it is most reasonable to base predictions of use rates for new vaccines on observed voluntary rates and the multiplicative: multiplicative score combination method (column 4 of Table 6.7). Adoption of other plausible methods of score combination usually will result in similar predictions of likely vaccine use.

The committee suggests that NIAID consider the development of polling methods to determine likely attitudes toward new vaccines among target populations and vaccine providers. Methods could be developed to incorporate into the HBM the effects of legislative mandates, combinations of vaccines, and promotional campaigns. The practicality of combining desirable new vaccines of low predicted acceptance with existing vaccines that have high utilization rates should be assessed further.

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7

Calculation and Comparison of the Health Benefits and Costs Associated with Candidate Vaccines

This chapter presents the method used to calculate and compare the reductions in morbidity and mortality that could be produced by the 20 vaccine candidates evaluated in this report, and the costs associated with their development and use. The proposed method has two principal components: (a) calculation of values for the health benefits and costs that would occur at a time when the annual yield of such benefits has reached a steady state, and (b) adjustment of these values for factors such as the probability of successful development and the number of years required to achieve the steady state.

A central analysis is presented in this chapter. Sensitivity analyses involving some of the factors used in the base case are discussed in Chapter 9.

Procedures

The steps for calculating expected health benefits and morbidity cost reductions from the vaccine candidates are listed below and illustrated in Figures 7.1 and 7.2.

1. Estimation of vaccine preventable illness (VPI) for each vaccine candidate. This is defined as the number of cases, complications, sequelae, and deaths that could be prevented (in the steady state) by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.
2. Calculation of the direct (treatment) cost imposed by the VPI, using methods described in Chapter 4.
3. Calculation of vaccine preventable illness values for each vaccine. These values incorporate both VPI estimates and a factor expressing the undesirability of the conditions prevented by the vaccine. Infant mortality equivalence (IME) values, described in Chapter 4, are used to quantify these value judgments. The calculations are identical to those used to produce disease burden values. Two sets of IME values are employed throughout this report: one expresses a median of committee member perspectives and the other is an age-neutral perspective. The effects of adopting alternative

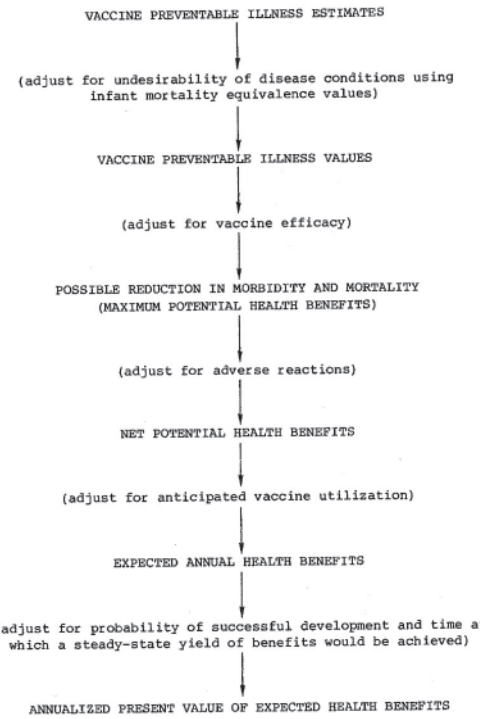

FIGURE 7.1 Calculation of expected health benefits.

perspectives in these calculations would be similar to that described in Chapter 4.

4. Calculation of the possible reduction in morbidity and mortality (PRMM) for each vaccine. These figures represent vaccine preventable illness values adjusted for the predicted efficacy of the vaccine. For diseases in which vaccine efficacy is expected to be the same for all conditions, calculation of PRMM simply involves multiplying the vaccine preventable illness values (one for each IME perspective) by the efficacy. If the vaccine is expected to have different efficacies for different conditions, the calculations are more complex. PRMM values must be calculated separately for each morbidity category/age group combination and then added together.

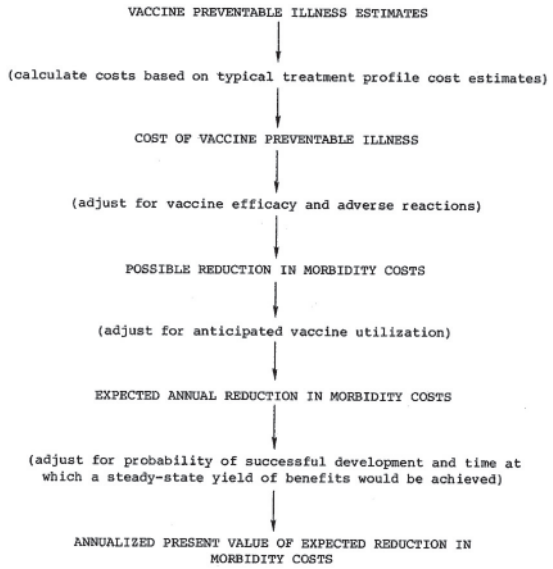

FIGURE 7.2 Calculation of expected reduction in morbidity costs.

5. Calculation of the vaccination program costs; as illustrated in Figure 7.3.
6. Estimation of the adverse effects of each vaccination program. The predicted incidence of adverse reactions, the annual number of potential new vaccinees, and the IME values for the types of adverse conditions predicted are used to calculate values representing the vaccine-induced morbidity and mortality (if any). The costs of vaccine-induced illness also are calculated—where necessary—by the procedures described in Chapter 4.
7. Calculation of the net potential health benefits. These values are PRMM figures adjusted for the adverse effects of a vaccination program.
8. Calculation of the expected annual health benefits. This step involves adjustment of net potential benefit values for anticipated vaccine utilization.
9. Calculation of the annualized present value of expected health benefits. These values represent an adjustment of the expected health benefits to take account of the probability of successful development

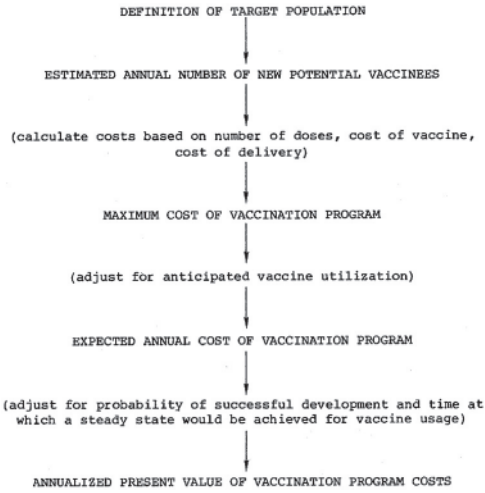

FIGURE 7.3 Calculation of vaccination program costs.

of the vaccine and the time at which a steady-state yield of benefits would be achieved.

10. Calculation of the annualized present value of expected reduction in morbidity costs; as illustrated in Figure 7.2. This procedure can also be applied to the costs of adverse effects calculated as noted under (6) above.
11. Calculation of the net costs associated with each vaccine. The net totals represent the reductions in morbidity costs (taking into account vaccine efficacy, utilization, probability of success, and time to steady-state yield of benefits, Figure 7.2), adjusted for the actual cost of the vaccination program (at the predicted utilization rate, Figure 7.3), the annualized cost of vaccine development (see Chapter 3), and, where necessary, the actual cost of adverse effects (i.e., at the predicted utilization rate).

A more detailed explanation of some elements used in the calculations and a discussion of certain assumptions adopted to simplify the process appear below.

Vaccine Characteristics

The vaccine characteristics used in this comparison are described in Chapter 5, Table 5.1. Detailed information on specific vaccines is included in Appendixes C through P.

Target Population

Target populations for the vaccines are described in the relevant appendixes and briefly outlined in Table 5.1. The number of new potential vaccine recipients entering the target population each year must be determined to calculate the number of adverse effects and the costs associated with each vaccination program. These calculations are based on the envisaged target population and the 1984 population projections (Bureau of the Census, 1984). Background information used to determine the number of new potential recipients of each vaccine is shown in Table 7.1.

Vaccine Preventable Illness

For each disease, estimates of vaccine preventable illness are derived from an examination of the distribution of the disease burden; the envisaged target population; the characteristics of the vaccine (e.g., the number of doses); the likely age of vaccine delivery; and for some diseases (e.g., hepatitis B and influenza), the proportion of the disease falling in the identified high-risk group.

Estimates of vaccine preventable illness for each disease are discussed and included in Appendixes C through P. These estimates, based on steady-state utilization, are derived from disease burden estimates judged to reasonably represent 1984 levels (see Chapter 4 and below).

Trends in Disease Burden and Population Numbers

Calculations of morbidity, mortality, and costs assume that the effects of trends in disease burden and population size (between 1984 and the achievement of steady-state benefits) would not be of sufficient magnitude to obscure differences between diseases. The effects of such trends could be examined, if desired, within the model proposed. These assumptions apply only to diseases under study and the current population projections: if other disease candidates are added to the list, the assumptions should be re-examined. Because of the trend towards greater numbers of individuals in the 25–59 years and 60 years and over age groups, the major effect of adopting these assumptions would be to somewhat underestimate the benefits of vaccines reducing disease in these age groups, assuming incidence rates remain constant.

Adverse Reactions

The maximum number of adverse reactions is calculated from the predicted incidence of adverse reactions (Table 5.1), assuming delivery of the required number of doses to the annual number of new potential vaccinees (Table 7.1). IME values appropriate for the conditions

TABLE 7.1 The Basis for Estimation of the Annual Number of New Potential Vaccines and the Delay in Vaccination Benefits

Pathogen	Vaccine Envisaged	Target Population	Individuals Entering Target Population [a]	Delay in Vaccination Benefits
Bordetella pertussis	Acellular	Infants	Birth cohort: 3,788,337	Probable age of vaccination (<1 year) to peak of disease (without vaccine ~3-4 years of age), i.e., 3 years
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	20 million reside in endemic area; age of vaccination likely to be ~15 years because disease incidence rises rapidly after that age (Fraser et al. 1979). Assuming 10% of residents are at high risk, i.e., 2 million, number of individuals entering target population is number of 14-year olds in this group, or 32,000 (1.6% of 2,000,000)	Probable age of vaccination (15 years) to midpoint of age range in which most disease occurs (25-75 years) i.e., ~35 years
Cytomegalovirus	Attenuated live virus	Seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas	See Appendix E: ~1408	CMV illness usually occurs within 2 years of onset of immunosuppression, i.e., ~1 year
		Nonpregnant adolescent females	Females, 14 years of age: 1,830,707	Probable age of vaccination (~14 years) to peak of birth rate (~24 years) (assumed to coincide with peak of congenital and perinatal CMV illness), i.e., ~10 years
	Glycoprotein produced by recombinant DNA technology	All children	Birth cohort: 3,788,337	Probable age of vaccination ~1-2 years to peak of birth rate (~24 years, assumed to coincide with peak of congenital and perinatal CMV illness), i.e., ~23 years
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	Birth cohort: 3,788,337	Probable age of vaccination (<1 year) to peak of most serious disease (~2-3 years), i.e., 2 years

TABLE 7.1 (Continued)

Pathogen	Vaccine Envisaged	Target Population	Individuals Entering Target Population [a]	Delay in Vaccination Benefits
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	Birth cohort: 3,788,337	Probable age of vaccination (~4-5 years) to peak of illness (20-29 years), i.e., ~20 years
	Subunit	Susceptibles of all ages (routine for children)		
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	Current estimate of the high-risk population is 8.7 million.[b] It is assumed that all individuals at high risk are in the 20-49 year age group, which numbers 104, 849, 663. The high risk population thus comprises 8.3% of this population. There are 4,199,218 individuals 20 years of age of whom 8.3% would be the number of potential new vaccinees, i.e., ~348,540	Probable age of vaccination in steady state (i.e., individuals ~20 years, entering high-risk group/target population) to a time intermediate between the peaks of acute (~20-29 years) and chronic illness (which occurs later in life) i.e., 15 years
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	Birth cohort: 3,788,337	Probable age of vaccination (1-3 years) to peak of genital illness (~20-25 years), i.e., 20 years
	Attenuated live virus	Children up to age 12 and older susceptibles	Birth cohort: 3,788,337	Probable age of vaccination (1-3 years) to peak of genital illness (~20-25 years), i.e., 20 years
Herpesvirus varicellae	Attenuated live virus	Recipients of organ and bone marrow transplants and persons under age 25 with lymphomas and leukemias	See Appendixes E and J: ~12,757	Varicella usually occurs within 2 years of the onset of immunosuppression, i.e., ~1 year
		Normal susceptibles, routine for children (booster for adults)	Birth cohort: 3,788,377	Probable age of vaccination or booster to peak of illness; for varicella, ~1-10 years; for zoster, middle age to early old age, i.e., ~10 years
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	As defined by CDC: 48,000,000. Revaccination needed each year because of strain changes	With annual vaccination, illness would be arrested within subsequent year, i.e., ~1 year
	Attenuated live virus	High-risk population as currently defined (see Appendix K)		

Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	Individuals 15 years of age: 3,669,254	Probable age of vaccination (~15 years) to peak of illness (~20-24 years), i.e., 7 years
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	Birth cohort: 3,788,337	Probable age of vaccination (<3 months) to peak of illness (~2 years), i.e., ~2 years
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	Birth cohort: 3,788,337	Probable age of vaccination (<3 months) to peak of illness (<2 years), i.e., 1 year
	Attenuated live virus	Infants	Birth cohort: 3,788,337	Probable age of vaccination (<3 months) to peak of illness (<2 years), i.e., 1 year
Rotavirus	Attenuated live bovine virus	Infants	Birth cohort: 3,788,337	Probable age of vaccination (~<1 year) to peak of illness (~2-3 years), i.e., 2 years
	Attenuated live human or reassortment virus	Infants	Birth cohort: 3,788,337	
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	Approximate birth cohort: 3,788,337	Benefits of vaccinating the mother during pregnancies accrue to the neonate up to ~3 months of age, i.e., within 1 year

[a]Based on 1984 population data.
[b]McIntosh, personal communcation (1983).

resulting from the adverse reactions are used to calculate values representing the potential burden of vaccine-induced illness. Where applicable, these values are then used to adjust PRMM values in the derivation of estimates for net potential health benefits (Figure 7.1).

An example of such a calculation is included in Appendix C to illustrate the procedure. Only three vaccine candidates are expected to have adverse reactions that might be equivalent to conditions serious enough to be included in the morbidity categories described in this report. Preliminary calculations of adverse reaction values for the three vaccines resulted in all cases in values less than one-half of one unit (generally well under 1 percent of the PRMM). All were considered negligible in relation to the total PRMM values for the vaccines.

In the tables and discussion that follow in this chapter, adverse reaction values and their costs are not included for the reasons described above. If other vaccine candidates are added to the analysis, however, their potential for adverse reactions should be evaluated.

The Time at Which Health Benefits and Cost Savings Associated With the Vaccines Will Occur

The purpose of the program of accelerated vaccine development is to expedite the realization of the benefits theoretically possible with various vaccines. It is appropriate, therefore, to consider the times at which benefits and costs associated with vaccine development and use would occur. This is normally done through a process termed discounting (Weinstein and Stason, 1977). Discounting can be applied both to the health benefits (of morbidity and mortality averted) and the costs involved (saved or incurred) in vaccine development and use.

Time to Licensure Factors affecting the predictions of the time it will take to develop the vaccine candidates are discussed in Chapter 5. The predictions are related to probability of success and other issues discussed in that chapter and shown in Table 5.1.

Time to Adoption and Steady-State Yield of Benefits After licensure, the utilization of a vaccine increases until it reaches a steady state. The costs of the vaccination program also increase to reach a steady state (as would the numbers of adverse effects, if applicable). The rate at which a vaccine is adopted depends on physician and target population attitudes toward the new vaccine. The issues determining these are similar to those discussed in Chapter 6.

The Centers for Disease Control, under the auspices of the United States Public Health Service's 1990 prevention objectives (1980), has adopted a goal of 50 percent or greater utilization for new vaccines at a time five years after licensure. While the utilization rate predicted by the committee for some vaccines is less than 50 percent,

the five-year point is a useful frame of reference for judging what the likely time of adoption would be. Predictions on the time to adoption (at the rate of utilization predicted in Chapter 6) are shown in Table 7.2. These times may be affected by factors such as federal purchase or promotional programs, by the combination of new vaccines with current vaccines that have high utilization rates, or by legislation. These factors have been excluded from consideration in arriving at the times in Table 7.2, but the effects of adopting alternative values could be evaluated easily (see Appendix R).

Considerable discussion took place regarding the acceptance and the likely time to adoption of an attenuated live influenza virus vaccine that would be used mostly in adults and require intranasal drop administration. The values finally selected (Table 7.2 and Chapter 6) reflect the consensus that this unfamiliar method of delivery would take a relatively long time to be adopted, but ultimately would be more acceptable than the injection required for the subunit vaccines.

The time between the age at which a vaccine would be most likely to be administered and the age at which the disease probably would have occurred without vaccination is termed the delay of vaccination benefits. This time must be determined separately for each vaccine—consider the difference between the Hemophilius influenzae type b vaccine for delivery to infants and the vaccine proposed for adolescent females to avert congenital CMV infection. The delay of vaccination benefits is a component of the total time to the steady-state yield of vaccine benefits. Information used to determine the delay is shown in Table 7.1 and the derivation of the time to steady-state yield of benefits is shown in Table 7.2.

In the calculations at the end of this chapter, the present value of the vaccination program costs are calculated on the assumption that they are incurred from the time at which a steady-state use of vaccine has been achieved. The present values of health benefits and expected reduction in morbidity costs are calculated on the assumption that they occur at the time of steady-state yield of vaccine benefits. Equations for deriving present values are given in Chapter 3.*

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* If desired, a more exact procedure can be used for these calculations. It takes account of the presumably linear increase from zero at the time of licensure to the values at the steady state. This is accomplished by substituting in the discounting process (Chapter 3) an adjusted time, T*, for the time to adoption or for the time after licensure to a steady-state yield of benefits (time to adoption plus delay of vaccination benefits). The general equation defining T* is

$$T^* = -1/r \ln[1/2 (1 + e^{-rT})]$$

where T is the time to adoption or the time from licensure to steady-state yield of benefits, and r is the discount rate.

In this analysis, the discount rate adopted is 0.05 so

$$T^* = -20 \ln[1/2 (1 + e^{-0.05T})].$$

TABLE 7.2 Various Times Connected with Vaccine Use and Benefits

Pathogen	Vaccine Envisaged	Target Population	Time to Licensure (years)	Time After Licensure to Adoption (years)	Total Time to Steady State of Vaccine Use	Delay of Vaccination Benefits (years)	Total Time to Steady-State Yield of Benefits (years)
Bordetella pertussis	Acellular	Infants	4	0	4	3	7
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	6.5	10	16.5	35	51.5
Cytomegalovirus	Attenuated live virus	Seronegative (SN) recipients of bone marrow and organ transplants and SN persons with leukemias and lymphomas	3	3	6	1	7
		Nonpregnant adolescent females	7	10	17	10	27
	Glycoprotein produced by recombinant DNA technology	All children	8.5	5	13.5	23	36.5
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	3	3	6	2	8
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	4	5	9	20	29
	Subunit	Susceptibles of all ages (routine for children)	5	5	10	20	30
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	1.5	5	6.5	15	21.5
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	5	5	10	20	30

	Attenuated live virus	Children up to age 12 and older susceptibles	8	10	18	20	38
Herpesvirus varicellae	Attenuated live virus	Recipients of organ and bone marrow transplants and persons under age 25 with leukemias and lymphomas	2	3	5	1	6
		Normal susceptibles, routine for children (booster for adults)	4	5	9	10	19
Herpesvirus varicellae	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	4	2	6	1	7
Influenza viruses A & B	Attenuated live virus	High-risk population as currently defined (see Appendix K)	6	6	12	1	13
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	10	5	15	7	22
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	5	5	10	2	12
Respiratory syncytial virus	Glycoprotein produced by recombinant UNA technology	Infants	5	5	10	1	11
	Attenuated live virus	Infants	5	5	10	1	11
Rotavirus	Attenuated live bovine virus	Infants	2.5	5	7.5	2	9.5
	Attenuated live human or reassortment virus	Infants	3	5	8	2	10
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	7	2	9	1	10

Costs

Calculation of the annual costs associated with each of the vaccine candidates entails three major components: 1) the reduction in morbidity costs; 2) the vaccination program costs; and 3) the costs of development of the vaccine. The costs of adverse reactions also should be calculated, if applicable.

Reduction in Morbidity Costs The general procedure for calculation of the direct costs associated with each disease is discussed in Chapter 4. The protocols developed to represent the typical treatment of each disease's cases, complications, and sequelae are presented in Appendixes C through P. The annual costs associated with vaccine preventable illness are calculated in a similar fashion and are included in the relevant appendixes. The costs associated with vaccine preventable morbidity are adjusted for various factors as shown in Figure 7.2, to derive an annualized present value of expected reductions in morbidity costs.

Vaccination Program Costs Calculation of the vaccination program costs is shown in Table 7.3. The annual number of new potential vaccine recipients is derived as shown in Table 7.1. Table 5.1 indicates the predicted cost/dose of each vaccine to the private sector and the number of doses required.

Program costs have been calculated for a fully private sector vaccine delivery program and for the situation that the committee considers most likely, namely, federal and state intervention to support certain (pediatric) vaccine programs. For the latter situation (termed a mixed public-private program), which is used in the central analysis, it is assumed that half of the total number of doses of pediatric vaccines would be delivered through public programs, and that bulk purchase would reduce the price of the vaccine (for those doses) by half. (The average cost per dose would thus be reduced to 75 percent of the cost predicted in Table 5.1.)

Surveys of charges for vaccine administration indicate differences between public and private settings and between pediatric and adult patients (Office of Technology Assessment, 1981). Calculations are made assuming a delivery charge per dose for pediatric vaccines of $15 in a private setting and $5 in a public program. (Thus, with a 50:50 mixed publie-private program for pediatric vaccines the average delivery charge would be $10.) The charge per dose for adults is assumed to be $10. Any delivery of adult vaccines through public programs is considered to be too limited to affect the price per dose or the average cost of delivery. The charges noted above are consistent with charges reported by the Office of Technology Assessment (1981), adjusted to 1984 levels using an annual inflation rate of 10 percent.

For the improved pertussis vaccines, incremental costs are calculated rather than total costs. The cost of delivery of a new

pertussis vaccine is considered to be 0, because it would simply replace the current pertussis vaccine in the DPT program. Utilization at about 95 percent is expected to be the same. The cost of the pertussis component of the current DPT vaccine is now about $3.00 per dose (Hinman and Koplan, 1984; Lederle Laboratories, 1984), and is subtracted from the predicted cost of the new vaccine, about $10 per dose.

For the improved influenza vaccines, incremental costs also are calculated. The method used to predict vaccine utilization suggests likely use rates of 0.25 and 0.31 for the subunit and attenuated live virus vaccines, respectively, and indicates a rate of 0.16 for the current vaccine (see Table 6.7). Thus, the incremental use rates would be 0.09 and 0.15.

To calculate the incremental costs of private sector programs using the new influenza vaccines, it is assumed that 9 percent of the target population (for the subunit vaccine) or 15 percent of the target population (for the live attenuated vaccine) would receive the new vaccine at the full cost of vaccine and delivery. The cost of the new subunit vaccine is expected to be $15, the cost of the live attenuated vaccine is expected to be $10, and the cost of delivery is expected to be $10. For 16 percent of the target population, the new vaccine would substitute for the existing vaccine. The incremental delivery charge for these persons would be zero, and the incremental cost of vaccine would be the cost of the new vaccine minus the cost of the current vaccine ($3 per dose when updated for inflation [Office of Technology Assessment, 1981]). Because the target population for influenza vaccine is overwhelmingly adult, the cost of the program is not altered if one assumes the mixed public-private program scenario. It is assumed that annual readministration of influenza vaccines (one dose for either) will be necessary to combat antigenic drift or shift.

Thus, the incremental costs of the two programs, assuming a target population of 48,000,000, would be:

Subunit vaccine

```
48,000,000 x 0.09 x ($15 + $10)
+ 48,000,000 x 0.16 x [$(15-3) + 0]
= $200,160,000
```

Attenuated live virus vaccine

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48,000,000 x 0.15 x ($10 + $10)
+ 48,000,000 x 0.16 x [$(10 - 3) + 0]
= $197,760,000
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The cost of the live attenuated cytomegalovirus vaccine for immunocompromised patients may be unrealistically low, if this project is viewed as independent from the further development of this vaccine for a larger market, i.e., adolescent females. Without the prospect of a wider market, its commercial development is unlikely.

TABLE 7.3 Annual Costs of Vaccination Programs

Pathogen	Vaccine Envisaged	Target Population	Annual Number of New Potential Vaccinees	Doses/Course	Cost of Private Sector Programs[a] Costs/Dose (dollars) Vaccine	Delivery	Total	Maximum Cost of Vaccination Program (dollars)	Approximate Maximum Program Cost ($ millions)
Bordetella pertussis	Acellular	Infants	3,788,337	5	7	0	7	132,591,795	133
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	32,000	3	10	10	20	1,920,000	2
Cytomegalovirus	Attenuated live virus	Seronegative (SN) bone marrow and organ transplant recipients and SN persons with leukemias and lymphomas	1,408	1	25	10	35	49,280	0.05
		Nonpregnant adolescent females	1,830,707	1	25	15	40	73,228,280	73
	Glycoprotein produced by recombinant DNA technology	All children	3,788,337	3	25	15	40	454,600,440	455
Hemophilus Hemophilus influenzae type b	Conjugated polysaccharide	Infants	3,788,337	4	20	15	35	530,367,180	530
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	3,788,337	1	15	15	30	113,650,110	114
	Subunit	Susceptibles of all ages (routine for children)	3,788,337	3	20	15	35	397,775,385	398
Hepatitis B virus	Glycoptotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	348,540	3	30	10	40	41,824,800	42

Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	3,788,337	4	20	15	35	530,367,180	530
	Attenuated live virus		3,788,337	1	20	15	35	132,591,795	133
Herpesvirus Varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias or lyirphomas	12,757	2	25	10	35	892,990	0.89
		Normal susceptibles, routine for children (booster for adults)	3,788,337	2	25	15	40	303,066,960	303
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	48,000,000	a	a	a	a	200,160,000	200
	Attenuated live virus	High-risk population as currently defined	48,000,000	a	a	a	a	197,760,000	198
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	3,669,254	3	20	10	30	330,232,860	330
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	3,788,337	2	15	15	30	227,300,220	227
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	3,788,337	2	15	15	30	227,300,220	227
	Attenuated live virus	Infants	3,788,337	1	15	15	30	113,650,110	114
Rotavirus	Attenuated live bovine virus	Infants	3,788,337	1.5	10	15	25	142,062,638	142
	Attenuated live human or reassort-ment virus	Infants	3,788,337	1.5	10	15	25	142,062,638	142
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	3,788,337	1	22.5	10	32.5	123,120,953	123

TABLE 7.3 (Continued)

Pathogen	Vaccine Envisaged	Target Population	Annual Number of New Potential Vaccinees	Doses/Course	Coat of Mixed Public-Private Programs: Average Costs/Dose (dollars) Vaccine	Delivery	Total	Maximum Coat of Vaccination Program (dollars)	Approximate Maximum Program Cost ($ millions)
Bordetella pertussis	Acellular	Infants	3,788,337	5	5.25	0	5.25	99,443,846	99
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	32,000	3	10	10	20	1,920,000	2
Cytomegalovirus	Attenuated live virus	Seronegative (SN) bone marrow and organ transplant recipients and SN persons with leukemias and lymphomas	1,408	1	25	10	35	49,280	0.05
		Nonpregnant adolescent females	1,830,707	1	18.75	10	28.75	52,632,826	53
	Glycoprotein produced by recombinant DNA technology	All children	3,788,337	3	18.75	10	28.75	326,744,066	327
Hemophilus influenzas type b	Conjugated polysaccharide	Infants	3,788,337	4	15	10	25	378,833,700	379
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	3,788,337	1	11.25	10	21.25	80,502,161	81
	Subunit	Susceptibles of all ages (routine for children)	3,788,337	3	15	10	25	284,125,275	284
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	348,540	3	30	10	40	41,824,800	42

Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	3,788,337	4	15	10	25	378,833,700	379
	Attenuated live virus		3,788,337	1	15	10	25	94,708,425	95
Herpesvirus varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias or lymphomas	12,757	2	25	10	35	892.990	0.9
		Normal susceptibles, routine for children (booster for adults)	3,788,337	2	18.75	10	28.75	217,829,378	218
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	48,000,000	a	a	a		200,160,000	200
	Attenuated live virus	High-risk population as currently defined	48,000,000	a	a	a		197,760,000	198
Nelsseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	3,669,254	3	20	10	30	330,232,860	330
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	3,788,337	2	11.25	10	21.25	161,004,323	161
Respiratory syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	3,788,337	2	11.25	10	21.25	161,004,323	161
	Attenuated live virus	Infants	3,788,337	1	11.25	10	21.25	80,502,161	81
Rotavirus	Attenuated live bovine virus	Infants	3,788,337	1.5	7.5	10	17.5	99,443,846	99
	Attenuated live human or reassort-ment virus	Infants	3,788,337	1.5	7.5	10	17.5	99,443,846	99
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	3,788,337	1	22.5	10	32.5	123,120,953	123

[a] See text for explanation of the assumptions underlying these calcuations. Costs are upper limits; they are not adjusted for anticipated utilization.

Results

Presented below are the results of the central analysis, which assumes the probability of successful vaccine development and other vaccine characteristics (e.g., cost) described in Chapter 5, the predicted utilization rates (with no combination or promotion) presented in Chapter 6, the mixed public-private vaccination program described above, and a discount rate of 0.05.

Health Benefits

Table 7.4 shows values representing the health benefits that could result from the development of each vaccine candidate. Values are shown for two perspectives to illustrate the influence of judgments involved in developing IME values.

Vaccine preventable illness values represent the burden of illness that could be averted by delivering a hypothetical vaccine that is 100 percent effective to the whole target population.

The values for the possible reduction in morbidity and mortality take into account the vaccine's predicted efficacy, and the expected annual health benefit values are adjusted for the anticipated utilization. The annualized present value of the expected health benefits incorporates the probability of successful development and the time at which benefits would occur. Use of these values to compare health benefits from these vaccines is discussed in Chapter 9.

An Illustration of the Process Figure 7.4 illustrates the sequence of calculations involved in the proposed method for comparing the health benefits expected from two vaccine candidates using the committee median IME perspective. Chapter 3 and the foregoing text describe the specific computations involved at each stage.

If an age-neutral IME perspective such as that shown in Table 4.6 is adopted in place of the committee median the relationship between values indicating the health benefits of the two vaccines changes. The annualized present value for expected health benefits of the gonococcal vaccine becomes 201 and that for parainfluenza virus vaccine becomes 117. This change is predominantly due to the fact that the age-neutral IME perspective (shown in Table 4.6) equates a first trimester fetal death with all other deaths. If, in the age-neutral perspective, the value for the relative undesirability of fetal deaths is changed to 100 (its value in the committee median perpsective) the relative values for annualized present value of expected health benefits become 5 for the N. gonorrhoeae vaccine, and 117 for the parainfluenza vaccine.

This case clearly illustrates how the relative importance attached to certain conditions or events can, in some cases, change the ranking on health benefits. Other differences in the rankings on health benefits with the committee median and age-neutral perspectives (generally not as dramatic as that just described) are shown in Table 7.4, and the rank orders presented in Table 9.2. The potential effect

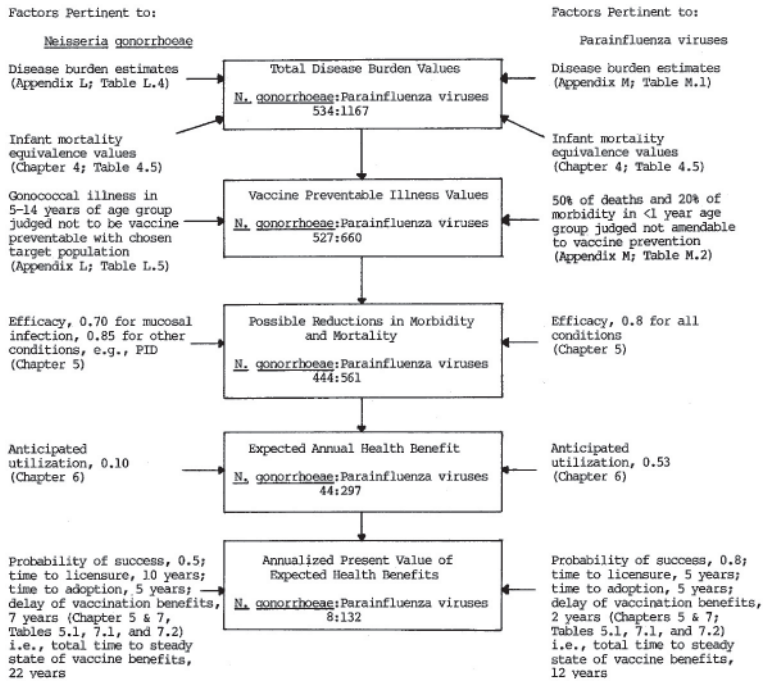

FIGURE 7.4 The Sequence of Calculations for Comparison of Health Benefits from Two Vaccine Candidates: Committee Median Perspective

on rankings of adopting alternative IME perspectives is discussed in Chapter 4.

Costs

Table 7.5 shows the costs associated with achieving the health benefits produced by each vaccine candidate.

The costs of vaccine preventable illness and the various reductions in morbidity costs parallel the health benefits values shown in Table 7.4. possible reductions in morbidity costs take account of the vaccine's efficacy; expected annual reductions in morbidity costs are adjusted further to reflect anticipated utilization. The annualized present value of expected cost reductions also incorporates the proba-

TABLE 7.4 Health Benefits Associated with Various Vaccines

Pathogen	Vaccine Envisaged	Target Population	Probability of Successful Development	Total Time to Steady-State Yield of Benefits (years)	Predicted Protective Efficacy	Anticipated Utilization
Bordetella pertussis	Acellular	Infants	0.9	7		
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	0.5	51.5	0.7	0.005
Cytomegalovirus	Attenuated live virus	seronegative (SN) bone marrow and organ transplant recipients and SN persons with leukemias and lymphomas	0.5	7	0.7	0.95
		Nonpregnant adolescent females	0.5	27	0.8	0.04
	Glycoprotein produced by recombinant DNA technology	All children	0.5	36.5	0.8	0.46
Hemophilus influenzae type b	Conjugated polysaccharide	Infants	0.9	8	0.8	0.76
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	0.95	29	0.9	0.12
	Subunit	Susceptibles of all ages (routine for children)	0.95	30	0.9	0.04
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	0.95	21.5	0.9	0.89
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	0.9	30	0.45	0.36
	Attenuated live virus	Children up to age 12 and older susceptibles	0.5	38	0.65	0.24

Herpesvirus varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias and lymphomas	0.99	e	0.9	0.95
		Normal susceptibles, routine for children (booster for adults)	0.95	19	0.9	0.4
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuramindase proteins)	High-risk population as currently defined (see Appendix K)	0.9	7	0.85	0.09
	Attenuated live virus	High-risk population as currently defined	0.7	13	0.85	0.15
Neisseria Neisseria qonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	0.5	22	0.85	0.1
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	0.8	12	0.8	0.53
Respiratory Syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	0.8	11	0.8	0.32
	Attenuated live virus	Infants	0.8	11	0.8	0.53
Rotavirus	Attenuated live bovine virus	Infants	0.95	9.5	0.9	0.27
	Attenuated live human or reassort-ment virus	Infants	0.9	10	0.9	0.27
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	0.65	10	0.8	0.11

TABLE 7.4 (Continued)

			Committee Median Perspective				Age-Neutral Perspective			
Pathogen	Vaccine Envisaged	Illness Target Population	Vaccine Preventable Illness Value [a]	Possible Reductions in Morbidity and Mortality [b]	Expected Annual Health Benefits	Annualized Present Value of Expected Health Benefits [d]	Vaccine Preventable Illness [a]	Possible Reductions in Morbidity and Mortality [b]	Expected Annual Health Benefits [c]	Annualized Present Value of Expected Health Benefits [d]
Bordetella pertussis	Acellular	Infants		62	62	40		60	60	38
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	334	234	1	0.0	260	182	1	0.0
Coccifiodes immitis	Attenuated live virus	Seronegative (SN) bone marrow and organ transplant recipients and SN persons with leukemias and lymphomas	488	342	325	115	351	246	234	83
Cytomegalovirus		Nonpregnant adolescent females	1184	947	38	5	1163	931	37	5
	Glycoprotein produced by cecombinant DNA technology	All children	1389	1111	511	43	1327	1061	488	41
Hemophilus influenzae Hemophilus influenzae type b	Conjugated polysaccharide	Infants	1807	1446	1099	669	1766	1413	1074	654
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	181	162	19	4	176	159	19	4
	Subunit	Susceptibles of all ages (routine for children)	181	162	6	1	176	159	6	1
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	2936	2642	2351	782	2832	2549	2269	755
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	1841	828	298	62	1263	568	204	43
	Attenuated live virus	Children up to age 12 and older susceptibles	1841	1197	287	22	1263	821	197	15

Herpesvirus varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias and lymphomas	558	337	320	237	372	231	219	162
		Normal susceptibles, routine for children (booster for adults)	1391	1112	445	167	960	746	298	112
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuramindase proteins)	High-risk population as currently defined (see Appendix K)	10644	9048	814	521	28225	23991	2159	1381
	Attenuated live virus	High-risk population as currently defined	10644	9048	1357	504	28225	23991	3599	1336
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	527	444	44	8	13811 (347)	11738 (294)	1174 (29.4)	201 (5)
Parainfluenza viruses	Trivalent, subunit vaccine (must contain fusion protein)	Infants	660	561	297	132	584	496	263	117
Respiratory Syncytial virus	Glycoprotein produced by recombinant DNA. technology	Infants	3827	3062	980	458	3775	3020	966	452
	Attenuated live virus	Infants	3827	3062	1623	759	3775	3020	1601	749
Botavirus	Attenuated live bovine virus	Infants	281	253	68	41	227	204	55	33
	Attenuated live human or reassort-ment virus	Infants	281	253	68	38	227	204	55	30
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	3570	2856	314	125	3528	2823	311	124

[a] See text and appendixes for explanation and derivation.
[b] Adjusted for vaccine efficacy; see text for explanation where efficacy varies with conditions.
[c] Adjusted for anticipated utilization.
[d] Adjusted for probability of success and time at which steady state of benefits would be achieved.

TABLE 7.5 Costs Associated with Various Vaccines

Pathogen	Vaccine Envisaged	Target Population	Probability of Development	Cost of Development ($ millions)	Total Tims to Steady State of Vaccine Use	Total Time to Steady-State Yield of Benefits (years)	Predicted Protective Efficacy[a]	Anticipated Utilization	Cost of Vaccine Preventable Illnessa (5 millions)
Bordetella pertussis	Acellular	Infants	0.9	10	4	7	—	0.95	—
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	0.5	10	16.5	51.5		0.005	
Cytomegalovirus	Attenuated live virus	Seronegative (SN) bone marrow and organ transplant recipients and SN persons with leukemias and lymphomas	0.5	10	6	7	–	0.95	–
							0.7		49.5
		Nonpregnant adolescent females	0.5	10	17	27		0.04	
							0.7		30
	Glycoprotein produced by recombinant DNA technology	All children	0.5	45	13.5	36.5		0.46	392
							0.8		
Heroophilus influenzae influenzae type b	Conjugated polysaccharide	Infants	0.9	30	6	8	0.8	0.76	824.1
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages {routine for children)	0.95	15	9	29	0.8	0.12	395
	Subunit	Susceptibles of all ages {routine for children)	0.95	25	10	30	0.9	0.04	104.6
Hepatitis B virus	Glycoprotein produced by recombinant DMA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	0.95	10	6.5	21.5	0.9	0.89	104.6
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	0.9	30	10	30	0.9	0.36	145.1 310.4
	Attenuated live virus	Children up to age 12 and older susceptibles	0.5	30	18	38	0.45 0.65	0.24	310.4

Herpesvirus varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias and lymphomas	0.99	5	5	6	0.9	0.95	69.2
		Normal susceptibles, routine for children (booster for adults)	0.95	5	9	19	0.9	0.4	202.9
Influenza viruses A & B	Subunit vaccine (purified heraagglutinin/ neuraminidase proteins)	High-risk population as currently defined (see Appendix K)	0.9	20	6	7	0.85	0.09	2129.9
	Attenuated live virus	High-risk population as currently defined (see Appendix K)	0.7	20	12	13	0.85	0.15	2129.9
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	0.5	50	15	22	0.85	0.1	921.9
Parainfluenza viruses	Trivalent, subunit vaccine {must contain fusion protein)	Infants	0.8	25	10	12	0.8	0.53	323.3
Respiratory Syncytial virus	Glycoprotein produced by recombinant DNA technology	Infants	0.8	25	10	11	0.8	0.32	274.1
	Attenuated live virus	Infants	0.8	25	10	11	0.8	0.53	274.1
Rotavirus	Attenuated live bovine virus	Infants	0.95	10	7.5	9.5	0.9	0.27	116.8
	Attenuated live human or reassort-ment virus	Infants	0.9	20	8	10	0.9	0.27	116.8
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	0.65	40	9	10	0.8	0.11	681.2

TABLE 7.5 (Continued)

Pathogen	Vaccine Envisaged	Target Population	Possible Reduction in Morbidity Costsb	Expected Annual Reduction in Morbidity Costsc	Annualized Present Value of Expected Reduction in Morbidity Coats d	Maximum Annual Cost of Mixed Public-Private Sector Vaccination Program e ($ millions)	Expected Annual Cost of Vaccination Program c	Annualized Present Value of Expected Vaccination Program Costsd	Annualized Present Value of Expected Net Costsd
Bordetella pertussis	Acellular	Infants	--	18.7	12	99	94	70	58
Coccidioides immitis	Killed spherule preparation	High-risk individuals residing or working in endemic areas	35	0.2	0.01	2	0.01	0.002	0.5
	Attenuated live virus	Seronegative (SN) bone marrow and organ transplant recipients and SN persons with leukemias and lymphomas	21	20	7	0.05	0.05	0.02	-7
Cytomegalovirus		Nonpregnant adolescent females	314	13	2	53	2	0.5	-1
	Glycoprotein produced by recombinant DNA technology	All children	659	303	26	327	150	39	16
Henophilus influenzae type b	Conjugated polysaccharide	Infants	316	240	146	379	288	193	49
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	94	11	3	81	10	6	4
	Subunit	Susceptibles of all ages (routine for children)	94	4	1	284	11	7	7
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	131	116	39	42	37	26	-12
Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	140	50	10	379	136	75	66
	Attenuated live virus	Children up to age 12 and older susceptibles	202	48	4	95	23	5	2

Herpesvirus varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias and lymphomas	62	59	44	0.9	1	1	-43
		Normal susceptibles, routine for children (booster for adults)	183	73	27	218	87	53	26
Herpesvirus Varicellae	Subunit vaccine (purified hemagglutinin/ neuraminidase proteins)	High-risk population as currently defined {see Appendix K)	1810	163	104	a	200	134	31
Influenza viruses A & B	Attenuated live virus	High-risk population as currently defined (see Appendix K)	1810	272	101	a	198	77	-23
Neisseria gonorrhoeae	A small number of promising options need investigation to determine best approach	Adolescents and adults age 15 and over	784	78	13	330	33	8	-3
Parainfluenza viruses	Trivalent, subunit vaccine {must contain fusion protein)	Infants	259	137	61	161	85	42	-18
Respiratory Syncytial virus	Glycoptotein produced by recombinant DNA technology	Infants	219	70	33	161	52	25	-6
	Attenuated live virus	Infants	219	116	54	81	43	21	-32
Rotavirus	Attenuated live bovine virus	Infants	105	28	17	99	27	18	1
	Attenuated live human or reassort-ment virus	Infants	105	28	16	99	27	16	2
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	545	60	24	123	14	6	-16

See text and appendixes for derivation.

[b] Adjusted for efficacy.

[c] Adjusted for anticipated utilization.

[d] Adjusted for probability of successful development and the time at which steady-state yield of benefits would be achieved.

[e] From Table 7.4.

[f] Adjusted for the probability of successful development, and the times at which vaccine use and the yield of benefits would reach a steady state.

bility of successful development and the time at which benefits would occur.

The vaccination program costs used in calculating net costs are those of a mixed public-private program, because this type of delivery system appears to be the most likely to develop.*

All expected costs are adjusted to take into account the anticipated utilization of vaccines. The annualized present value of expected net costs also is adjusted to reflect the probability of each vaccine's successful development and the time that costs and benefits would occur.

These calculations of costs can be used to compare vaccine candidates from a variety of viewpoints, as discussed in Chapter 9. Sensitivity analyses described in that chapter also show the effects on the rankings of assumptions other than those used in the central analysis.

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* Any delivery of adult vaccines through public programs is considered to be too limited to affect the price per dose or the average cost of delivery. Thus, the assumption of a mixed public-private program has the effect of lowering the costs of pediatric vaccination programs relative to adult programs.

8

Additional Issues in the Selection of Priorities for Accelerated Vaccine Development

The selection of candidates for accelerated vaccine development requires consideration of several non-quantifiable factors in addition to the potential benefits described in previous chapters. These factors encompass both ethical issues and questions about private sector incentive structures.

Equity Considerations in the Calculation of Disease Burdens and Vaccine Benefits

The methods used to compare disease burdens (Chapter 4) and vaccine benefits (Chapter 7) intentionally incorporate the opportunity for individuals to attach different weights to events that occur at different ages through the infant mortality equivalence mechanism. These weights have a direct effect on both disease burden values and calculations of possible reductions in morbidity and mortality. For example, if the death of one child less than one year of age is considered to be equivalent to the deaths of ten persons over age 60, then a disease that kills 1,000 young infants annually would impose the same disease burden as another disease that kills 10,000 elderly persons annually.

The model allows decision makers to assess the impact of different infant mortality equivalence trade-offs. For those individuals who may be uncomfortable with any suggestion that one life is worth more than another, Chapters 4 and 7 also illustrate the use of an "age-neutral" perspective.

Lives vs. Cases vs. Days

The age-neutral perspective used in this report is neutral with respect both to morbidity and mortality. It would be possible, however, to construct a perspective in which all deaths were considered equal, but morbidity was weighted differently for different age groups. For example, days of hospitalization in adult life might be weighted more heavily than days of hospitalization in childhood. Use of the infant mortality equivalence scheme allows decision makers to vary trade-off values within age groups as well as among them.

The Aggregate Nature of the Disease Burden Calculations

Infant mortality equivalence values assigned to specific morbidity category/age group combinations do not differentiate with respect to gender, race, ethnic origin, socioeconomic class, place of residence, occupation, or lifestyle. Often, however, diseases occur more frequently in some parts of the population than in others. The size of these high-risk groups may play a significant role in determination of the national disease burden. For example, if disease A attacks 10 percent of the white population of the United States and disease B attacks 60 percent of the black population, and if the sequelae of the two diseases are equivalent, then on a national basis disease A will produce a greater disease burden than disease B because whites are so much more numerous. Examples of diseases with higher attack rates or more serious sequelae for particular groups are presented in Table 8.1.

One method for going beyond a single, national burden-of-illness comparison is to construct individual disease burden profiles for specific groups, for example:

- American Indians
- women
- persons whose income levels fall below the poverty line
- children in their first year of life
- hospital patients
- homosexual men.

These multiple burden-of-illness profiles might not lead directly to new public policy recommendations, but they would serve as a reminder that the national profile is an aggregate that obscures differential effects in definable population groups. The multiple profiles also could be used to deal openly with issues such as the extent to which one's behavior places one in a vulnerable group (e.g., drug abusers), and whether or not society wishes to devote special attention to meeting the needs of the more vulnerable groups, however those groups are defined.

The adoption of special campaigns for delivering vaccine(s) to high-risk groups might be one solution to the problem of differential risks; another method to meet the needs of these groups might involve the portfolio approach, described below.

The Portfolio Approach for Ranking vaccines for Research and Development Support

In establishing consistent methods for setting priorities for vaccine research and development support, some consideration should be given to ranking within a group (or portfolio) of candidate vaccines. It may not be desirable or appropriate to have a single priority list based on final numerical (expected benefits) scores for all possible vaccines that need developmental support. This concept is reflected in the committee's charge to rank vaccines separately for use in the United States and for use in developing countries. Perhaps grouping of

TABLE 8.1 Examples of Diseases Affecting Certain High-Risk Groups

Disease	High-Risk Group	Problem
Gonorrhea	Women	More serious sequelae than in men
Hemophilias influenzae type b meningitis	American Indians	Higher than average incidence
Streptococcus group B	Lower socio-economic groups	Higher than average incidence
Hepatitis A S B, cytomegalovirus, herpes	People who have numerous sexual partners	Higher than average incidence
Varicella, cytomegalovirus	Immunosuppressed children (e.g., those on chemo-therapy)	More serious sequelae than in the average child
Coccidioides immitis	Inhabitants of certain regions	Higher than average incidence

vaccines for use within the United States also should be considered. Possible classification categories include:

1. Stage of vaccine development*
   a. improvement of existing or available vaccines (e.g., pertussis and influenza)
   b. Vaccines at an advanced stage of development that are already in, ready, or almost ready for clinical and/or field trials (e.g., hepatitis A and varicella)
   c. Vaccines at an early stage of development that require significantly more basic study before any large scale clinical or field trials would be possible (e.g., respiratory syncytial virus)
2. Expected recommendations for vaccine use
   a. Vaccines for the entire population
   b. Vaccines for routine pediatric care
   c. Vaccines primarily for adults
   d. Vaccines for specific high-risk groups

A third classification scheme might be to integrate and combine the above groupings, but the results would be fairly cumbersome.

* The committee has partially adopted this concept in opting to define a limited slate of candidates for accelerated vaccine development and a separate list of pathogens for which more basic research is necessary before vaccine development even at stage C above is foreseeable (see Appendix B).

The rationale for developing some type of classification system is based on practical program and political considerations. For example, an objective scoring formula might give malaria vaccine development a very high priority because of the huge incidence and public health importance of the disease; yet the prospects for such a vaccine might depend on some unknown technological breakthrough. While the probability of successful development could be incorporated into the ultimate ranking, the selection of a balanced portfolio of vaccine candidates might be better served by setting priorities within categories divided by stage of development (the vaccines most advanced in development generally have the highest probability of success).

On the other hand, development of an improved pertussis vaccine or a vaccine for acquired immune deficiency syndrome (when the etiologic agent is confirmed) might score quite low by objective measures, while policy considerations indicate that these vaccines should receive high priority (see below for discussion of pertussis vaccine). Limited selected use vaccines, the "orphan vaccines," will have to be ranked in a separate grouping if any of them are to receive developmental support.

The Pertussis Vaccine Problem

Setting a priority for the development of an improved vaccine against Bordetella pertussis presents unique problems that involve some of the issues discussed above. This situation recently has been summarized by Fulginiti (1984) and Linnemann et al. (1983).

The efficacy of the current pertussis vaccine is high and only marginal improvement is possible. Utilization is also high because of state requirements for immunization of children entering school, which are likely to continue. However, use of the vaccine is associated with certain adverse side effects.

The success of the immunization program against pertussis has reduced the annual number of cases to a low level, which the public may interpret as a low risk of illness to infants. This perception is erroneous, however, because the reservoir for infection remains (consider the reappearence of pertussis epidemics in the United Kingdom after a decline in vaccine acceptance levels). The public's mistaken view of the risk-benefit ratio for the current pertussis vaccine may be due in part to imbalanced news media coverage.

The committee believes that the side effects of pertussis vaccination may be causing widespread misconceptions about the relative risks and benefits of vaccination programs in general. In this situation, the small reduction in morbidity and mortality that would result from introduction of an improved pertussis vaccine (one with fewer side effects) would underestimate the overall benefits it could produce. Thus, treatment of an improved pertussis vaccine as a special case in setting priorities for development may be justified.

Industry Interest and Activity: The Respective Roles of the Public and Private Sectors

The charge to the committee included consideration of how the level of industry interest in certain vaccines should affect the National Institute of Allergy and Infectious Disease's (NIAID) selection of candidates for accelerated development. Various ways in which such interest might affect the ultimate availability or speed of development of new vaccines have been identified. Potential profitability presumably is the motivating force for private sector activity focused on the hepatitis and Herpes simplex vaccines, for example (Gunby, 1983; Wilson, 1984). One of the major disincentives for development in the private sector, other than potential lack of profitability, is potential liability resulting from clinical trials or widespread use (e.g., this may be a problem in the development of a streptococcus group B vaccine to be given to pregnant women).

Industry willingness to manufacture vaccines that are licensed and to invest in research and development directed towards new vaccines are among the topics being addressed by the Institute of Medicine's Committee on Public-Private Sector Relations in Vaccine Innovation. The results of that study may lead to changes in the factors that govern industry interest in vaccine innovation. The level of industry interest in specific vaccines also may change over time as new development techniques are refined.

This committee understood that it probably was not aware of all pertinent vaccine-related activity in the private sector. Given this situation, no formal attempt was made to incorporate the level of industry interest in individual vaccines into the mechanism designed for selecting priorities for accelerated development.

The committee suggests, however, that NIAID decisions on how to implement the program of accelerated vaccine development should incorporate a review of relevant activity in the private sector. This review should be focused on (1) identification of projects on which mutual collaboration might facilitate industrial development of a needed vaccine (e.g., on clinical trials), and (2) identification of high priority vaccines for which obvious disincentives exist (e.g., special liability issues or limited market size).

Periodic reassessment of this aspect of the program of accelerated vaccine development, preferably biennially, is particularly desirable because of current rapid changes in technological capabilities for producing new vaccines.

Findings, Conclusions, and Recommendations

A variety of legitimate perspectives exist on the relative undesirability of death and morbidity in different age groups. The method proposed for calculating the benefits to be expected from various vaccines allows those setting the priorities to observe the effects of adopting any particular perspective on the final rankings. The problem of deciding what relative weights different perspectives should receive is inherently a policy or political question, not a scientific one.

The benefits from new vaccines may not be distributed evenly across age or ethnic groups, between sexes, or among other subsets of the population. The method designed by the committee can provide useful information on the distribution of benefits that could accrue from different courses of action, but the committee recommends that decisions regarding selection of an equitable course of action should be addressed in a broader political/public policy forum.

The public perception of adverse reactions to the current pertussis vaccine is damaging generally to efforts to promote immunization, and thus development of an improved pertussis vaccine merits special consideration.

In implementing the program of accelerated vaccine development, NIAID periodically should review activity in the private sector to identify projects on which public-private collaboration might expedite development; and to overcome industry-scientific disincentives to development of high priority vaccines.

In the ultimate selection of a portfolio of candidates for accelerated vaccine development, information obtained from the analysis described in Chapters 3, 7, and 9 must be integrated with the non-quantifiable considerations discussed above.

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9

Findings, Conclusions and Recommendations

This chapter presents the results obtained from the priority assessment system described in the preceding chapters. Health benefits and net costs have been calculated for each of the 22 vaccine projects,* and the candidates have been ranked accordingly. These rankings reflect assumptions made in the central analysis, presented in Chapters 1 through 7 and reiterated below. To illustrate the use of other assumptions (all considered plausible by the committee), several sets of sensitivity analyses have been performed. These examine the effects on the rankings of different perspectives on the undesirability of morbidity and death, of different discount rates, and of alternative assumptions on the probability of successful development, likely utilization, and vaccine cost.

The rankings discussed below should be used as a guide to the selection of development priorities after consideration of the assumptions and issues outlined in Chapters 3 and 8. The committee believes that one of the major strengths of this analysis is that it encourages those using it to examine all judgments and assumptions involved in the decision process. New data should be incorporated as they become available. Alternative assumptions regarding variables in the model may be incorporated as appropriate, depending on the purposes for which decision makers are using this tool.

The Central Analysis

The central analysis described below incorporates the following:

1. Vaccine and development characteristics described in Chapter 5, including predictions on the target population, efficacy, and vaccine cost.
2. The anticipated utilization rate estimated for a "no combination, no promotion" situation (Chapter 6).

* The 22 projects involve 20 vaccines: the attenuated live cytomegalovirus vaccine and the varicella vaccine each have two separate target populations.

3. The mixed public-private vaccination program described in Chapter 7.
4. Times to licensure and adoption, and delay of vaccination benefits presented in Chapter 7.
5. Calculations of health benefits and costs as described in Chapters 4 and 7, and Appendixes C through P (including calculation of the incremental benefits from new influenza vaccines and the benefits of an improved pertussis vaccine, i.e., the elimination of current adverse effects).
6. Use of a 5 percent discount rate for future health benefits and costs.
7. Adoption, for illustrative purposes only, of the committee median perspective on the undesirability of various morbidity conditions and mortality.
8. Consideration of the development of each vaccine candidate (for each target population) as an independent project.
9. Expression of health benefits in units considered equivalent in undesirability to the death of an infant (i.e., infant mortality equivalents, IMEs) (see Chapter 4).

Findings

The results of the central analysis, using the committee median perspective (Chapter 7 and Tables 9.1 and 9.2), have been interpreted for a hypothetical situation in which five vaccines are to be selected for highest priority (with no more than one vaccine per disease/target population combination).

First, we rule out vaccines that are dominated in both benefits and costs by another vaccine against the same disease (Table 9.2, columns 1 and 3). Thus, the RSV glycoprotein vaccine is dominated by the RSV attenuated live virus (ALV) vaccine; the hepatitis A subunit vaccine is dominated by the hepatitis A ALV vaccine; and the human rotavirus ALV vaccine is dominated by the bovine rotavirus ALV vaccine.

Table 9.3 displays the patterns of dominance between the remaining 19 vaccine candidates. Procedures described in Chapter 3 are used to select the desired number of candidates.

Thus, of the remaining 19 vaccines, we can as a second step rule out those that are dominated by at least five other vaccines (see Table 9.3). On this basis, we eliminate from consideration: CMV (all target populations); herpes simplex (all vaccines); B. pertussis; N. gonorrhoeae; hepatitis A; rotavirus (bovine ALV); and Coccidioides immitis.

These two steps leave the following nine vaccines (eight diseases) in contention for the top five positions: hepatitis B; RSV (ALV); Hemophilus influenzae type b; influenza (subunit or ALV); Herpesvirus varicellae (for high-risk individuals); Herpesvirus varicellae (for normals and children); streptococcus group B; parainfluenza viruses. RSV dominates six others, so it must be among the top five, regardless of the weight given to benefits and costs.

The selection of the remaining four vaccines depends on the relative weight of health benefits versus costs. In particular, if the

objective is solely to maximize the expected health benefit (Table 9.2, column 1), the top five vaccines are:

Hepatitis B
RSV (ALV)
H. influenzae type b
Influenza (subunit)
Herpesvirus varicellae (high-risk individuals)

The choice of the subunit vaccine over the ALV vaccine for influenza, however, is reasonable only if there is a willingness to pay an extra $54 million ($31 million plus $23 million) to gain 17 (521 minus 504) IME units of health benefit, or about $3.2 million per IME compared to the ALV vaccine. If this appears unreasonable, the ALV influenza vaccine would be a better choice.

It can be shown that the other vaccines in the top five would remain the best choices as long as the willingness to pay to save an IME is at least $125,000. (Below this willingness to pay, parainfluenza would replace H. influenzae type b on the priority list; below $6,000, streptococcus group B would replace hepatitis B.) It can be shown that for no range of willingness to pay would Herpesvirus varicellae (normals and children) enter the top five, although it ranks sixth for any willingness to pay above $1.3 million per IME. Thus, if the objective is to select five vaccines:

- If resource cost is not a concern, select:
  Hepatitis B
  RSV (ALV)
  H. influenzae type b
  Influenza (subunit)
  Varicella (high-risk individuals)

- If resource cost is of secondary concern, but $3.2 million is deemed excessive to save an IME, select:
  Hepatitis B
  RSV (ALV)
  H. influenzae type b
  Influenza (ALV)
  Varicella (high-risk individuals)

- If resource cost is enough of a concern that it is not deemed appropriate to spend even $125,000 to save an IME, select:
  Hepatitis B
  RSV (ALV)
  Influenza (ALV)
  Varicella (high-risk individuals)
  Parainfluenza

  (Only if it were felt that it was not worth paying even $6,000 to save an IME would streptococcus group B vaccine displace hepatitis B on the list.)

TABLE 9.1 Cost-Effectiveness Ratios for Vaccine Candidates: Central Analysis

Pathogen	Vaccine Envisaged	Target Population	Annualized Present Value of Expected Net Costs ($millions)	Annualized Present Value of Expected Health Benefits		Cost-Effectiveness Ratio ($1,000 per IME value) a	
				Committee Median Perspective	Age-Neutral Perspective	Committee Median Perspective	Age-Neutral Perspective
Bordetella	Acellular	Infants	58	40	3a	1,450	1,526
Coccidioides	Killed spherule preparation	High-risk individuals residing or working in endemic areas	0.5	0.05	0.04	10,000	12,500
Bordetella pertussis	Attenuated live virus	Seronegative (SN) bone marrow and organ transplant recipients and SN persons with leukemias and lymphomas	-7	115	83	b	b
		Nonpregnant adolescent females	-1	5	5	b	b
Coccidioides iimiitis	Glycoprotein produced by recombinant DNAtechnology	All children	16	43	41	372	390
Cytomegalovirus	Conjugated polysaccharide	Infants	49	669	654	73	75
Hemophilus influenzae type b		Susceptibles of all ages (routine for children)	4	4	4	1,000	1,000
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages (routine for children)	7	1	1	7,000	7,000
	Subunit						
Hepatitis B virus	Glycoprotein produced by recombinant DNA technology	High-risk groups (health professionals, homosexuals, IV drug users, etc.)	-12	782	755	b	b

Herpes simplex viruses 1 & 2	Glycoprotein produced by recombinant DNA technology	Children up to age 12 and older susceptibles	66	62	43	1,065	1,535
	Attenuated live virus	Children up to age 12 and older susceptibles	2	22	15	91	133
Herpesvirus varicellae	Attenuated live virus	Recipients of bone marrow and organ transplants and persons under age 25 with leukemias and lymphomas	-43	237	162	b	b
		Normal susceptibles, routine for children (booster for adults)	26	167	112	156	232
Influenza viruses A & B	Subunit vaccine (purified hemagglutinin/ neuratninidase proteins)	High-risk population as currently defined (see Appendix K)	31	521	1381	60	22
	Attenuated live virus	High-risk population as currently defined	-23	504	1336	b	b
Neisseria gonorchoeae	A few promising options need investigation to determine best approach	Adolescents and adults age 15 and over	-3	8	201	b	b
Neisseria gonorchoeae	Trivalent, subunit vaccine (must contain fusion protein)	Infants	-18	132	117	b	b
Parainfluenza viruses	Glycoprotein produced by recombinant DNA technology	Infants	-6	458	452	b	b
Respiratory syncytial virus	Attenuated live virus	Infants	-32	759	749	b	b
Rotavirus	Attenuated live bovine virus	Infants	1	41	33	24	30
	Attenuated live human or reassort-ment virus	Infants	2	38	30	53	67
Streptococcus group B	Conjugated polysaccharide	Pregnant women for fetuses and neonates	-16	125	124	b	b

[a] Infant mortality equivalent.
[b] Cost-effectiveness ratio undefined because net costs are negative.

TABLE 9.2 Benefits and Net Costs of Vaccine Candidates: Central Analysis

Annualized Present Value of Expected Health Benefits (Infant-Mortality Equivalents)				Annualized Present Value of Expected Net Costs	
Coimmittee Median Perspective		Age-Neutral Perspective			
Vaccine	Value	Vaccine	Value	Vaccine	Costs ($ millions)
Hepatitis B virus	782	Influenza viruses A & B (subunit)	1,381	Herpesvirus varicellae (high-risk individuals)	-43
Respiratory syncytial virus (ALV) a	759	Influenza viruses A & B (ALV)	1,336	Respiratory syncytial virus (ALV)	-32
Henraphilus influenzae type b	669	Hepatitis B virus	755	Influenza A & B (ALV)	-23
Influenza viruses A & B (subunit)	521	Respiratory syncytial virus (ALV)	749	Parainfluenza virus	-18
Influenza viruses A & B (ALV)	504	Hemophilus influenzae type b	654	Streptococcus group B	-16
Respiratory syncytial virus (glycoprotein)	458	Respiratory syncytial virus (glycoprotein)	452	Hepatitis B virus	-12
Herpesvirus varicellae (high-risk individuals)	237	Neisseria gonorrhoeae	(201) b	Cytomegalovirus (ALV: high-risk individuals)	-7
Herpesvirus varicellae (normal, children)	167	Herpesvirus varicellae	162	Respiratory syncytial virus (glycoprotein)	-6
Parainfluenza virus	132		124	Neisseria gonorrhoeae	-3
Streptococcus group B	125	Herpesvirus varicellae	117	Cytomegalovirus (ALV: nonpregnant adolescent females)	-1
Cytomegalovi rus (ALV: high-risk individuals)	115	[illegible]	112	Coccidioides inmitis	0.5
		[illegible] group a			

Herpes simplex viruses 1 & 2 (glycoprotein)	62	Cytomegalovirus (ALV: high-risk individuals)	83	Rotavirus (bovine ALV)	1
Cytomegalovirus (glyooprotein: children)	43	Herpes simplex viruses 1&2 (glycoprotein)	43	Herpes simplex viruses 1 & 2 (ALV)	2
Rotavirus (bovine ALV)	41	Cytomegalovirus (glycoprotein, children)	41	Rotavirus (human ALV)	2
Bordetella pertussis	40	Bordetella pertussis	38	Hepatitis A virus (ALV)	4
Rotavirus (human ALV)	38		33	Hepatitis A virus (subunit)	7
Herpes simplex viruses 1 & 2 (ALV)	22	Bordetella Pertussis Rotavirus (bovine ALV)	30	Cytomegalovirus (glycoprotein: children)	16
Neisseria gonorrhoeae	8	Rotavirus (human ALV)		Herpesvirus varicellae (normal, children)	26
	5	Herpes simplex virus 1 & 2 (ALV)	15	Influenza viruses A & B (subunit)	31
Neisseria gonorrhoeae Cytomegalovirus (ALV: nonpregnant adolescent females)	4	(Neisseria gonorrhoeae)	(5)[b]	Hemophilus influenzae type b	49
Hepatitis A virus (ALV)	1	Neisseria gonorrhoeae	5	Bordetella pertussis	58
Hepatitis A virus (subunit)		Cytomegalovirus (ALV: nonpregnant adolescent females)	4	Bordetella Pertussis	
Coccidioidps inmitis	<1	Hepatitis A virus (ALV)	1	Herpes simplex viruses 1 & 2 (glycoprotein)	66
		Hepatitis A virus (subunit)			
		Coccidioides uimitis	<1		

[a] Attenuated live virus.

[b] Value is 201 if IME for first trimester fetal deaths is 1; value is 5 if IME for first trimester fetal deaths is 100.

TABLE 9.3 Vaccine Dominance: Committee Median Perspective (column dominates row)

19 vaccine Candidates	A	B	C	D	E	F	G	H	I	J	K	L	K	N	O	P	Q	R	S	Number Dominated by
A. Respiratory syncytial virus (ALV)																				0
B. Hetpesvirus varicellae [HRII																				0
C. Hepatitis B virus																				0
D. Influenza viruses A & B (ALV)	X																			1
E. Parainfluenza viruses	X	X		X																3
F. Streptococcus group B	X	X		X	X															4
G. Cytomegalovirus (HR)	X	X	X	X	X	X														6
H. Rotavirus	X	X	X	X	X	X	X													7
I. N, Gonorrohoeae	X	X	X	X	X	X	X													7
J. H. influenzae type B	X		X																	2
K. Influenza viruses A & B (subunit)	X		X																	2
L. Herpesvirus varicellae L. Herpesvirus varicellae (normals)	X	X	X	X																4
M. Cytomegalovirus (glycoprotein)	X	X	X	X	X	X	X													7
N. Herpes simplex 1 & 2 (ALV)	X	X	X	X	X	X	X	X												8
O. Cytomegalovirus (adolescents)	X	X	X	X	X	X	X		X											8
P. Coccidioides immitis	X	X	X	X	X	X	X		X											8
p. Coccidioides immitis	X	X	X	X	X	X	X			X	X	X								10
Q, Herpes simplex 1 & 2 (glycoprotein)	X	X	X	X	X	X	X	X	X					X	X					11
R. Hepatitis A	X	X	X	X	X	X	X	X		X	X	X	X							12
E. Bordetella pertussis S. Bordetella Pertussis	16	13	13	13	11	10	9	3	3	2	2	2	1	1	1	0	0	0	0	
Number dominated																				

Notes: One vaccine dominates another if it is superior on one dimension (costs or benefits) and at least as desirable on the other dimension; when one vaccine against a disease dominates another vaccine against the same disease, only the dominating candidate is listed. HR denotes high-risk individuals.

Similar logic to that described above would apply if other numbers of vaccines were to be chosen.

Sensitivity Analyses

Adoption of Age-Neutral Versus Committee Median Perspective

The age-neutral perspective on morbidity and mortality was adopted as an alternative to the committee median perspective (see Chapter 4 for explanation of these perspectives). The results are shown in Chapter 7 and Tables 9.1 and 9.2.

Use of the age-neutral perspective IME values does not markedly change the selection of the top five. For any willingness to pay to save an IME of at least $125,000, the priority list remains:

Hepatitis B
RSV (ALV)
H. influenzae type b
Influenza
Varicella (high-risk individuals)

The ALV influenza vaccine would be preferred over the subunit vaccine unless one were willing to pay more than $1.2 million per incremental IME saved. Parainfluenza vaccine would displace H. influenzae type b if the willingness to pay per IME saved were less than $125,000; streptococcus group B vaccine would replace hepatitis B vaccine if the willingness to pay were as little as $6,000; none of the other vaccines would become contenders for the top five positions at any willingness to pay. Thus, for the candidates considered, the ranking of the top five vaccines does not depend on whether the committee median weights or the age-neutral weights are used.

Discount Rate

The committee believes that incorporation of a discounting procedure for future health benefits and costs is justified because it reflects the preference for benefits achieved sooner rather than later (a basic concept in the establishment of a program of accelerated vaccine development). The effect of placing greater or lesser weight on achieving early benefits was examined by selecting discount rates higher (0.10) and lower (0.02) than that used in the central analysis.

The results with these discount rates are compared to the central analysis in Tables 9.4 and 9.5.

Using discount rates of 10 percent or 2 percent would not materially affect the rankings, nor would it affect the choices of the top five.

TABLE 9.4 Sensitivity Analysis: Annualized Present Value of Expected Health Benefit

	Discount Rate					
	Central Analysis (0.05)		0.02		0.1	
Vaccine	Rank	Value	Rank	Value	Rank	Value
Hepatitis B virus	1	782	1	1,459	4	288
Respiratory syncytial virus (ALV)	2	759	2	1,044	2	455
Hemophilus influenzae b	3	669	3	844	1	461
Influenza viruses A & B (subunit)	4	521	5	638	3	376
Influenza viruses A & B (ALV)	5	504	4	734	6	275
Respiratory syncytial virus (glycoprotein)	6	458	6	630	5	275
Herpesvirus varicellae (high-risk individuals)	7	237	8	281	7	179
Herpesvirus varicellae	8	167	7	290	11	69
	9	132	9	188	10	76
Herpesvirus Varicellae	10	125	10	168	9	79
(normal, children)	11	115	12	141	8	83
Parainfluenza viruses	12	62	11	148	15	15
Streptococcus group B						
Cytomegalovirus (ALV! high-risk individuals)	13	43	13	124	16	8
Herpes siirplex viruses 1 & 2 (glycoprotein)						
Cytomegalovirus (glycoprotein: children)	14	41	15	54	13	26
Rotavirus (bovine ALV)	15	40	17	49	12	29
Bordetella Dertussis						
Rotavirus (human ALV)	16	38	16	50	14	24
Herpes simplex 1 & 2 (ALV)	17	22	14	68	17	4
Neisseria gonorrhoeae	18	8	18	14	18	3
Cytomegalovirus (ALV: nonpregnant adolescent females)	19	5	19	11	19	1
Hepatitis A virus (ALV)	20	4	20	10	20	1
Hepatitis A virus (subunit)	21	1	21	3	21	<1
Coccidioides immitis	22	<1	22	0.2	22	<1

TABLE 9.5 Sensitivity Analysis: Annualized Present Value of Expected Net Costs at Various Discount Rates

	Discount Kate					
	central Analysis (0.05)		0.02		0.10	
Vaccine	Rank	Value ($millions)	Rank	Value ($millions)	Rank	Value ($millions)
Herpesvirus varicellae (high-risk individuals)	1	-43	1	-51	1	-32
Respiratory syncytial virus {ALV)[a]	2	-32	2	-46	2	-17
Influenza viruses A & B (ALV)	3	-23	4	-37	3	9
Parainfluenza viruses	4	-18	5	-30	5	-6
Streptococcus group B	5	-16	6	-24	4	-7
Hepatitis B virus	6	-12	3	-41	15	6
Cytomegalovirus (ALV: high-risk individuals)	7	-7	10	-8	6	-4
Respiratory syncytial virus (glycoprotein)	8	-6	9	-11	7	-1
Neisseria gonorrhoeae	9	-3	8	-12	13	4
Cytomegalovirus (ALV: nonpregnant adolescent females)	10	-1	12	-3	9	1
Coccidioides immitis	11	0.5	15	0	8	1
Rotavirus {bovine ALV)	12	1	13	0	10	3
Herpes simplex viruses 1 & 2 (ALV)	13	2	11	-3	12	4
Rotavirus (human ALV)	14	2	14	0	11	3
Hepatitis A virus (ALV)	15	4	16	2	14	5
Hepatitis A virus (subunit)	16	7	17	7	16	6
Cytomegalovirus (glycoprotein: children)	17	16	7	-15	17	21
Herpesvirus varicellae (normal, children)	18	26	18	22	18	24
Influenza viruses A & B (subunit)	19	31	19	33	19	28
Hemophilus influenzae type b	20	49	20	46	20	48
Bordetella pertussis	21	58	21	64	22	50
Herpes simplex viruses 1 & 2	22	66	22	76	21	48

[a] Attenuated live virus.

Alternative Development Scenario

The central analysis employs the probability of successful development indicated for each vaccine in Chapter 5. The effect of adopting a more optimistic but not unreasonable view was examined by assuming a 100 percent chance of successful development within the period set for likely time to licensure. The results are shown in Table 9.6. Such an assumption would not materially affect the choice of the top five vaccines.

As another sensitivity analysis, by way of example, we considered the effects of lowering the probability of successful development for a single, highly ranked, vaccine—RSV-ALV (Table 9.7). The original estimate reflected in Tables 9.1 and 9.2 was 80 percent. In order to eliminate RSV-ALV vaccine from the top five (based on expected health benefit: committee median perspective, Table 9.2), this probability would have to be less than 25 percent, in which case Herpesvirus varicellae vaccine (for normals and children) would surpass it.

Alternative Utilization Scenario

Anticipated utilization rates used in the central analysis are those estimated by the method described in Chapter 6. These are for voluntary acceptance. They assume that new vaccines will not be used in combination with existing vaccines, and that use will reflect presently prevailing attitudes towards the diseases. Higher utilization rates probably could be achieved by combining vaccines or by instituting promotional/educational campaigns. To determine the effect of possible increased use on rankings, an optimistic utilization scenario was developed. In this scenario, it is assumed that the use rate for pediatric vaccines (including the attenuated live cytomegalovirus vaccine for adolescent females) is raised to 90 percent by vaccine combination or some other means. For adult vaccines (including the N. gonorrhoeae vaccine), the scenario assumes that the use rate is raised to 33 percent by promotional campaigns. If the estimated use rate is higher than the rate assumed in the optimistic scenario, the higher rate is used in the sensitivity analysis. Incremental vaccination program costs are recalculated for influenza vaccine (at 33 percent utilization) as described in Chapter 7.

The effects on the ranking of adopting this optimistic utilization scenario are shown in Table 9.8.

Assuming optimistic utilization rates would leave RSV, influenza, hepatitis B, and H. influenzae type b vaccines in the top five based on expected health benefit, and would move gonococcal vaccine into the top five as well, in place of varicella vaccine for high-risk persons. In addition, the subunit vaccine against influenza becomes much more cost-effective, being preferred to the ALV vaccine for willingness to pay value of greater than $33,000 per IME saved. Moreover, streptococcus group B vaccine replaces H. influenzae type b vaccine for willingness to pay values below $275,000 per IME. Herpesvirus varicellae vaccine (high-risk individuals) replaces hepatitis B vaccine for

TABLE 9.6 Sensitivity Analysis: Alternative Development Scenario

	Annualized Present Value of Expected Health Benefits (committee median perspective)					Annualized Present Values of Expected Net Costs ($million)			
	Predicted probability of Successful Development (central analysis)		100% probability of Successful Development			Predicted Probability of Successful Development (central analysis)		100% Probability of Successful Development	
Vaccine	Rank	Value	Bank	Value	Vaccine	Rank	Value	Bank	Value
Hepatitis B virus	1	782	2	824	Herpesvirus varicellae (high-risk individuals)	1	-43	1	-43
Respiratory syncytial virus (ALV)	2	759	1	949	Respiratory syncytial virus (ALV) .	2	-32	2	-40
Hemophilus influenzae type b	3	669	3	744	Influenza viruses A & B (ALV)	3	-23	3	-33
Influenza viruses A & B (subunit)	4	521	5	579	Parainfluenza viruses	4	-18	5	-23
Influenza viruses A & B (ALV)	5	504	4	720	Streptococcus group B	5	-16	4	-26
Respiratory syncytial virus (glycoprotein)	6	458	6	573	Hepatitis B virus	6	-12	7	-13
Herpesvirus varicellae (high-risk individuals)	7	237	7	239	Cytomegalovirus (ALV: high-risk individuals)	7	-7	6	-14
Herpesvirus varicellae (normals, children)	8	167	10	176	Respiratory syncytial virus (glycoprotein)	8	-5	8	-8
Parainfluenza viruses	9	132	11	166	Neisseria gonorrhoeae	9	-3	9	-8
Streptococcus group B	10	125	9	193	Cytomegalovirus (ALV: nonpregnant adolescent females)	10	-1	10	-2
Cytomegalovirus [ALV: high-risk individuals)	11	115	8	231	Coccidioides immitis	11	0.5	11	0.5
Herpes simplex viruses 1 $ 2 (glycoprotein)	12	62	13	69	Rotavirus (ALV bovine)	12	1	12	1
Cytomegalovirus (glycoprotein: children)	13	43	12	86	Herpes simplex viruses 1 & 2 (ALV)	13	2	14	3
Rotavirus (ALV bovine)	14	41	16	43	Rotavirus (ALV human)	14	2	13	2

TABLE 9.6 (Continued)

	Annualized Present *Value* of Expected Health Benefits (committee median perspective)					Annualized Present Values of Expected Net Costs ($million)			
	Predicted Probability of Successful Development (central analysis)		100% Probability of Successful Development			Predicted Probability of Successful Development (central analysis)		100% Probability of Successful Development	
Vaccine	Rank	Value	Bank	value	Vaccine	Bank	Value	Rank	Value
Bordetella pertussis	15	40	15	44	Hepatitis A virus (ALV)	15	4	15	4
Rotavirus (ALV human)	16	38	17	42	Hepatitis ft virus (subunit)	16	7	16	7
Herpes simplex 1 & 2 (ALV)	17	22	14	45	Cytomegalovirus (glycoprotein: children)	17	16	18	29
Neisseria gonorrhoeae	18	*8*	18	15	Herpesvirus varicellae (normal, children)	18	26	17	28
Cytomegalovirus (ALV: nonpregnant adolescent females)	19	5	19	10	Influenza viruses A & B (subunit)	19	31	19	34
Hepatitis ft virus (ALV)	20	4	20	5	Hemophilus influenzae type b	20	49	20	54
Hepatitis A virus (subunit)	21	1	21	1	Bordetella pertussis	21	58	21	65
Coccidioides immitis	22	<1	22	<1	Herpes simplex viruses 1 & 2 (glycoprotein)	22	66	22	74

TABLE 9.7 Effect of Varying Probability of Success on Health Benefits and Net Costs of RSV-ALV Vaccine

	Central Analysis	
Probability of Success	Annualized Present Value of Expected Health Benefits—Committee Median (IME units)	Annualized Present Value of Expected Net Costs ($millions)
1.0	949	-40
0.9	854	-36
0.8[a]	759	-32
0.7	664	-28
0.6	569	-24
0.5	474	-20
0.4	380	-15
0.3	285	-11
0.2	190	-7
0.1	95	-3
0.0	0	1.0

[a] Probability used in central analysis.

willingness to pay values below about $50,000 per IME, parainfluenza vaccine replaces Neisseria gonorrhoeae vaccine below $30,000 per IME, and CMV vaccine (ALV, nonpregnant adolescent females) replaces influenza vaccine below $12,000 per IME.

Low Vaccine Cost Scenario

The effect on the rankings of assuming a lower vaccine cost per dose (50 percent of that predicted; Chapter 5) is shown in Table 9.9.

This assumption does not materially affect the ranking of vaccine candidates.

Conclusions

Final decisions on the number of vaccines to be selected for accelerated development and on the ultimate choices must incorporate a

TABLE 9.8 Sensitivity Analysis: Optimistic Utilization Scenario

	Annualized Present Value of Expected Health Benefits (committee median perspective)					Annualized Present Value of Expected Net Costs ($million)			
	Predicted Utilization (central analysis)		Optimistic Utilization			Predicted Utilization (central analysis)		Optimistic Utilization	
Vaccine	Rank	Value	Rank	Value	Vaccine	Rank	Value	Rank	Value
Hepatitis B virus	1	782	6	755	Herpesvirus varicellae (high-risk individuals)	1	-43	3	-43
Respiratory syncytial virus (ALV)	2	759	4	1,271	Respiratory syncytial virus (ALV)	2	-32	1	-55
Hemophilus influenzae type b	3	669	5	775	Influenza viruses A & B (ALV)	3	-23	5	-29
Influenza viruses A & B (subunit)	4	521	1	2,609	Parainfluenza viruses	4	-18	4	-31
Influenza viruses A & B (ALV)	5	504	2	1,514	Streptococcus group B	5	-16	2	-53
Respiratory syncytial virus (glycoprotein)	6	458	3	1,271	Hepatitis B virus	6	-12	9	-12
Herpesvirus varicellae (ALV: high-risk individuals)	7	237	11	162	Cytomegalovirus (ALV: high-risk individuals)	7	-7	10	-7
Herpesvirus varicellae (normals, children)	8	167	9	252	Respiratory syncytial virus (glycoprotein)	8	-6	7	-20
Parainfluenza viruses	9	132	10	199	Neisseria gonorrhoeae	9	-3	8	-16
Streptococcus group B	10	125	8	372	Cytomegalovirus (ALV: nonpregnant adolescent females)	10	-1	6	-27

Cytomegalovirus (ALV: high-risk individuals)	11	115	16	83
Herpes simplex viruses 1 & 2 (glycoprotein)	12	62	14	106
Cytomegalovirus (glycoprotein: children)	13	43	17	80
Rotavirus (ALV bovine)	14	41	13	110
Bordetella pertussis	15	40	19	38
Rotavirus (ALV human)	16	38	15	101
Herpes simplex viruses 1 & 2 (ALV)	17	22	18	58
Neisseria gonorrhoeae	18	8	7	662
Cytomegalovirus (ALV: nonpregnant adolescent females)	19	5	12	112
Hepatitis A virus (ALV)	20	4	20	33
Hepatitis A virus (subunit)	21	1	21	31
Coccidioides immitis	22	<1	22	2.4

Coccidioides immitis	11	0.5	11	0.2
Rotavirus (ALV bovine)	12	1	14	3
Herpes simplex viruses 1 & 2 (ALV)	13	2	15	5
Rotavirus (ALV human)	14	2	13	3
Hepatitis A virus (ALV)	15	4	16	26
Hepatitis A virus (subunit)	16	7	21	132
Cytomegalovirus (glycoprotein: children)	17	16	17	28
Herpesvirus varicellae (normals, children)	18	26	20	59
Influenzae viruses A & B (subunit)	19	31	12	3
Hemophilus influenzae b	20	49	18	57
Bordetella pertussis	21	58	19	58
Herpes simplex viruses 1 & 2 (glycoprotein)	22	66	22	164

TABLE 9.9 Sensitivity Analysis: Lowering Vaccine Costs

	Lowering Present Value of Expected Net Costs ($million)			
	Predicted Vaccine Cost (central analysis)		50% of Predicted Vaccine Cost	
Vaccine	Rank	Value	Rank	Value
Herpesvirus varicellae (high-risk individuals)	1	-43	1	-43
Respiratory syncytial virus (ALV)	2	-32	2	-38
Influenza viruses A & B (ALV)	3	-23	3	-32
Parainfluenza virus	4	-18	4	-29
Streptococcus group B	5	-16	7	-18
Hepatitis B virus	6	-12	5	-22
Cytomegalovirus (high-risk individuals)	7	-7	10	-7
Respiratory syncytial virus (glycoprotein)	8	-6	8	-13
Neisseria gonorrhoeae	9	-3	11	-6
Cytomegalovirus (nonpregnant adolescent females)	10	-1	14	-1
Coccidioides immitis	11	0.5	15	0.5
Rotavirus (ALV bovine)	12	1	12	-3
Herpes simplex viruses 1 & 2 (ALV)	13	2	16	1
Rotavirus (ALV human)	14	2	13	-2
Hepatitis A virus (ALV)	15	4	17	2
Hepatitis A virus (subunit)	16	7	19	5
Cytomegalovirus (glycoprotein, children)	17	16	18	3
Herpesvirus varicellae (normal, children)	18	26	20	9
Influenza viruses A & B (subunit)	19	31	6	-21
Hemophilus influenzae type B	20	49	9	-10
Bordetella pertussis	21	58	21	24
Herpes simplex viruses 1 & 2 (glycoprotein)	22	66	22	44

variety of non-quantifiable factors, as well as information provided by the rankings derived with the proposed system for calculating benefits and costs. The additional factors include but are not limited to:

- the goals of the agency and its time frame for achieving them
- the ethical questions that must be considered in the distribution of benefits
- the most appropriate points at which the agency can exert influence
- the extent of private sector activities
- the balance of the desired development portfolio (e.g., pediatric vs. adult vaccines; national vs. regional diseases)
- the arguments that can be made for treating certain vaccine development projects as unique because of their potential impact on immunization in general. (The committee believes that an improved pertussis vaccine merits unique treatment because of its potential for restoration of public confidence in immunization programs.)

These are discussed in more detail in Chapter 8. The analyses presented in this chapter indicate that vaccines for hepatitis B, RSV (ALV), H. influenzae type b, influenza (probably ALV), and Herpesvirus varicellae (for high-risk individuals) rank at or near the top of priority lists for accelerated development under a wide range of assumptions, although streptococcal group B vaccine and Neisseria gonorrhoeae vaccine would move up considerably if utilization predictions were more optimistic. The slate of top choices among the vaccine candidates remains stable when alternative but plausible assumptions are adopted regarding discount rates and perspectives on morbidity and mortality. Many vaccines fail to enter the top five under even the most extreme assumptions. Additional sensitivity analyses, discussed below, can be performed to identify elements which may alter decisions.

Under the central analysis, the top choices also remain stable for a wide range of willingness-to-pay values per IME, i.e., between $125,000 per IME and several million dollars per IME. White (1983) has reported that most estimates of how much individuals would be willing to pay to save a life lie well within this range.

Discussion

Scientific opinion differs as to some of the judgments incorporated into the proposed method and uncertainty surrounds other factors. The system has been applied using the best estimates and data that the committee could develop within its resources. The attempt in the above described exercise to be explicit about certain estimates should not be interpreted as indicating that a high degree of precision, unanimity, or certainty in comparisons is possible with existing methods or data, or the need where data are unavailable to resort to expert judgment. The implications of gaps in the information required by the method and differences of opinion over estimates are discussed more fully in Chapter 1. In this light, additional analyses are suggested to provide

further information on the key elements that may alter decisions or on which more information is desirable.

Ideally, to fully assess the effect of alternative IME profiles on the rankings it is desirable to conduct calculations using the whole range of individual sets of IME values. Because of resource and time constraints this was not possible in the present study. Two perspectives were adopted to illustrate how potential variation in opinion might affect results. The committee, however, does not endorse either the median of its valuations or the age-neutral perspective for policy formulation in this area. The effect of adopting different IME values is discussed in Chapter 4.

A practicable solution to further examination of how differences in opinion on the undesirability of conditions might affect vaccine rankings would be to select or construct a small number of profiles which have distinct differences to the committee median or age-neutral set. For example, IME profiles that show greater or lesser aversion to chronic or acute morbidity than the median set and an alternately constructed age-neutral profile (i.e., for each morbidity category calculate the geometric mean of median IME values across different age groups). Examination of the results of the ranking process using these profiles would identify the extent to which a difference of opinion in this area could alter rankings.

A number of further sensitivity studies around the central analysis are also possible. These include the effect on the rankings of different predictions about the number of doses needed with a vaccine (which would affect vaccination program, and hence, net costs), and of variation in the predictions on individual vaccines, e.g., the probability of success of development of vaccines.

The impact on rankings could also be tested employing alternative assumptions on the choice of target population for some vaccines (e.g., gonococcal); this would, however, entail more extensive recalculations including re-estimation of vaccine preventable illness.

Recommendation

The National Institute of Allergy and infectious Diseases and other agencies should consider means of improving the epidemiologic data on which disease comparisons can be based. Lack of data in some areas and the variable quality of data in other areas are serious impediments to the development of a comprehensive priority selection scheme.

Reference

White, L.J. 1983. Public decision-making with respect to atmosphericPAH sources and emissions. Pp. D1–D26 in Polycyclic AromaticHydrocarbons. National Academy of Sciences. Washington, D.C.:National Academy Press.

APPENDIXES

Appendix

A

SOME EXAMPLES OF THE APPLICATION OF PROJECT SELECTION METHOD

Allocating Resources to Medical Technologies

Cost-effectiveness analysis and benefit-cost analysis have been applied in the evaluation of several medical technologies, including vaccines (Koplan et al., 1979; Schoenbaum et al., 1976; Willems et al., 1980). Weinstein and Stason (1977) have reviewed these applications. The premise underlying the use of such methods is that the rankings supplied by the cost-effectiveness ratios, if obtained by uniform methods, could offer a guide to the allocation of limited resources by health care providers.

Application of cost-effectiveness analysis to the setting of priorities for clinical research also has been suggested and methods have been outlined by Mosteller and Weinstein (1981). These methods have been applied informally to set priorities for clinical trials at the National Heart, Lung, and Blood Institute (Levy and Sondik, 1982).

A decision-analytic approach to priority setting for health programs has been used in Ghana (Ghana Health Assessment project Team, 1981). It was proposed that priority setting for disease prevention could be guided by the impact of target diseases measured on an index called "days of healthy life lost," in which days of morbidity were weighted on a 0–1 scale and then aggregated with days of life lost. This example, like many others based on the impact of illness, considers only potential benefits and does not consider the costs and effectiveness of specific disease interventions, nor does it consider economic benefits or costs.

Priorities for Biomedical Research

Cost-effectiveness analysis has been proposed to help set priorities for biomedical research (Keeler, 1970). For this purpose, the numerator of the cost-effectiveness ratio is the cost of the research itself, while the denominator is a benefit-cost estimate of the net expected reduction in the economic cost of the disease, multiplied by the subjective probability of successful research. Keeler's study contains an example based on a comparison (as of 1970) of hepatitis versus rubella vaccines.

Selection of Chemicals for Toxicity Testing and Regulation

Several multiattribute scoring systems have been developed in response to the need for government agencies to set priorities for testing chemicals for toxic effects, including carcinogenicity. The agencies directly involved have been the National Toxicology Program in the Department of Health and Human Services, and the Environmental Protection Agency (EPA), which is required under the Toxic Substances Control Act to publish every six months a list of the highest priority chemicals it has identified for mandatory testing in the private sector.

A committee of the National Research Council/National Academy of Sciences reviewed a number of the scoring systems that had been developed (National Academy of Sciences, 1981). One of the more sophisticated systems developed for the Environmental Protection Agency is described in the report of the Toxic Substances Control Act Interagency Testing Committee (1977). This scoring system is based on two groups of attributes: exposure-related and biological. The exposure score used in this method consists of a weighted combination of four factors: quantity of production; quantity released; number of persons occupationally exposed; and number of persons generally exposed. The "quantity released" factor score is a composite of two subfactor scores (quantity and persistence), and the factor score for "extent to which the general population is exposed" is a composite of four subfactor scores (number of people exposed, frequency of exposure, exposure intensity, and penetrability). Interestingly, although the latter four subfactor scores are added, they are quantified on a quasi-logarithmic scale so that the process approximates a multiplicative combination, which would be the approach dictated by decision analysis.

The biological scores used in the method seem more arbitrary and are actually used only informally (i.e., in a multiattribute accounting mode) in the selection process. Ultimately, a list of the few dozen top candidates, as identified by the scoring system, is reviewed by the committee, and the final selection is based on informal judgment, not the formal scores. This subjective final step is necessary because no attempt is made earlier to incorporate within the scores several key objectives, including feasibility of testing and regulation.

Cost-effectiveness analysis also has been suggested for the testing priorities problem (Weinstein, 1979), and multiattribute scoring systems have been proposed for setting priorities for regulating toxic chemicals (Squire, 1981).

Priorities for Hazardous Waste Sites Under Superfund

A recent example of a multiattribute scoring system for project selection has been developed at the EPA in response to legislation that sets aside a certain amount of money for the clean-up of the highest priority hazardous waste sites in the nation—the so-called Superfund. The scoring system, called the Hazard Ranking System (HRS), is part of

the National Oil and Hazardous Substances Contingency Plan (Environmental Protection Agency, 1982).

The scoring system consists of a hierarchy containing five main scores, several "factor category" scores within each main score, and several "factor" scores within each factor category. The main scores are: potential for harm from migration of a substance away from the site by air (S_A), surface water (S_{SW}), and groundwater (S_{GW}); potential for hazards of fire or explosion (S_{FE}); and potential for direct contact at the site (S_{DC}). Each main score is normalized to a 0–100 scale. A composite score for potential for harm from migration (S_M) is derived as the normalized root-mean-square of the scores for the three routes of exposure:

$$S_M = \sqrt{\frac{S_A^2 + S_{SW}^2 + S_{GW}^2}{3}}.$$

Within each main score, several factor category scores (0–100 scale) are multiplied and then renormalized on a 0–100 scale. The multiplicative combination of factor category scores can be viewed as an approximation of the more rigorous decision-analytic approach in which one would express the hazard posed by a waste facility as the product of the probability of a harmful occurrence and the magnitude of the potential damage. In general, though the HRS does not directly quantify the probability of harm from a facility or the magnitude of potential harm, the factors have been defined to approximate both of these elements.

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Appendix

B

PATHOGENIC AGENTS FOR WHICH ACCELERATED VACCINE DEVELOPMENT DOES NOT APPEAR APPROPRIATE

Judging the Feasibility of Accelerated Vaccine Development

The selection of candidates for accelerated vaccine development depends in part on the mechanisms used to promote development. In the broadest sense, accelerated development could refer to any increase in emphasis or funding at any point along the continuum from disease definition and basic research through clinical trials to licensure.

In the early phases of vaccine development, the questions that need to be answered and the methods most appropriate for answering them may be difficult to define. A diversity of approaches may be desirable until a scientific consensus emerges on the research directions most likely to be productive. Once the pathways for development have been set, however, the tasks needed to bring the vaccine to licensure are easier to identify and place in a uniform framework.

The National Institute of Allergy and Infectious Diseases' (NIAID) influence to accelerate development is most likely to be effective in the latter stages of the continuum, probably through the contract mechanism. One of the committee's first responsibilities was to identify vaccine candidates "ready" for this type of support. Candidates were included in the ranking exercise described in Chapter 3 if committee members and knowledgeable consultants believed that their successful development was probable within ten years. Candidates excluded from the analysis are described briefly, in alphabetical order, later in this appendix. (In several cases, reasonable vaccine candidates were excluded because they do not have a significant disease burden in the United States. These will be included in a separate report on vaccine development for technologically less developed countr ies.)

The knowledge required to determine the feasilibity of accelerated development covers a wide spectrum, from characteristics of the pathogen to the composition of the target population. The latter is important not only for cost-effective vaccine delivery, but also to determine whether there is sufficient motivation to achieve reasonable utilization. No checklist can replace experienced judgment in assessing vaccine feasibility, but it is possible to identify certain factors that generally facilitate vaccine development (although all may not be essential):

- knowledge of clinical signs and symptoms of the disease to allow differentiation from similar syndromes
- identification of the pathogen and its major characteristics, including the existence of strains and serotypes, their infectivity, their virulence, their antigenicity, and the nature of essential immunogens
- the existence of specific techniques for cultivation of the pathogen
- identification of non-human models of infection
- knowledge of the human immune response to the pathogen, including the duration and type of response (e.g., serum antibody, mucosal antibody, or cell-mediated immunity)
- definition of the target population.

All aspects of the knowledge base that involve technical feasibility must be reassessed frequently: a vaccine not foreseeable today may become reality because of one unexpected development in the laboratory. This is especially true in the fields relevant for vaccine development, because the capacity of modern biotechnology has only begun to be explored.

Accelerated vaccine Development and Basic Research priorities

The criteria for selection of candidates for accelerated vaccine development do not address the general question of which vaccines are most needed in the United States. For some diseases that impose major burdens on the U.S. population, the knowledge base is not sufficient to allow consideration for accelerated vaccine development by NIAID. Nevertheless, portions of the analysis described in this report can be applied to these disease problems to gain useful information about long-term goals and potential benefits. The description of disease burden considerations in Chapter 4 and the discussion of utilization patterns in Chapter 6 may be especially helpful in this regard.

The committee hopes that the selection of candidates for accelerated vaccine development will not divert funds from long-term basic research programs. For these programs, the scientific merit of the research proposal should continue to be the dominant criterion for funding.

Pathogens not Included on the Slate of Candidates

Acquired Immune Deficiency Syndrome Agent

During the tenure of this committee, research has led to rapid generation of new knowledge about the suspected etiology of Acquired Immune Deficiency Syndrome (AIDS). The committee decided, however, that speculation in this report regarding the future availability and efficacy of an AIDS vaccine would not be useful.

Recent investigations suggest that the retroviruses Human T-Cell Leukemia Virus (HTLV-III) and Lymphadenopathy Associated Virus (LAV) may be the agents (or agent, if they prove to be identical) responsible for AIDS (Centers for Disease Control, 1984). Large-scale production techniques to produce virus and virus antigens in sufficient quantities to develop diagnostic kits for detection of antibody already are under licensure from the National Institutes of Health (NIH) to at least five commercial companies. Panels of scientists at the NIH and the Food and Drug Administration are proceeding as rapidly as possible with studies of the relevant etiologic relationships, and their results could provide the information necessary to begin development of possible vaccines.

Consideration of a candidate AIDS vaccine under the formula developed by the Committee would be influenced markedly by the high mortality rate associated with AIDS as studied to date. Two years after diagnosis, more than 70 percent of patients have died. Estimates indicate that the total number of persons affected is now about 5,000.

The availability of stable cell lines and a lymphoblastoid cell line in which HTLV-III and LAV replicate further augments the capacity for vaccine development. Robert Gallo and his colleagues at the National Cancer Institute have suggested that analysis of a specific viral protein antigen, common to all HTLV-III isolates examined to date, might be a suitable beginning for research leading to a possible vaccine. It is important to remember that previous attempts to prepare immunizing agents against animal retroviruses have not been very successful, but they have never been fully exploited. AIDS, if it is indeed a human retrovirus-induced disorder, certainly will provide the incentive necessary for new work in this area.

Live virus vaccines seem unlikely with agents so readily integrated into the host cell genome. Inactivated virus or component antigens are promising and certainly should be safe. Eventual decisions regarding investment in vaccine development obviously would include consideration of a number of the factors discussed in Chapter 8, "Additional issues in the Selection of Priorities for Accelerated Vaccine Development."

Adenovirus (respiratory disease)

Adenovirus causes acute respiratory disease in children and military recruits, gastrointestinal disease, and conjunctivitis. Efforts to produce vaccines for these illnesses have been reviewed briefly by Foy and Grayston (1982).

Early work involving inactivated vaccines for military recruits encountered problems with variable vaccine potency, which resulted from poor virus growth in the monkey cell cultures used for propagation. Other researchers have shown that subunit vaccines are possible (Kasel et al., 1966), but both of these approaches have been abandoned in favor of attempts to stimulate immunity to respiratory infection with live oral vaccines.

Multivalent live oral vaccines are licensed for the strains responsible for disease in military recruits, but these are different from

the strains responsible for most disease in civilian populations. Also, the strains used in the live oral vaccine are not significantly attenuated. While no spread of infection has been found in military use, spread was observed among children when the live oral vaccines were tested (Foy and Grayston, 1982). The potential problem of respiratory illness developing in contacts of recipients of the oral unattenuated adenovirus vaccine and questions about the oncogenic potential of adenoviruses remain obstacles to future vaccine development.

Anaerobic Bacteria

Bacteroides fragilis This organism is regarded as the most important anaerobe in clinical medicine because of its prevalence in intra-abdominal sepsis, its frequent association with bacteremia, and its resistance to antibiotics. B. fragilis is also the only anaerobic bacterium capable in experimental animal model systems of inducing abscess alone rather than in combination with a facultative aerobic organism (Washington, 1971). The organism has a polysaccharide capsule that is immunogenic, and animal experiments have shown that vaccination induces antigen specific T-cell dependent immunity to abscesses. The principal factor limiting pursuit of a polysaccharide vaccine for this organism is that only 70 percent of intra-abdominal infections involve B. fragilis (Shapiro et al., 1982). In animal models, however, immunization with capsular polysaccharide leads to development of an antigen specific lymphokine capable of protecting against abscesses caused by B. fragilis. Pursuit of a vaccine of cellular rather than bacterial origin offers promise for reducing the incidence of intra-abdominal abscesses (Kasper, personal communication, 1984).

Clostridium botulinum The disease caused by this organism is relatively rare in the United States (50 to 100 cases per year) and most cases occur in young infants. A vaccine is available, but its efficacy in children under age six months (against the infant botulism form of the disease) is uncertain. Use of the vaccine is now restricted to older, high-risk individuals, such as those doing experimental work with the organism.

Clostridium difficile This agent is the most common cause of antibiotic-associated colitis. Its two toxins, designated A and B, are immunogenic, but it is not yet known if antigenic experience confers protection. The high prevalence and serious morbidity associated with C. difficile disease make it a likely candidate for vaccine development in the future.

Clostridium perfringens This organism is a common cause of food-borne outbreaks of gastrointestinal illness, but the disease is usually brief, self-limited, and not life threatening except in some regions. The enterotoxin is immunogenic and a vaccine is available outside the United States.

Clostridium tetani Tetanus toxoid is now administered routinely to most children in the United States. Hence, cases of tetanus in the United States may occur in the elderly, who may not have been immunized. The elderly seem to have a blunted response to booster doses of tetanus toxoid; this problem with efficacy in a portion of the population probably does not call for development of a new vaccine.

Chlamydia

The Chlamydia trachomatis species contains various strains that are the etiologic agents of lymphogranuloma venereum (LGV), trachoma, and various other syndromes. There are at least 15 serotypes of C. trachomatis: three are associated with LGV and 12 are considered trachoma strains, although the symptoms they produce range from acute and chronic eye disease, urethritis in males, and genital tract infection in females, to acute ocular and respiratory tract infections in newborns and young infants (Grayston and Wang, 1978). C. trachomatis is now considered a major cause of sexually transmitted disease (e.g., mucopurulent cervicitis).

C. trachomatis is not a suitable candidate for vaccine control at this time for both biological and public health reasons (NIAID, 1984). There is little evidence of natural immunity. Results from trials with an inactivated vaccine suggest that chronic eye disease with pannus formation may result from heterotypic infection: eye disease was accentuated in vaccine recipients who later became infected with another serotype (Craighead, 1975). Field studies in Taiwan and India with multiple doses of an inactivated vaccine failed to show long-term protection (Grayston and Wang, 1978).

The number of genital and neonatal infections caused by C. trachomatis strains probably could be reduced substantially by standard public health measures, including contact tracing. Efforts also are underway to modify some antibiotic treatment protocols, i.e., for gonorrhea to ensure killing of chlamydiae which are often isolated either alone or with gonococci from cultures of patients with urethritis (Bowie and Holmes, 1979).

Entamoeba histolytica

The E. histolytica ameba frequently is found living as a commensal in the lumen of the human large intestine, producing large numbers of infective cysts that are transmitted by the fecal-oral route. It also may produce invasive amebiasis, however, with symptoms ranging from mild dysentery to life-threatening fulminant, hemorrhagic infection with high fever. Liver invasion with abscess formation also may occur.

While amebiasis is not common in the U.S., loci exist in both institutional and non-institutional settings (Krogstad et al., 1978). Prevalence rates among male homosexuals may range from 20 to 30 percent in some large cities (Kean, 1976, 1981; Phillips et al., 1981; Pomerantz et al., 1980).

Little is known about the pathogenic mechanisms of the disease, the factors governing commensal or invasive behavior, or the nature of the host response. Although surface differences have been reported between commensal and invasive infectious agents (Martinez-Palomo and Martinez-Baez, in press), much basic research needs to be conducted before vaccine prevention of amebiases can be considered.

Epstein-Barr Virus

Epstein-Barr virus (EBV), a member of the herpes group of viruses, is the principal cause of infectious mononucleosis in young adults. It also has been implicated as a causal factor in the development of Burkitt lymphoma in Africa and of nasopharyngeal carcinoma in immunogenetically susceptible persons in the Far East (Evans and Neiderman, 1982).

EBV appears to be a suitable pathogen for vaccine control: natural infection affords a high degree of protection, involving both humoral and cell-mediated immunity. In technologically less developed countries, where EBV antibody usually is acquired in early childhood following mild or asymptomatic infections, clinical infectious mononucleosis is rare.

Unfortunately, major technical problems remain to be solved before development of an EBV vaccine can proceed. Virus cultivation has been successful only in suspension cultures of primate lymphocytes, and the yield of extracellular virus is usually quite low. This limits research efforts in general, and especially those concerned with attenuation of the virus. A subunit vaccine consisting of a component of the viral membrane antigen complex could circumvent this problem. Researchers have made substantial progress in determining the structure of gp340, an EB viral envelope glycoprotein that induces virus-neutralizing activity in experimental animals (Morgan et al., 1983).

Uncertainty about the oncogenic and transforming potential of EBV may inhibit the development and use of a live attenuated virus vaccine. More information is needed on how the virus interacts with the immune system at different ages and in different populations.

Escherichia coli

Immune prophylaxis for diarrheal diseases caused by E. coli was excluded from consideration in the domestic (U.S.) phase of this study. It will be included in the discussion of vaccines for technologically less developed countries.

Experimental work with animal models suggests that development of a vaccine to prevent upper and lower urinary tract infections in infants and children may be feasible (Robbins, personal communication, 1983). Various types of E. coli antigens elicit protective immunity in animal models: the K (acidic) 1, 2, 3, 12, 13 capsular polysaccharide and the mannose resistant globeside-binding pili. The process of defining which antigens should be incorporated into a candidate vaccine is

underway, so it is recommended that vaccine prospects in this area be reviewed regularly.

Giardia lamblia

Immune prophylaxis against giardiasis was excluded from consideration in the domestic phase of this study; it will be included in the discussion of vaccines for technologically less developed countries.

Hospital Acquired Infections (gram-negative bacteria)

Hospital-acquired infections due to gram-negative bacteria are an extremely serious problem in the U.S. They are a major cause of interrupted and complicated treatment protocols in patients undergoing chemotherapy. Treatment is difficult, prolonged, expensive and often fails to prevent significant morbidity and mortality.

The most common causes of these infections are Escherichia coli, Klebsiella spp., Pseudomonas aeruginosa, and Serratia marcescens. Although experimental data in laboratory animals suggest that surface antigens of these bacteria may be protective, they are too diverse for use as immunoprophylactic agents.

Basic research into the structure of lipopolysaccharides (essential macromolecules on the outer membranes of all gram-negative bacteria) has revealed that the region close to the lipid A ("core") is antigenically similar in most gram-negative species. Antibodies to this deep "core" region exert complement-mediated anti-bacterial effects that include promotion of opsonization, phagocytosis, and bacteriolysis, and neutralization of "endotoxic" activities including vasomotor collapse. Mutants have been isolated that have this specific structure exposed. Immunization of volunteers with these mutants has produced hyper immune globulins that, when administered passively, confer protection against both morbidity and mortality caused by gram-negative bacteremia.

Clinical trials of this hyper immune plasma and/or globulin probably will be initiated by commercial firms in the near future. If early reports about this hyperimmune plasma are verified, then these products could be on the market within several years.

NIAID could stimulate progress in this important area by supporting studies to characterize these protective antibodies and to develop new ways to elicit them.

Non-Typable Hemophilius influenzae (NTHI)

NTHI is the second leading cause of acute otitis media in children. It also causes sinusitis, conjunctivitis, and exacerbations of chronic bronchitis and cystic fibrosis. In neonates and immunocompromised adults it may cause bacteremia, with or without meningitis.

Several major problems impede development of a vaccine for NTHI. First, the NTHI organisms appear to be quite heterogeneous (Anderson,

personal communication, 1984). No standard methodology exists to identify specific isolates or to distinguish them from the progeny of capsulated H. influenzae strains (some of which may carry only traces of capsular antigen). Vaccine development will depend in part on identification of an antigenic structure that is common to most NTHI strains and that is immunogenic in both children and adults.

The second problem is that NTHI pathogens usually cause disease on mucosal surfaces rather than invasive infections. The role of mucosal immune factors in protection against these organisms is poorly understood (Gilsdorf, personal communication, 1984). For otitis, the development of specific immunity may be less important than the maturation of non-specific barriers.

Non-A, Non-B Hepatitis (NANBH)

The major stumbling block to development of a non-A, non-B hepatitis vaccine is that despite many years of intensive effort the nature of the infective agent or agents remains a mystery. Inactivation and physical characterization experiments seem to indicate that NANBH is caused by some type of relatively conventional virus (Feinstone and Purcell, 1983), but no one has been able to identify an antigen-antibody system.

One explanation for this failure might be the very low infectivity titers found in patients and animal models (titers seldom exceed 10^2 to 10^3 infectious units per ml). At these titers, the virus would not be detected by even the most sensitive radioimmunoassays unless there were a large excess of viral antigen in the plasma (Purcell, personal communication, 1984). Another explanation might be that patients do not develop an antibody to the agent. NANBH often causes chronic infection and cases that appear to be self-limiting may actually be asymptomatic chronic infections. If, as in chronic hepatitis B virus infections, no antibody is produced to surface antigens, then the virus would not be detectable using an immunoassay.

Some laboratories are now turning to molecular virology in an attempt to identify nucleic acids unique to non-A, non-B hepatitis agents. If and when such a genome is identified, it should be possible to clone it, sequence it, search for open reading frames, prepare NANBH virus-associated antigens (either by expression in appropriate vectors or by synthesis of peptides), and study the antigens and their respective antibodies. At that point, an NANBH vaccine might be possible.

Histoplasma capsulatum

Serological studies indicate that only about 1 percent of those infected with H. capsulatum have severe disease. Whether this is the result of variation in virulence of the pathogen, an inoculum effect, or variation in the host response is not clear (Medoff, personal communication, 1984). Hence, more research is needed on the pathogen

and the immune response to better define the prospects for immune prophylaxis and the population at risk of illness.

Human Papilloma Virus

Growing evidence of an association between human papilloma virus (HPV) and human cervical cancers has increased interest in the development of an HPV vaccine. Apparent malignant transformation caused by HPV has been found with urogenital condylomata (Crum et al., 1984; Fletcher and Norval, 1983), and with a rare form of squamous cell carcinoma linked to the wart syndrome epidermodysplasia verruciformis. Isolation of HPV genomes in these studies was made possible by recombinant DNA technology; prior to the late 1970s, HPV research was hampered by an inability to grow the virus in tissue culture.

Development of an HPV vaccine will require greater knowledge about the immunogenicity of viral proteins. HPV has 15 known types and subtypes (Fletcher and Norval, 1983), but only some of these appear to have oncogenic potential.

Kawasaki Disease Agent

The first case of Kawasaki disease, which generally affects children under five years of age, was recognized in the United States in 1971. The true incidence of the disease is not known, however, because it is difficult to diagnose. Its symptoms include high fever, red eyes, a strawberry tongue, swollen lymph nodes, and a rash, it may have serious complications, including liver, brain, artery, or heart damage.

If the suggested causative bacterium, Propionibacterium acnes (Kato et al., 1983), is confirmed, further research on the immune response to the organism and on its spread will be needed before the prospects for vaccine prevention become clear.

Legionella spp. (Legionnaire's disease)

The most common manifestation of legionellosis is pneumonia, which may be caused by any of several species of Legionella. Other symptoms have been recognized. Information on the epidemiology, transmission, and pathogenesis of legionellosis has been reviewed by Fraser (1982). Transmission is usually by the airborne route. Some evidence suggests that humoral antibody is protective; additionally, a cell membrane fraction containing lipid, carbohydrate, and protein induces immunity to challenge in animal models (Fraser, 1982; Wong et al., 1979). No attempt at immunization of humans has been reported, however.

More research is needed to define the circumstances under which Legionella pose a threat to health. This information would help identify a potential vaccine population.

Mycobacterium tuberculosis

Vaccination against tuberculosis currently consists of intracutanous inoculation with BCG (bacillus Calmette-Guerin), an organism developed from an attenuated strain of Mycobacterium bovis in the early part of this century (Comstock, 1982). However, in the United States there is little need for the kind of protection that a vaccine can provide. Case-finding programs, chemotherapy, and chemoprophylaxis provide a wide measure of control. In addition, effective BCG vaccination would negate the diagnostic value of the tuberculin test, which probably should be protected in countries with low infection rates.

The need for improvement of BCG or development of other vaccines against tuberculosis is to be considered in the second volume of this study in which the committee addresses diseases of importance to technologically less developed countries.

Mycoplasma pneumoniae

Efforts to develop a vaccine to prevent M. pneumoniae infections have been prompted primarily by their frequent failure to respond to antibiotics. Inactivated vaccines prepared from whole organisms have been tested in a number of groups, particularly young adults. In one study, Mogabgab detected neutralizing antibodies in almost two-thirds of recipients, but found a protection rate of only 45 percent in follow-up studies (Mogabgab, 1973; Wenzel et al., 1976). Similar vaccines have been prepared and studied by other investigators with comparable results. Live attenuated vaccines, including temperature sensitive mutants, also have been developed and some have been tested in small groups of volunteers (Greenberg et al., 1974).

More recent work has focused on the role of a specific surface protein. This protein (P1) is located on a specialized terminal structure responsible for attachment of the organism to host cell membranes. Antibody to P1 protein has been shown to inhibit attachment of virulent M. pneumoniae to respiratory epithelium in tracheal organ cultures, which suggests that P1 might be an effective vaccine component.

Progress with all potential M. pneumoniae vaccines has been hampered by lack of knowledge about the natural pathophysiology and immunology of mycoplasma infection in man (Foy, 1982).

Neisseria meningitidis Group B

The major obstacle to preparation of a vaccine against this important cause of meningococcal meningitis is that the group B capsular polysaccharide, an alpha 2 8 linked homopolymer of N-acetyl neuraminic acid, is not an effective immunogen in mice or humans (Frasch, personal communication, 1984; Wyle et al., 1972). Attempts to increase its immunogenicity by noncovalent linkage to the outer membrane proteins

have been only minimally successful (Zollinger et al., 1979, 1982, 1983). Although the resultant vaccine stimulates antibodies, they are all of the IgM class, they usually do not persist beyond a few weeks, and they are variably bactericidal with human complement.

Efforts to improve the polysaccharide's immunogenicity using adjuvants or by covalent linkage to proteins must be pursued with caution because certain structures in the human fetal and newborn brain contain short oligosaccharides of sialic acid with the same alpha 2 8 linkage (Finne et al., 1983; Soderstrom et al., 1984; Zollinger et al., 1979). This potential crossreactivity may explain, in part, the poor immunogenicity of the group B polysaccharide.

The serotype proteins of the outer membrane, when prepared properly, induce a more promising antibody response. The antibodies persist for at least eight months, appear to be of reasonably high avidity, and are bactericidal with human complement (Zollinger et al., 1979, 1982, 1983). However, their protective efficacy remains unproven. The drawback is that these antibodies are primarily type specific, and probably would not provide protection against heterologous group B strains. More research needs to be done to determine how many serotypes would be required in a vaccine to provide a reasonable level of protection, the rate at which new serotypes appear, and the breadth of antigenic specificity of each of the membrane proteins. However, only a few serotypes, principally types 2 and 15, are associated with most group B meningococcal disease.

In addition to pursuing more information on outer membrane/group B polysaccharide vaccines, researchers are evaluating other surface antigens (e.g., lipopolysaccharides, pili, and iron binding proteins) that may be common to all group B strains.

Final resolution of questions involving how best to use meningococcal vaccines in the general population requires more information on the factors that influence risk of disease in individuals, occurrence of disease in specific localities, and disease spread. However, vaccines are available against serogroups A, C, Y, and W and the feasibility of employing them to prevent at least a proportion of meningococcal disease needs examination.

Rhinovirus

Between 30 and 50 percent of common colds in adults are caused by rhinovirus infections. Unfortunately, two major problems have inhibited rapid development of a vaccine to prevent these illnesses (Douglas, personal communication, 1984). The first is the large number of serotypes: a protective vaccine probably would have to be effective against at least 105 serotypes.

The second problem involves the need to elicit a local (nasal) antibody response. Several studies have shown that while inactivated rhinovirus vaccines elicit high serum antibody responses when administered parenterally, they are not protective because the resultant nasal antibody

responses are low. Inactivated rhinovirus material must be administered repeatedly to the nasal mucosa to elicit a local antibody response, but the clinical efficacy of such an approach has not yet been tested.

Experience with influenza virus vaccines suggests that administration of a live attenuated virus would stimulate the necessary local immunity, but the effort required to develop attenuated stains of 105 different serotypes would be considerable.

Rickettsia rickettsii (Rocky Mountain Spotted Fever)

Early vaccines against R. rickettsii, the etiologic agent of Rocky Mountain Spotted Fever, consisted of homogenates of infected ticks (Spencer and Parker, 1924); later they were composed of ether extracts of organisms grown in the yolk sacs of embryonated eggs (Cox, 1939). These proved relatively ineffective in the prevention of infection in direct challenge tests or on inadvertent exposure of laboratory workers. Although they prolonged the incubation period, shortened the course of illness, reduced the rate of relapse, and stimulated an early rise of antibodies, they did not prevent disease and they provided minimal prophylactic efficacy.

A third vaccine was prepared from R. rickettsii grown in tissue cultures of chick embryo fibroblasts (Kenyon and Pederson, 1975). They were formalin-inactivated and purified by sucrose density gradient centrifugation. In guinea pigs and rhesus monkeys, serologic responses to this vaccine were detectable at levels suggesting that it was immunogenically superior to the older vaccines. Preliminary studies in human volunteers revealed cellular immune and antibody responses after two or three injections. Once again, however, direct challenge tests disclosed a lack of clinical protection.

Rocky Mountain Spotted Fever continues to cause morbidity and mortality in selected areas of the nation (approximately 1,000 cases and 40 deaths each year). Vaccine would be advantageous for people in states most affected (including North Carolina, South Carolina, Georgia, Virginia, Maryland, Tennessee, and Oklahoma). Prior natural illness provides significant immunity. Research is needed at a basic level to characterize the antigens of the rickettsia, the host immune response, and the critical factors in protection against disease.

Salmonella spp. (nontyphoidal)

The committee elected to consider the prospects for nontyphoidal Salmonella vaccines along with other vaccines whose major use would be in technologically less developed countries.

Shigella spp.

The low incidence of shigella in the United States prompted the committee to include this disease in its consideration of candidates for accelerated vaccine development for technologically less developed countr ies.

Staphylococcus aureus

Staph. aureus causes a variety of clinical diseases, ranging from boils and wound infections to food poisoning, bacteremia, and toxic shock syndrome (Sheagren, 1984a,b). In a recent survey conducted by the Centers for Disease Control, Staph. aureus ranked second behind Escherichia coli as a cause of all types of hospital-acquired infections.

Despite many years of intensive research to find ways of controlling Staph. aureus, the prospects for vaccine development remain slim. Researchers have just begun to understand the role of the "antiphagocytic" capsule on some strains, and the significance of certain exotoxins. The relative importance of the organism's pathogenic mechanisms remains a mystery. In addition, neither antibodies nor cell-mediated immunity appears to play a major role in host defenses against the organism (Ruben, personal communication, 1984). Previous attempts to develop vaccines against Staph. aureus have not been successful. Passive immunity might be a more practical alternative, but even this is uncertain.

Streptococcus Group A

The incidence of acute rheumatic fever (ARF) has decreased dramatically in the United States and other industrialized nations, but the disease remains the leading cause of cardiovascular morbidity and mortality among young people in much of the rest of the world (Bisno, 1984). For this reason, the committee decided to deal with the ARF etiologic agent, group A streptococcus, in its consideration of candidates for accelerated vaccine development for technologically less developed countries.

The principal virulence antigen of the group A streptococci is the M protein. There are more than 80 M protein serotypes, but recent evidence suggests that strains vary in their rheumatogenicity, so a vaccine to prevent all clinical group A streptococcal infections would not have to be hopelessly multivalent. Moreover, certain subunits of the molecule appear to contain antigens that mediate cross-reactive protection between types. An M protein fragment as small as 13 amino acids has now been chemically synthesized (Beachey et al., 1984).

The primary challenge for researchers will be to isolate and identify subpeptides of the M protein that elicit protection but that do not cross-react with human heart tissue. Although the pathogenetic significance of heart-reactive antibodies in ARF is unknown, a vaccine containing antigens that elicit heart-reactive antigens probably would be unacceptable. Fortunately, current techniques in molecular biology provide the tools necessary to identify the cross-reactive antigens and exclude them.

Streptococcus mutans

Numerous studies in rodents, primates, and humans have implicated Streptococcus mutans as the primary etiologic agent of dental caries (Hamada and Slade, 1980; McGhee and Michalek, 1981). Caries immunity has been induced successfully in laboratory animals, but the development of a caries vaccine for humans remains problematic.

One of the major problems impeding this effort is lack of knowledge about the immune system of external secretions and how it relates to serum-derived immunity. Dental caries develop in an environment that is bathed continuously by saliva. The principal immunoglobulin in saliva and other human external secretions is secretory IgA (sIgA). Ingestion of S. mutans has been shown to induce serotype-specific sIgA in humans, but the effect of this induced sIgA on bacterial colonization of tooth surfaces has not been investigated fully.

Development of a caries vaccine also will require better characterization of S. mutans antigens. This is especially important because it has been reported that sera from rabbits hyper immunized with S. mutans may cross-react with human heart tissue. Any potential cross-reactive antigens must be identified before development of a caries vaccine can proceed.

Adverse side effects would not be acceptable from a caries vaccine because dental caries is not a life-threatening disease. The challenge is to produce an effective vaccine that consists of nontoxic, relevant antigens.

Streptococcus pneumoniae

The development of an improved pneumococcal vaccine (for use in children) will be addressed in the phase of the study evaluating vaccines for use in technologically less developed countries. Although this vaccine candidate was omitted from this initial application of the proposed method to domestic (U.S.) diseases (because of resource limitations), it is recommended that it be included in future applications.

Treponema pallidum (syphilis)

Lack of knowledge about T. pallidum virulence factors and host responses to the organism make it unclear whether an immunoprophylactic approach to syphilis will be possible. Technical problems include the fact that the organism cannot be grown in culture; intratesticular passage in rabbits is the only animal model available (Baseman and Alderete, 1983).

Numerous reports indicate that the temporal appearance of humoral antibody and cell-mediated immunity during T. pallidum infection is abnormal, but the significance of this is unclear. In addition, recent evidence suggests that the organism acquires a surface coat of host macromolecules, but the biological significance of this avidly bound

host material is unknown. The surface coat might contribute to the pathophysiology of the disease by inducing autoimmune reactions to host-treponemal complexes.

Treponema-like Spirochete of Lyme Disease

Lyme disease is a tick-borne infection that was first recognized in 1975 (Steere et al., 1983). The most specific manifestation of the disease is erythema chronicum migrans (ECM), an expanding anular skin lesion accompanied by fever, headache, and myalgias. In untreated patients, the initial ECM lesion is followed by involvement of the joints, nervous system, and/or heart.

Reports from several investigators indicate that the disease is caused by a spirochete first isolated from I. dammini ticks in 1982. It is very difficult at this time to make predictions about vaccine development for Lyme disease because so little is known about the infectious agent, the pathogenesis of the disease, the host immune response, or the epidemiology of the disease. Some patients with the disease demonstrate temporal abnormalities of specific IgM and IgG responses, but the significance of these abnormalities is not clear. The late manifestations of Lyme disease may mimic several immune-mediated disorders, including juvenile rheumatoid arthritis, rheumatic fever, and multiple sclerosis. This suggests that the spirochete may trigger a self-propagating inflammatory host response.

Better understanding of the pathogenic process may indicate that vaccination will not be an appropriate form of prophylaxis for Lyme disease. Undoubtedly, one problem will be definition of an appropriate vaccine target population.

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Appendix

C

PROSPECTS FOR IMMUNIZING AGAINST BORDETELLA PERTUSSIS

Any discussion of the prospects for an improved vaccine against Bordetella pertussis must include a review of the history of the existing pertussis vaccine. The efficacy of this vaccine is well documented, but its association with a significant rate of adverse effects has made it a focus of controversy. Widespread discussion of the risks of the current pertussis vaccine may be eroding confidence in childhood immunization programs in general (see Chapter 8). A forthcoming report from the Institute of Medicine's Committee on Public-Private Sector Relations in Vaccine Innovation will address the frequency of untoward reactions to vaccines and problems arising from their occurrence. Hence, these issues will be mentioned only briefly in this appendix. The disease burden and benefits sections of this appendix are somewhat different from those of the other appendixes, because the analysis of pertussis vaccine benefits focuses on incremental rather than total benefits.

Disease Description

Pertussis (whooping cough) is a bacterial infection caused by Bordetella pertussis, and characterized by severe paroxysmal coughing that persists for weeks (Mortimer, 1982). The disease primarily affects infants and young children, and its morbidity and mortality rates generally are inversely related to age. Infants do not acquire adequate maternal immunity, so they are highly susceptible to infection.

The infection is localized in the respiratory tract, especially on the epithelial surfaces of the bronchial tree. The cause of the paroxysms of coughing (the whoop) is uncertain: it may be a result of the tenacious nature of the secretions, or a direct effect of the organism or its toxins on the central nervous system. Immediate complications include encephalopathy and convulsions, pulmonary atelectasis, and

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secondary infections such as pneumonia and otitis media. Developmental retardation and bronchiectasis may be permanent sequelae (Mortimer, 1982).

Pertussis responds poorly to treatment with antimicrobial drugs (Mortimer, 1982). Erythromycin and ampicillin, the two most commonly used antibiotics, are effective only if given in the earliest stages, although secondary complications caused by organisms other than Bordetella pertussis usually respond satisfactorily.

In the United States, morbidity and mortality due to pertussis declined rapidly following widespread adoption of the pertussis vaccine in the 1940s, and its official standardization in 1949. By 1967, the crude mortality rate from pertussis in this country had decreased to less than 1 percent of the 1930 rate; between 1970 and 1974, only 52 pertussis deaths occurred in the U.S. (Mortimer, 1982). Epidemiological studies show that the vaccine played an important role in these reductions, although not all of the decline can be attributed to its use (some decline in morbidity and mortality from pertussis was observed in industrialized nations prior to the start of immunization).

Recently, the incidence of pertussis has increased in Sweden, England, and Japan, where use of the vaccine has decreased because of the fear of severe reactions, or because vaccine of low potency has been used (Fulginiti, 1984). Pertussis remains a significant contributor to infant mortality in developing countries.

Although the incidence of pertussis in the U.S. is low, the disease is ubiquitous. In 1983, 2,258 cases (provisional total) were reported to the Centers for Disease Control (CDC) (Centers for Disease Control, 1984). This total probably represents only a fraction of all pertussis infections occurring in the country, however, for the following reasons: cases frequently go unreported or are not recognized; verification of infection by isolation of the organism requires culture methods not used routinely in many diagnostic laboratories; serologic testing is not feasible for routine diagnosis; and infection in immunized or partially immunized children may cause bronchitis, but without the typical whooping.

The current pertussis vaccine is composed of inactivated whole cells of B. pertussis. In the United States it is used exclusively in combination with diphtheria and tetanus toxoids, adsorbed with alum. The efficacy of the DPT vaccine against pertussis following primary immunization is about 90 percent (Broome, 1984; Centers for Disease Control, 1982). About 95 percent of infants and children in the U.S. receive the DPT vaccine according to schedules recommended by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics (1982).

The safety of the current whole cell pertussis vaccine component has been the subject of considerable debate within the medical literature and within the public arena (Fulginiti, 1984). Low grade fever and local tenderness appear frequently after injection. Severe or disturbing untoward reactions, including shock, convulsions, encephalopathy, and persistent high-pitched screaming, are rare complications (Hinman and Koplan, 1984). The rates of these adverse reactions are difficult to determine precisely, at least in part because they often

are not reported. Nevertheless, as morbidity and mortality from pertussis have declined, these reactions have drawn considerable attention. The frequency of fatal reactions has been estimated to be 1 to 2 cases per 10 million injections, and the frequency of serious neurologic disorders such as encephalopathy to be 1 case per 110,000 infections, with persistent neurological dysfunction one year later at 1 case/310,000 infections (Cody et al., 1981; Miller et al., 1981). The rate of adverse reactions is considered by all to be higher than desirable, and by a few to be unacceptable (Fulginiti, 1984).

Pathogen Description

Several serotypes of Bordetella pertussis have been defined, but there are no definitive data indicating that protection is serotype-specific. The development of improved pertussis vaccines has been hindered in the past by incomplete understanding of the pathogenesis of the disease, by the lack of a suitable animal model, and by uncertainty surrounding the pathogenic roles played by several exotoxins and cell wall components of the pertussis organism. Considerable progress has been made recently in characterizing some of these products, including pertussis toxin, lymphocytosis promoting factor, filamentous hemagglutinin (FHA), adenylate cyclase, lipopolysaccharide (LPS), dermonecrotic toxin, and the various agglutinogens that define the "serotype" of B. pertussis (Robbins, 1984). However, the roles played by these components and the potential benefits of antibodies manufactured against them remain unclear.

Host Immune Response

It has not been possible to define the host immune response to B. pertussis in contemporary immunologic terms, because so little is known about the antigens that induce protection. Studies reported by the British Medical Research Council in the 1950s showed good correlation between standard potency (mouse protection) test results and clinical protection (Medical Research Council, 1956). Based on these results and those of other studies, the mouse potency test was selected as an indication of efficacy in lieu of immunologic data or field studies (Robbins, 1984).

Agglutination titers of the sera of those vaccinated in the British studies also were found to correlate well with efficacy. Agglutination titers of 1:320 or better were associated with protection. One notable exception was observed with a partially purified soluble antigen, the first soluble antigen pertussis vaccine ever used. This vaccine was highly effective in terms of clinical protection, but did not result in an agglutinin response except to the specific serologic strain that was used in production of the soluble antigen. In other studies, protection has been found in the presence of low agglutination titers. Hence, it is unclear whether the absence of agglutinins predicts susceptibility.

The duration of vaccine-induced immunity is known only by inference. Occasional outbreaks of pertussis have been reported among young adults, particularly health care personnel caring for pediatric populations in which pertussis was prevalent. This information suggests that vaccine-induced immunity is not life-long, but the major morbidity and mortality of pertussis definitely occurs in infants and small children. The disease burden incurred by waning immunity in adults probably is minor.

Magnitude of Disease Burden

Benefits from an improved pertussis vaccine are likely to arise from the elimination of adverse side effects rather than from a further decrease in the already reduced disease incidence. Researchers do not expect to produce significant increases in vaccine efficacy, immunogenicity (at lower ages), or utilization. Therefore, no effort has been made to document the current burden of pertussis illness or to calculate what the burden would be in the absence of the current vaccination program, if desired, these calculations could be made with methods devised by Hinman and Koplan (1984).

For this report, the burden of illness that could be eliminated by an improved pertussis vaccine is considered to be equivalent to the adverse effects arising from the current vaccine. The manner in which this has been calculated is described below in the section "Vaccine Preventable Illness."

Vaccine Target Population

The target population for an improved pertussis vaccine would be identical to the target population for the existing vaccine: the entire cohort of infants born every year in the United States. Indeed, simple substitution of an improved pertussis component for the existing whole cell pertussis component in the DPT vaccine would be the desirable goal. This would maintain the present simplicity of immunization patterns for infants and small children. All 50 states have mandatory immunization laws requiring completion of primary immunization prior to school entry.

With an improved, less reactive vaccine it might be possible to offer immunization to older individuals who were, for some reason, not vaccinated. This is not possible with existing vaccines because of adverse reactions with increasing age.

Suitability for Vaccine Control

The documented efficacy of the existing pertussis vaccine, when given as recommended, clearly indicates the suitability of pertussis for vaccine control.

Vaccine Preventable Illness

The illness that could be averted by an improved pertussis vaccine is considered to be equal to the burden of adverse side effects arising from the current vaccination program. This is calculated from incidence rates for adverse effects determined by Hinman and Koplan (1984), assuming that 95 percent of the projected 1984 birth cohort receive the recommended five doses (three in the first year of life and the remaining two before the age of five). Hence, the annual number of doses is 3,788,337×0.95×5=17,994,600; and episodes are distributed between the under one year and the 1–4 years age groups in a ratio of 3:2.

Minor reactions (Morbidity Category A illness) occur at a rate/dose of 1:2.5; hence, a total of 7,197,840 episodes are expected. These are assumed to last two days.

Reactions falling into Morbidity Category B occur at rates of 1:1,750 for both convulsions and collapse, and 1:926 for high-pitched crying. These result in estimates of 10,283 cases of convulsion, 10,283 cases of collapse, and 19,433 cases of high-pitched crying per year. Thus, the total in Category B is 39,999 episodes, each assumed to last two days.

Hospitalizations (for two days) are estimated to result from 25 percent of physician contacts for convulsions and collapse (which are estimated to be half of the total number of convulsions and collapse), i.e., 0.25×2×10,283×0.5=2,570 cases. Hospitalizations (for approximately two days) are estimated to result from 10 percent of the cases with unusual crying that seek medical care (estimated to be 25 percent of all cases); i.e., 0.1×0.25×19,433=485 cases. Encephalitis occurs at a per dose rate of 1:110,000 and results in 164 cases requiring hospitalization for an estimated 15 days. The total number of hospitalizations is therefore 3,219 cases distributed between the under 1 and 1–4 years age groups in a ratio of 3:2 (doses under one year:doses over one year, i.e., 1,931:1,288). The average weighted duration of these hospitalizations is three days.

Chronic sequelae from encephalitis occur at a per dose rate of 1:310,000, resulting in a total of 58 cases. These have been distributed among Morbidity Categories D, E, and F, and in a ratio of 3:2 between the under 1 year and the 1–4 years age groups.

Table C.1 summarizes the burden of illness arising from adverse vaccine reactions that could be eliminated with an improved pertussis vaccine. This burden is potentially preventable if an improved vaccine with equal efficacy could be substituted for the existing vaccine.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence" is used to standardize disease burden values (see Chapter 4). Vaccine preventable illness values for pertussis reflect the total elimination of side effects caused by the current vaccine. They are calculated using the estimates in Table C.1 and the two sets of IME values used throughout this

TABLE C.1 Vaccine Preventable Illness: Current Adverse Effects of Pertussis Vaccine

Morbidity Category	Description	Number Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Local reactions	4,318,704	2	2,879,136	2								
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Collapse, convulsions, crying	24,000	2	15,999	2								
C	Requiring hospitalization	Hospitalization for collapse, convulsions, encephalitis	1,931	3	1,288	3								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	CBS sequalae of encephalitis	12	n.a.	B	n.a.								
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	CNS sequalae of encephalitis	12	n.a.	8 n.a. 8 n.a.									
F	Total impairment		12	n.a.	8	n.a.								
G	Reproductive impairment resulting in infertility													
H	Death													

Note: n.a.=not applicable.

report. Using IME values based on a median of committee member perspectives, the vaccine preventable illness value for an improved pertussis vaccine is 62; with the age-neutral perspective, the value is 60.

Possible Reduction in Morbidity and Mortality (PRMM)

The basis for calculating the reduction in morbidity and mortality that could be achieved with an improved pertussis vaccine is different from that used to calculate PRMM for totally new vaccines, and is described above.

The improved vaccine is anticipated to have the same efficacy and target population as the existing vaccine, so the maximum possible reduction in morbidity and mortality is the elimination of adverse effects—as expressed in the VPI values above.

Adverse Reactions

The PRMM calculation does not recognize, however, that the new vaccine also will cause some adverse reactions (Table 5.1). To determine how these side effects will affect the benefits from the new vaccine, it is necessary to estimate the number of episodes in each age group and then adjust them using the appropriate infant mortality equivalence values. Five to 10 percent of vaccinees are expected to have mild local reactions (which are considered less significant than illness in Morbidity Category A) and 0.1 percent are expected to have moderate systemic reactions that will fall into Morbidity Category B and last for two days. Applying these percentages to the estimated number of doses (assuming 95 percent of the predicted 1984 birth cohort of 3,788,337 receives five doses, three in the first year of life and two more between one and five years of age), gives a total of $3{,}788{,}337 \times 0.95 \times 3 \times 0.001 = 10{,}797$ adverse episodes in infants under one year of age. In the 1–4 years age group, the total is $3{,}788{,}337 \times 0.95 \times 2 \times 0.001 = 7{,}198$.

Assuming a two-day duration and using appropriate IME values, the adjusted figure for adverse effects of the improved vaccine using the committee median perspective would be

$$\frac{10{,}797 \times 2}{100{,}000} + \frac{7{,}197 \times 2}{50{,}000} = 0.50.$$

Using the age-neutral perspective, it would be

$$\frac{10{,}797 \times 2}{100{,}000} + \frac{7{,}197 \times 2}{100{,}000} = 0.36.$$

These values do not significantly change the net potential benefit values for the new pertussis vaccine. They remain 62 and 60 using the committee median and age neutral perspectives, respectively.

Use of these values for comparing vaccines is described in Chapter 7.

Prospects for Vaccine Development

The adverse side effects associated with the whole cell pertussis vaccine prompted the Japanese to stop using it, which led to an increased incidence of the disease (Kanai, 1980). To overcome this problem, Japanese scientists developed an acellular vaccine with high levels of two protein antigens that seems to induce a protective immune response (Sato et al., 1981). These antigens are the lymphocytosis-promoting factor (LPS) and the filamentous hemagglutinin (FHA). This acellular product, now manufactured by several firms, has been used in Japan since 1980. As anticipated, these vaccines cause considerably fewer systemic and local reactions than the previous whole cell vaccines, but their overall safety and clinical efficacy have not been reported formally.

The National Institute of Allergy and Infectious Diseases (NIAID) has approached the problem in two ways. First, it has offered the use of its vaccine evaluation units for studies of the safety and immunogenicity of any candidate preparations developed by commercial manufacturers. One American manufacturer has obtained bulk vaccine from a Japanese manufacturer, and evaluation of this product is in progress. In addition, several other United States manufacturers are developing their own acellular vaccines, and discussions are underway regarding future field testing. The NIAID's second approach has been to advertise for a contractor to develop and improve acellular vaccines; one award was made during FY 1983.

Based on this information, the committee believes that an improved acellular pertussis vaccine is a realistic possibility, that five years will be necessary to bring such a product to the point of licensure, and that the cost of development will be about $20 million. If the existing Japanese acellular vaccine proves to be both safe and effective, one to two years of developmental time might be saved, as well as up to half of the cost. In any event, the probability of success for the development of an improved acellular pertussis vaccine is estimated to be 90 percent.

The one potential problem in this otherwise optimistic scenario relates to the clinical trials. Clinical trials of an improved acellular pertussis vaccine will be attended by logistic, legal, and ethical problems, primarily because it will be difficult to identify a meaningful control group. It would hardly be justifiable to use a placebo control when an effective and generally safe vaccine already exists. In addition, the incidence of the disease in the United States is already so low that a field trial in this country, comparing safety and efficacy of the existing whole cell vaccine to a new acellular vaccine, would be almost impossible. It has been suggested that efficacy studies of new pertussis vaccines be carried out in parts of the world that still have high pertussis morbidity and mortality; again, the selection of a control vaccine other than the existing whole cell pertussis vaccine would raise serious ethical problems.

It is not clear whether United States manufacturers or even the NIAID could commit the resources necessary to establish a medical, epidemiological, and laboratory staff to assess the effectiveness of a

new pertussis vaccine over a prolonged period. On the other hand, Robbins (1984) has argued that extensive field trials to study the efficacy of a new pertussis vaccine may not be necessary if the proposed vaccine passes the appropriate potency and toxicity requirements; can be characterized fully in biochemical, biophysical, and immunologic terms; and can be shown to meet a series of additional biochemical standards. Such an approach presumes that quantitative serologic assays for antibodies to pertussis components could be established and standardized, and that a relationship between antibody response and the existing potency standards could be established.

It must be recognized that should an improved, less reactogenic vaccine become available, it will be exceptionally difficult to define the frequency (if any) of rare but potentially catastrophic reactions without administration of the vaccine to millions of children. The difficulties involved in differentiating vaccine-caused neurological problems from similar events that occur naturally in some children in the first six months of life will continue to exist.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used in predicting vaccine utilization are described in Chapter 6, where scores assigned to various vaccines are displayed together to facilitate comparison.

Lay Acceptance

Lay persons undoubtedly perceive the risk of pertussis as very low, although they continue to believe that the disease is serious if it occurs. Most individuals assume that the vaccine is effective.

Concern about adverse reactions has been a significant barrier in countries other than the U.S. during recent years. The vaccine's safety has been debated widely in both medical and lay publications. An example of this phenomenon occurred in the U.S. in April 1982: a single television program aired on the East Coast resulted in a transient decline in pertussis vaccine usage in the viewing area.

Nevertheless, usage of the DPT vaccine in the U.S. remains high, supported by strong recommendations from the American Academy of Pediatrics and the CDC's Advisory Committee on Immunization Practices. Inclusion of the improved acellular pertussis component in the vaccine will strengthen this acceptance. Existing school-entry immunization laws will ensure a high level of utilization.

Provider Acceptance

Provider perceptions of the risk of pertussis may be slightly higher than that of the lay community, but other scores on health belief model parameters will be similar.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparative exercise. The total costs should be taken only as an approximation of the direct cost of this disease.

Costs Related to Adverse Effects of Current Vaccine

Category A

# of cases = 7,197,840		
approx. 2% of cases receive 1 phys. visit at $30		= $ 4,319,000
	TOTAL (A)	= $ 4,319,000

Category B

Convulsions - following immunization		
# of cases = 10,283		
approx. 50% of cases receive 1 phys. visit at $30		= $ 154,000
	TOTAL	= $ 154,000
Collapse - following immunization		
# of cases = 10,283		
approx. 50% of cases receive 1 phys. visit at $30		= $ 154,000
	TOTAL	= $ 154,000
Unusual crying - following immunization		
# of cases = 19,433		
approx. 25% of cases receive 1 phys. visit at $30		= $ 146,000
	TOTAL	= $ 146,000
	TOTAL (B)	= $ 454,000

Category C - receive physician contact

total # of cases = 3,219		
Convulsion		
# of cases = 1,285		
100% of cases receive 2 days hospitalization at $400/day		= $ 1,028,000
	TOTAL	= $ 1,028,000
Collapse		
# of cases = 1,285		
100% of cases receive 2 days hospitalization at $400/day		= $ 1,028,000
	TOTAL	= $ 1,028,000

Unusual crying
# of cases = 486
100% of cases receive 2 days hospitalization
at $400/day = $ 389,000
TOTAL = $ 389,000

Encephalitis

approx. # of cases = 164
100% of cases typically receive 2 days ICU
hospitalization at $600/day, and = $ 197,000
13 days normal hospitalization at $400/day = $ 853,000

100% of cases typically receive additional diagnostic
testing/treatment at rate equivalent to daily
inclusive hospital rate
2 days at $600/day = $ 197,000
13 days at $400/day = $ 853,000
TOTAL = $ 2,100,000
TOTAL (C) = $ 4,545,000

Category D

# of cases = 20
total annual costs for treatment and/or care
= $2,000/case; assuming a duration of 20 years
at 5% discount rate, total present value/case
= $26,000 = $ 520,000
TOTAL (D) = $ 520,000

Category E

# of cases = 20
total annual costs for treatment and/or care
= $5,000/case; assuming a duration of 20 years
at 5% discount rate, total present value/case
= $65,000 = $ 1,300,000
TOTAL (E) = $ 1,300,000

Category F

# of cases = 20
total annual costs for treatment and/or care
= $20,000/case; assuming a duration of 50 years
at 5% discount rate, total present value/case
= $383,000 = $ 7,660,000
TOTAL (F) = $ 7,660,000

TOTAL COST = $18,798,000

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Appendix

D

PROSPECTS FOR IMMUNIZING AGAINST COCCIDIOIDOMYCOSIS

Disease Description

Coccidioidomycosis (valley fever, San Joaquin fever) is caused by the dimorphic fungus Coccidioides immitis. This fungus grows in the soil and produces spores (arthroconidia), which are carried by air currents and inhaled by humans and lower animals. In the united States, Coccidioidomycosis is endemic to California, Arizona, New Mexico, parts of Nevada and Utah, and southwestern Texas.

The population of the endemic areas is estimated to be about 20,000,000 (Chin, personal communication, 1983; Pappagianis, personal communication, 1983), but temporary visitors to these areas also may develop the disease. Individuals in occupations that involve working with the soil (e.g., agriculture, construction, and oil drilling) appear to be at increased risk (Chin, personal communication, 1983; Cox, 1983; Pappagianis, personal communication, 1983). Morbidity and mortality rates also are higher among certain racial and ethnic groups: black, Asian (especially Filipino), and Mexican males are at greater risk of disseminated disease than white males, for example (Pappagianis, 1980). The disease affects all age groups; the highest incidence is in males over the age of 25.

Less than half of those who become infected develop clinical signs of disease. The primary lesion is usually pulmonary. In those who become ill, clinical symptoms of fever, malaise, cough, and chest pain follow an incubation period of 7 to 28 days (typically 10 to 16 days). Night sweats and anorexia may occur also. The disease is usually self-limited, particularly in adults. A few individuals may develop residual cavitary disease, and sometimes nodules or pulmonary abscesses. The pulmonary cavities usually heal spontaneously. Chronic progressive pulmonary disease, resembling histoplasmosis or tuberculosis, occurs in a small number of patients.

Allergic manifestations also appear in some cases. Erythema nodosum or erythema multiforme may develop a few days or a few weeks

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after infection. The appearance of these manifestations coincides with the development of delayed hypersensitivity to proteins of the infecting fungus, which is a characteristic feature of this disease.

Progressive, disseminated disease occurs in a very small percentage of infected persons, and almost any tissue or organ may be involved. Disseminated disease and chronic progressive pulmonary disease probably develop more readily in patients undergoing immunosuppressive therapy or in those with an underlying condition that lowers their immune competence, but these conditions also occur in individuals without such recognized conditions.

Pathogen Description

Coccidioides immitis is a dimorphic fungus of the subdivision Deuteromycotina (Huppert and Sun, 1980). The resistance engendered by vaccine prepared from a single strain protects in several animal species against challenge with a wide variety of strains of diverse morphological characteristics. C. immitis can be cultured easily as a mycelial fungus on dextrose-peptone agar; most strains grow more rapidly than other fungi that cause systemic disease (Huppert and Sun, 1980). The fungus also can be cultured on liquid media, under aerobic conditions. In infected hosts, C. immitis maintains a spherule endospore cycle that can be reproduced in vitro only under special physiochemical conditions. Protective antigens have not been identified. Growth and development of the spherule is associated with increased immunogenicity and the principal immunogens appear to reside in the spherule wall.

Host Immune Response

Infection with C. immitis induces both cell-mediated and humoral immune responses. Epidemiological studies indicate that recovery from primary, non-disseminated infection with C. immitis, whether symptomatic or asymptomatic, virtually always produces resistance to exogenous reinfection (Smith et al., 1948); although rare, documented reinfections have occurred in laboratory workers (Overholt and Hornick, 1964; Sorensen and Cheu, 1964).

Coccidioidin, a crude filtrate of a mycelial culture, is used in skin tests, precipitin reactions, and complement-fixation (CF) assays (Kobayashi, 1980). A positive coccidioidin skin test indicates that coccidioidal infection has occurred in the past. The close correlation between the intensity of the skin test response and immunologic competence permits the coccidioidin skin test to be used as a direct immunologic index of clinical prognosis in patients known to have coccidioidomycosis. Spherulin, a new antigenic extract from the spherule phase of the organism, appears to detect about one-third more skin test reactors than coccidioidin (Pappagianis, 1980).

In vitro parameters of cell-mediated immunity also correlate with disease activity. The macrophage inhibitory factor (MIF) is negative

in most patients with active disease and is therefore not a helpful index of severity. The lymphocyte transformation reaction is negative in the most severe cases; in milder cases, lymphocyte transformation often does not correlate well with other tests of immune response. In vitro test responses, like the skin test, may convert to positive with clinical improvement, though they do not always do so simultaneously. Serum blocking factors have been described that can depress skin test or lymphocyte transformation reactivity, but their effects on clinical disease, severity, and prognosis are uncertain (Pappagianis, 1980).

In 80 percent of infections, the precipitin test detecting IgM is positive within two weeks of the onset of symptoms. A precipitin response is considered pathognomonic of infection with C. immitis. Over 90 percent of positive reactions revert to negative within six months, although a few patients with disseminated disease will have persistent or late positive precipitins.

The complement fixation test appears to reflect the presence of IgG antibody and is positive in only ten percent of patients by the second week of symptoms; it is positive in almost all patients within two months. The complement-fixing antibody titer correlates inversely with the competence of cell-mediated immunity. In one study, 80 percent of patients with a coccidioidin complement fixation titer of 1:32 or less had a positive coccidioidin skin test, compared to only 41 percent of those with higher serologic titers (Pappagianis, 1980).

Magnitude of Disease Burden

An estimated 80,000 primary coccidioidal infections occur each year in endemic areas of the United States (Chin, personal communication, 1983; Pappagianis, personal communication, 1983). About 40 percent of primary infections are symptomatic and approximately half of these cases require medical attention (Cox, 1983; Pappagianis, personal communication, 1983). About 90 percent (28,800) of symptomatic individuals have mild pulmonary or systemic symptoms, such as cough, chest pain, fever, headache, anorexia, myalgia, or malaise (Morbidity Category B), that last for about 18 days (Catanzaro and Drutz, 1980a, 1980b). Cases involving acute pulmonary sequelae (about 10 percent of symptomatic cases) are associated with more serious pulmonary lesions and it is assumed that all of these cases require hospitalization (Morbidity Category C: Morbidity Categories are described in Table D.2).

Fraser and coworkers (1979) have estimated the age-specific national incidence of initial hospitalizations for coccidioidomycosis (Table D.1). Based on these estimates of incidence and the 1984 U.S. population projections, it is estimated that about 4,517 initial hospitalizations will occur in 1984 in the United States (see Table D.1).* About 5 percent of hospitalizations result from cases of

* This estimated national incidence is higher than the 3,200 hospitalizations that would be expected to occur on the incidence of infection in endemic areas.

TABLE D.1 Derivation of Age Distribution for Coccidioidomycosis

	Age Group (years)					
	Cinder 1	1-4	5-14	15-24	25-59	60 and over
Hospitalizations (Morbidity Category C)						
Incidence[a] (cases per 10^6 population)	2	2	3	15	26	27
Number of cases	7	29	67	605	2,756	1,053
Percentage of all hospitalizations	0.2	0.6	2	13	61	23
Non-hospitalized cases[b] (Morbidity Category B)	58	173	576	3,744	17,568	6,624
Deaths[c] (Morbidity Category H)	1	2	5	34	157	59

a Age-specific national incidence of initial hospitalizations from Fraser et al. (1979).
b Age distribution assumed identical to age distribution of hospitalized cases. Total from Pappagianis (personal communication, 1983).
c 5.7 percent of hospitalizations.

symptomatic or acute pulmonary disease that disseminate into one or more organ systems (e.g., skin, lymph nodes, spleen, liver, bone, kidneys, meninges, or brain). The incidence of disseminated disease varies considerably among racial groups. In adult white males it is about 2 percent of symptomatic cases; in adult black and non-Filipino Asian males, it is about 15 percent; and in adult Filipino males it is about 50 percent (Pappagianis, personal communication, 1983). The incidence in females is unknown, but is thought to be somewhat lower.

About one-third of cases of disseminated disease result in meningitis, which is fatal about half the time (Pappagianis, personal communication, 1983). The number of non-fatal cases of meningitis is small and has been judged insignificant for these disease burden calculations, information on chronic sequelae in survivors of meningitis are not available, so these consequences also have been excluded from estimates of disease burden.

Fraser and coworkers (1979) have estimated that the case fatality rate for all hospitalized cases, including cases of disseminated disease, is about 5.7 percent. Survivors of disseminated disease may have chronic or recurrent sequelae (e.g., chronic pulmonary, cutaneous, ophthalmic, or genitourinary symptoms), however the percentage of cases with long-term sequelae is thought to be quite low and these cases are not included in the calculation of disease burden.

Chronic pulmonary disease may be recognized weeks, months, or years after apparent recovery from acute pulmonary disease. Chronic disease may last for years and can be fatal. Disseminated disease may occur a year or more following even an asymptomatic infection. Data

on the incidences of such occurrences are not available; however, they are thought to be quite rare and have been judged insignificant for the purpose of calculating disease burden.

Table D.2 summarizes the disease burden for coccidioidomycosis.

Uncertainty in the Disease Burden Estimates

Coccidioidomycosis is not officially notifiable to the Centers for Disease Control; among the endemic areas, only California and Arizona have reporting requirements. Very little data on the incidence and age distribution of disease, specific complications, and chronic morbidity associated with coccidioidomycosis are available in the literature. Estimates of the number of cases of disease in endemic areas were provided by Pappagianis (personal communication, 1983) and Stevens (1980) and estimates of the national incidence and age distribution of hospitalizations for coccidioidomycosis were derived from data reported by Fraser and coworkers (1979). For the disease burden calculation, it has been assumed that the age distribution of non-hospitalized cases and deaths is the same as the age distribution of hospitalized cases reported by Fraser and coworkers (1979). No basis was found on which to make specific estimates of the incidence of chronic morbidity and such estimates are not included in the disease burden.

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for Coccicioides immitis are calculated using estimates from Table D.2 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 343 (committee median perspective) and 268 (age-neutral perspective).

Target population

Although the total population living in the endemic areas is approximately 20,000,000, and several million temporary visitors per year are at some risk of contracting the disease, the total population at which immunization efforts might be directed probably would be between 1 and 2 million. This is because many long-term residents in the endemic areas are already immune and it is unlikely that attempts would be made to immunize temporary visitors. Immunization probably would be targeted at members of specific occupational groups (e.g., agricultural, oil field, and construction workers) who are at greatest risk of becoming infected. This group is arbitrarily assumed to comprise 10 percent of the population of endemic areas.

TABLE D.2 Disease Burden Summary: Coccidioides immitis

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Symptomatic disease	SB	18	173	18	576	18	3,744	18	17,568	18	6,624	18
c	Requiring hospitalization	Acute pulmonary disease; disseminated disease	7	12	29	12	67	12	605	12	2,756	12	1,053	12
D	Mild chronic disability (not requiring hospitaliaation, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability {requiring hospitalization, special care, or other major limitation of normal activity)									n.a.				
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		<1	n.a.	2	n.a.	5	n.a.	34	n.a.	157	n.a.	59	n.a.

Note: n.a.=not applicable.

The incidence of coccidioidomycosis rises rapidly in persons over the age of 15. Fraser and coworkers (1979) have reported that the incidence of hospitalization for coccidioidomycosis begins to rise at age 15 and shows a steady increase until age 25, after which the overall incidence remains fairly stable. Immunization efforts probably would be directed at 15-year-olds, although initially older persons would be vaccinated too. Younger target populations might be considered in some cases where substantial exposure occurs at an earlier age, e.g., some native American populations.

Suitability for Vaccine Control

The natural course of most coccidioidomycosis infections suggests that the disease is suitable for vaccine control. An effective vaccine would be expected to induce satisfactory immunity, because primary natural infection usually provides resistance to exogenous reinfection.

Alternatives to vaccine prevention are unsatisfactory: avoidance of infection in endemic areas is virtually impossible. The disease could be prevented if it were possible to decontaminate infected soil (because infection is transmitted primarily by inhaled arthroconidia), but it is not. Also, the therapeutic alternatives for treatment of coccidioidomycosis are limited. Amphotericin B is the standard drug for chemotherapy and has been used for more than 20 years in pulmonary coccidioidomycosis. In practice, however, it appears that while amphotericin has a fungicidal activity in vitro, it is only fungistatic in concentrations that are clinically attainable in body fluids (Stevens, 1980). It is also highly toxic, so its benefits must be weighed carefully against its toxicity.

While the disease burden in terms of number of cases is relatively small compared to that associated with many other infectious diseases, treatment costs are significant (see below). Effective vaccination strategies probably could be designed for some subsets of the population at risk (e.g., some occupational groups), and these strategies might significantly reduce costs associated with the disease. It is important to note, however, that some of the groups at highest risk, especially migrant workers, would be difficult to reach.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the possible reduction in morbidity and mortality that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

On the basis of the suggested target population, described above, all illness occurring in persons older than age 15 is considered

potentially vaccine preventable. Table D.3 summarizes the VPI for coccidioidomycosis.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). The vaccine preventable illness value for Coccidioides immitis is calculated using estimates from Table D.3 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the vaccine preventable illness value is 334. Using the age-neutral perspective, the value is 260.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the possible reduction in morbidity and mortality (the maximum potential health benefit) that could be produced by the Coccidioides immitis vaccine candidate described in Table 5.1, the vaccine preventable illness value is multiplied by the predicted efficacy of the vaccine, which is 70 percent. Using the vaccine preventable illness value based on a median of committee member perspectives, the potential reduction in morbidity and mortality is 234. Using the age-neutral perspective, the value is 182.

These values are not adjusted for vaccine adverse effects or anticipated utilization. Use of these values for comparing vaccines is described in Chapter 7.

Prospects for Vaccine Development

The ideal vaccine for coccidioidomycosis would be a live, attenuated isolate of C. immitis; however, attempts to isolate a stable, attenuated mutant in the 1960s failed (Kong and Levine, 1967a; Pappagianis, et al., 1961) and few further studies have been done in this area (Walch and Kalvoda, 1971).

The use of killed vaccines in mice and monkeys has been investigated by Levine, Kong, and Pappagianis (Kong and Levine, 1967b; Kong et al., 1966; Levine et al., 1960; Levine et al., 1961; Levine et al., 1965; Pappagianis et al., 1979). These studies have established that killed spherules protect against lethal progression of coccidioidomycosis and typically limit the number, size, and distribution of lesions on intraperitoneal or intranasal challenge with viable arthroconidia. Vaccines made from spherules were more protective than those made from mycelia or arthroconidia (Kong and Levine, 1967b; Levine et al., 1960; Levine et al., 1961), and spherule cell walls were more protective than intact spherules (Kong et al., 1963; Levine et al., 1961).

It is important to note that although spherules are highly protective, they also cause moderately severe local reactions (Pappagianis

TABLE D.3 Vaccine Preventable Illness: Coccidioides immitis

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Number Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
6	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Symptomatic disease							3,744	1B	17,568	1B	6,624	*lB*
C	Requiring hospitalization	Acute pulmonary disease; disseminated disease							605	12	2,756	12	1,053	12
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death								34	n.a.	157	n.a.	59	n.a.

et al., 1961; Pappagianis et al., 1979). Researchers have found that the amount of killed spherules that can be tolerated as a single dose administered intramuscularly in humans is, on a body weight basis, less than 1/400 (0.25 percent) of the dose required to protect mice (Pappagianis et al., 1979).

Because of the toxicity of spherules, efforts have been made to isolate the Coccidioides component(s) that confers protection to this disease. Pappagianis and coworkers reported in 1979 on a subcellular vaccine derived from the whole spherule vaccine. That particular antigen was difficult to prepare in sufficient quantities, however, and did not appear to be as effective as the original vaccine from which it was derived.

Studies by Lecara and Cox (Cox, personal communication, 1984; Lecara et al., 1983) have shown that C-ASWS, an alkali-soluble, water-soluble cell wall antigen of Coccidioides mycelia (designated C-ASWS-M) and spherules (designated C-ASWS-S) protect mice against intraperitoneal challenge with 3,000 viable arthroconidia (p 0.0001 as compared to control mice). These soluble extracts afford less but still significant protection against intranasal challenge with 1,000 arthroconidia (p 0.025). Decreased protection to intranasal as opposed to intraperitoneal challenge may be attributed to the solubility of the C-ASWS extracts. That is, administration of C-ASWS in complete Freund adjuvant fails to effect a mobilization of T-lymphocytes and/or activated macrophages within lung tissues. This same problem has been encountered with soluble vaccines of other microbes where immunity involves a cellular response. In an attempt to effect a pulmonary response, Lecara and Cox (Cox, personal communication, 1984) plan to insolubilize the C-ASWS antigen using glutaraldehyde cross linkage or precipitation with alum. The insoluble antigens will be administered intramuscularly, followed by an intranasal instillation prior to challenge of mice with viable arthroconidia.

The vaccine efficacy of killed spherules is now being evaluated in a double-blind, randomized trial of human volunteers in California and Arizona. At last report (Nichols, 1983), a total of 2,090 persons had enrolled in the study. The vaccine is given in a series of three intradeltoid doses. Reactions to the 5,016 injections administered have ranged from nothing to mild discomfort in 79 percent of participants, moderate discomfort in 17 percent, and marked or unacceptable reactions in 3.4 percent. Six coccidioidal cases have been reported among the recipients; however, because this is a double-blind study, it is not known whether these cases occurred in vaccine recipients or in subjects receiving placebo injections.

Pappagianis and coworkers are continuing efforts to obtain a soluble or subcellular antigen following two lines of investigation (Pappagianis, personal communication, 1984):

- Use of a neutral extraction method to obtain antigen from spherules. New extracts are now available, but their immunogenicity has not been determined.

- Examination of the culture supernatant of the in vitro endospore spherule endospore cycle for the presence of high molecular weight antigen liberated from the cells.

Using acrylamide gel electrophoresis, Pappagianis and coworkers have found evidence of soluble, high molecular weight components, which appear to be at least partially protein, early in the culture cycle (Pappagianis, personal communication, 1984). The immunogenicity and protective efficacy of these components are not known.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to various vaccines are displayed together to facilitate comparison.

Lay Acceptance

Lay perceptions of the risk and severity of coccidioidomycosis are judged to be very low, primarily because the public is thought to be unfamiliar with the disease and because many of the persons at highest risk are migrant agricultural workers with limited access to the medical care system. The perception of benefits also is judged to be very low because of the relatively low efficacy of the vaccine and the mild or asymptomatic nature of most infections. Perceived barriers to vaccination are judged to be high because of the moderate incidence of adverse reactions to the vaccine and the predicted number of required doses (3).

Provider Acceptance

Physicians in areas of the United States in which coccidioidomycosis is endemic probably have become more aware of the risk of disease and more familiar with its clinical manifestations in recent months because of clinical trials of the vaccine candidate now being conducted in Arizona and California. Their perceptions of risk and severity of disease are judged to be moderate. Perceived benefits of the vaccine are likely to be relatively high, although moderated somewhat by the relatively low predicted efficacy of the vaccine. Perceived barriers are judged to be moderate because of the moderate incidence of adverse reactions to the vaccine.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on

certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparative exercise. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden

Category A n/a	
Category B - Benign symptomatic disease; acute pulmonary disease	
# of cases = 28,743	
100% of cases typically receive 2 phys. visits at $30/visit	= $ 1,725,000
100% of cases typically receive diagnostic procedure at $120 [skin test, serology, immunodiffusion, chest x-ray, blood count]	= $ 3,449,000
TOTAL (B)	= $ 5,174,000
Category C - Acute pulmonary disease	
# of cases = 4,517	
100% of cases typically receive 12 days normal hospitalization at $400/day	= $21,682,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 12 days at $400/day	= $21,682,000
100% of cases typically receive treatment with one vial amphotericin B/day for 21 days (at $13/vial)	= $ 1,233,000
# of cases of meningitis = 75*	
100% of cases typically receive 14 days normal hospitalization at $400/day	= $ 420,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 14 days at $400/day	= $ 420,000
100% of cases typically receive treatment of 2 vials amphotericin B/day for 21 days ($13/vial)	= $ 41,000
TOTAL (C)	= $45,478,000
Categories E - G n/a	
TOTAL COST	= $50,652,000

*38 patients die

Category A n/a

Category B - Benign symptomatic disease; acute pulmonary disease

# of cases = 27,936

100% of cases typically receive 2 phys. visits at $30/visit	= $ 1,676,000
100% of cases typically receive diagnostic procedure at $120 [skin test, serology, immunodiffusion, chest x-ray, blood count]	= $ 3,352,000
TOTAL (B)	= $ 5,028,000

Category C - Acute pulmonary disease

# of cases = 4,414

100% of cases typically receive 12 days normal hospitalization at $400/day	= $21,187,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 12 days at $400/day	= $21,187,000
100% of cases typically receive treatment with one vial amphotericin B/day for 21 days (at $13/vial)	= $ 1,205,000

# of cases of meningitis = 75*

100% of cases typically receive 14 days normal hospitalization at $400/day	= $ 420,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 14 days at $400/day	= $ 420,000
100% of cases typically receive treatment of 2 vials amphotericin B/day for 21 days ($13/vial)	= $ 41,000
TOTAL (C)	= $44,460,000

Categories E - G n/a

TOTAL COST = $49,488,000

*38 patients die

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Appendix

E

PROSPECTS FOR IMMUNIZING AGAINST CYTOMEGALOVIRUS

Disease Description

Human cytomegalovirus (CMV) does not cause identifiable disease in the vast majority of infections. The major problems result from congenital cytomegalovirus infection. Only 5 to 10 percent of congenital infections are symptomatic, but 1 to 2 percent of these are fatal. Almost 90 percent of symptomatic infections leave sequelae in the survivors. Between 5 and 17 percent of congenitally infected children who are asymptomatic at birth have late sequelae. The acute manifestations of congenital cytomegalovirus infection include hepatic disease, resulting in jaundice, and multiorgan involvement including ocular and cerebral infections (Weller, 1971).

Cytomegalovirus infection also can be acquired in the newborn period, through inoculation of virus from the birth canal during delivery or by ingestion of infected breast milk (Stagno et al., 1980). The disease spectrum associated with perinatal infection has not been well defined, but appears to be less serious than that of congenital infections, although children may develop delayed complications.

Acute infection in a normal host induces antibodies and a specific cell-mediated immune response, but viral shedding may persist for months or even years, and the virus may become latent. Reactivation of CMV infection with viral shedding may occur in asymptomatic patients.

Symptomatic illness after early childhood, resulting from reactivation of the virus or primary infection, usually occurs in immunocompromised hosts. Cytomegalovirus pneumonia and other manifestations may be especially severe and are often fatal in patients who have undergone bone marrow transplants and other procedures that require suppression of the immune system.

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Description of the Pathogen

Human cytomegalovirus, a member of the herpesvirus group, consists of double-stranded DNA inside an icosahedral capsid made up of 162 capsomeres. The capsid is surrounded by a lipid-containing envelope. These virus particles are large and complex; analysis of their antigenic structure has just begun. Neither the number of strains nor the significance of their antigenic differences is known (Gold and Nankervis, 1982).

Host Immune Response

The normal immunocompetent host develops both humoral and cell-mediated immune reponses to primary cytomegalovirus infection (Gold and Nankervis, 1982). Despite these responses, virus shedding can persist for weeks or months, often followed by latent infection. Periodic reactivation of infection usually is asymptomatic, but may cause extensive disease in the immunocompromised host. Interstitial pneumonia is the most serious manifestation in these individuals, and is usually associated with fever. Infections of the liver, the gastrointestinal tract, and the retina also are observed in immunocompromised hosts.

Magnitude of Disease Burden

The following groups are those primarily at risk: (a) fetuses subject to congenital infection; (b) infants subject to perinatal infection; (c) recipients of multiple transfusions of whole blood; (d) recipients of organ and bone marrow transplants; (e) persons with leukemia; and (f) normal adults who may contract CMV mononucleosis or other febrile illnesses. Some of these groups overlap; however, because of the lack of data on the extent of overlap the committee chose to consider them separately in the disease burden estimates.

Congenital Cytomegalovirus Infection

CMV infection occurs in an estimated 0.4 to 2.3 percent of live births in the United States (Alford, personal communication, 1983; Lang, 1980; Plotkin, personal communication, 1983; Plotkin et al., 1983; Stagno et al., 1983). To simplify this analysis, the following calculations are based on an estimate of 1 percent or 37,883 infected infants. Most infected infants are asymptomatic at birth, but late sensorineural sequelae may occur.

Infants Symptomatic at Birth An estimated 7.5 percent (2,841) of congenitally infected infants are symptomatic at birth (see Tables E.1 and E.2). Symptoms of cytomegalic inclusion disease (CID) include

TABLE E.1 Congenital CMV Infection

	Estimated Figure
Number of infected infants (1% of live births in U.S.)	37,883
Symptomatic at birth (7.5%)	2,841
Fatal disease (25%)	710
Number with CNS sequelae (82.5% of survivors)[a]	1,758
Asymptomatic at birth (92.5%)	35,042
Number with late sequelae (15%)[b]	5,256

Note: Adapted from Stagno et al., 1983. Data also provided by Alford (personal communication, 1983), Hanshaw (personal communication, 1983), Losonsky (personal communication, 1983), Plotkin (personal communication, 1983), and Polk (personal communication, 1983).

aMicrocephaly 70 percent; psychomotor retardation 60 percent; neuromuscular disorders 35 percent; hearing abnormalities 30 percent; ocular abnormalities 22 percent (Pass et al., 1980).

bHearing loss, minimal brain damage, learning disorders, behavioral disorders (Pass et al., 1980).

hepatosplenomegaly, jaundice, petechiae, pneumonia, and chorioretinitis; central nervous system symptoms and other neurological deficits also may be present at birth (Alford, personal communication, 1983; Gold and Nankervis, 1982; Hanshaw, personal communication, 1983; Ho, 1982; Losonsky, personal communication, 1983; Plotkin, personal communication, 1983; Polk, personal communication, 1983). The duration of hospitalization is estimated to be 7 days for two-thirds of patients with CID and 14 days for one-third of patients with CID, giving an average weighted duration of 9 days.

Approximately 25 percent (710) of infants symptomatic at birth die before the age of one year as a result of CMV infection. About 82.5 percent of survivors (1,758) develop mild to severe chronic sensorineural sequelae (Categories D and E). Data reported by Pass et al. (1980) and estimates by Losonsky (personal communication, 1983), Polk (personal communication, 1983), and Whitley (personal communication, 1984) have been used to place these cases in appropriate Morbidity Categories and age groups as shown in Table E.2. (Morbidity Categories are described in Table E.3.)

Infants Asymptomatic at Birth An estimated 15 percent (5,256) of congenitally infected infants who are asymptomatic at birth later develop chronic sensorineural sequelae (see Table E.1), including

TABLE E.2 Assumed Age Distribution of Morbidity Associated with Congenital CMV Disease

	Age (years)	
	Under 1	1-4
Symptomatic at birth (2,841 cases)		
Cytomegalic inclusion disease (2,841 cases)		
100% in Morbidity Category C	2,841	
25% in Morbidity Category H (deaths)	710	
Sensorineural sequelae (1,758 cases)		
75% progress to Morbidity Category D	660	660
25% progress to Morbidity Category E	220	220
Asymptomatic at birth (35,042 cases)		
100% in Morbidity Category B	35,042	
Late sensorineural sequelae (5,256 cases)		
75% in Morbidity Category D		3,942
25% in Morbidity Category E		1,314

Note: See text for sources.

hearing loss, minimal brain damage, and learning and behavioral disorders. About 75 percent of these chronic disorders are mild (Category D) and 25 percent are moderate to severe (Category E) (see Table E.2). Most late sequelae become apparent before four years of age (Losonsky, personal communication, 1983; Pass et al., 1980; Polk, personal communication, 1983).

Perinatal Cytomegalovirus Infection

Although about 12 percent (454,600 in 1984) of all newborns in the United States acquire CMV infection at birth or during the early months of life, most do not develop acute disease (Alford, personal communication, 1983; Plotkin, personal communication, 1983; Stagno et al., 1983). Of those infected, about 2 percent (9,092) develop interstitial pneumonia or other respiratory disease (Plotkin, personal communication, 1983). The infection also may cause late appearing sequelae, but this potential has not been assessed adequately and data on which to base estimates of the incidence of such sequelae are not available. For the purpose of estimating disease burden, all cases of perinatal respiratory disease associated with CMV are assumed to occur in infants under the age of one year. The majority of cases do not require

TABLE E.3 Disease Burden: CMV Congenital and Perinatal Infections

			Under 1 Year		1-4 Years		5-14 Tears		15-24 Years		25-59 Years		60 Years and over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Natal/perinatal respiratory disease	7,092	6										
C	Requiring hospitalization	Cytomegalic inclusion disease; natal/perinatal respiratory disease	4,841	10										
D	Mild chronic disability {not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Psychomotor retardation; neuromuscular disorders; hearing abnormalities; ocular abnormalities	660	n.a.	4,602	n.a. n.a.								
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Microcephaly; psychomotor retardation; neuromuacular disorders; ocular abnormalities	220	n.a. n.a.	1,534	n.a.								
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death	Cytomegalic inclusion disease; natal/perinatal respiratory disease		n.a.										
			910											

Notes: Durations are weighted averages.n.a.=not applicable.

hospitalization; these are included in Morbidity Category B for a duration of six days. Whitley (personal communication, 1984) estimates that about 2,000 infected infants are hospitalized (Morbidity Category C), half for 7 days and half for 14 days. About 10 percent of these cases are fatal (Hanshaw, personal communication, 1984).

Table E.3 summarizes the disease burden associated with congenital and perinatal CMV disease.

CMV Mononucleosis and Other Febrile Illnesses

The incidence of mononucleosis in the U.S. population is estimated to be 0.25 to 0.50 cases per 1,000; CMV causes between 5.0 and 7.5 percent of these cases (Gold and Nankervis, 1982; White, 1980). The estimate of the number of cases of CMV mononucleosis used in this report (7,650 cases) is intermediate between Plotkin's estimate of 10,000 (personal communication, 1983) and the number derived by applying the approximate mid-points (0.375 cases per 1,000 and 6 percent) of the ranges above to the 1984 population projection.

Although the disease is known to occur in infants and children, it is rare (Ho, 1982). Therefore, all cases are assumed to occur in the age groups 15–24 years and 25–59 years. Cases are distributed between these two age groups in proportion to the percentage of the projected 1984 population that each group represents (i.e., 15–24 years, 27.7 percent; 25–59 years, 72.3 percent). The duration of the typical case of mononucleosis (Category B) is estimated to be four days, with 35 days of convalescence (Category A). These figures are approximate averages of estimates provided by Gold and Nankervis (1982), Ho (1982), Rook and Quinnan (1982), and Stewart (personal communication, 1983). It is estimated that about 5 percent of all cases will require five days of hospitalization (Category C) for diagnostic purposes (fever of unknown origin), and that all of these cases will occur in the 25–59 years of age group (Losonsky, personal communication, 1983; Polk, personal communication, 1983).

CMV is also thought to cause various other febrile illnesses, ranging from mild illnesses with symptoms of fever and malaise to more severe cases involving varying degrees of hepatitis, respiratory or gastrointestinal symptoms, or central nervous system disease (Gold and Nankervis, 1982). An estimated 40,000 such illnesses occur annually, and it is assumed that all are in the 15–24 years and 25–59 years age groups. The distribution of cases between these age groups is calculated in the same manner as that for CMV mononucleosis (see above). It is estimated that 25 percent of cases require hospitalization (Category C) for five days, and that the remaining cases fall into Category B (Losonsky, personal communication, 1983; Polk, personal communication, 1983). Durations in each category are assumed to be the same as those estimated for CMV mononucleosis. Table E.4 shows the estimated distribution of cases of disease (including convalescence) between morbidity categories and age groups.

Table E.5 summarizes disease burden associated with CMV mononucleosis and other febrile illnesses.

TABLE E.4 Distribution of Cases of CMV Mononucleosis and Other Febrile Illnesses

Morbidity Category	Condition	Age (years) 15-24	25-59
A	Mononucleos is (convalescence from B)	2,119	5,531
	Mononucleos is/PUO[a] (convalescence from B)		383
	Other febrile illnesses (convalescence from B)	11,080	28,920
B	Mononucleosis (typical case)	2,119	5,531
	Mononucleosis/FUO (convalescence from C)		383
	Other febrile illnesses (75 percent of typical cases)	8,310	21,690
	Other febrile illnesses (convalescence from C)	2,770	7,230
C	Mononucleos is/FUO		383
	Other febrile illnesses (25 percent of typical cases)	2,770	7,230

[a]Fever of unknown origin.

Post-Transfusion infection

Recipients of transfusions of whole blood are at increased risk of primary or secondary infection with CMV; the risk of infection appears to correlate with the number of units transfused (Ho, 1982). Infection acquired in this manner causes a self-limited, usually mild mononucleosis, similar to that produced by Epstein-Barr virus. The duration of symptoms (typically fever, malaise, splenomegaly, or hepatitis of variable degree) is 1 to 4 weeks (Rook and Quinnan, 1982). For the disease burden estimate, the midpoint of this range (2.5 weeks) is used to represent the duration of the typical case; the disease is assumed to prolong hospitalization (Morbidity Category C) by 10 days (Stewart, personal communication, 1983).

To obtain a reasonable estimate of the number of units likely to be transfused in 1984, an average has been calculated from data on the number of units of whole blood transfused in 1979 (2,160,000) and 1980 (1,930,000), provided by the National Heart, Lung, and Blood Institute

TABLE E.5 Disease Burden: CMV Mononucleosis and Other Febrile Illnesses

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	[federate localised pain, mild systemic reaction, or impairment requiring minor change in normal activities	Mononucleos is and other febrile illnesses (convalescence from B)							13,199	35	34,834	35		
B	Moderate pain moderate or impairment requiring moderate change in normal activities, e.g., housebound or in bed	Mononucleos is (typical case); other febrile illnesses (75% of typical cases); mononucleosis (convalescence from C); other febrile illnesses (convalescence from C)							13,199	4	34,834	4		
C	Requiring hospitalization	Mononucleosis (with FUO); other febrile illnesses (25% of typical cases)							2,770	5	7,613	5		
D	Mild chronic disability {not requiring hospitalization, institutionalization, or other major limitation of normal activity]													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death													

(in press).* It is estimated that each recipient receives three units of blood (Plotkin, personal communication, 1983), and that 4 percent (26,105) of recipients become symptomatically infected (Ho, 1982).

Data on the age distribution of recipients are not available. Transfusions are assumed to be distributed across age groups in proportion to the percentage of the population projected to be in each age group in 1984.

Transfusions in Very Low Birthweight Infants Based on data reported by Adler and coworkers (Adler et al., 1983) and information provided by Losonsky (personal communication, 1983), it is estimated that about 25 percent of very low birthweight (less than or equal to 1,250 g) infants receive blood transfusions from multiple donors and that 20 percent of these infants acquire CMV infection. Of those infected, approximately 40 percent show symptomatic disease (e.g., hepatitis, respiratory disease, or hepatosplenomegaly: Morbidity Category C, duration 10 days) and in 20 percent of these the disease is fatal. Approximately 25 percent of symptomatic infants suffer moderate to severe chronic impairment (Morbidity Category E) and 25 percent suffer total impairment (Morbidity Category F). Estimated morbidity and mortality associated with CMV infection in these infants is summarized in Table E.6.

Table E.7 summarizes disease burden associated with CMV in recipients of transfusions.

CMV and Organ Transplantation

Recipients of organ transplants (renal, liver, cardiac, and bone marrow) can develop CMV infections in two different ways. Transmission of blood elements containing CMV from the donor can produce a primary CMV infection, or the immunosuppression required for transplantation can lead to reactivation of a latent infection (Gold and Nankervis, 1982; Ho, 1982; Rook and Quinnan, 1982). Infection may be inapparent or may result in clinical disease ranging from mild mononucleosis to severe multiorgan system disease; the severity of disease may be related to the vigor of immunosuppresive therapies employed to prevent graft rejection (Alford, personal communication, 1983; Stewart, personal communication, 1983).

Renal Transplants Data on the number and age distribution of renal transplants performed annually in the U.S. have been obtained from the Health Care Financing Administration (HCFA, 1983). Between 1978 and

* The number of units (87,136) estimated to be given to very low birthweight infants has been subtracted from the total number of units transfused, because this group of patients is considered separately in estimating disease burden.

TABLE E.6 Estimated Morbidity and Mortality Associated With CMV in Multiply Transfused infants

Number of VLBW[a] infants (less than or equal to 1,500 g) (1.15% of 1984 births)[b]	43,566
Number receiving multiple transfusions (25% of 43,566)	10,892
Number infected with CMV (20% of 10,892)	2,178
Number with symptomatic CMV disease (40% of 2,178)	871
Number with moderate to severe chronic disability (25% of 871)	218
Number with total impairment (25% of 871)	218
Fatal disease (20% of 871)	174

[a] very low birthweight.

[b] Source: McCormick (1983). Data on the number of infants weighing less than 1,250 g are not available; it is assumed for purposes of estimating disease burden that the number of such infants is not significantly different from the number of infants weighing 1,500 g or less.

1982, the average annual percent increase in the number of transplants was 8.0 percent. The projected figure of 6,250 renal transplants for 1984 assumes that this annual percent increase has not changed. Data on the age distribution of 1984 transplant recipients have been derived from HCFA data for 1981.* The derivation indicates that 88.5 percent of transplants occur in persons aged 25–59 years and 2 percent occur in persons aged 60 years or older. The remaining 9.5 percent are assumed to be divided equally between the 5–14 years and 15–24 years age groups, corresponding roughly to HCFA data. An estimated 70 percent of transplant recipients become infected (or show reactivation of prior infection) with CMV; 15 percent of those infected become ill as a result of CMV infection, 15 percent become seriously ill, and one-third of those seriously ill die (Losonsky, personal communication, 1983; Plotkin, personal communication, 1983; Polk, personal communication, 1983; Stewart, personal communication, 1983) (see Table E.8). CMV infection in transplant recipients is assumed to prolong hospitalization by 18 days (Losonsky, personal communication, 1983; Polk, personal communication, 1983; Stewart, personal communication, 1983).

* HCFA data on the number of transplants includes Medicare and non-Medicare patients; HCFA data on age distribution includes Medicare patients only. About 93 percent of transplants are covered by Medicare (Krakauer et al., 1983). It is assumed for the disease burden estimate that non-Medicare transplants have the same age distribution.

TABLE E.7 Disease Burden: CMV Post-Transfusion Syndrome

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Casee	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Hequiring hospitalization	Blood-transfusion recipients	1,289	10	1,592	10	3,707	10	4,464	10	11,643	10	4,307	10
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)		218	n.a.										
F	Total impairment		218	n.a.										
G	Reproductive impairment resulting in infertility													
H	Death		174	n.a.										

TABLE E.8 Renal Transplants in the United States

	Age (years)						
	Under 1	1-4	5-14	15-24	25-59	60 and Over	fill Ages
Estimated number (%) of renal transplants in age groups used in this report, projected to 1984[a]	1	1	297 (4.75)	297 (4.75)	5,531 (88.5)	125 (2.0)	6,250
Number with clinical CMV disease			31	31	581	13	656
Number with severe clinical CMV disease			31	31	581	13	656
Fatalities due to CMV infection			10	10	194	1	215

[a]Estimates derived from Health Care Financing Administration (1983) data.

Liver Transplants Over the past 20 years, about 540 liver transplants have been performed worldwide (Sherlock, 1983); but in 1984, 150 to 200 transplants are expected in the United States alone. The number of transplants probably will continue to increase (Scharschmidt, personal communication, 1984). About 31 percent of transplants in the United States are performed on patients under the age of 18, and the remainder on patients between the ages of 18 and 55 (Scharschmidt, personal communication, 1984). Data on the incidence of CMV infection and associated morbidity and mortality in recipients of liver transplants are not available; it is assumed that infection rates and morbidity and mortality in these patients are similar to those in recipients of renal transplants (see above). For the disease burden estimate, it is assumed that 175 liver transplants will occur in 1984; that 31 percent of transplants (54) will occur in persons in the age groups 1–4, 5–14, and 15–24 (reflecting the proportion of the United States population represented by each group); and that 69 percent of transplants (121) will occur in persons in the age group 25–59. Estimated morbidity and mortality due to CMV infection in recipients of liver transplants are summarized in Table E.9.

Cardiac Transplants The number of cardiac transplants performed annually in the U.S. over the past five years is estimated to be about 100 (Evans, personal communication, 1983). Data on the age distribution of transplant recipients are not available; it is assumed that all transplants occur in the 25–59 years age group. Morbidity and mortality due to CMV infection in these patients is assumed to be similar to that in renal transplant patients (Losonsky, personal communication, 1983; Polk, personal communication, 1983).

Table E.10 summarizes the disease burden associated with CMV in renal, liver, and cardiac transplant recipients.

TABLE E.9 Liver Transplants in the United States

	Age (years)			
	1-4	5-14	15-24	25-59
Number of transplants	9	21	25	121
Number with clinical CMV disease	2	4	6	26
Fatalities due to CMV disease	1	1	1	4

Note: Number of transplants estimated by Scharschmidt (personal communication, 1984). Age distribution derived from estimates provided by Scharschmidt (personal communication, 1984) and from distribution of projected 1984 United States population (Bureau of the Census, 1984).

Bone Marrow Transplants Estimates of the number of allogeneic bone marrow transplants performed annually in the U.S. from 1979 to 1982 were provided by the Statistical Center of the International Bone Marrow Transplant Registry (1983).* Assuming an average annual increase of 52 percent, the projected number of bone marrow transplants in 1984 is 1,848. The estimated age distribution of recipients was derived from data reported by Meyers et al. (1982). Hanshaw (personal communication, 1984) estimates that CMV infection occurs in about 77 percent of transplant recipients. About 25 percent of recipients develop CMV pneumonia and in 80 percent of these patients the infection is fatal (see Table E.11). Disease associated with CMV infection in marrow recipients is estimated to prolong hospitalization by 30 days (Stewart, personal communication, 1983).

Table E.12 summarizes disease burden associated with CMV in recipients of bone marrow transplants.

Patients with Malignancies

Patients with malignancies are at increased risk of acquiring CMV infection, primarily as a result of immunosuppressive therapies. CMV disease has been described best in children and adults with hematologic malignancies, especially leukemia. Data on the incidence of CMV disease in patients with other malignancies are limited and disease burden has been calculated only for patients with leukemia. Table E.13 shows the estimated morbidity and mortality associated with CMV disease in these patients.

* These data have not been reviewed or approved by the Advisory Committee of the IBMTR.

TABLE E.10 Disease Burden: CMV in Renal, Liver, and Cardiac Transplant Recipients

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hospitalization	Renal transplant recipients Cardiac transplant recipients Liver transplant recipients			2	18	66	18	68	18	1,208	18	26	18
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death						10	n.a.	11	n.a.	199	n.a.	1	n.a.

TABLE E.11 CMV Pneumonia in Recipients of Allogeneic Bone Marrow Transplants

	Age (years)						
	Under 1	1-4	5-14	15-24	25-59	60 and Over	All Ages
Number (%) of allogeneic bone marrow transplants[a,b]	30 (1.6)	118 (6.4)	490 (26.5)	601 (32.5)	536 (29.0)	74 (4.0)	1,849 (100)
Number of transplant recipients contracting CMV pneumonia[b] (about 25% of above)	8	30	123	150	134	19	464
Fatalities (80%)[c] due to CMV infection	6	24	98	120	107	15	370

[a] Number based on data for 1979–1982 provided by the Statistical center of the International Bone Marrow Transplant Registry (1983). These data have not been reviewed or approved by the Advisory Committee of the IBMTR. Figures have been projected to 1984 at an annual average increase of 52 percent.

[b] Age distribution derived from data reported in Meyers et al. (1982).

[c] Average of estimates of mortality provided by Alford (personal communication, 1983), Hanshaw (personal communication, 1983), and Plotkin (personal communication, 1983); and derived from data in Rook and Quinnan (1982) and Meyers et al. (1982).

TABLE E.12 Disease Burden; CMV in Bone Marrow Transplant Recipients

Morbidity Category	Description	Number Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hospitalization	Bone marrow transplants	8	30	30	30	123	30	150	30	134	30	19	30
D	Mild chronic disability {not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)											n.a.		n.a.
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		6	n.a.	24	n.a.	98	n.a.	120	n.a.	107	n.a.	15	n.a.

TABLE E.13 CMV Disease in Patients With Leukemia

	Age (years)						
	Under 1	1-4	5-14	15-24	25-59	60 and Over	All Ages
Number of patients with leukemia[a]		9,279[b]	900	820	5,497	22,257	38,753
Number infected with CMV (27%)		2,505	243	221	1,484	6,009	10,462
Number with viremia (30% of those infected)		752	73	66	445	1,803	3,139
Number with viremia and clinical disease (33% of those with viremia)		248	24	22	147	595	1,036
Number with fatal CMV disease (10% of above)		25	2	2	15	60	104

Note: Includes lymphocytic, granulocytic, monocytic, and "other" types of leukemia. Also includes aleukemic and subleukemic conditions.

[a]Derived from data in Young et al., 1981 and Bureau of the Census (1984).

[b]Young et al., 1981 reports incidence in children under 5. It is assumed here that all cases in children under 5 occur in the 1–4 years age group.

An estimated 27 percent of patients with leukemia become infected with CMV, 30 percent of those infected are viremic, and 33 percent of viremic patients have clinical disease (e.g., pneumonia) attributable to CMV (Pizzo, 1981). The infection is fatal in about 10 percent of patients with clinical disease (Losonsky, personal communication, 1983; Polk, personal communication, 1983). Disease associated with CMV infection in patients with leukemia is estimated to prolong hospitalization by 14 days (Losonsky, personal communication, 1983; Polk, personal communication, 1983; Stewart, personal communication, 1983).

Table E.14 presents the disease burden associated with CMV in patients with leukemia. Table E.15 summarizes the disease burden for all CMV disease.

Uncertainty in the Disease Burden Estimates

National data on the morbidity and mortality associated with cytomegalovirus infection are not collected by any agency, and could not be found in the literature. Estimates used in this appendix to calculate disease burden are based primarily on consultations with physicians knowledgeable about the epidemiology and clinical manifestations of disease associated with CMV infection. In addition, some published studies of CMV infection and sequelae were reviewed. Data on the size and age distribution of populations at increased risk of CMV disease are not available, so estimates were derived using the sources cited in the text.

Calculation of Comparative Total Disease Burden values

The method used in this study to compare the morbidity and mortality resulting from various diseases is described in Chapter 4.

Total disease burden values (TDBVs) for CMV are calculated using estimates from Table E.15 and employing infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 3,018 (committee median perspective) and 2,682 (age-neutral perspective).

Vaccine Target Populations

Congenital and Perinatal Infection

Immunizing susceptible females prior to pregnancy is the most effective way to prevent congenital and perinatal infection. Reactivation of CMV has been shown to cause infection in babies born to the same latently infected mother, but careful prospective studies by Stagno et al. (1983) have demonstrated that primary infection of the mother during pregnancy is more likely to be associated with symptomatic, congenital infection than reactivation of latent virus. Although

TABLE E.14 Disease Burden: CMV in Patients with Malignacies (Leukemias)

			Under 1 Year		1-4 Yeats		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duratior
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiting moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hoapitalization	Patients with leukemias			248	14	24	14	22	14	147	14	595	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)									n.a.				
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death				25	n.a.	2	n.a.	2	n.a.	15	n.a.	60	n.a.

TABLE E.15 Disease Burden Summary: Cytomegalovirus

Morbidity Category	Description	Condition[a]	Under 1 Year		1-4 Years		5-14 Yours		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities								13,199	35	34,834	35		
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed		7,092	6					13,199	4	34,834	4		
C	Requiring hospitalization		6,138	10	1,872	11	3,92D	11	7,474	8	20,745	9	4,947	11
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity}		660	n.a.	4,602	n.a.								
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)		438	n.a.	1,534	n.a.		n.a.						n.a.
F	Total impairment		218	n.a.										
G	Reproductive impairment resulting in infertility													
H	Death		1,090	n,a.	49	n.a.	110	n.a.	133	n.a.	321	n.a.	76	n.a.

Notes: Includes all cases associated with (a) congenital and perinatal infections; (b) CMV mononucleosis and other febrile illnesses; (c) post-transfusion CMV disease; (d) organ and bone marrow transplants; and (e) malignancies. Durations are weighted averages.

[a]See text and tables E.1 through E.14.

it is theoretically possible to develop a vaccination program aimed at pubertal females, similar to that in the United Kingdom for congenital rubella, difficulties may be encountered in achieving high immunization rates in that group. Some health professionals favor the strategy of administering a CMV vaccine simultaneously with current pediatric vaccines.

High-Risk Individuals

For seronegative persons who are going to receive a transplant from a seropositive donor and individuals with leukemias and lymphomas (subsequently referred to as "high-risk individuals"), it would seem desirable to offer some degree of protection against primary infection. Studies are underway in transplant recipients using the Towne live attenuated vaccine developed by Plotkin (Plotkin et al., 1984). The preliminary report on these studies indicates that of those vaccinated, 15 out of 16 seronegative recipients of renal transplants from seropositive donors had evidence of infection following transplantation, and nine manifested evidence of cytomegalovirus disease. Eleven of the 14 placebo recipients had evidence of infection and 10 showed clinical manifestations of CMV infection. The infection rate and the percentage of those infected showing symptoms did not differ significantly between the vaccine-treated and placebo-treated groups; however, a significantly higher percentage of placebo recipients showed evidence of severe CMV disease.

These preliminary studies suggest that this high-risk population is an appropriate, discrete target population (albeit small) to consider in CMV vaccine development.

Suitability for Vaccine Control

CMV infection occurs over a wide age range, so an effective vaccination program would have to involve either a vaccine that provides very long lasting protection or boosters at regular intervals. The need for frequent boosters, which is more likely with a subunit vaccine, could decrease utilization rates.

Congenital Infections

It appears that the best method for reducing the impact of congenital cytomegalovirus infection would be the induction of long lasting immunity in childhood. This would prevent primary infection during pregnancy. Immunization of pubertal females also would be effective if a high rate of vaccination could be achieved.

High-Risk Individuals

As noted above, questions exist regarding the ability of attenuated live vaccines to protect high-risk individuals against CMV infection. Other options might be useful in ameliorating CMV-related illness occurring during the post-transplant period. Cheeseman et al. (1979) have demonstrated that prophylactic administration of interferon may prevent cytomegalovirus infection following renal transplantation. In an analogous situation, it has been demonstrated that the administration of antiviral compound can decrease post-transplant complications caused by herpes simplex infection. Thus, it is possible that antiviral drugs or interferon may offer sufficient temporary protection to the transplant recipient during the period of greatest risk.

Vaccine Preventable Illness

Defining the target population is the first step in calculating the possible reduction in morbidity and mortality that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

Live Attenuated Vaccine for Nonpregnant Adolescent Females

The primary purpose of immunizing nonpregnant adolescent females would be to prevent disease associated with congenital and perinatal CMV infection, so only that portion of the total CMV disease burden is considered here. The vaccine also may protect recipients from CMV disease; however, to simplify the calculations of vaccine preventable illness, the potential reduction in disease burden in recipients of the vaccine is not considered. The degree to which this simplification underestimates the potential benefits of the vaccine is considered minor, but could be calculated using the estimates of disease burden provided in this report.

Because reactivation of maternal infection contracted prior to administration of the vaccine could result in congenital or perinatal infection, it is estimated that even if the entire target population were immunized, some congenital and perinatal infection and disease would continue to occur. In calculating the extent of vaccine preventable illness, it is assumed that 10 percent of symptomatic congenital and perinatal infections result from reactivation of virus. Thus, 90 percent of the symptomatic congenital and perinatal infections are assumed to be potentially vaccine preventable.

Live Attenuated Vaccine for High-Risk Individuals

Preliminary evidence reported by Plotkin and coworkers (1984) indicates that while a live, attenuated vaccine might not reduce the rate of primary CMV infection following renal transplantation, it might reduce the severity of CMV disease following primary infection. Because the vaccine would not prevent disease associated with reactivation of infection, only illness occurring in initially seronegative patients is considered in estimating the potential benefits of the vaccine.

It is assumed that about half of all transplant patients and half of all leukemia patients are initially seronegative, and that the vaccine potentially could prevent all disease associated with CMV in these patients.

Glycoprotein Vaccine for Normal Children

Only disease occurring in normal immunocompetent persons is considered in calculating the potential benefits of this vaccine. This simplification underestimates the potential benefits of the vaccine because it excludes the potential reduction in illness that might occur in recipients who are normal at the time of immunization but later develop conditions that require immunosuppressive therapies. The degree to which this simplification underestimates the potential benefits of this vaccine is considered minor because the number of such persons is relatively small.

Adopting this approach, it is estimated that 100 percent of CMV disease associated with blood transfusions in persons older than one year (the approximate age at which vaccination would occur), 100 percent of CMV mononucleosis and other febrile illnesses, and 100 percent of congenital and perinatal disease could be prevented with this vaccine.

The estimates of vaccine preventable illness are shown in Tables E.16, E.17, and E.18.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Vaccine preventable illness values for CMV are calculated using estimates from Tables E.16, E.17, and E.18, and the two sets of IME values employed throughout this report, using IME values based on a median of committee member perspectives, the vaccine preventable illness values are 1,184 for the live attenuated vaccine for nonpregnant adolescent females; 488 for the live attenuated vaccine for high-risk patients; and 1,389 for the glycoprotein vaccine for normal children. Using the age-neutral perspective, the values are 1,163, 351, and 1,327, respectively, for the same vaccines.

TABLE E.16 Vaccine Preventable Illness: Cytomegalovirus—Live Attenuated Vaccine for Nonpregnant Adolescent Females

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localised pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Natal/perinatal respiratory disease	6,383	6										
C	Requiring hospitalization	Congenital and natal/ perinatal disease	4,357	10										
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Sequelae of congenital infections	594	n.a.	4,142	n.a. n.a.								
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Sequelae of congenital infections	198	n.a. n.a.	1,381	n.a.								
F	Total impairment	Sequelae of congenital infections												
G	Reproductive impairment resulting in infertility													
H	Death	Death from congenital and natal/perinatal disease	819	n.a. n.a.										

Notes: For discussion, see text. Durations are weighted averages.

TABLE E.17 Vaccine Preventable Illness: Cytomegalovirus—Live Attenuated Vaccine for High-Risk Individuals

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hospitalization	Transplant recipients and patients with leukemias	4	30	140	16	107	25	120	25	745	19	15	15
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)					n.a.		n.a.				n.a.		
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		3	n.a.	25	n.a.	55	n.a.	67	n.a.	161	n.a.	38	n.a.

Notes: For discussion, see text. Durations are weighted averages.

TABLE E.18 Vaccine Preventable Illness: Cytomegalovirus—Glycoprotein Vaccine for Normal Children

Morbidity Category	Description	Condition[a]	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities								13,199	35	34,834	35		
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed		7,092	6					13,199	4	34,834	4		
C	Requiring hospitalization		4,841	10	1,592	10	3,707	10	7,234	8	19,256	8	4,307	10
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)		660	n.a.	4,602	[illegible] n.a.								
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)		220	[illegible]	1,534	[illegible]								
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		910	[illegible] n.a.										

Notes: For discussion, see text. Durations are weighted averages.

[a]See text and tables E.3, E.5, and E.7.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by each of the three cytomegalovirus vaccine candidates, the two vaccine preventable illness values for each vaccine are multiplied by the predicted efficacy of that vaccine. Using vaccine preventable illness values based on a median of committee member perspectives, the potential morbidity and mortality reductions are 947 for the live attenuated vaccine for nonpregnant adolescent females (efficacy=0.8); 342 for the live attenuated vaccine for high-risk patients (efficacy= 0.7); and 1,111 for the glycoprotein vaccine for normal children (efficacy=0.8). Using the age-neutral perspective, the values are 931, 246, and 1,061, respectively, for the same vaccines.

These values are not adjusted for vaccine adverse effects or anticipated utilization.

Use of PRMM values for comparing vaccines is described in Chapter 7.

Prospects for Vaccine Development

Opinions vary considerably on the knowledge base necessary for successful development of cytomegalovirus vaccines. The size of the virus, its ability to become latent and then reactivated in both subclinical and clinical infections, and its poorly understood antigenic structure have been major obstacles to vaccine development. To a lesser degree, concern has been expressed about the theoretical possibility that, as a herpes virus, CMV could be associated with transformation of human cells. Although Albrecht and Rapp (1973) reported that cytomegalovirus could transform hamster cells, there has never been evidence of an epidemiologic association between cytomegalovirus and human malignancy.

Some scientists have expressed concern about the strength of immunity that could be induced by the live attenuated virus vaccines. The most advanced CMV vaccine candidate employs the Towne live attenuated strain developed by Plotkin et al. (1983, 1984). Preliminary trials with this vaccine are underway in renal transplant patients. The vaccine induces local reactions in almost half of seronegative recipients but does not appear to induce systemic reactions in this group.

Concern over reactivation of "attenuated" viruses has led some scientists to propose the development of a glycoprotein CMV vaccine (discussed further below). Such an approach would be technically more difficult because the protective antigens are not defined and because the induction of immunity would require multiple doses of antigen, possibly with adjuvants.

Clinical Studies The performance of clinical trials with an attenuated live CMV vaccine presents major problems, whether the target population consists of nonpregnant adolescent females or high-risk individuals (as defined above).

In the first case, the problems stem from the fact that the target population is different from the population at risk of disease. Infection with cytomegalovirus often is not apparent, so it will be necessary to follow large numbers of initially seronegative women (both vaccinated and unvaccinated controls) before, during, and immediately after pregnancy, in addition, the children of these women will have to be followed from birth to about five years of age. To identify late developing sequelae, it will be necessary to examine these children repeatedly, both for physical impairments such as hearing loss and for impaired cognitive development.

The problems associated with vaccine trials in high-risk individuals are different but no less worrisome. Clinical evaluation of patients with multiple abnormalities is complex. Preliminary trials in this population with the Towne live attenuated strain (Plotkin et al., 1983, 1984) have shown that seronegative renal transplant recipients who get organs from seropositive donors develop evidence of CMV infection whether or not they receive the vaccine. The difference between the vaccinees and the placebo group appears to be in the severity of CMV disease following primary infection, but the data are not yet complete.

Predictions About Vaccine Development The probability of successful development of an attenuated live virus vaccine for nonpregnant adolescent females and high-risk patients is estimated to be 50 percent, with an investment of about $50 million over seven years. Less time would be needed for a vaccine for renal transplant patients (about three years), because some data for this group already exist.

The estimate of the probability of success is lower than that for some other vaccines because of the questions that remain about the structure of the CMV virus, the characteristics of protective antigens, the nature of the latent state, and the elements of host immunity that control infection. The protective efficacy of the vaccine in terms of decreased damage from congenital infections is estimated to be 80 percent. A lesser degree of efficacy, approximately 70 percent, is expected in the high-risk population (e.g., prior to immunosuppression).

Although genetic analysis of cytomegalovirus is in the early stages, it is possible by analogy with other viruses (e.g., Herpes simplex virus and hepatitis B virus) to predict that a vaccine eventually could be produced by recombinant DNA technology. Identification and isolation of the genes coding for major viral surface glycoprotein antigens would allow their insertion into a suitable host system, e.g., yeast. This would permit production of the antigens independently from the viral DNA, which could reduce concerns over the possible oncogenicity and potential for latency of live virus vaccine preparations. Considerable research needs to be conducted, however, to determine the feasibility of this approach. In addition to the areas mentioned above, researchers need to learn more about the extent and significance of variations between CMV viral strains, the immune control of CMV infection, and the nature of host-virus interactions.

Predictions on vaccine development are shown in Chapter 5.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity of illness, benefits of immunization, and barriers to vaccination) used to predict vaccine utilization are described in Chapter 6, in which scores assigned to various vaccines are displayed together for comparison.

Live Attenuated Vaccine for Nonpregnant Adolescent Females

Lay Acceptance Lay perception of the risk of illness is judged to be quite low, primarily because it seems that most parents of adolescents do not consider their own children to be at risk of having a mentally retarded child. Lay perception of the severity of mental retardation and of the benefits of a vaccine that might prevent it are considered to be quite high. Because of the relatively high frequency of adverse reactions to the vaccine, lay perception of the barriers to vaccination also are judged to be relatively high.

Provider Acceptance Because most congenital and perinatal CMV infections are clinically inapparent, physician perception of the risk of illness is judged to be low. Perception of the severity of disease caused by congenital and perinatal infection is judged to be high and a vaccine with the potential to prevent severe neurological disease probably would be perceived as having relatively high benefits, moderated somewhat by the relatively low predicted efficacy of the vaccine. The high frequency of adverse reactions to the vaccine may result in relatively high perceived barriers to its administration.

Live Attenuated Vaccine for High-Risk Individuals

Lay Acceptance Lay perceptions of the risk and severity of disease and of the benefits of the vaccine are judged to be quite high, primarily because of physician cueing and because the consequences of disease caused by CMV, including graft rejection, may be quite severe. The perception of barriers to vaccination is judged to be low, as a result of the serious nature of the underlying diseases in these patients, the perceived severity of the possible consequences of CMV disease, and the experience of these patients with intensive medical treatment.

Provider Acceptance Physician perceptions of the risk and severity of disease caused by CMV in this group of patients are judged to be quite high, because of the severe disease and relatively high fatality

rate associated with CMV infection in these patients. Even though the vaccine is predicted to have a lower efficacy in this group, when it is efficacious it may prevent very severe or fatal outcomes; thus, the perceived benefits are judged to be moderately high and the perceived barriers low.

Glycoprotein Vaccine for Normal Children

Lay Acceptance Lay perception of the risk of illness caused by CMV is judged to be quite low, primarily because the public is thought to be unfamiliar with the potential for CMV infection and disease. Perception of the severity of disease (e.g., mononucleosis) is judged to be moderate, and perception of the likely benefits of the vaccine is judged to be moderately high, based on the predicted efficacy of the vaccine in preventing disease of moderate severity. Perceived barriers to vaccination are judged to be moderate, based on the relatively high cost of vaccination and the predicted number of required doses (3).

Provider Acceptance Perceptions of the risk and severity of disease caused by CMV are judged to be high because of the high probability of infection over a lifetime and because the illnesses caused by CMV include some that may have severe sequelae. The perceived benefits of the vaccine are judged to be moderately high, based on the predicted efficacy of the vaccine in preventing disease associated with severe outcomes. Perceived barriers are judged to be relatively low because no adverse reactions are expected; the predicted number of required doses (3) may increase perceived barriers slightly.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden
Congenital and Perinatal CMV infection

Category A n/a

Category B - perinatal respiratory disease*		
# of cases = 7,092		
approx. 50% of cases receive 1 phys. visit at $30	= $	106,000
approx. 20% of cases receive diagnostic procedures at $55	= $	78,000
[chest x-ray]		
approx. 10% of cases receive treatment at $5	= $	4,000
TOTAL (B)	= $	188,000
Category C - cytomegalic inclusion disease (CID) and perinatal respiratory disease		
CID		
# of cases = 2,841		
67% of cases typically receive 7 days hospitalization at $400/day	= $	5,330,000
33% of cases typically receive 14 days hospitalization at $400/day	= $	5,250,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate,		
for 67%, 7 days at $400/day	= $	5,330,000
for 33%, 14 days at $400/day	= $	5,250,000
100% of cases typically receive inpatient workups and tests at an additional $200/day,		
for 67%, 7 days	= $	2,665,000
for 33%, 14 days	= $	2,625,000
[culture, serologies, x-rays, blood gases]		
100% of cases typically receive 2 follow-up phys. visits at $30/visit	= $	170,000
TOTAL	= $	26,620,000
Perinatal respiratory disease		
# of cases = 2,000		
10% of cases typically receive 14 days of neonatal ICU at $800/day	= $	2,240,000
40% of cases typically receive 6 days ICU at $600/day plus 8 days normal hospitalization at $400/day	= $	5,440,000
50% of cases typically receive 4 days ICU at $600/day plus 3 days normal hospitalization at $400/day	= $	3,600,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate,		
for 10%, 14 days at $800/day	= $	2,240,000

*Cost and treatment estimates based on data gathered for parainfluenza respiratory tract disease (Category B) cost calculations.

for 40%, 6 days at $600/day plus 8 days at $400/day		= $ 5,440,000
for 50%, 4 days at $600/day plus 3 days at $400/day		= $ 3,600,000
100% of cases typically receive 6 follow-up phys. visits at $30/visit		= $ 360,000
	TOTAL	= $ 22,920,000
	TOTAL (C)	= $ 49,540,000

Category D - cytomegalic inclusion disease (chronic neurologic sequelae) [assuming typical lifetime duration of 70 years]

# of cases = 5,262		
total annual costs for treatment and/or care $2,000/case; for 70* year duration at 5% discount rate, total present value/case = $41,000		= $ 215,742,000
[physician/specialist visits, continuous medication and testing for seizures, physical therapy, aid for learning/behavioral disabilities]		
	TOTAL (D)	= $ 215,742,000

Category E - cytomegalic inclusion disease (chronic neurologic sequelae) [assuming lifetime duration 75% of typical]

# of cases = 1,754		
total annual costs for treatment and/or care $5,000/case; for 53 year duration at 5% discount rate, total present value/case = $97,000		= $ 170,138,000
[see Category D]		
	TOTAL (E)	= $ 170,138,000
	TOTAL COST	= $ 435,608,000

Mononucleosis and Other Febrile Illnesses

Category A - convalescence from B

# of cases = 48,033		
[costs/case associated with 35 day convalescence period]		
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 1,441,000
	TOTAL (A)	= $ 1,441,000

*Although most chronic Category D and E cases occur in the age group 1–4, the standard 70-year life expectancy figure is used to simplify calculations.

Category B - mononucleosis (typical case) and other febrile illnesses (convalescence from C)

# of cases = 48,033		
[costs associated with 4 day duration of illness]		
100% of cases typically receive diagnostic workup at $175 [serologies, urine/throat cultures, CBC/chemistries]	= $	8,406,000
100% of cases typically receive 2 phys. visits at $30/each	= $	2,882,000
TOTAL (B)	= $	11,288,000

Category C - mononucleosis and other febrile illnesses (hospitalized cases)

# of cases = 10,383		
100% of cases typically receive 5 days hospitalization at $400/day	= $	20,766,000
hospitalized cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate, 5 days at $400/day	= $	20,766,000
TOTAL (C)	= $	41,532,000

Categories D - G n/a

TOTAL COST	= $	54,261,000

Post-Transfusion Infection

Category C

# of cases = 27,002		
1.5% of cases typically receive 10 days neonatal ICU at $800/day	= $	3,240,000
3% of cases (very low birthweight infants) typically receive 10 days neonatal ICU at $800/day	= $	6,480,000
95.5% of cases typically receive 10 days ICU at $600/day	= $	154,721,000
hospitalized cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate		
for 4.5%, 10 days at $800/day	= $	9,721,000
for 95.5%, 10 days at $600/day	= $	154,721,000
100% of cases typically require diagnostic testing at $1000 [serologies, cultures, CBC/chemistries]	= $	27,002,000
TOTAL (C)	= $	355,885,000

Category E

# of cases = 218
total annual costs for treatment and/or care = $5,000/case; assuming lifetime duration of 53 years at 5% discount rate, total present value/case = $97,000 = $ 21,146,000

TOTAL (E) = $ 21,146,000

Category F

# of cases = 218
total annual costs for treatment and/or care = $20,000/case; assuming lifetime duration of 35 years at 5% discount rate, total present value/case = $344,000 = $ 74,992,000

TOTAL (F) = $ 74,992,000

TOTAL COST = $ 452,023,000

Renal, Cardiac, Liver Transplants

Category C

# of cases = 1,370
100% of cases typically receive 18 additional days ICU at $600/day = $ 14,796,000
100% of cases typically receive additional diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rates 18 days at $600/day = $ 14,796,000

TOTAL COST = $ 29,592,000

Bone Marrow Transplant Recipients

Category C

# of cases = 464
100% of cases typically receive 18 additional days ICU at $400/day = $ 3,341,000
100% of cases typically receive additional diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate 18 days at $400/day = $ 3,341,000

TOTAL COST = $ 6,682,000

Category C

# of cases = 1,036	
100% of cases typically receive 18 additional days ICU at $600/day	= $ 11,189,000
100% of cases typically receive additional diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate 18 days at $600/day	= $ 11,189,000
TOTAL COST	= $ 22,378,000
TOTAL COST FOR CMV	= $1,000,544,000

Cost of Vaccine Preventable Illness

Glycoprotein Vaccine for Normal Children

100% of congenital and perinatal infection	= $435,608,000
100% of mononucleosis and other febrile illnesses	= $ 54,261,000
100% of post-transfusion disease in people over 1 year, but 0% in infants under 1 year (25,713 in Category C only)	= $334,269,000
TOTAL COST	= $824,138,000

Live Attenuated Vaccine for High-Risk Individuals

50% of all disease burden in IC patients (transplant recipients, patients with malignancies)	= $ 29,826,000
TOTAL COST	= $ 29,826,000

Live Attenuated Vaccine for Nonpregnant Adolescent Females

90% of congenital and perinatal infection	= $392,047,000
TOTAL COST	= $392,047,000

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Appendix

F

PROSPECTS FOR IMMUNIZING AGAINST HEMOPHILUS INFLUENZAE TYPE b

Hemophilus influenzae type b is a major cause of meningitis in young children. Neurological sequelae, including hearing and vision loss, motor abnormalities, seizure disorders, severe mental retardation, and quadriplegia, may follow the meningitis (Norden, 1982). The case-fatality ratio is approximately 5 percent with adequate treatment, and almost 90 percent without proper care. Other invasive forms of the disease include epiglottiditis, pneumonia, bacteremia, and cellulitis.

Studies indicate that H. influenzae first colonizes the nasopharynx and then penetrates the mucosa. Capsulated H. influenzae strains are responsible for most severe illness, although non-capsulated strains occasionally have been associated with infection. Of the six encapsulated strains, type b is by far the most common cause of invasive disease (Norden, 1982). Host intervention through the production of anticapsular antibodies can prevent disease.

The mechanism by which virulent H. influenzae organisms gain access to the blood is not known, but a bacteremic phase that is generally asymptomatic precedes invasion of the meninges. Whether the organism will go on to cause meningitis depends on its virulence and the immune status of the host. Invasion of the cerebrospinal fluid is followed by the usual symptoms of bacterial meningitis, which if not treated promptly is often fatal.

Pathogen Description

Nonencapsulated H. influenzae strains, although common, are largely avirulent. There are six serotypes of H. influenzae with immunochemically distinct capsular polysaccharides (Egan et al., 1982). They are identified as types a, b, c, d, e, and f. Almost all invasive H. influenzae disease is caused by type b (Norden, 1982). Thus, a vaccination program can be directed against a single type.

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Studies on the noncapsular surface antigens of H. influenzae type b in several laboratories have revealed a number of distinct strains within type b (Hansen et al., 1982a; Loeb and Smith, 1980). The relative prevalence of these different strains as a cause of disease varies with geographic locale. More than 20 different subtypes have been identified, but 5 or 6 account for most H. influenzae type b illness (Hansen et al., 1982a; Loeb and Smith, 1980). Subtyping is primarily of epidemiologic value, because all type b strains are killed by anti-type b polysaccharide antibodies. The type b polysaccharide has been purified and its structure determined. The repeating unit is •3)-˜ -D-ribose-(1•1)-D-ribitol-5-phosphate.

Host Immune Response

Protection against invasive H. influenzae disease is due primarily to humoral immunity (Solotrovsky and Lynn, 1978). Protective antibodies are induced to both the capsular polysaccharide and major outer membrane surface proteins. Classic studies by Fothergill and Wright (1933) demonstrated an inverse relationship between the development of bactericidal antibodies and the age-related incidence of H. influenzae disease. The same inverse relationship has been demonstrated for antibodies directed against the type b capsular polysaccharide (Anderson et al., 1977).

Following the decline of maternally acquired immunity between two and three months of age, bactericidal antibodies generally are not detectable for about three years. They then rise slowly, reaching adult levels by about age eight. However, there is considerable individual variability in the pattern of antibody changes.

Clinical studies suggest a positive correlation between the presence of anti-type b antibodies and the relative absence of H. influenzae disease in children older than five years of age (Peltola et al., 1977). Passive protection studies in animals, primarily the infant rat, provide further evidence for the protective effects of antibodies against type b polysaccharide (Myerowitz and Norden, 1977).

There is strong evidence from the Finnish studies of the capsular polysaccharide (polyribophosphate) vaccine for the protective role of antibody in older children (Peltola et al., 1984). However, the committee believes the focus should be directed towards a vaccine that would be effective in younger children because of the distribution of the disease described below.

Magnitude of Disease Burden

Estimates of the disease burden imposed by H. influenzae type b are based primarily on information from Cochi (personal communication, 1983), Hill (1983), and Norden (1982). All cases of invasive illness caused by the organism are assumed to fall into generic Morbidity Category C. (Morbidity Categories are defined in Table F.2.)

The Centers for Disease Control receives case reports on meningitis from 27 states, but there is believed to be considerable underreporting. An average of 1,500 cases per year were reported between 1978 and 1981.

To estimate the number of cases of H. influenzae type b meningitis that will occur in 1984, an incidence range was derived from rates cited in Hill (1983), and Norden (1982). The approximate midpoint of that range was then applied to population projections for 1984. The estimate of 9,000 cases corresponds well to that made by Cochi, i.e., 8,000 to 10,000 cases. These rates may need revision in light of ongoing studies described below. It is also important to note that incidence rates among certain groups are higher than that for the general population:. fourfold higher for blacks; fivefold for Navaho Indians; and tenfold for Alaskan Eskimos (Norden, 1982).

The number of cases of non-meningitic H. influenzae type b invasive disease is more difficult to estimate. Various studies have reported that non-meningitic conditions account for 30 to 80 percent of invasive illness caused by all types of H. influenzae (Dajani et al., 1979; Granoff and Basden, 1980; Todd and Bruhn, 1975; Ward et al., 1982). Comprehensive studies on this question are now underway in Minnesota (Osterholm et al., 1983), Atlanta (Cochi, personal communication, 1983), and Alaska (Ward, personal communication, 1983).

Pending publication of these studies, the ratio of meningitis to non-meningitic invasive disease for H. influenzae type b is assumed to be 55:45. Thus, the number of cases of non-meningitic invasive disease in 1984 is projected to be 7,364.

Table F.1 shows the presumed age distribution for cases of meningitis and non-meningitic invasive disease. These figures represent a composite of information from several sources (e.g., Cochi, personal communication, 1983; Granoff and Basden, 1980). The result is somewhat simplified, but has been judged sufficiently accurate for the purposes of these calculations.

For age groups under 15 years the total number of cases in Morbidity Category C includes cases of meningitis (under 1 year, 4,050; 1–4 years, 4,050; 5–14 years, 900) and cases of non-meningitic invasive disease (under 1 year, 1,841; 1–4 years, 3,314; 5–14 years, 736). Cases in Category C in age groups beyond age 14 consist entirely of non-meningitic invasive disease. The durations shown in Table F.2 are weighted to reflect the typical duration of hospitalization for the type of illness that predominates in the total number of cases (i.e., meningitis, 13 days; other invasive disease, 10 days).

The case-fatality rate for all types of invasive disease is assumed to be 5 percent on the basis of estimates in Hill (1983) and Norden (1982), and information supplied by Cochi (personal communication, 1983).

The number of cases of long term sequelae of meningitis have been calculated as follows: 28 percent of survivors are assumed to incur chronic disability distributed between Morbidity Categories D (10 percent), E (13 percent), and F (5 percent). These figures are based on studies by Munoz et al. (1983) and Sell (1983), and on the review by Granoff and Squires (1982).

TABLE F.1 Assumed Age Distribution of H. influenzae Invasive Disease Cases (Percentages)

Age Group (years)	Meningitis (percent)	Other Invasive Disease (percent)
Under 1	45	25
1-4	45	45
5-14	10	10
15-24		4
25-59		12
60 and over		4

The occurrence of chronic sequelae arising from other invasive H. influenzae type b infections was not noted by Norden (1982) and is assumed to be negligible in this disease comparison.

Estimates of the disease burden imposed by H. influenzae type b, based on the assumptions outlined above, are shown in Table F.2. These estimates should not be taken as a definitive statement on the incidence and distribution of H. influenzae type b illness, however, because time and resource limitations necessitated the adoption of certain simplifying assumptions. These have been judged not to compromise the utility of the estimates for comparative purposes within this study, but the committee cautions against use of these estimates for other purposes.

Uncertainty in the Disease Burden Estimates

As noted above, several studies have reported different incidence rates for meningitis and for non-meningitic invasive disease. Uncertainty thus exists regarding both the true national incidence of these illnesses and the appropriate rates to employ for estimating deaths and the incidences of chronic sequelae.

Estimates used in calculations in this report may require revision when final results are available from studies described above.

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare the morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for H. influenzae type b were calculated using estimates from Table F.2 and infant mortality equivalence values based on a median of committee member perspectives

TABLE F.2 Disease Burden Summary: H. Influenzae Type b

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hospitalization	Meningitis and other invasive disease	5,891	13	7,364	12	1,636	12	295	10	884	10	295	10
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Bearing loss	385	n.a.	385	n.a.	86	n.a.						
E	Moderate to severe chronic disability {requiring hospitalization, special care, or other major limitation of normal activity]	Vision impairment, motor abnormalities, mental retardation, seizure disorders	500	n.a.	500	n.a.	111	n.a.		n.a.		n.a.		n.a.
F	Total impairment	Severe mental retardation, guadriplegia	192	n.a.	192	n.a.	43	n.a. n.a.						
G	Reproductive impairment restating in infertility					n.a.		n.a.						
H	Death		295	n.a.	368	n.a.	82	n.a.	15	n.a.	44	n.a.	15	n.a.

or on an age-neutral perspective. TDBVs thus obtained are 1,986 (committee median perspective) and 1,919 (age neutral perspective).

Vaccine Target Population

The distribution of H. influenzae illness is described above. Up to two to three months of age, most infants exhibit maternal antibodies. Although some cases of the disease appear between three and six months, most illness occurs between six and twelve months of age. Hence, the target population for active immunization probably will be all children at about three months of age. An earlier age of initial immunization may be practicable if a vaccine can be developed that induces immunity in younger infants.

H. influenzae generally has not been considered to be associated with outbreaks, but this may change with changing lifestyles in the United States. Studies are underway to determine the risk of primary disease and secondary spread in day care centers (Cochi, personal communication, 1983; Osterholm et al., 1983). Recent studies in Colorado have shown that the relative risk of developing H. influenzae type b disease is up to 12-fold higher in children who attend day care centers than in age matched controls (Istre et al., 1983). Thus, infants and children in day care centers may require special attention.

Suitability for Vaccine Control

Invasive disease caused by H. influenzae type b is well suited to control by active immunization because antibody appears to provide protection, and because an opportunity to induce immunity exists between the decline of maternal antibodies (two to three months) and the peak of illness (after six months). Current treatment regimens are not satisfactory because chronic central nervous system sequelae often occur despite antibiotic therapy (Hill, 1983).

Chemoprophylactic agents (e.g., rifampin; Band et al., 1984) and passive immunization (with hyperimmune globulin) are possible post-exposure means of controlling secondary spread of disease. These methods were not considered further because secondary disease probably represents a small proportion of the total disease burden and because the methods are not directly relevant to the committee charge.

Success in vaccine prevention of invasive disease, particularly meningitis, will depend on the development of a vaccine capable of inducing immunity in infants. Progress towards this goal is described below.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the benefits that could be produced by a vaccine candidate. This definition can be then translated into an estimate for vaccine

preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

The H. influenzae type b vaccine probably would be administered first at about two to three months of age when maternal antibody has declined. Because the immune response at this age is limited, no vaccine would be likely to reach full protective efficacy until after six months of age, by which time further doses could have been administered. About 20 percent of illness in the first year of life occurs before six months, against which only partial protection could be expected. Thus, it is judged that only about 90 percent of illness in the first year of life is potentially preventable with the candidate vaccine. All illness in age groups 1–4 years and 5–14 years is considered vaccine preventable. Illness in older age groups is not considered vaccine preventable because it is rare and individuals at risk are not easily identified. Hence, special efforts probably would not be made to extend the target population to prevent such disease. Estimates of vaccine preventable illness are shown in Table F.3.

Vaccine Preventable illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Total vaccine preventable illness values for H. influenzae type b are calculated using estimates from Table F.3 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the total vaccine preventable illness value for H. influenzae type b is 1,807; with the age-neutral perspective the value is 1,766.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality (the maximum potential health benefit) that could be produced by a vaccine candidate, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of the vaccine. For the H. influenzae type b vaccine candidate, the predicted efficacy is 80 percent. Thus, the potential reduction in morbidity and mortality is 1,446 using the committee median perspective and 1,413 using the age-neutral perspective.

Use of these unadjusted potential benefits numbers for comparing vaccines is described in Chapter 7.

Prospects for Vaccine Development

Two major approaches have been taken toward development of an effective vaccine against invasive H. influenzae type b disease: (1)

TABLE F.3 Vaccine Preventable Illness: H. Influenzae Type b

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hospitalization	Meningitis and other invasive disease	5,302	13 n.a.	7,364	12	1,636	12 n.a.						
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Hearing loss	347	n.a. n.a.	385	n.a.	86	n.a. n.a.						
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major Limitation of normal activity)	Vision impairment, motor abnormalities, mental retardation, seizure disorders	450	n.a. n.a.	500	n.a.	111	n.a.						
F	Total impairment	Severe mental retardation, quadriplegia	173	n.a.	192		43	n.a.						
G	Reproductive impairment resulting in infertility													
H	Death		266	n.a.	368	n.a. n.a.	82	n.a.						

Note: For discussion, see text.

use of the purified type b capsular polysaccharide, and (2) preparation of polysaccharide-protein or oligosaccharide-protein conjugates. A third approach has been to use outer membrane protein vaccines. The first two approaches have been evaluated clinically; a major field trial utilizing the purified capsular polysaccharide was carried out in 1974 in Finland (Peltola et al., 1977). The outer membrane protein vaccines have been examined only in animal models, and are protective in these models (Hansen et al., 1982b; Shenep et al., 1983).

The Finnish study involved use of an H. influenzae type b polysaccharide vaccine as a control in a group A meningococcal polysaccharide vaccine field trial. The Hemophilus vaccine was administered to approximately 49,000 children three months to five years of age (Makela et al., 1977; Peltola et al., 1977). There were no significant adverse reactions to the vaccine, but erythema and tenderness at the injection site were common.

The vaccine proved to be effective in preventing H. influenzae type b disease in children over about 18 months of age; but the vaccine was without protective effect in younger children (Peltola et al., 1984; Pincus et al., 1982). From these efficacy studies, it appears that this purified polysaccharide vaccine (which is not yet licensed in the U.S.) could prevent a substantial amount of invasive H. influenzae type b disease, but a conjugated vaccine (as envisaged in Table 5.1) probably would improve on this (especially in preventing meningitis) for the reasons discussed below.

Antibody studies on children immunized with the polysaccharide vaccine show an age-related response: fewer than 10 percent of infants less than six months of age respond, about 40 percent between six and twelve months respond, and 80 percent or better respond after twelve months of age (Pincus et al., 1982). The success of the polysaccharide vaccine is thus limited by its poor immunogenicity in the age groups at greatest risk. For this reason, several alternative approaches have been investigated (Hill, 1983). They include: 1) mixing the polysaccharide with pertussis organisms (Williams et al., 1982); 2) covalently coupling the polysaccharide to a protein carrier (Schneerson et al., 1980); 3) covalently coupling oligosaccharides derived from the type b polysaccharide to a protein carrier (Anderson, 1983); and 4) use of outer membrane protein vaccines (Shenep et al., 1983).

The first alternative, mixture of the polysaccharide with Bordetella pertussis cells as an adjuvant, has been evaluated as single and multiple injections in infants and young children (Williams et al., 1982). In some studies the combination appeared to be more immunogenic than the type b polysaccharide alone, but these vaccines were significantly more reactogenic than the pure polysaccharide.

The polysaccharide-protein conjugate vaccines hold considerable promise as candidate vaccines. These vaccines are based on observations that coupling of polysaccharide antigens to protein carriers can alter the immune response to the polysaccharide (Schneerson et al., 1980). The polysaccharide is converted from a T-cell independent antigen to one that can recruit T-helper cells. Clinical trials have demonstrated that conjugate vaccines, prepared using high molecular weight polysaccharide attached to either diphtheria or tetanus toxoid,

are clearly superior to the polysaccharide alone in children under three years of age. They induce antibody levels well over those considered to be protective in 100 percent of children over 9 months of age (Lepow and Gordon, 1984), and 90 percent of infants (Zahradnik and Gordon, 1984). Further studies on the acceptability of conjugate vaccines for general use are in progress. The lower age limit for induction of protective antibody levels by these vaccines remains to be precisely determined.

The other approach to conjugate vaccines is to couple small oligosaccharides, derived from the type b polysaccharide, to diphtheria toxoid (Anderson, 1983). These vaccines also are immunogenic in young children.

Neither conjugate vaccine appears to be reactogenic in children (King et al., 1981); however, additional studies are required to determine their overall acceptability. Preliminary studies suggest that concurrent use of the polysaccharide-protein conjugate vaccine with the DTP vaccine has been shown to enhance the immune response to the free toxoid (Zahradnik and Gordon, 1984).

In conclusion, the purified type b polysaccharide has been demonstrated to be effective in children over 18 months of age, but not useful in children under 18 months of age. The polysaccharide-protein and oligosaccharide-protein conjugate vaccines are clearly more immunogenic than the polysaccharide alone in younger children.

Predictions on the further development of a vaccine for H. influenzae type b appear in Chapter 5.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to various vaccines are displayed together to facilitate comparison.

Lay Acceptance

Parental recognition of H. influenzae type b illness, or meningitis, as a threat to their child is probably mistakenly low, hence, a low score has been assigned to the perceived risk of illness. In contrast, high scores have been assigned in the severity and vaccination benefits categories because meningitis is recognized as a severe condition (possibly with physician cueing), and there is a strong belief in the benefits of pediatric vaccines in general. The need for more than one dose if the vaccine is administered to infants or young children is probably the only major perceived barrier to obtaining vaccination, so a moderately low score appears in that category.

Provider Acceptance

Provider recognition of H. influenzae type b as a cause of meningitis and other disease states is believed to be reasonably accurate, involving a moderate risk of a range of severe illnesses. Physician perception of the benefits of an adequately tested vaccine with the envisaged efficacy (see Chapter 5) and ability to induce early immunity would be favorable and any barriers (e.g., the number of doses) would be low because efficacy and safety testing could be conducted reasonably easily. Efficacy trials of the vaccine may be in a high risk population, and this may engender some reservations about relevance to the general population.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparative exercise. The total costs should be taken only as a rough approximation of the direct costs of this disease.

Cost of Total Disease Burden

Categories A & B n/a

Category C

Meningitis

# of cases = 9,000	
67% of cases typically receive 13 days hospitalization at $400/day	= $ 31,356,000
approx. 33% of cases receive 10 days normal hospitalization at $400/day and 3 days ICU at $600/day	= $ 17,226,000
100% of cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate	
for 67%, 13 days at $400/day	= $ 31,356,000
for 33%, 10 days at $400/day and 3 days at $600/day	= $ 17,226,000
[spinal taps, blood chemistries, antibiotics (ampicillin/chloramphenicol), blood cultures, additional cultures, severe cases may require CAT scan]	
100% of cases typically receive 1 follow-up phys. visit at $30	= $ 270,000
TOTAL	= $ 97,434,000

Other invasive disease

# of cases = 7,364	
90% of cases typically receive 10 days hospitalization at $400/day	= $ 26,510,000
approx. 10% of cases receive 8 days normal hospitalization at $400/day and 2 days ICU at $600/day [intubation for epiglottiditis]	= $ 3,240,000
100% of cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate	
for 90%, 10 days at $400/day	= $ 26,510,000
for 10%, 2 days at $600/day and 8 days at $400/day	= $ 3,240,000
[spinal taps, blood chemistries, antibiotics (ampicillin/chloramphenicol), blood cultures, additional cultures, severe cases may require CAT scan]	
100% of cases typically receive 1 follow-up phys. visit at $30	= $ 221,000
TOTAL	= $ 59,721,000
TOTAL (C)	= $157,155,000

Category D - hearing loss (assuming 20 year duration)

# of cases = 856	
total annual costs for treatment and/or care $2000/case; for 20 year duration at 5% discount rate, total present value/case = $26,000 [physician/specialist visits, continuous medication and testing for seizures, physical therapy, aid for learning disabilities]	= $ 22,256,000
TOTAL (D)	= $ 22,256,000

Category E - vision impairment, motor abnormalities, mental retardation, seizure disorders (assuming 20 year duration)

# cases = 1,111	
total annual costs $5,000/case; for 20 year duration at 5% discount rate, total present value/case = $65,000 [see Category D]	= $ 72,215,000
TOTAL (E)	= $ 72,215,000

Category F - severe mental retardation, quadriplegia (for lifetime, assuming 70 years duration)

# of cases = 427
total annual costs $20,000/case; assuming lifetime of 70 years at 5% discount rate, total present value/case = $406,000 [institutionalization] = $173,362,000

TOTAL (F) = $173,362,000

Category G n/a

TOTAL COST = 424,988,000

Cost of Total Vaccine Preventable Illness

Categories A & B n/a

Category C

Meningitis

cases = 8,595 (55% of total cases under age 15)
67% of cases typically receive 13 days hospitalization at $400/day = $ 29,945,000
approx. 33% of cases receive 10 days normal hospitalization at $400/day and 3 days ICU at $600/day = $ 16,451,000
100% of cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate
for 67%, 13 days at $400/day = $ 29,945,000
for 33%, 10 days at $400/day and 3 days at $600/day = $ 16,451,000
[spinal taps, blood chemistries, antibiotics (ampicillin/chloramphenicol), blood cultures, additional cultures, severe cases may require CAT scan]
100% of cases typically receive 1 follow-up phys. visit at $30 = $ 258,000

TOTAL = $ 93,050,000

Other invasive disease

# of cases = 5,697
90% of cases typically receive 10 days hospitalization at $400/day = $ 20,509,000
approx. 10% of cases receive 8 days normal hospitalization at $400/day and 2 days ICU at $600/day = $ 2,507,000
[intubation for epiglottiditis]
100% of cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate

for 90%, 10 days at $400/day = $ 20,509,000
for 10%, 2 days at $600/day and 8 days at $400/day = $ 2,507,000
[spinal taps, blood chemistries, antibiotics (ampicillin/chloramphenicol), blood cultures, additional cultures, severe cases may require CAT scan]
100% of cases typically receive 1 follow-up phys. visit at $30 = $ 171,000
TOTAL = $ 46,203,000

TOTAL (C) = $139,253,000

Category D - hearing loss (assuming 20 year duration)

# of cases = 818
total annual costs for treatment and/or care $2,000/case; for 20 year duration at 5% discount rate, total present value/case = $26,000 = $ 21,268,000
[physician/specialist visits, continuous medication and testing for seizures, physical therapy, aid for learning disabilities]

TOTAL (D) = $ 21,268,000

Category E - vision impairment, motor abnormalities, mental retardation, seizure disorders (assuming 20 year duration)

# of cases = 1,061
total annual costs $5,000/case; for 20 year duration at 5% discount rate, total present value/case = $65,000 = $ 68,965,000
[see Category D]

TOTAL (E) = $ 68,965,000

Category F - severe mental retardation, quadriplegia (for lifetime, assuming 70 years duration)

# of cases = 408
total annual costs $20,000/case; assuming lifetime of 70 years at 5% discount rate, total present value/case = $406,000 = $165,648,000
[institutionalization]

TOTAL (F) = $165,648,000

Category G n/a

TOTAL COST = $395,134,000

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Appendix

G

PROSPECTS FOR IMMUNIZING AGAINST HEPATITIS A VIRUS

Disease Description

Hepatitis A virus (HAV) infection is a more prevalent but somewhat less serious disease than that caused by the hepatitis B virus. It has a worldwide distribution and often occurs in epidemic clusters. HAV is spread primarily by the fecal-oral route; outbreaks often may be traced to contaminated food or community water supplies. Secondary epidemic waves may follow a known outbreak when close personal contacts of the original victims develop the disease (McCollum, 1982). Some researchers suspect that HAV also may be spread by the respiratory route, but there is no conclusive evidence to support this theory.

The age distribution of HAV infection depends on the level of sanitation. In developing countries, infection and acquisition of antibodies occur early, when the disease is usually mild. As sanitation improves and the incidence of disease declines, infection may be delayed to an age at which symptoms are far more severe.

In young children, HAV illness is often anicteric and may be entirely subclinical. When symptoms do occur, they may include jaundice, fever, malaise, fatigue, headache, anorexia, nausea, vomiting, and abdominal pain. Adults with HAV illness may be sick enough to require hospitalization. The disease has no known sequelae and is rarely fatal. Apart from the transient viremia that occurs during early HAV infections, there has been no identification of viremic carriers (Mosley, 1975). Risk factors for hepatitis A infections include involvement in day care, homosexuality, personal contact with infected individuals, and foreign travel.

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Pathogen Description

The HAV is an enterovirus about 28 nm in diameter (McCollum, 1982). It contains a single-stranded RNA and four polypeptides. Comparative studies of HAV from different geographic areas have been limited, but it appears that only one serotype exists. This simplifies potential vaccine development.

Fecal excretion of infected virus begins about 25 days after oral infection with HAV. Peak infectivity probably occurs before the onset of symptoms in the fourth week after exposure.

Host Immune Response

The host immune response to HAV infection involves both IgM and IgG (McCollum, 1982). Anti-HAV IgM appears as virus excretion begins to subside. Shortly thereafter, IgG levels begin to rise. IgG persists while IgM levels fall over the next three to six months. Cell-mediated immunity to HAV infection has not been reported.

Disease Burden Estimates

Estimates of the numbers of cases of illness, hospitalization, and death due to HAV are based on information supplied by Alter (personal communication, 1983), in which hepatitis figures reported to the Centers for Disease Control (Centers for Disease Control, 1983; Francis et al., 1984) were adjusted on the basis of more precise data gathered in the Sentinel County Study. This system facilitates estimation of underreporting, age-specific incidence, and the true distribution of cases between hepatitis A and hepatitis B.

Estimates given below include only icteric cases. (Estimates in Appendix H for hepatitis B include other symptomatic cases.) Calculations based on the sources cited above indicate that there are 35,000 non-hospitalized and 13,000 hospitalized cases of HAV illness and 152 deaths each year.

The distribution of cases among age groups in Table G.1 is based on calculations using data reported to the CDC. Application of these percentages to the estimated total number of cases, hospitalizations, and deaths produces the figures shown in Table G.2. The number of episodes of illness included in Category B is comprised of both typical cases and cases convalescing from hospitalization. Durations of typical cases are based on advice from a number of sources; durations of hospitalizations are from the CDC data (Alter, personal communication, 1983).

Uncertainty in the Disease Burden Estimates

Estimates included in Table G.2 may be low because anicteric cases (with symptoms other than jaundice) have not been included. No data could be found on which to base estimates of the numbers of these cases.

TABLE G.1 Clinically Symptomatic Illness Caused by Hepatitis A Virus in Specific Age Groups (Percentages)

Age Group (years)	Cases Not Hospitalized[a] (percent)	Hospitalizations (percent)	Deaths (percent)
Under 5	4.4	2.0	0
5-14	20.0	10.0	8.0
15-24	46.0	26.0	7.0
25-59	25.0	49.0	29.0
60 and over	4.7	13.0	56.0
All ages	100	100	100

aAssumed to have a distribution the same as that for all reported cases. Cases of unknown age are assumed for the purposes of this report to occur proportionally in the three largest groups. All cases under 5 years of age are assumed to occur in the 1–4 years age group.

The Sentinel County Study (Francis et al., 1984), when coupled with surveillance data reported to the CDC, provides a reasonable basis on which to estimate the true incidence of hepatitis A; however, some errors may have been introduced in the extrapolation to derive national estimates.

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for hepatitis A are calculated using estimates from Table G.2 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. The TDBVs for HAV are 181 (committee median perspective) and 176 (age-neutral perspective).

Vaccine Target Population

The target population for an HAV vaccine is the entire cohort of babies born in the United States. The accessibility of this population has been demonstrated by the success of the DPT and MMR inoculation programs. Childhood vaccination also would benefit adults because herd immunity plays a significant role in this disease.

TABLE G.2 Disease Burden Summary: Hepatitis A Virus

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Jaundice, including convalescence from Category C (total)			1,800	14	8,300	14	19,480	30	15,120	30	3,335	60
C	Requiring hoapitalization	Severe hepatitis			260	8	1,300	8	3,380	8	6,370	8	1,690	8
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring bospitalization, special care, or other major limitation of normal activity)							n.a.		n.a.				
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death	Death following fulminant hepatitis					12	n.a.	11	n.a.	44	n.a.	85	n.a.

Suitability for Vaccine Control

The human immune response to HAV infection and vaccine studies in experimental animals both suggest that the virus is an ideal candidate for vaccine control. Natural infection with HAV appears to induce long lasting immunity. In addition, small doses of pooled human immune globulin are highly effective in preventing or ameliorating HAV infection in contacts of cases and in persons regularly exposed to known endemic settings (McCollum, 1982).

Studies in marmoset and chimpanzee models with both killed and live attenuated virus vaccines have been quite successful. Both vaccines induced neutralizing antibody against the virus; subsequently, the animals were totally protected against parenterally administered challenge virus (Provost et al., 1982, 1983).

While improved sanitation is an effective technique for reducing the incidence of HAV infection, and immune globulin administration can diminish or eliminate symptoms in exposed individuals, only a vaccination program will allow true control of the disease.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the benefit that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

The HAV vaccine would be administered to infants and young children, well before the disease usually occurs, so all cases and complications of the illness would be potentially vaccine preventable. Thus, the VPI estimates are identical to the disease burden estimates shown in Table G.2.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Total vaccine preventable illness values for hepatitis A virus are calculated using estimates from Table G.2 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the total vaccine preventable illness value for hepatitis A virus is 181; with the age-neutral perspective the value is 176.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by the hepatitis A vaccine candidates, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of the vaccine(s). For both hepatitis A virus vaccines (live attenuated virus and subunit), the predicted efficacy is 0.90. The potential reduction in morbidity and mortality available with either vaccine is 162 using the committee median perspective and 159 using the age-neutral perspective. These values are not adjusted for vaccine adverse reactions or anticipated utilization.

Use of these unadjusted potential benefits numbers for comparing vaccines is described in Chapter 7.

Prospects for Vaccine Development

The major stumbling block to HAV vaccine development was lack of a suitable animal model. This was overcome when Holmes et al. (1969) first unequivocally demonstrated the infection of marmosets with HAV. Subsequently, Provost et al. (1975) demonstrated that the virus derived from marmoset liver was readily inactivated by treatment with formaldehyde. This finding led to preparation of the first killed HAV vaccine. Tests of this vaccine in marmosets demonstrated that it could stimulate antibody and that the resulting antibody was protective (Provost and Hilleman, 1978).

The next advance in hepatitis A vaccine research came in the late 1970s, when several laboratories reported reliable propagation of the virus in cell culture. Since then, it has become apparent that the virus grows in a variety of cells, including the WI-38 and MRC-5 human diploid strains (Provost and Hilleman, 1979; Provost et al., 1982). Sequential passage of the virus in cell culture attentuated it for both marmosets and chimpanzees, yet it retained the ability to elicit antibodies (Provost et al., 1983). Clinical studies are now underway to find the optimal level of attenuation for a human vaccine.

An alternative vaccine might employ subunit antigens of the virus prepared by recombinant DNA technology in commercial yeast cells. One of these noninfective subunits might be ideal for inclusion in a complex vaccine against multiple agents. A possible combination would include an HAV subunit and agents of the herpesvirus family (e.g., herpes simplex, cytomegalovirus, and varicella-zoster).

A single injection of live virus vaccine would be expected to induce lifetime immunity. The non-infective antigens might have to be administered intermittently. Predictions on the prospects of vaccine development are shown in Table 5.1.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine

utilization are described in Chapter 6 where scores assigned to various vaccines are displayed together to facilitate comparison.

Lay Acceptance

The perceived risk of acquiring HAV infection among the lay population is probably quite small because most people do not associate hepatitis with children. The perceived severity is probably moderate, because most adults are familiar with the limitation of normal activities associated with the disease, but do not know that symptoms are usually milder in children. The perceived benefits of the vaccines probably would be moderately high, as a result of the general belief in the efficacy of pediatric vaccines. The perception of risks probably would be moderately low; it would stem primarily from concerns about the potential risk of any live virus.

Provider Acceptance

The perceived risk of illness among providers is probably slightly higher than among the lay population, primarily because of greater knowledge about the existence of subclinical infections. More information also plays a role in the slightly lower score for perceived severity. In contrast, perceived benefits probably would be higher as a result of provider awareness of the benefits of herd immunity. Provider perception of barriers probably would be somewhat lower than that of the lay population.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden and Vaccine Preventable Illness

Category A n/a

Category B - nausea, fever, jaundice, abdominal pain, anorexia

total # of cases = 48,035

Originial cases		
# of cases = 35,035		
100% of cases typically receive diagnostic tests at $150 [IgM, SGGTx2, SGPTx2, Bilirubin]		= $ 5,255,000
100% of cases typically receive 2 follow-up phys. visits at $30/each and testing (enzymes) at $20/visit		= $ 3,504,000
	TOTAL	= $ 8,759,000
Convalescent cases - from Category C		
# of cases = 13,000		
100% of cases typically receive 2 follow-up phys. visits at $30/each and testing (enzymes) at $20/visit		= $ 1,300,000
	TOTAL	= $ 1,300,000
	TOTAL (B)	= $ 10,059,000

Category C - severe hepatitis

# of cases = 13,000		
100% of cases typically receive 8 days of normal hospitalization at $400/day		= $ 41,600,000
approx. 10% cases receive additional 7 days ICU at $600/day [usually in greater than 60 age group]		= $ 5,460,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate		
for 100% of cases, 8 days at $400/day		= $ 41,600,000
for 10% of cases, 7 days at $600/day		= $ 5,460,000
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 390,000
	TOTAL (C)	= $ 94,510,000

Categories D - G n/a

TOTAL COST = $104,569,000

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Appendix

H

PROSPECTS FOR IMMUNIZING AGAINST HEPATITIS B VIRUS

An effective, plasma-derived hepatitis B vaccine has been available commercially since 1982, but its acceptance by the targeted high-risk populations has been quite low. This may be because of cost and concerns related to its source, i.e., plasma from donors who may be at high risk of other infections. The need for a less expensive vaccine that would be more acceptable to potential recipients prompted the committee to include a new hepatitis B vaccine as a candidate in this report.

One additional reason for the need for a new hepatitis B vaccine is that with use of the present vaccine plus immune globulin, the domestic (U.S.) source of the present vaccine, i.e., infected individuals, could considerably diminish or even disappear. In fact, to the extent that effective modalities are found for dealing with chronic HBsAg carriers, a conflict of interest could arise concerning preservation of vaccine "source material."

Disease Description

Symptoms of acute hepatitis B virus (HBV) infection include nausea, vomiting, abdominal pain, generalized myalgia with occasional joint pain, urticarial rash, and jaundice. HBV infection also is associated with certain immune complex diseases (polyarteritis nodosa and glomerulonephritis) and with acrodermatitis in young children. Severe cases of hepatitis B may require hospitalization, and death usually follows fulminant hepatitis. Infection is subclinical in one-third of all cases (Francis and Maynard, 1979). Of symptomatic cases in otherwise healthy adults, approximately half involve jaundice, and the other half involve more generalized symptoms. Children infected with HBV are much less likely to have symptoms of hepatitis; probably less than one in a

The advice and assistance of M.J.Alter, J.L.Dienstag, D.P.Francis, and G.Schatz in the preparation of this appendix are gratefully acknowledged. The committee assumes full responsibility for any judgments or assumptions.

hundred HBV infections in newborns is symptomatic (Schweitzer et al., 1973; Stevens et al., 1975).

Approximately 10 percent of healthy adults infected with HBV develop a chronic carrier state that may be either asymptomatic or result in chronic active hepatitis. Chronic infection can follow HBV infection and is most common in immunosuppressed adults (e.g., dialysis patients) and newborn infants (Prince et al., 1978; Schweitzer et al., 1973; Stevens et al., 1975). Chronic infection may result (usually after a period of many years) in cirrhosis or primary hepatocellular carcinoma, either of which can lead to death.

Pathogen Description

HBV is a small (42 nanometer) virus particle consisting of an outer coat and a central core with an unusual circular, partially double-stranded DNA (Dane et al., 1970; Gerin and Wai-Kuo Shih, 1978; Robinson, 1978). The central core contains two antigenic components, the core antigen (HBcAg) and a soluble component of the core antigen, the so-called e antigen (HBeAg). The coat protein is designated the surface antigen (HBsAg) of the virus. In addition to the whole virus particle, the blood of infected individuals contains smaller (20 to 22 nanometer) spherical and tubular forms that consist entirely of HBsAg. HBsAg has several major antigenic determinants. The a antigen is shared by virtually all strains of HBV. In addition, there are two sets of mutually exclusive antigenic determinants (d/y and w/r) that, in combination, produce the four major viral subtypes, adw, adr, ayw and ayr. Additional subtype classifications and variants of each of the above major determinants have been described, but their importance for HBV infection or for immunity to infection is unclear (Gerin et al., 1982).

Host Immune Responses

The immune response to HBV infection involves antibody production to all the HBV antigens: anti-HBc, anti-HBe, and anti-HBs. Anti-HBs usually appears only after resolution of HBsAg infection and is the only antibody that is considered protective (Francis and Maynard, 1979). nata/perinatal and anti-HBe may be present during acute or chronic HBV infection, as well as following resolution, and thus appear to play no part in protection against HBV. Individuals who recover from HBV infection usually develop substantial anti-HBs levels, which probably persist for life. The major humoral immune response following infection is to the common a antigenic component (anti-HBs/a) (McAuliffe et al., 1982). Thus, most individuals who have recovered from infection with one subtype of HBV will have subtype cross-protection. Rarely, anti-HBs/a fails to develop; when this occurs, the patient may remain susceptible to the other subtypes.

Disease Burden Estimates

Disease burden estimates given below are based on information supplied by Alter (personal communication, 1983), in which numbers of cases of hepatitis reported to the CDC (Centers for Disease Control, 1983) were adjusted on the basis of more precise data gathered in the Sentinel County Study (Francis et al., 1984). This system facilitates estimation of underreporting, age-specific incidence, and the proportion of cases caused by HAV and HBV.

Serological surveys and other data suggest that about 15 to 20 percent of clinically apparent cases are reported and that only one-half to two-thirds of infections actually result in clinical symptoms (Francis and Maynard, 1979). (Disease burden estimates in this report are based on the assumption that about two-thirds of cases are symptomatic.) The total number of clinically apparent hepatitis B infections in the United States (128,000, including hospitalizations) has been derived by adjusting the number of cases reported to the CDC (22,177 in 1982) for suspected underreporting. This results in a total of 194,000 infections overall (about 200,000 per year). The number of infections in children less than one year old and from one to four years old probably are underestimated by this approach because of the high proportion of asymptomatic infections in these age groups. Estimates of the number of hospitalizations (15,000) are based on information from the National Hospital Discharge Survey (Alter, personal communication, 1983). The age distributions for hospitalized and non-hospitalized cases are assumed to be identical to those derived from reports to the CDC, shown in Table H.1.

These distributions are applied to the number of hospitalizations to obtain age-specific estimates for Morbidity Category C (Morbidity Categories are defined in Table H.2.), and to the number of non-hospitalized cases (128,000 minus 15,000) to obtain estimates for Morbidity Category B. The numbers in each age group in Category B (Table H.2) include both non-hospitalized cases and individuals convalescing from hospitalization.

Chronic sequelae are estimated to result from 10 percent of all HBV infections (Francis and Maynard, 1979). The HBsAg carrier rate is higher in some groups (e.g., 40 to 50 percent in dialysis patients and 90 percent in newborn infants) and lower in others (e.g., probably less than 5 percent in healthy women). For this report, an average carrier rate of 10 percent has been assumed. This yields a total of 19,400 chronic cases. The asymptomatic carrier state and chronic persistent hepatitis are designated as mild chronic disability (Category D); such cases (12,800) are estimated to comprise about two-thirds of the total number of individuals with chronic infection. Chronic active hepatitis leading to cirrhosis or primary hepatocellular carcinoma, which accounts for the other third of chronic cases (6,596), is assumed to impose moderate to severe chronic disability. Of severe chronic cases, about 28 percent involve chronic active hepatitis, about 68 percent involve cirrhosis, and about 4 percent involve hepatoma. Of deaths from severe chronic cases, about 80 percent die from cirrhosis and 20 percent from hepatoma (Alter, personal communication, 1983).

Table H.1 Distribution of Acute Illness and Hospitalizations Due to Hepatitis B infection (Percentages)

Age (years)	Non-Hospitalized Cases[a] (percent)	Hospitalizations[b] (percent)
Under 1		
1-4	0.6	0.5
5-14	1.4	1.2
15-24	35.2[c]	36
25-59	56.4[c]	53.5[c]
60 and over	6.3	9.3

[a]Assumed to have a distribution the same as that for all reported cases (Alter, 1983). All non-hospitalized cases in children under 5 years are assumed to occur in the 1–4 years age group.

[b]From Alter (personal communication, 1983). All hospitalizations in children under 5 years of age are assumed to occur in the 1–4 years age group.

[c]The age distribution of cases, supplied for the 15–29 years and 30–59 years age groups, has been adjusted based on population figures to correspond to the desired format, i.e., 15–24 years and 25–59 years.

The age at which chronic sequelae and deaths associated with these sequelae occur probably is dependent on the age of initial infection and the lag time between initial infection and the onset of severe sequelae and death. The likelihood of hepatoma or cirrhosis probably is considerably higher when mother to infant infection occurs. Data available on the age distribution of infections (as opposed to illness) and on the lag time are insufficient to calculate the actual age distribution of chronic sequelae, hence a distribution of these events between the 14–24 years, 25–59 years, and 60 years and over age groups based on population size is assumed. Deaths following chronic sequelae (3,958) are assumed to be distributed between the 25–59 years and the 60 years and over age groups on the same basis.

The number of reported deaths resulting from fulminant hepatitis (113) is assumed to be a reasonable indicator of actual deaths. To derive the distribution of such deaths among age groups, the following fatality rates per 100 cases have been applied: age groups under 15 years, 1.2; 15–24 years, 0.6; 25–59 years, 0.9; 60 years and over, 2.9. These rate estimates have been used by the CDC for roughly similar age groups (i.e., under 15 years; 15–29 years; 30–44 years; over 44 years). Applying the rates to estimated cases yields 147 deaths. The difference between this figure and the 113 deaths reported probably is due to underreporting. The distribution of deaths from fulminant hepatitis estimated using this procedure is as follows: under one year, 0; 1–4 years, 1; 5–14 years, 2; 15–24 years, 32; 25–59

TABLE H.2 Disease Burden Summary: Hepatitis B Virus

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Jaundice, nausea, fever, etc.			753	14	1,762	14	45,176	301	71,757	30	8,514	60
C	Requiring hospitalization	Severe hepatitis			75	9	180	9	5,400	9	8,025	9	1,395	9
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Carrier state, chronic persistent hepatitis							2,789	n.a.	7,311	n.a.	2,638	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Chronic active hepatitis, cirrhosis, primary hepatocellular carcinoma							1,440	n.a.	3,766	n.a.	1,389	n.a.
F	Total Impairment													
G	Reproductive impairment resulting in infertility													
H	Death	Death following fulminant hepatitis and chronic sequelae			1	n.a.	2	n.a.	32	n.a.	2,864	n.a.	1,106	n.a.

Note: n.a.=not applicable.

years, 72; 60 years and over, 40. These are included in the total number of deaths, which in the older age groups arise mostly from chronic sequelae.

Estimates of the disease burden imposed by hepatitis B, based on the above assumptions, are shown in Table H.2.

Uncertainty in the Disease Burden Estimates

The National Hepatitis Surveillance System and the Sentinel County Study provide a reasonable basis on which to estimate the true incidence of hepatitis B infections and illness in the U.S. The major uncertainties in the disease burden arise from lack of information about the age distribution of chronic sequelae of infection. The number of deaths from primary hepatocellular carcinoma, as estimated from hospital data, may be up to twice that derived by the methods described above (Schatz, personal communication, 1984). Such possible discrepancies in estimates derived from different sources need further study.

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for hepatitis B are calculated using estimates from Table H.2 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 5,866 (committee median perspective) and 5,665 (age-neutral perspective).

Vaccine Target Population

The hepatitis B virus is most often transmitted parenterally, through intimate sexual contact, or perinatally from infected mothers to their newborn infants. Other routes of transmission may occur, but probably require close personal contact with exchange of body fluids. Although high-risk groups for HBV infection have been clearly identified, the CDC's Sentinel County Study revealed that only half of all reported hepatitis B patients appeared to belong to a high-risk group (Francis et al., 1984).

The groups at high risk because of parenteral exposure include health care personnel who have contact with blood and/or blood-contaminated instruments; dialysis patients; drug addicts; and multiply transfused children and adults (e.g., those with hemophilia or some form of chronic anemia). Individuals at risk because of sexual exposure to HBV are homosexual men with multiple sex partners, spouses and other sex partners of people with acute or chronic HBV infections, and possibly prostitutes.

A newborn infant is at risk of perinatal HBV infection if its mother is either a chronic HBsAg carrier or if she has an acute HBV infection near the time of delivery. Infants with the highest incidence of perinatal HBV infection are those whose mothers are members of high-risk groups (e.g., immigrants from endemic areas, medical personnel, and drug addicts).

Others who are considered at high risk of HBV infection are family contacts of HBsAg carriers and the residents and staff of some institutions (e.g., prisons and schools for the mentally retarded). Travelers in endemic areas may be at risk of HBV infection if they have intimate contact with the local population or receive indigenous medical care (a possible source of parenteral exposure).

Because of the difficulty in identifying and reaching some of those in groups at risk of hepatitis B (homosexual men, IV drug users, heterosexual contacts of infectious people), and because a substantial portion of patients with hepatitis B do not fit into any identifiable group, it may be necessary to administer HBV vaccine to all children to effectively control this disease. Should the safety record of current (or new) vaccines continue to be good and should the price of vaccine decrease, universal vaccination could be re-evaluated.

Suitability for Vaccine Control

The current hepatitis B vaccine has been available commercially since June of 1982, but its acceptance by the targeted high-risk populations has been disappointing (Hilleman et al., 1982; McAuliffe et al., 1982). In addition to the cost of immunization, barriers to vaccine use have been the general reluctance of adults to use any vaccine; inaccurate perceptions of the risk of HBV infection and the significance of hepatitis and its sequelae; and the fear of side effects. The latter was aggravated by the recent appearance of acquired immune deficiency syndrome (AIDS) and the concern that it might be caused by a blood-transmissible agent present in plasma-derived vaccines. Although this fear has proved unwarranted (Stevens, 1983), many who need protection are not yet convinced and have not taken the vaccine.

This is unfortunate because no satisfactory treatment exists for an established acute or chronic HBV infection. Approaches to control other than immunization, such as standard hygiene measures, use of disposable medical equipment, and screening of blood donors for HBsAg, reduce the risk of exposure but do not provide complete protection. Passive immunization with hepatitis B immune globulin (HBIG) is only partially effective as a means of post-exposure prophylaxis (Seeff, 1982).

The plasma-derived hepatitis B vaccine (composed of purified HBsAg 20 nanometer particles adsorbed onto an alum adjuvant) has minimal side effects and is at least 90 percent effective in preventing HBV infection and providing subtype cross-protection in healthy adults (Coutinho et al., 1983; Desmyter et al., 1983; Francis et al., 1982; Guesry et al., 1982; Szmuness et al., 1980, 1982). In combination

HBIG, it is 85 to 95 percent effective in preventing perinatal HBV infection (Szmuness et al., 1982). Immunocompromised individuals do not respond as well to the current vaccines. Only 50 to 60 percent of dialysis patients and an even lower proportion of oncology patients develop anti-HBs following complete immunization (Crosnier et al., 1981; Desmyter et al., 1983; Stevens et al., in press [a]). Moreover, efficacy of the current vaccine in these groups has not been clearly established.

Hepatitis B occasionally occurs despite administration of vaccine. Thus far, such cases have been limited to the initial immunization period (i.e., before protective antibody develops) and to nonresponders to the vaccine (less than 5 percent of those immunized). Long-term follow-up of vaccine recipients indicates that detectable, vaccine-induced anti-HBs persists for at least four to five years in 90 percent or more of vaccine responders (Stevens et al., in press [b]).

When HBV infection is prevented, the risk of chronic HBV infection also is prevented. Thus, effective immunization of those at risk eventually should produce the secondary benefit of reducing the pool of chronic HBsAg carriers, the primary source of HBV.

Hepatitis B vaccine currently is recommended in the United States only for high-risk groups. Although this approach seems reasonable for the moment (with limited supplies of a fairly expensive vaccine), it restricts the number of hepatitis B cases that can be prevented. The actual proportion of cases prevented is probably far less than 50 percent, because many people at high risk are not recognized by the physician (e.g., infants and close contacts of undetected HBsAg carriers) or do not identify themselves (e.g., some homosexual men and drug addicts).

The need for a new generation of hepatitis B vaccines is clear. The goals in developing these vaccines would be to enhance immune responsiveness (especially for immunocompromised populations), to make available an unlimited resource of antigenic material, to reduce the cost of immunization, and to reduce the fear of side effects.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the benefit that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

The CDC Sentinel County Study results indicate that approximately 50 percent of illness from hepatitis B occurs in the high-risk target population and this is the portion considered vaccine preventable in this study (Alter, 1983; Francis et al., 1984). The estimates of VPI are shown in Table H.3.

TABLE H.3 Vaccine Preventable Illness: Hepatitis B Virus

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Jaundice, nausea, fever, etc.			376	14	881	14	22,588	301	36,878	20	4,257	60
C	Requiring hospitalization	Severe hepatitis			38	9	90	9	2,700	9	4,013	9	698	9
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Carrier state, chronic persistent hepatitis							1,395	n.a.	3,656	n.a.	1,349	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Chronic active hepatitis, cirrhosis, primary hepatocellular carcinoma							720	n.a.	1,883	n.a.	695	n.a.
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death	Death following fulminant hepatitis and chronic sequelae					1	n.a.	16	n.a.	1,482	n.a.	553	n.a.

Vaccine Preventable Illness values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Total vaccine preventable illness values for hepatitis B are calculated using estimates from Table H.3 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the total vaccine preventable illness value for hepatitis B is 2,936; with the age-neutral perspective the value is 2,832.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by the hepatitis B vaccine candidate, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of the vaccine. For hepatitis B vaccine, the predicted efficacy is 0.90. The potential reduction in morbidity and mortality for the hepatitis B vaccine is 2,642 using the committee median perspective and 2,549 using the age-neutral perspective.

Prospects for New Vaccine Development

Three approaches to the development of new hepatitis B vaccines already are under investigation: the identification of alternate methods for production of plasma-derived vaccines (subunit or micelle vaccines) (Dreesman et al., 1982a; Howard et al., 1982; Sanchez et al., 1982), the use of recombinant DNA technology (Burrell et al., 1979; McAleer et al., 1984; Miyanohara et al., 1983; Valenzuela et al., 1979), and the production of synthetic polypeptide vaccines (Dreesman et al., 1982b; Gerin et al., 1983a; Gerin et al., 1983b; Hopp, 1981; Lerner et al., 1981). It is unlikely that the alternate plasma-derived vaccines ever will be utilized. Many of the barriers affecting the use of current vaccines would still apply. Moreover, the development of recombinant or polypeptide vaccines presumably would make plasma derived vaccines obsolete.

Several groups have introduced the HBsAg genome of HBV into different microorganisms. Thus far, the most successful have been those that express HBsAg in yeast (McAleer et al., 1984). At least one of these recombinant vaccines is permitted for investigational use in humans by the United States Food and Drug Administration. Studies of its safety and immunogenicity began in late 1983. Scolnick et al. (1984) report that in two groups of healthy, low-risk volunteer adults the vaccine was highly effective. The thirty-seven subjects each received a 10 g dose of HBsAg at 0, 1, and 6 months. By three months, 80 to 100 percent of vaccinees were antibody positive. Large boosts in titer followed the third dose. There have been no serious reactions attributable to the vaccine. Based on these results and other find-

ings, it is estimated that a recombinant vaccine made from yeast will be available in two to three years.

The HBsAg genome also has been incorporated into the vaccinia virus, which then expresses HBsAg on its surface (Smith et al., 1983). Studies in chimpanzees of the resulting vaccine, its safety and immunogenicity, and its ability to protect against challenge with wild HBV already have begun. The advantages of using vaccinia as a vehicle for immunization against hepatitis are presumed ease of production (no need for procedures to inactivate HBV or to remove extraneous immunogens), low cost (technologies already are in place for vaccine production), and the use of live replicating virus. Potential barriers to the use of this vaccine include: (1) the fact that vaccinia vaccine for smallpox prophylaxis has been abandoned worldwide—some countries might be reluctant to reintroduce it; (2) the inherent danger of potential side effects in individuals with dermatitis or unrecognized immune deficiencies; and (3) uncertainty about successful "takes" following administration and the effectiveness of booster doses.

Several laboratories have identified the major antigenic site of HBsAg, a hydrophilic sequence of 8 to 12 amino acids (Dreesman et al., 1982a; Gerin et al., 1983a; Gerin et al., 1983b; Hopp, 1981; Lerner et al., 1981). Polypeptides of various sequences have been synthesized and studies of immunogenicity in animals have begun. The major barrier to successful development of synthetic vaccines is the poor immune response to small polypeptides. Current investigations are directed at enhancing immunogenicity, either through structural modifications (e.g., the circular polypeptide developed by investigators at Baylor) or by attaching the peptide to larger carrier molecules and adjuvants. Whether or not these efforts will succeed and how long they will take remains to be seen. Most estimates place the development time at six to ten years.

Anticipated improved vaccine Utilization

It is anticipated that improved hepatitis B vaccines would be as effective as current vaccines (or more so for some populations) and that some barriers now deterring use of plasma-derived vaccines would no longer apply. Therefore, utilization should be better. It is expected that both providers and potential recipients in the high-risk groups will have a high perception of the risk of infection (a score of eight out of ten), that physicians will have a somewhat higher perception of the severity of the disease than will lay people (a score of eight versus seven out of ten), and that both groups will have high expectations of the vaccine's efficacy (a score of nine out of ten). Some barriers to utilization may persist. A high cost would inhibit some from being vaccinated. Compliance is usually worse for vaccines targeted for adults rather than for children, and this barrier may remain unless educational programs can overcome it. The modest degree of difficulty involved in initiating and completing immunization (e.g., the possible need for pre-immunization testing for HBV markers) may remain a barrier for some individuals.

Complete control of HBV infection in high-risk populations probably will continue to be impeded, regardless of the source of vaccine, by the difficulties inherent in getting vaccine to those who need it most (e.g., health care workers entering the workforce and young, newly active homosexual men). Moreover, for reasons discussed above, control of HBV infection in the United States probably will not be achieved as long as the target population remains limited to high-risk groups. Thus, the long-term goal for control of hepatitis B in the United States, as in the highly endemic areas of the world, is the development of a vaccine that can be used universally in childhood.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this disease comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden*

Category A n/a

Category B - jaundice, nausea, fever, etc.

total # of cases = 127,962		
Original cases		
# of cases = 112,887		
100% of cases typically receive diagnostic lab testing at $150 [HBSAG, SGOTx2, SGPTx2, Bilirubin]		= $ 16,933,000
100% of cases typically receive 4 phys. visits at $30/visit		= $ 13,546,000
	TOTAL	= $ 30,479,000
Convalescent cases - from Category C		
# of cases = 15,075		
100% of cases typically receive 4 phys. visits at $30/visit and testing (serology) at $40/visit		= $ 4,221,000
	TOTAL	= $ 4,221,000
	TOTAL (B)	= $ 34,700,000

* More comprehensive estimates of the costs arising from hepatitis B infection have recently been made by Schatz et al. (in press). Some estimates in this section do not correspond to those made by Schatz et al., but differences do not materially affect the values carried forward to comparisons in Chapters 4 and 7.

Category C - severe hepatitis

# of cases = 15,075

100% of cases typically receive 9 days of normal hospitalization at $400/day	= $ 54,270,000
2% of cases typically receive 7 additional days of ICU at $600/day	= $ 1,266,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate	
for 100% of cases, 9 days at $400/day	= $ 54,270,000
for 2% of cases, 7 days at $600/day	= $ 1,266,000
100% of cases typically receive 1 follow-up phys. visit at $30	= $ 452,000
TOTAL (C)	= $111,524,000

Category D - asymptomatic carrier state, chronic persistent hepatitis

Of approx. 200,000 new infections/year, approx. 10% or 20,000 cases become carriers and belong in Category D, E, or F. Approx. 60% of carriers (approx. 12,000) do not manifest symptoms and belong specifically in Category D (Schatz, in press)

total # of cases chronic Category D = 12,800 (Alter, 1983)

of these asymptomatic cases, approx. 25% are discovered and receive outpatient screening annually for 25 years duration at $130/year (1 phys. visit plus $100 diagnostics) total present value/case = $2,000	= $ 6,400,000
approx. 80% of these cases which receive annual screening are chronic persistent, requiring annual weighted cost/case of $750 (Schatz, in press). Assuming additional cost of $620/year, for total cost of approx. $1,400/year, and 25 years duration from onset at a 5% discount rate, total present value/case = $21,000	= $ 53,760,000
200,000 high risk pregnant women screened at $25	= $ 5,000,000
TOTAL (D)	= $ 65,160,000

Category E - chronic active hepatitis, cirrhosis, primary hepatocellular carcinoma

total # of cases = 6,595 (Schatz et al., in press)

Chronic active hepatitis

# of cases = 1,847 (28% of total Category E) total annual weighted cost/case = $1,320 (Schatz, in press). Assuming 20 years expected lifetime duration at a 5% discount rate, total present value/case = $17,000	= $ 31,399,000
TOTAL	= $ 31,399,000

Cirrhosis cases (Francis, personal communication, 1984)
# of cases = 4,485 (68% of total Category E)
approx. total annual weighted cost/case = $500.
Assuming 9 years duration at a 5% discount rate,
total present value/case = $4,000 = $ 17,940,000
after approx. 9 year period, hospitalization
(typically ending in death) for 100% of cases
present value/case = $5,000 = $ 22,425,000
TOTAL = $ 40,365,000

Primary hepatocellular carcinoma cases*
# of cases = 264 (4% of total Category E)
approx. total weighted hospitalization costs/case
= $5,500 (typically ending in death within 6
months to 1 year) = $ 1,452,000
TOTAL = $ 1,452,000
TOTAL (E) = $ 73,216,000

TOTAL COST = $284,600,000

Cost of Total Vaccine Preventable Illness**

Category A n/a

Category B - jaundice, nausea, fever, etc.

total # of cases = 64,980
Original cases
# of cases = 57,441
100% of cases typically receive diagnostic lab
testing at $150 = $ 8,616,000
[HBSAG, SGOTx2, SGPTx2, Bilirubin]
100% of cases typically receive 4 phys. visits at
$30/visit = $ 6,893,000
TOTAL = $ 15,509,000

*See discussion of "Uncertainty in the Disease Burden Estimates."

**More comprehensive estimates of the costs arising from hepatitis B infection have recently been made by Schatz et al. (in press). Some estimates in this section do not correspond to those made by Schatz et al., but differences do not materially affect the values carried forward to comparisons in Chapters 4 and 7.

Convalescent cases - from Category C	
# of cases = 7,539	
100% of cases typically receive 4 phys. visits at $30/visit and testing (serology) at $40/visit	= $ 2,111,000
TOTAL	= $ 2,111,000
TOTAL (B)	= $ 17,620,000
Category C - severe hepatitis	
# of cases = 7,539	
100% of cases typically receive 9 days of normal hospitalization at $400/day	= $ 27,140,000
2% of cases typically receive 7 additional days of ICU at $600/day	= $ 633,000
100% of cases typically receive additional diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate	
for 100% of cases, 9 days at $400/day	= $ 27,140,000
for 2% of cases, 7 days at $600/day	= $ 633,000
100% of cases typically receive 1 follow-up phys. visit at $30	= $ 226,000
TOTAL (C)	= $ 55,772,000
Category D - asymptomatic carrier state, chronic persistent hepatitis	
Of approx. 200,000 new infections/year, approx. 10% or 20,000 cases become carriers and belong in Category D, E, or F. Approx. 60% of carriers (approx. 12,000) do not manifest symptoms and belong specifically in Category D (Schatz, in press)	
total # of cases chronic Category D = 6,400	
of these asymptomatic cases, approx. 25% are discovered and receive outpatient screening annually for 25 years duration at $130/year (1 phys. visit plus $100 diagnostics)	
total present value/case = $2,000	= $ 3,200,000
approx. 80% of these cases which receive annual screening are chronic persistent, requiring annual weighted cost/case of $750 (Schatz, in press). Assuming additional cost of $620/year, for total cost of approx. $1,400/year, and 25 years duration from onset at a 5% discount rate, total present value/case = $21,000	= $ 26,880,000
200,000 high-risk pregnant women screened at $25	= $ 5,000,000
TOTAL (D)	= $ 35,080,000
Category E - chronic active hepatitis, cirrhosis, primary hepatocellular carcinoma	
total # of cases = 3,298	

Chronic active hepatitis		
# of cases = 923 (28% of total Category E)		
total annual weighted cost/case = $1,320 (Schatz, in press). Assuming 20 years expected lifetime duration at a 5% discount rate, total present value/case = $17,000		= $ 15,691,000
	TOTAL	= $ 15,691,000
Cirrhosis cases (Francis, personal communication, 1984)		
# of cases = 2,243 (68% of total Category E)		
approx. total annual weighted cost/case = $500. Assuming 9 years duration at a 5% discount rate, total present value/case = $4,000		= $ 8,972,000
after approx. 9 year period, hospitalization (typically ending in death) for 100% of cases present value/case = $5,000		= $ 11,215,000
	TOTAL	= $ 20,187,000
Primary hepatocellular carcinoma cases*		
# of cases = 132 (4% of total Category E)		
approx. total weighted hospitalization costs/case = $5,500 (typically ending in death within 6 months to 1 year)		= $ 726,000
	TOTAL	= $ 726,000
	TOTAL (E)	= $ 36,604,000
	TOTAL COST	= $145,076,000

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*See discussion of "Uncertainty in the disease Burden Estimates."

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Appendix

I

PROSPECTS FOR IMMUNIZING AGAINST HERPES SIMPLEX VIRUSES 1 AND 2

Disease Description

Illness caused by herpes simplex viruses 1 and 2 generally is characterized by cutaneous and mucosal lesions; however, initial infections in some individuals are asymptomatic, while others experience severe systemic disease. Infection is complicated by lifelong retention of virus or viral genetic material in the ganglia. The latent virus may cause recurrences of the disease when activated by factors such as sunlight, fever, menstruation, stress, or drugs. The virus also may be shed asymptomatically. The disease may be severe and generalized when it occurs in immunocompromised persons, neonates, or those with atopic dermatitis. Infections of the eye may lead to blindness, and herpesvirus encephalitis can be fatal. Herpes simplex, especially type 2, has been linked epidemiologically with cervical cancer in women (Nahmias et al., 1982).

The two serotypes of HSV differ in their most frequent sites of infection and their prevalence at different ages. HSV-2 traditionally has been regarded as a virus transmitted primarily by venereal contact or by maternal genital infection to a newborn; these infections occur most often during adolescence or early adulthood. HSV-1 is found at body sites above the waist, usually the mouth, and is most common in childhood, it is usually transmitted by non-venereal contact, but can be transmitted venereally. The initial illness usually is more severe than recurrences, although, as noted above, first infections can be subclinical.

Pathogen Description

HSV-1 and HSV-2 belong to a family of DNA viruses that has over 60 members affecting a wide range of hosts. Herpes viruses in humans

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include cytomegalovirus, Herpesvirus varicellae (varicella-zoster virus), and Epstein-Barr virus. All have the capacity for persistence in the human host (Nahmias and Josey, 1982).

HSV-1 and HSV-2 are complex viruses containing a large, double-stranded DNA genome coding for about 50 viral proteins. About half of HSV-1 and HSV-2 sequences are homologous. There has been some progress recently towards identifying the genes responsible for latency and carcinogenicity (Roizman et al., 1984).

Of particular importance to the prospects for immunization are the surface glycoproteins of the HSV-1 and HSV-2 viral envelopes. Herpes simplex viruses carry five major surface glycoproteins—designated gB, gC, gD, gE, and gG. Some of these glycoproteins (e.g., gD, gB, and gC) are known to induce high level neutralizing antibodies in naturally infected individuals, and are thought to be potential candidates for subunit vaccines. Genes coding for gD have been cloned and expressed in mammalian cell lines (Lasky et al., 1984).

Host Immune Response

The immunology of HSV infections has been reviewed recently by Shore and Nahmias (1981). In primary HSV infections, humoral antibodies can be detected within 1 to 3 weeks and assays of cellular immunity in vitro have demonstrated a cell-mediated response after a similar period.

It is not clear which of these responses leads to curtailment of primary infection in normal individuals. HSV infections in immunocompromised hosts tend to be severe and chronic.

Recurrence of latent HSV infection takes place in spite of the presence of circulating antibodies, probably because of the factors responsible for latency, about which very little is known. Hence, it probably will be necessary to stimulate immunity prior to exposure to achieve protection.

Vaccines containing viral glycoprotein surface antigens, prepared in chick embryo culture, have been shown to be effective in stimulating immunity and preventing disease in experimentally infected animals (Hilleman et al., 1981). Trials in humans are discussed below.

Disease Burden

Estimates for the disease burden are based on information from Nahmias and Josey (1982), and the National Institute of Allergy and Infectious Diseases (1980, 1983); on advice from Bryson (personal communication, 1983), Cates (personal communication, 1983), Corey (personal communication, 1984), Guinan (personal communication, 1984), Johnson (personal communication, 1983), Nahmias (personal communication, 1984), and Whitley (personal communication, 1984); and on the specific references cited. The Morbidity Categories referred to below are defined in Chapter 4 and Table I.9.

The Centers for Disease Control (CDC) has developed a cumulative incidence model for genital herpes infections from serological data provided by Stavraky and colleagues (1983) (Cates, personal communication, 1983; Johnson, personal communication, 1983). Stavraky et al. (1983) conducted a serological survey of a representative sample of white residents of Toronto, Canada, aged 35 to 55, which provides the best estimates available of HSV-2 infection in a relatively unselected North American population. An HSV-2 seropositivity incidence of 0.152 was reported. To derive age-specific incidence densities, it was assumed that the 0.152 prevalence provided an accurate measure of past genital herpes infection. It also was assumed that the age-specific incidence density of genital herpes infections is proportional to the age-specific incidence of reported gonorrhea, i.e., that genital herpes has the same probability distribution by age as gonorrhea:

$$ID(HSV)_i = kID(GC);$$

where $ID(HSV)_i$ = genital herpes incidence density for age interval i
$ID(GC)_i$ = gonorrhea incidence density for age interval i
k = proportionality constant

Cumulative incidence is related to age-specific incidence density by the formula:

$$CI_m = 1 - \exp -k \sum_{i=1}^{m} (ID(GC)_i \times \Delta t_i)$$

where CI_m = cumulative incidence at end of age interval m

t_i = width of age interval i

The proportionality constant (k) was estimated by substituting 0.152 for $CI_{30"35}$ and gonorrhea cases reported to the CDC in 1980 for the ID $(GC)_i$. The gonorrhea ID $(GC)_i$ was then multiplied by k to obtain ID $(HSV)_i$ for genital herpes.

Although the assumptions for these calculations cannot be tested, the incidence density-cumulative incidence estimates are consistent with the physician visit estimates derived independently as described below. Using the cumulative incidence model, the CDC has calculated the proportion of the population that would become infected by the time individuals attain the upper age in various categories and has estimated the number of new genital herpes infections each year. These are shown in Table I.1.

The survey by Stavraky et al. (1983) represents the best available basis on which to estimate the incidence of HSV infection. Nevertheless, the estimates presented below must be used with caution and with regard for their limitations. Although the authors employed probability sampling of low, middle, and high socioeconomic strata of an urban North American population (Toronto, Canada), the survey sample

TABLE I.1 Incidence and Prevalence of Genital Herpes Infections

Age (years)	Cumulative Incidence (proportion of group infected by end of period)	Estimated Number of New Infections
0–9	0.0006	2,000
10–14	0.0024	6,000
15–19	0.0427	175,000
20–24	0.1030	278,000
25–29	0.1364	148,000
30–34	0.1522	65,000
35 and over	0.1522	50,000
5–14		8,000[a]
15–24		453,000
25–59		263,000[b]
All ages		724,000

Note: Estimates provided by the Centers for Disease Control (Cates, personal communication, 1983).

a For this disease burden comparison, all infections in the age groups under 15 years are included in the 5–14 years age group.

b For this disease burden comparison, all infections occurring over age 35 are included in the 25–59 years age group.

clearly was not representative of the total U.S. population. Additionally, the serological tests used to identify HSV-2 infection did not have the level of sensitivity and selectivity that might be desired. Further, it should be recognized that the comparison of HSV to gonorrhea may not be entirely justified because changes in the incidence of the two diseases in subsets of the populations (e.g., whites and blacks) may not have been similar.

Information on physician visits for genital herpes is reported in the National Disease and Therapeutic Index, a survey of a probability sample of U.S. office-based medical practitioners conducted by International Marketing Services (Philadelphia, Pennsylvania). Projections from these data by the CDC, based on findings that physicians in private practice diagnose between one-third and one-half of gonorrhea cases in the U.S., resulted in a range of 510,000 to 764,000 visits to physicians for genital HSV. Considering that some new infections do not result in a physician visit, and that some recurrences do, it is reasonable to assume that an estimated total of 724,000 new genital

infections and recurrences each year could generate 510,000 to 764,000 physician visits annually.

It is known that symptomatic primary disease can be followed by episodes of asymptomatic infection and vice-versa (Reeves, et al., 1981). On the basis of data reported by Stavraky et al. (1983) and the work of Nahmias (personal communication, 1984) an average of about one-third of all primary genital infections are assumed to result in clinical illness, i.e., 241,333. The estimate of the number of infections derived from Stavraky et al. (1983) is for HSV-2 infections, which have been presumed to be genital. It is important to note, however, that an unknown (but probably minor) proportion of all primary genital infections are caused by HSV-1. In this report, the number of such infections that produce clinical symptoms is assumed to be encompassed in the estimate cited above (241,333), because the figure derived from the analysis of Stavraky et al. is probably higher than the true number of HSV-2 infections (this could have resulted from poor selectivity of the serological test).

Two-thirds of initial cases of genital herpes are assumed to fall into Morbidity Category A and one-third into Category B for the 15–24 and 25–59 years age groups. In the 5–14 years age group, a higher proportion of the morbidity is likely to be more severe because more first cases in this age group are likely to be primary responses to HSV than at later ages, when a prior type-1 infection would decrease the morbidity associated with type-2 genital infection. Genital herpes in this age group is also likely to be more disturbing to both child and parents. Hence, one-third initial non-hospitalized cases of genital herpes in the 5–14 years age group are assigned to Category A and two-thirds to Category B. The distribution of initial non-hospitalized illnesses resulting from genital herpes, using the assumptions outlined above, is shown in Table I.2. Some primary genital herpes cases will progress to illness requiring hospitalization and are included in Table I.2.

Limited information is available from which the annual number of recurrent episodes of genital herpes can be calculated, particularly with respect to the period after the initial episode over which recurrences are distributed. Information from Bryson (personal communication, 1983), Corey et al., 1983, and Reeves et al. (1981), indicates that a high proportion (50 to 90 percent) of individuals experience recurrences when followed for six months to a year after the initial clinical episode; however, there is great variability in the recurrence rate among individuals (Bryson, personal communication, 1983; Corey, personal communication, 1984) and between types. The average number of recurrences per year falls about 50 percent after four years (Corey, personal communication, 1984).

To calculate the total number of recurrences per year, it is assumed that there will be an average of two recurrences per year for 10 years for each initial clinical case. Thus, in any one year there will be a ten-year cohort of one-third of the 724,000 persons infected (i.e., 241,333 initial clinical cases) experiencing two recurrences per year. This means that the number of annual recurrences of genital

TABLE I.2 Distribution of Initial Nonhospitalized Cases of Genital Herpes

Morbidity Category	Age Group (years) 5–14	15–24	25–59	All Ages
A	889	100,667	58,444	160,000
B	1,778	50,333	29,222	81,333

herpes can be estimated as 724,000×0.333×10×2, i.e., 4,826,667. These recurrent episodes have been judged to fall into Category A.

In the absence of data, genital HSV recurrences are assumed to be distributed in a 1:3 ratio between the 15–24 years (1,206,667) and 25–59 years (3,620,000) age groups.

Nahmias and Josey (1982) have estimated that approximately 500,000 cases of (predominantly primary) oral herpes (including gingivostomatitis) and about 100 million episodes (predominantly recurrences) of labial herpes occur annually in the U.S. For this disease comparison, these were judged to fall into Morbidity Categories B and A, respectively, with assumed age distributions as shown in Table I.3.

The National Advisory Eye Council (1983) estimates that about 500,000 cases of (initial ocular) herpetic keratitis occur annually. Of these, nearly one-half have a recurrence within two years; recurrences may lead to corneal damage, and blindness is a rare but serious consequence (Howard and Kaufman, 1962). Initial cases of herpetic keratitis are judged to fall into Morbidity Category B, and assumed to last about 14 days. The assumed distribution of cases, calculated from data reported by Wilhelmus et al. (1981), is shown in Table I.4.

To calculate the number of recurrences (also judged to fall into Morbidity Category B), it is assumed on the basis of observations reported by Wilhelmus et al. (1981) that 10 percent of initial cases have one recurrence per year for five years. Thus, there is a cohort of 50,000 experiencing one recurrence per year. The age distribution of recurrences, assumed to follow that of primary episodes, is shown in Table I.4.

An unknown proportion of cases of herpetic keratitis may result in corneal damage severe enough to necessitate corneal transplantation. Blindness may follow recurrences with or without corneal transplantation. Data reported by the Society for the Prevention of Blindness (1980), indicate that of 47,000 new cases of blindness annually, an estimated 850 result from infectious diseases. Removal of rubella (150 cases), syphilis (200 cases), and toxoplasmosis (150 cases) from this total leaves 350 cases with an unspecified infectious causation. Of blindness due to corneal disease (1,250 cases annually) about 50 percent, i.e., about 625 cases, may be due to herpetic keratitis (Helmson, personal communication, 1984). For the purposes of this comparison, it has been assumed that 500 cases of blindness due to

TABLE I.3 Estimated Distribution of Episodes of Oral (Primary), Labial (Recurrent), and Herpetic Keratitis Herpes Illness

		Oral Herpes Cases		Labial Herpes Cases		Herpetic Keratitis Cases		
							Number	
Age (years)	Percentage of Population[a]	Assumed Distribution[b] (percent)	Number	Assumed Distribution[c] (percent)	Number	Assumed Distribution[d] (percent)	New	Recurrences
Under 1	1.6	10	50,000					
1-4	6.1	50	250,000					
5-14	14.2	20	100,000	15	15,000,000	5	25,000	25,000
15-24	17.1	5	25,000	25	25,000,000	7	35,000	35,000
25-59	44.6	10	50,000	45	45,000,000	55	275,000	275,000
60 and over	16.4	5	25,000	15	15,000,000	33	165,000	165,000
All ages			500,000		100,000,000		500,000	500,000

[a] Based on projected 1984 population.
[b] Based on information in Juretic (1966).
[c] Based on the observation that labial herpes (fever blisters) in children under 5 years is extremely rare and the hypothesis that there is a 5–15 year lapse between the time of acquiring oral herpes and the occurrence of fever blisters.
[d] Based on data reported by Wilhelmus et al. (1981).

TABLE I.4 Contribution of HSV-Associated Illness Falling into Morbidity Categories A and B

	Age (years)						
Illness	Under 1	1-4	5-14	15-25	25-59	60 and Over	All Ages
Category A							
Genital HSV (initial)			889	100,667	58,444		160,000
Genital HSV (recurrences)				1,206,667	3,620,000		4,826,667
Labial HSV (recurrences)			15,000,000	25,000,000	45,000,000	15,000,000	100,000,000
Herpetic keratitis (recurrences; excluding neonates)			25,000	35,000	275,000	165,000	500,000
Total			15,025,889	26,342,334	48,953,444	15,165,000	
Category B							
Oral HSV (primary)	50,000	250,000	100,000	25,000	50,000	25,000	500,000
Genital HSV (severe initial)			1,778	50,333	29,222		81,333
Herpetic keratitis (new cases; excluding neonates)			25,000	35,000	275,000	165,000	500,000
Total	50,000	250,000	126,778	110,333	354,222	190,000	

herpetic keratitis occur annually. Most of these are cases in which corneal transplantation has failed to prevent ultimate loss of sight. These cases are included under Category E and distributed according to the age distribution for herpetic keratitis (other than that occurring in neonates) shown in Table I.4, i.e., under 1 year, 0; 1–4 years, 0; 5–14 years, 25; 15–24 years, 35; 25–59 years, 275; 60 years and over, 165. These are included in the totals in Summary Table I.9.

No estimates of herpes of the skin or respiratory herpetic illness are included because these conditions have been judged to be generally not as significant as those conditions discussed above.

Contributions of the various HSV illnesses to the total disease burden falling into Morbidity Categories A and B are shown in Table I.4. An average duration of 7 days is assumed for all Category A illnesses and a duration of 14 days for Category B illnesses.

Analysis of data from the National Center for Health Statistics indicates that approximately 17,000 hospitalizations annually are associated with HSV infections. This number includes neonatal HSV, encephalitis in adults, severe oral HSV, and other HSV infections as discussed below.

The estimates for neonatal herpes described below were based on information on diagnosed cases supplied by Whitley (personal communication, 1984) from an ongoing, multicenter collaborative study, and advice from other sources. This information is considered a more accurate reflection of the current situation (e.g., regarding fatality rates) than published data, because treatment modalities for this disease have changed in recent years. The precision of these estimates is discussed further under "Uncertainty in the Disease Burden Estimates."

The incidence of neonatal HSV infection varies with region but averages about 1 case per 10,000 births. Thus, about 380 cases would be predicted for the 1984 birth cohort of 3,788,337. Overall the case fatality rate is about 20 percent; 40 percent of cases have mild (skin) disease and 40 percent of cases have disseminated severe disease. Mild disease results in less frequent CNS complications. Of 40 survivors having mild disease (from 100 cases), one would have severe CNS sequelae, one moderate CNS sequelae, and two mild CNS sequelae. Of the 40 survivors having severe disease (from 100 cases), 15 would have severe CNS sequelae, 5 moderate CNS sequelae, and 5 mild CNS sequelae. Hence, from an estimated 380 cases of neonatal HSV, 100 percent would fall into Category C; overall, 7 percent (i.e., 27) would have mild CNS sequelae; 6 percent (i.e., 23) would have moderate to severe CNS sequelae; 16 percent (i.e., 61) would have very severe CNS sequelae; and 20 percent (i.e., 76) would die.

HSV encephalitis at older ages is estimated to occur in the U.S. at an annual rate of one case per 250,000 persons (Whitley, personal communication, 1983), for a total of approximately 946 cases. Forty-five percent are assumed to die, and 60 percent of survivors incur chronic disability equally distributed among Morbidity Categories D, E, and F. The numbers of cases derived with these assumptions and the observed age distribution (Whitley, personal communication, 1983) are shown in Table I.5.

TABLE I.5 HSV Encephalitis and its Consequences in Adults

Age (years)	Percentage Distribution of Cases[a]	Number of Cases	Deaths	Chronic Disability (Cases)		
				Category D	Category E	Category F
Under 1						
1-4	2	19	9	2	2	2
5-14	3	28	13	3	3	3
15-25	15	143	64	16	16	16
25-59	70	662	298	72	72	72
60 and over	10	95	43	10	10	10
All ages	100	946	427	103	103	103

[a]Whitley (personal communication, 1983).

The remaining hospitalized cases of HSV infection (about 15,000) consist of severe primary oral herpes (gingivostomatitis) and disseminated HSV, usually occurring in severe genital infections or in immunocompromised hosts. The committee estimates that about 1 percent of oral herpes cases progress to disease severe enough to require hospitalization, i.e., 5,000 cases. The age distribution of these cases, assumed to be the same as that for all oral herpes cases, is shown in Table I.6.

The age distribution of the remaining hospitalized cases (mostly involving immunocompromised individuals) is assumed to be similar to that observed for HSV encephalitis. The resulting distribution is shown in Table I.7. Contributions to total hospitalization figures and the assumed durations of hospitalization are shown in Table I.8.

Table I.9 summarizes the aggregate totals of the various contributions to the disease burden resulting from HSV-1 and HSV-2 infections. Numbers of cases include:

- for Category A: primary and recurrent genital herpes, labial herpes, and recurrent herpes keratitis
- for Category B: oral herpes, new herpes keratitis cases, and severe genital herpes
- for Category C: hospitalizations for neonatal HSV, HSV encephalitis, severe genital infection, severe oral herpes (gingivostomatitis), and disseminated HSV infections (mostly in immunocompromised individuals)
- for Categories D, E, and F: chronic CNS impairment from neonatal and encephalitic illness, and blindness from herpetic keratitis in. Category E.

Uncertainty in the Disease Burden Estimates

HSV 1 and 2 infections cause a wide range of illnesses, most of which are not reportable. Hence, it should be emphasized that many of the estimates included in the HSV disease burden are highly speculative. Certain conditions, such as recurrences of genital herpes, vary considerably, i.e., from none to very frequent recurrences. There is little data, however, on which to base averages or the length of time over which recurrences occur.

Application of the cumulative incidence model to the data of Stavraky et al. (1983) leads to some apparent inconsistencies in the numbers of infections in groups over the age of 30 years. Application of the model to more complete serologic data on the U.S. population is in progress and should lead to more reliable estimates (Cates, personal communication, 1984; Johnson, personal communication, 1984).

For some conditions no data could be found on age distributions, so they were estimated based on the advice of those with relevant clinical experience. Improvements and changes in the treatment of some conditions, e.g., encephalitis or disseminated herpes, may alter the pattern of consequences (e.g., deaths or length of hospitalization). Improvements and changes in the treatment of some conditions,

TABLE I.6 Hospitalized Oral Herpes Cases

Age Group (years)	Percentage Distribution of Cases[a]	Number of Cases
Under 1	10	500
1-4	50	2,500
5-14	20	1,000
15-24	5	250
25-59	10	500
60 and over	5	250
All ages	100	5,000

[a]Based on information in Juretic, 1966.

such as neonatal HSV infection, encephalitis, and disseminated herpes, may alter the pattern of consequences (e.g., deaths, length of hospitalization, and distribution of long-term sequelae). The figures for neonatal HSV infection also may be affected by underreporting (of non-diagnosed cases). These issues need further assessment. Sources of information on blindness resulting from herpes keratitis need further investigation because this estimate is based on arbitrary assumptions applied to limited data, and the cases are in a Morbidity Category that is highly disfavored.

It is recommended that the disease burden from HSV be reevaluated when studies in progress are completed.

Calculation of Total Disease Burden Values

The method used to compare morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for HSV-1 and HSV-2 are calculated using estimates from Table I.9 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 2,684 (committee median perspective) and 1,857 (age-neutral perspective).

Target Population

The optimal approach to control of HSV infections is vaccination in infancy or early childhood to prevent (or at least reduce) the replication of virus during primary infection. This also should eliminate or ameliorate recurrences.

TABLE I.7 Other Hospitalized Cases of HSV Infection

TABLE I.7 Other Hospitalized Cases of HSV Infection

Age Group (years)	Percentage Distribution of Cases[a]	Number of Cases
Under 1		
1-4	2	210
5-14	3	315
15-24	15	1,575
25-59	70	7,350
60 and over	10	1,050
All ages		10,500

Note: Excluding neonatal HSV, encephalitis, and hospitalized oral cases.

Suitability for Vaccine Control

Some progress has been made in antiviral chemotherapeutic control of HSV primary infections with drugs such as acyclovir (Corey and Holmes, 1983; Gunby, 1983). However, such approaches do not prevent the virus from establishing latency, which would be the ultimate goal of vaccination. An immunization approach that could prevent both primary infections and recurrences would be the most desirable form of control. The feasibility of this is discussed under "Vaccine Preventable Illness."

It should be stressed that HSV and other human herpes viruses, which rapidly become shielded from the immune response in the dorsal root ganglia, present a more difficult problem in vaccine development than other agents for which the target organ is distant to the portal of entry. To protect effectively against these viruses, the level of immunity resulting from vaccination must be very high. Achievement of these high levels of immunity probably will require that subunit glycoprotein vaccines be administered periodically. This may pose a problem of maintaining immunity in young adults, who probably have a low frequency of physician visits for other purposes.

Corey and Mertz (in press) have discussed the concepts and problems involved in developing vaccines against HSV.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the possible reduction in morbidity and mortality (or the maximum potential health benefit) that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). For HSV, VPI is defined as the number of cases,

TABLE I.8 Contributions to HSV Hospitalizations (Category C)

	Neonatal HSV		Encephalitis		Severe Oral		Other Severe Disease[a]			
Age (years)	Cases	Duration[b] (days)	Cases	Duration[b] (days)	Cases	Duration[c] (days)	Cases	Duration[c] (days)	Total Cases Per Age Group	Weighted Duration
Under 1	380	20			500	5			880	11
1-4			19	20	2,500	5	210	5	2,729	5.5
5-14			28	20	1,000	5	315	5	1,343	5.5
15-24			143	20	250	5	1,575	5	1,968	6.0
25-59			662	20	500	5	7,350	5	8,512	6.0
60 and over			95	20	250	5	1,050	5	1,395	6.0
All ages	380		946		5,000		10,500			

[a] Mostly in immunocompromised individuals; includes severe genital infections.
[b] Approximate average durations for all cases; see cost calculations for durations related to severity of condition.
[c] Regular care.

TABLE I.9 Disease Burden Summary: Herpes Simplex Viruses 1 & 2

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Genital (primary and recurrences), labial, keratitis (recurrences)	—	7	—	7	15,025,889	7	26,342,334	7	40,993,444	7	15,165,000	14
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Genital, oral, keratitis (initial)	50,000	14	250,000	14	126,778	14	110,333	14	354,222	14	190,000	14
C	Requiring hospitalization	Neonatal HSV, severe genital, encephalitis, severe oral, disseminated HSV	880	11	2,729	5.5	1,343	5.5	1,980	6	8,512	6	1,395	6
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Mild CNS impairment	27	n.a.	2	n.a.	3	n.a.	16	n.a.	72	n.a.	10	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Moderate to severe CNS impairment, blindness	23	n.a.	2	n.a.	28	n.a.	51	n.a.	347	n.a.	175	n.a.
F	Total impairment	Very severe CNS impairment	61	n.a.	2	n.a.	3	n.a.	16	n.a.	72	n.a.	10	n.a.
G	Reproductive impairment resulting in infertility													
H	Death		76	n.a.	9	n.a.	13	n.a.	64	n.a.	298	n.a.	43	n.a.

Note: n.a.=not applicable.

complications, sequelae, and deaths that could be prevented by immunization of the entire target population with the most effective vaccine possible.

Current knowledge about the immunology of herpes infections and recurrences suggests that immune prophylaxis of HSV illness will not totally prevent the disease because repeated HSV infections are known to occur, e.g., initial HSV-2 genital infections occur in individuals with antibody to HSV-1. Little relevant data exist from which to predict the effects of vaccines against HSV in humans; the vaccine effects could vary among individuals just as the severity of disease varies. The committee chose to formulate its predictions on HSV in terms of total numbers of disease-related events prevented, rather than attempt to foresee the probable effects in individuals. The committee estimates that the best that a vaccine could achieve would be a 50 percent reduction in the number of symptomatic primary infections, a 75 percent reduction in the number of recurrences, and a reduction in severity of episodes averaging about 60 percent.

To calculate the number of cases, complications, and sequelae of HSV infections that are potentially vaccine preventable, it is assumed: (1) that the first dose of vaccine would be delivered to infants and that the proportion of illness occurring during the period of partial protection (i.e., before subsequent doses could be administered) would be negligible; (2) that neonatal infections result in equal proportions from primary and recurrent infections (Nahmias, personal communication, 1984; Whitley, personal communication, 1984); (3) that encephalitis and other severe hospitalized illnesses (except for severe primary oral infections) result from primary and recurrent episodes of HSV in equal proportions; and (4) that chronic sequelae result about equally from primary and recurrent infections. Thus, for conditions in categories 2, 3, and 4, the vaccine would produce about 62.5 percent reduction in the number of such cases.

It is also assumed that most first cases of ocular herpes occur in individuals with prior HSV-1 (presumably oral) infections (Nahmias, personal communication, 1984); hence, the efficacy of the ideal vaccine against these infections and their possible ultimate consequence, blindness, is assumed to be 75 percent.

Table I.10 shows the number of potentially vaccine preventable episodes of HSV illness in Morbidity Categories A and B (derived from Table I.4). Table I.11 shows numbers of HSV hospitalizations that are potentially vaccine preventable (derived from Table I.8). Summary Table I.12 combines data from Tables I.10 and I.11 with estimates of vaccine preventable sequelae from neonatal and adult encephalitis and cases of blindness (Categories D, E, and F), and with vaccine preventable deaths (Category H). Estimates of chronic illness in Table I.12 have been calculated from estimates of the total disease burden described above, assuming 75 percent are vaccine preventable.

Treatment of the anticipated reduction in severity of HSV illness is described in the section "Possible Reductions in Morbidity and Mortality."

TABLE I.10 Episodes of HSV-Associated Illness Falling into Morbidity Categories A and B That Are Potentially Vaccine Preventable

Illness	Under 1	1-4	5-14	15-24	25-59	60 and Over	All Ages
Category A							
Primary genital			444	50,334	29,222		80,000
Labial (recurrences)			11,250,000	18,750,000	33,750,000	11,250,000	75,000,000
Keratitis (recurrences; excluding neonates)			18,750	26,250	206,250	123,750	375,000
Genital (recurrences)				905,000	2,715,000		3,620,000
Total			11,269,194	19,731,584	36,700,472	11,373,750	
Category B							
Oral (primary)	25,000	125,000	50,000	12,500	25,000	12,500	250,000
Genital (severe primary)			889	25,167	14,611		40,667
Keratitis (new cases; excluding neonates)			18,750	26,250	206,250	123,750	375,000
Total	25,000	125,000	69,639	63,917	245,861	136,250	

Note: Derived from Table I.4 using assumptions described in the text.

TABLE I.11 Potentially Vaccine Preventable HSV Hospitalizations (Category C)

	Neonatal HSV		Encephalitis		Severe Oral		Other Severe Disease[a]			
Age (years)	Cases	Duration[b] (days)	Cases	Duration (days)	Cases	Duration[c] (days)	Cases	Duration[c] (days)	Total Cases Per Age Group	Weighted Duration
Under 1	238	20			250	5			488	12
1-4			12	20	1,250	5	131	5	1,393	5
5-14			18	20	500	5	197	5	715	5.5
15-24			89	20	125	5	984	5	1,198	6.0
25-59			414	20	250	5	4,593	5	5,257	6.0
60 and over			59	20	125	5	656	5	840	6.0
All ages	238		592		2,500		6,562			

Note: Derived from Table I.8 using assumptions described in the text.

[a] Mostly immunocompromised; includes severe genital.
[b] Approximate average durations for all cases: see cost calculations for durations related to severity of condition.
[c] Regular care.

TABLE I.12 Vaccine Preventable Illness: Herpes Simplex Viruses 1 & 2

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Genital (primary and recurrences), labial, keratitis (recurrences					11,269,194	7	19,734,584	7	36,700,472	7	11,373,750	7
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Genital, oral, keratitis (initial)	25,000	14	125,000	14	69,639	14	43,917	14	245,861	14	136,250	14
C	Requiring hospitalization	Neonatal HSV, severe genital, encephalitis, severe oral, disseminated HSV	448	12	1,393	5	705	5.5	1,198	6	5,257	6	840	6
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Mild CNS impairment	17	n.a.	1	n.a.	2	n.a.	10	n.a.	45	n.a.	6	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Moderate to severe CNS impairment, blindness	14	n.a.	1	n.a.	21	n.a.	36	n.a.	251	n.a.	129	n.a.
F	Total impairment	Very severe CNS impairment	38	n.a.	1	n.a.	2	n.a.	10	n.a.	45	n.a.	6	n.a.
G	Reproductive impairment resulting in infertility													
H	Death		48	n.a.	6	n.a.	8	n.a.	40	n.a.	186	n.a.	27	n.a.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapters 4 and 7). Total vaccine preventable illness values for HSV are calculated using estimates from Table I.12 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the vaccine preventable illness value for HSV is 1,841; with the age-neutral perspective the value is 1,263.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by each of the HSV vaccine candidates, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of the vaccine.

For the HSV calculations it is assumed that the glycoprotein and live attenuated vaccines will be 45 percent and 65 percent effective, respectively, in achieving the maximum possible reductions in the number of episodes of morbidity and mortality (see above discussion of vaccine preventable illness).

For the glycoprotein vaccine, the values for potential reduction in morbidity and mortality are 828 (committee median perspective) and 568 (age neutral perspective); for the live attenuated virus vaccine, they are 1,197 (committee median perspective) and 821 (age-neutral perspective).

These values are not adjusted for vaccine adverse reactions or anticipated utilization. They may underestimate to a certain extent the benefits of the respective vaccines because they do not take into account the expected reduction in severity of episodes. The smallest differentiation between IMEs for adjacent Morbidity Categories within an age group is one order of magnitude, however, so a 60 percent reduction in severity presumably would not be likely to move episodes between categories. Hence, the change would be negligible for the purposes of this comparison.

Use of the PRMM or maximum potential health benefit figures for comparing vaccine benefits is described in Chapter 7.

Prospects for Vaccine Development

Studies of the therapeutic efficacy of inactivated whole virus vaccines have been conducted over the years with little success (Hilleman, 1976). Subsequent efforts have focused on vaccines containing glycoprotein surface antigens prepared in chick embryo cell cultures because fragments of the DNA of the viral genome in inactivated preparations might pose an oncogenic hazard. These have been shown to be effective in stimulating immunity (when administered with adjuvants), reducing disease, and preventing death in experimentally

challenged mice (Hilleman et al., 1981.) Such vaccines also induce antibody in humans (Hilleman et al., 1981). Studies are underway to measure the vaccine's ability to prevent infection in adults not previously infected with HSV-2 whose sexual partners suffer from recurrent genital herpes (Mertz et al., in press).

The glycoprotein vaccines are being actively pursued by a number of groups working to prevent herpesvirus infections and disease in man. The current thrust is to prepare the glycoproteins by recombinant DNA techniques in host species such as yeast or mammalian cell cultures (Gunby, 1983; Lasky et al., 1984). The ultimate vaccine probably will include at least two glycoproteins each from serotypes 1 and 2.

Advances in molecular biology also have made possible the development of genetically engineered attenuated live virus vaccines against HSV (Roizman et al., 1984). These vaccines, which have been tested in experimental animals, are expected to produce longer lasting immunity than the subunit vaccines. Some researchers believe that objections to the use of live HSV vaccines will diminish as genetic engineering makes possible the removal of regions of the genome responsible for cell transformation.

Clinical trials of vaccine candidates pose no major problems with regard to study populations because sexual partners of persons already infected provide an easily identifiable and accessible test group.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to various vaccines are displayed together to ease comparison.

Lay Acceptance

The perception among parents of the risk of illness caused by HSV-1 and HSV-2 to their children is believed to be low to moderate. The perception of the clinical and social consequences of the associated illnesses (possibly with some physican cueing on CNS complications) have been rated as moderately high. Perceptions of the benefits of vaccination probably also would be moderately high because there are no cures for these diseases. Several potential barriers exist, however, including the long delay in some of the major benefits from childhood to the sexually active adult years; the realization by parents that they would be protecting their children against a disease for which the risk rises with promiscuity; and the probable number of injections involved in maintaining immunity through early adult life.

Differences between lay perceptions of glycoprotein and live attenuated vaccines are expected to be minimal.

Provider Acceptance

Providers of medical care might score the risk of illness somewhat higher than the public because they would be knowledgeable about the consequences of asymptomatic infection and shedding. Providers probably would score severity lower, however, because they should be less affected by recent media attention concerning the social consequences of genital HSV. The benefits of vaccination probably would be rated as moderate by providers for similar reasons. Barriers perceived by providers with the glycoprotein vaccine would be fairly low, mostly relating to a disinclination on the part of some providers to deal with sexually transmitted diseases. Barriers to the use of a live vaccine would include concern over potential oncogenicity, probably not fully dispelled by licensure testing. The barriers score for the live vaccine is thus moderate.

Costs of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Total Cost of Disease Burden

Category A - genital, oral and labial, primary and recurrences

Primary genital		
# of cases = 160,000		
approx. 50% of cases receive 1 phys. visit at $30		= $ 2,400,000
approx. 10% of cases receive diagnostic culture procedure at $30		= $ 480,000
approx. 50% of cases receive treatment/medication (topical acyclovir) at $35		= $ 2,800,000
	TOTAL	= $ 5,680,000
Recurrent genital		
# of cases = 4,826,667		
approx. 1% of cases receive 1 phys. visit at $30		= $ 1,448,000
approx. 25% of cases receive treatment/medication (topical acyclovir or other treatment*) at $20		= $ 24,133,000
	TOTAL	= $ 25,581,000

*See Chapter 4, "Comparison of Direct Costs Resulting from Disease."

Labial
# of cases = 100,000,000 (recurrences of oral)
approx. 0.1% of cases receive 1 phys. visit at $30 = $ 3,000,000
approx. 0.1% of cases receive treatment/medication
(topical acyclovir or other treatment*) at $20 = $ 2,000,000
TOTAL = $ 5,000,000

Herpetic keratitis recurrences
# of cases = 500,000
100% of cases typically receive 2 specialist phys. visits at $50/each = $ 50,000,000
100% of cases typically receive medication (vidarabidine, trifluridine, idoxuridine) or treatment (debridement) at a total of $100 = $ 50,000,000
TOTAL = $100,000,000
TOTAL (A) = $136,261,000

Category B

Primary genital
# of cases = 81,333
100% of cases typically receive 1 phys. visit at $30 = $ 2,440,000
100% of cases typically receive medication at $35 = $ 2,847,000
TOTAL = $ 5,287,000

Primary oral
# of cases = 500,000
approx. 10% of cases receive 1 phys. visit at $30 = $ 1,500,000
[treatment involves domestically available fluids at no additional cost]
TOTAL = $ 1,500,000

Herpes keratitis
# of cases = 500,000
100% of cases receive 2 specialist phys. visits at $50/each = $ 50,000,000
100% of cases receive medication (vidarabidine, trifluridine, idoxuridine) or treatment (debridement) at a total of $100 = $ 50,000,000
TOTAL = $100,000,000
TOTAL (B) = $106,787,000

Category C - hospitalization, severe and disseminated HSV, encephalitis and neonatal HSV

*See Chapter 4, "Comparison of Direct Costs Resulting from Disease."

Neonatal HSV*

total # of cases = 380; 95% overall survive

Mild disease (of skin or eye)

# of cases = 190	
100% of cases typically receive 12 days in a special care nursery at $400/day	= $ 912,000
100% of cases typically receive diagnostic testing, treatment (antiviral drugs) and special care (isolation) equivalent to daily inclusive hospital rate, 12 days at $400/day	= $ 912,000
100% of cases typically receive 1 follow-up physician visit at $30	= $ 6,000

Severe disease (including disseminated infection)

# of cases = 190	
100% of cases typically receive 14 days neonatal ICU at $800/day	= $ 2,128,000
100% of cases typically receive 7 days additional normal hospitalization at $400/day	= $ 532,000
100% of cases receive diagnostic testing and treatment (antiviral drugs) as a cost equivalent to daily inclusive hospital rate,	
14 days at $800/day	= $ 2,128,000
7 days at $400/day	= $ 532,000
100% of cases typically receive 1 follow-up physician visit at $30	= $ 6,000
TOTAL (neonatal HSV)	= $ 7,156,000

Encephalitis

# of cases = 946	
100% of cases typically receive 14 days ICU at $600/day (65% survive)	= $ 7,946,000
approx. 65% of cases (all survivors) receive 20 additional days normal hospitalization at $400/day	= $ 4,919,000
all cases receive diagnostic testing and treatment (antiviral drugs) at rate equivalent to daily inclusive hospital rate	
for 100%, 14 days at $600/day	= $ 7,946,000
for 65%, 20 days at $400/day	= $ 4,919,000
65% of cases typically receive 1 follow-up phys. visit at $30	= $ 18,000
TOTAL (encephalitis)	= $ 25,748,000

*See discussion in text regarding uncertainty surrounding neonatal HSV estimates.

Severe oral
# of cases = 5,000
100% of cases typically receive 5 days normal hospitalization at $400/day. Additional diagnostic testing and treatment not significant. = $ 10,000,000
100% of cases typically receive 1 follow-up phys. visit at $30 = $ 150,000
TOTAL (severe oral) = $ 10,150,000

Immunocompromised/Severe and Disseminated HSV
# of cases = 10,500
100% of cases typically receive 5 days normal hospitalization or additional hospitalization at $400/day = $ 21,000,000
100% of cases typically receive diagnostic testing and treatment (acyclovir) at rate equivalent to daily inclusive hospital rate, 5 days at $400/day = $ 21,000,000
100% of cases typically receive 1 follow-up phys. visit at $30 = $ 315,000
TOTAL (IC and disseminated HSV) = $ 42,315,000

Corneal Transplants

The estimated 500 cases of blindness resulting from herpetic keratitis are probably cases in which corneal transplant ultimately failed to prevent loss of vision (possibly due to recurrence of disease). The estimated average cost of corneal transplantation is about $2,500 (Helmsen, 1984). Hence, costs due to corneal transplantation are $2,500 x 500 = $ 1,250,000
This value is recognized as a minimum estimate because it excludes that (unknown) proportion of the total annual number of corneal transplants that are required because of herpes keratitis and which are successful.
TOTAL (C) = $ 86,619,000

Category D - mild CNS impairment

Neonatal
# of cases = 27
total annual costs for treatment and/or care = $2,000/case; assuming a duration of 20 years and 5% discount rate, total cost/case = $26,000 = $ 702,000
TOTAL = $ 702,000

All other cases of HSV encephalitis
# of cases = 103
total annual costs for treatment and/or care = $2,000/case; assuming an average duration of 30

years and 5% discount rate, total cost/case = $32,000 = $ 3,296,000

TOTAL = $ 3,296,000

TOTAL (D) = $ 3,998,000

Category E - serious CNS impairment

Neonatal

# of cases = 23

total annual costs for treatment and/or care = $5,000/case; assuming a duration of 20 years and 5% discount rate, total cost/case = $65,000 = $ 1,495,000

TOTAL = $ 1,495,000

All other cases of HSV encephalitis

# of cases = 103

total annual costs for treatment and/or care = $5,000/case; assuming an average duration of 30 years and 5% discount rate, total cost/case = $81,000 = $ 8,343,000

TOTAL = $ 8,343,000

Blindness

# of cases = 500

total annual costs for treatment and/or care = $5,000/case; assuming a duration of 25 years and 5% discount rate, total cost/case = $74,000 = $ 37,000,000

TOTAL = $ 37,000,000

TOTAL (E) = $ 46,838,000

Category F - very severe CNS impairment

Neonatal

# of cases = 61

total annual cost for treatment and/or care = approx. $20,000/case; assuming a reduced lifetime duration of 20 years at 5% discount rate, total cost/case = $262,000 = $ 15,982,000

TOTAL = $ 15,982,000

All other cases of HSV encephalitis

# of cases = 103

total annual cost for treatment and/or care = approx. $20,000/case; assuming a duration of 30 years at 5% discount rate, total present value/case = $323,000 = $ 33,269,000

TOTAL = $ 33,269,000

TOTAL (F) = $ 49,251,000

Costs associated with culture for HSV during pregnancy in infected women

95% of the 3,783,337 projected live births for 1984 will receive medical attention (Binkin et al., 1984). 5% of those 3,594,170 births are at high risk (women with a history of genital herpes) and of those 179,709 women, 20% (35,942) will actually receive an average of 5 HSV cultures at $30/culture (Binkin et al., 1984).

35,942 women typically receive 5 cultures at $30/culture	= $ 5,391,000
Of the 35,942 women screened for HSV, approx. 7,500 will receive a Cesarean section at approx. $2,300 above the cost of a normal vaginal delivery (Binkin et al., 1984)	
7,500 women typically receive Cesarean section at $2,300 extra	= $ 17,250,000
TOTAL (SCREENING COSTS)	= $ 22,641,000
TOTAL COST	= $452,395,000

Total Cost of Vaccine Preventable Illness

Category A - genital, oral and labial, primary and recurrences

Primary genital

# of cases = 80,000	
approx. 50% of cases receive 1 phys. visit at $30	= $ 1,200,000
approx. 10% of cases receive diagnostic culture procedure at $30	= $ 240,000
approx. 50% of cases receive treatment/medication (topical acyclovir) at $35	= $ 1,400,000
TOTAL	= $ 2,840,000

Recurrent genital

# of cases = 3,620,000	
approx. 1% of cases receive 1 phys. visit at $30	= $ 1,086,000
approx. 25% of cases receive treatment/medication (topical acyclovir or other treatment*) at $20	= $ 18,100,000
TOTAL	= $ 19,186,000

Labial

# of cases = 75,000,000 (recurrences of oral)	
approx. 0.1% of cases receive 1 phys. visit at $30	= $ 2,250,000
approx. 0.1% of cases receive treatment/medication (topical acyclovir or other treatment*) at $20	= $ 1,500,000
TOTAL	= $ 3,750,000

*See Chapter 4, "Comparison of Direct Costs Resulting from Disease."

Herpetic keratitis recurrences
# of cases = 375,000
100% of cases typically receive 2 specialist phys. visit at $50/each = $ 37,500,000
100% of cases typically receive medication (vidarabidine, trifluridine, idoxuridine) or treatment (debridement) at a total of $100 = $ 37,500,000
TOTAL = $ 75,000,000
TOTAL (A) = $100,776,000

Category B

Primary genital
# of cases = 40,667
100% of cases typically receive 1 phys. visit at $30 = $ 1,220,000
100% of cases typically receive medication at $35 = $ 1,423,000
TOTAL = $ 2,643,000

Primary oral
# of cases = 250,000
approx. 10% of cases receive 1 phys. visit at $30 [treatment involves domestically available fluids at no additional cost] = $ 750,000
TOTAL = $ 750,000

Herpes keratitis
# of cases = 375,000
100% of cases receive 2 specialist phys. visits at $50/each = $ 37,500,000
100% of cases receive medication (vidarabidine, trifluridine, idoxuridine) or treatment (debridement) at a total of $100 = $ 37,500,000
TOTAL = $ 75,000,000
TOTAL (B) = $ 78,393,000

Category C - hospitalization, severe and disseminated HSV, encephalitis and neonatal HSV

Neonatal HSV*
total # of cases = 238; 95% overall survive

Mild disease (of skin or eye)
# of cases = 119
100% of cases typically receive 12 days in a special care nursery at $400/day = $ 571,000
100% of cases typically receive diagnostic testing, treatment (antiviral drugs) and special care

*See discussion in text regarding uncertainty surrounding neonatal HSV estimates.

(isolation) equivalent to daily inclusive hospital rate, 12 days at $400/day	= $ 571,000
100% of cases typically receive 1 follow-up physician visit at $30	= $ 4,000
Severe disease (including disseminated infection)	
# of cases = 119	
100% of cases typically receive 14 days neonatal ICU at $800/day	= $ 1,333,000
100% of cases typically receive 7 days additional normal hospitalization at $400/day	= $ 333,000
100% of cases receive diagnostic testing and treatment (antiviral drugs) as a cost equivalent to daily inclusive hospital rate,	
14 days at $800/day	= $ 1,333,000
7 days at $400/day	= $ 333,000
100% of cases typically receive 1 follow-up physician visit at $30	= $ 4,000
TOTAL (neonatal HSV)	= $ 4,482,000
Encephalitis	
# of cases = 592	
100% of cases typically receive 14 days ICU at $600/day (65% survive)	= $ 4,973,000
approx. 65% of cases (all survivors) receive 20 additional days normal hospitalization at $400/day	= $ 3,078,000
all cases receive diagnostic testing and treatment (antiviral drugs) at rate equivalent to daily inclusive hospital rate	
for 100%, 14 days at $600/day	= $ 4,973,000
for 65%, 20 days at $400/day	= $ 3,078,000
65% of cases typically receive 1 follow-up phys. visit at $30	= $ 12,000
TOTAL (encephalitis)	= $ 16,114,000
Severe oral	
# of cases = 2,500	
100% of cases typically receive 5 days normal hospitalization at $400/day. Additional diagnostic testing and treatment not significant.	= $ 5,000,000
100% of cases typically receive 1 follow-up phys. visit at $30	= $ 75,000
TOTAL (severe oral)	= $ 5,075,000
Immunocompromised/Severe and Disseminated HSV	
# of cases = 6,526	
100% of cases typically receive 5 days normal hospitalization or additional hospitalization at $400/day	= $ 13,052,000

100% of cases typically receive diagnostic testing and treatment (acyclovir) at rate equivalent to daily inclusive hospital rate, 5 days at $400/day = $ 13,052,000
100% of cases typically receive 1 follow-up phys. visit at $30 = $ 196,000
TOTAL (IC and disseminated HSV) = $ 26,300,000

Corneal Transplants
See notes under cost of total disease burden calculations. Seventy-five percent of the burden of herpetic keratitis is assumed to be vaccine preventable, hence, avoidable costs for corneal transplants are 0.75 x 500 x $2,500 = $ 938,000
TOTAL (corneal transplants) = $ 938,000
TOTAL (C) = $ 52,909,000

Category D - mild CNS impairment

Neonatal
# of cases = 17
total annual costs for treatment and/or care = $2,000/case; assuming a duration of 20 years and 5% discount rate, total cost/case = $26,000 = $ 442,000
TOTAL = $ 442,000

All other cases of HSV encephalitis
# of cases = 64
total annual costs for treatment and/or care = $2,000/case; assuming an average duration of 30 years and 5% discount rate, total cost/case = $32,000 = $ 2,048,000
TOTAL = $ 2,048,000
TOTAL (D) = $ 2,490,000

Category E - serious CNS impairment

Neonatal
# of cases = 14
total annual costs for treatment and/or care = $5,000/case; assuming a duration of 20 years and 5% discount rate, total cost/case = $65,000 = $ 910,000
TOTAL = $ 910,000

All other cases of HSV encephalitis
# of cases = 64
total annual costs for treatment and/or care = $5,000/case; assuming an average duration of 30 years and 5% discount rate, total cost/case = $81,000 = $ 5,184,000
TOTAL = $ 5,184,000

Blindness
# of cases = 375
total annual costs for treatment and/or care
= $5,000/case; assuming a duration of 25 years
and 5% discount rate, total cost/case = $74,000 = $ 27,750,000
TOTAL = $ 27,750,000
TOTAL (E) = $ 33,844,000

Category F - very severe CNS impairment

Neonatal
# of cases = 38
total annual cost for treatment and/or care
= approx. $20,000/case; assuming a reduced
lifetime duration of 20 years at 5% discount
rate, total cost/case = $262,000 = $ 9,956,000
TOTAL = $ 9,956,000

All other cases of HSV encephalitis
# of cases = 64
total annual cost for treatment and/or care
= approx. $20,000/case; assuming a duration of
30 years at 5% discount rate, total present
value/case = $323,000 = $ 20,672,000
TOTAL = $ 20,672,000
TOTAL (F) = $ 30,628,000

Costs associated with culture for HSV during pregnancy in infected women
The reduction in screening costs that might result
if a vaccine were available would not necessarily
correspond to the maximum possible reduction in
disease (50-75%): physicians would probably
continue to screen some vaccinated women. Hence,
25% of screening costs associated with the total
disease burden is arbitrarily assumed to be vaccine
preventable.
TOTAL (SCREENING COSTS) = 0.25(22,641,000) = $ 5,660,000

TOTAL COST = $310,361,000

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Appendix

J

PROSPECTS FOR IMMUNIZING AGAINST HERPESVIRUS VARICELLAE

Disease Description

Varicella (chicken pox) is an acute communicable disease, primarily of childhood, caused by Herpesvirus varicellae (the varicella-zoster virus). The incubation period ranges from 10 to 21 days, with a median of 12 to 14 days. Susceptibility is universal, and because varicella is one of the most highly communicable infections known, the disease is almost universal as well. Diagnosis is relatively easy because of the characteristic vesicular rash. The principal route of spread appears to be by aerosolized small droplet rather than by direct contact with vesicular fluid or with the dried crusts of the skin lesions; paradoxically, virus is difficult to detect in oropharyngeal secretions, but is present in high titer in vesicular fluid from the lesions (Weller, 1982).

In normal children other than neonates, varicella is almost always a benign illness. Encephalitis occurs occasionally, but the most serious apparent complication is Reye's syndrome. Although the nature of the relationship between varicella and Reye's syndrome is uncertain, it is clear that varicella either plays a direct role in the pathogenesis of the syndrome or acts as a surrogate or marker for some concurrent condition that predisposes children to the disorder.

Adults are much more likely to experience significant morbidity or even mortality due to varicella. Varicella pneumonia, which may or may not be complicated by secondary bacterial pneumonia, is the principal complication in adults, although encephalitis also occurs.

Varicella-zoster virus shares with other members of the herpesvirus group the property of persistence or latency. In the case of varicella-zoster, the sensory ganglia have been suggested as the principal site of latency, but this has not been proved (Weller, 1982). Reactivation of the virus secondary to advancing age, stress, immunosuppression, and perhaps other factors, results in herpes zoster (shingles), a painful and prolonged eruption of typical herpetic lesions involving

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dermatome(s) supplied by the involved ganglion. Generalized dissemination, involvement of motor neurons, and meningoencephalitis also may complicate typical herpes zoster (Weller, 1982).

Pathogen Description

The varicella-zoster virus has been described often: although certain genetic differences have been identified among strains, the differences evidently do not involve alteration of the relevant antigens that induce protection. Techniques for in vitro culture of this virus and vaccine production also have been described fully elsewhere (Weller, 1982, 1983a).

Host Immune Response

The host immune response following natural varicella involves IgG, IgM, and IgA antibodies (Weller, 1983a). They appear several days after onset of the rash, reach maximum titer during the second or third week after the illness, and decline thereafter. IgA and IgM disappear, usually within a year, but IgG persists at low levels. Humoral antibody levels probably are boosted from time to time by asymptomatic contact with the wild virus (the "streetcar" booster).

The role of humoral antibody in maintaining "latency" is not clear, but following the appearance of herpes zoster, there is a sharp rise in levels of IgG, IgM, and IgA (Weller, 1983a). The cellular immune response is even less well understood. Lymphocytes from otherwise healthly elderly people who develop herpes zoster show little blastogenic response to the viral antigen until several days after the appearance of zoster; specific responses then occur. It appears, therefore, that a depressed cellular immune state is a major factor in the end of latency "containment," and the pathogenesis of herpes zoster (Weller, 1983a).

Host immune responses to live attenuated varicella vaccine generally mimic those of the natural infection, although the duration of protection is not yet clear. Of even greater concern, however, is the nature of the latent state and the incidence of herpes zoster related to the use of live attenuated varicella-zoster vaccine. Experience with immunization of susceptible immunodeficient children is limited. Several vaccinated leukemic children in Japan have developed zoster (Asano et al., 1983), but there is no evidence that varicella vaccine causes an increase in the frequency or severity of zoster in immunodeficient recipients. The frequency and severity of zoster in normal recipients given varicella vaccine can be assessed only by long-term studies in vaccinated and naturally infected populations (McIntosh, 1984).

Magnitude of Disease Burden

Typical Cases of Varicella

It is estimated that under steady-state conditions, the annual number of cases of varicella approaches the birth cohort (3,788,337 in 1984), and is distributed among age groups as shown in Table J.1 (Preblud, 1983; Preblud, personal communication, 1983).

A typical case of varicella is classified as Morbidity Category B (Morbidity Categories are defined in Table J.5.) The duration of cases in persons under the age of 15 is estimated to be seven days (Preblud, personal communication, 1983); in persons older than 15, a prodrome of fever, malaise, headache, and other constitutional symptoms prior to onset of the rash is assumed to prolong total duration to nine days.

Complications Associated with Varicella

Although varicella has been associated with many types of complications, those most commonly reported are encephalitis, Reye's syndrome, secondary bacterial infections, and pneumonia. National data on the incidence of complications are available only for encephalitis, Reye's syndrome, and death (Preblud, 1983). The Centers for Disease Control (CDC), on the basis of an analysis of hospital discharge summaries provided by The National Center for Health Statistics, has estimated that there are approximately 6,500 hospitalizations annually for all complications associated with varicella (Preblud, 1983). Use of the incidence rates noted above to determine the distribution of causes of hospitalization suggests that complications, other than encephalitis and Reye's syndrome (e.g., pneumonia), are the major causes of hospitalizations and deaths—a finding not in accord with the perceptions of a number of individuals with clinical experience. This is discussed further under "Uncertainty in the Disease Burden."

The estimated distribution of hospitalizations for complications associated with varicella is shown in Table J.2.

Encephalitis The risk of encephalitis following varicella is estimated to be 1.7/100,000 cases in children from 1 to 14 years, and 15/100,000 cases in persons older than 20 years (Preblud, 1983).* Two percent of all cases of encephalitis are estimated to occur in infants under the age of one (Preblud, 1983). The duration of cases of encephalitis is estimated to be 14 days (Losonsky, personal communication, 1983; Polk, personal communication, 1983) and all cases are assumed to be hospitalized (Morbidity Category C).

*The disease burden calculations in this appendix assume that risks estimated by Preblud for persons 20 years of age or older also apply to persons in the 15–20 years age group.

TABLE J.I Distribution of Cases of Varicella

	Age (years)						
	Under 1	1–4	5–14	15–24	25–59	60 and Over	All Ages
Percentage of all cases	2	20	73	4	0.9	0.1	100
Number of cases	75,767	757,667	2,765,486	151,534	34,095	3,788	3,788,337

The case fatality rate is estimated to be 17 percent in infants under the age of one; 19 percent in children 1–4; 15 percent in children 5–14; 15 percent in young adults 15–24; and 29 percent in persons 25 years of age or older. Chronic neurological sequelae are estimated to occur in 60 percent of survivors; cases are assumed to be distributed equally between Morbidity Categories D (mild chronic sequelae), E (moderate to severe chronic sequelae), and F (total impairment) (Preblud, 1983; Preblud, personal communication, 1983). Estimated morbidity and mortality associated with encephalitis are summarized in Table J.3.

Reye's Syndrome The Centers for Disease Control estimates that approximately 900 cases of Reye's syndrome occur annually in the United States and that 25 percent (225) are associated with a varicella prodrome (Hurwitz, personal communication, 1983). Most cases (98 percent) occur in children between the ages of 1 and 14 years; 1 percent of cases occur in infants less than 1 year of age and 1 percent of cases occur in persons older than 14 years. Cases occurring between the ages of 1 and 14 are assumed to be distributed between the age groups 1–4 and 5–14 in proportion to the distribution of cases of varicella occurring in these age groups. It is estimated that the case fatality rate is 35 percent in infants under the age of 1; 25 percent in children 1–4; and 25 percent in children 5–14 (Hurwitz, personal communication, 1983). Almost half of survivors are estimated to suffer mild to severe chronic neuropsychologic problems (e.g., mental retardation, cranial nerve palsies, motor dysfunction) (Sullivan-Bolyai and Corey, 1981). All cases of Reye's syndrome are classified in Morbidity Category C, because they require hospitalization. The duration of hospitalization is estimated to be 30 days (Losonsky, personal communication, 1983). Cases in which chronic sequelae occur are assumed to be distributed evenly between Morbidity Categories D (mild chronic sequelae) and E (moderate to severe chronic sequelae). Estimated morbidity and mortality due to Reye's syndrome are summarized in Table J.4.

TABLE J.2 Estimated Hospitalizations Due to Complications of Varicella

	Age (years)						
	Under 1	1-4	5-14	15-24	25-59	60 and Over	All Ages
Percentage of all hospitalizations	2	47.2	32.8	4.5	10	3.5	100
Number of hospitalizations							
Encephalitis	2	13	47	23	5	0	90
Reye's syndrome	2	50	171	0	0	0	223
Other complications	126	3,005	1,914	270	645	228	6,188
Total	130	3,068	2,132	293	650	228	6,501
Duration of hospitalization (days)							
Encephalitis	14	14	14	14	14	n.a.	
Reye's syndrome	30	30	30	n.a.	n.a.	n.a.	
Other complications	5	5	5	5 (85%) 10 (15%)	5 (85%) 10 (15%)	5 (85%) 10 (15%)	
Weighted average	6	5	7	6	6	6	

Notes: Estimated on the basis of information provided by Losonsky (personal communication, 19831, Polk (personal communication, 1983), and Preblud (personal communication, 1983).
n.a.=not applicable.

TABLE J.3 Estimated Morbidity and Mortality Due to Encephalitis Associated With varicella

	Age (years)					
	Under 1	1–4	5–14	15–24	25–59	60 and Over
Incidence per 100,000 cases of varicella[a]	n.e.[b]	1.7	1.7	15	15	15
Number of cases of encephalitis (Morbidity Category C)	2[c]	13	47	23	5	1
Number (%) of Category C resulting in fatalities	1 (17)	2 (19)	7 (15)	3 (15)	1 (29)	
Number of cases with chronic sequelae (60% of survivors):						
Morbidity Category D	1	2	8	4	1	
Morbidity Category E	1	2	8	4	1	
Morbidity Category F	1	2	8	4	1	

[a] Source: Preblud (1983).
[b] n.e.=not estimated.
[c] Estimated to be two percent of all cases.

Fatalities The risk of death from complications associated with varicella is estimated to be 2.0/100,000 cases in children 1–14, and 50/100,000 in persons 20 years of age and older (Preblud, 1983). Infants under the age of 1 are estimated to account for 7 percent of all deaths (Preblud, 1983). The estimated distribution of deaths from all causes associated with varicella is summarized in Table J.5.

The estimate of the number of deaths derived using these rates is about 177; this is greater than the reported number (about 100). The discrepancy is probably due to underreporting, through misdiagnosis, or more likely through attribution of death to other causes, for cases in which varicella may have contributed to death, e.g., from congenital heart disease.

Table J.6 summarizes the disease burden associated with typical cases and complications of varicella in normal persons.

Herpes Zoster

Data on the occurrence of herpes zoster in the general population are not collected by any reporting agency and have not been found in a search of the published literature. The following disease burden calculations are based on data reported by Ragozzino and coworkers (1982), who conducted a population-based study of herpes zoster in 590 residents of Rochester, Minnesota, from 1945 to 1959. Data on the age distribution of patients who developed sequelae were not reported in that study; it is assumed that sequelae occur only in persons aged 25 years or older. Table J.7 shows the estimated age distribution of typical cases and sequelae of herpes zoster in normal persons and how

TABLE J.4 Estimated Morbidity and Mortality Due to Reye's Syndrome With Varicella Prodrome

	Age (years)		
	Under 1	1-4	5-14
Number (%) of cases of Reye's syndrome (Morbidity Category C)[a]	2 (1)	50 (22)	171 (76)
Number (%) of Category C resulting in fatalities[b]	1 (35)	13 (25)	43 (25)
Number with mild chronic sequelae (Morbidity Category D) (24% of survivors)[c]	1	9	31
Number with moderate to severe chronic sequelae (Morbidity Category E) (24% of survivors)[c]	1	9	31

[a]One percent of cases occur in persons older than 14 years; these cases are not included in disease burden estimates because the age group(s) in which they occur are unknown.
[b]Source: Hurwitz (personal communication, 1983).
[c]Percent based on estimates in Sullivan-Bolyai and Corey (1981).

the numbers of cases of sequelae have been calculated and distributed between Morbidity Categories.

The duration of typical cases of herpes zoster (Morbidity Category B) is estimated to be 14 days (Preblud, personal communication, 1983; Polk, personal communication, 1983; Losonsky, personal communication, 1983). Table J.8 shows the estimated distribution and duration of complications in normal persons and the Morbidity Categories under which they are classified.

Table J.9 summarizes the disease burden associated with typical cases and sequelae of herpes zoster in normal persons.

Table J.10 shows the total combined disease burden associated with varicella and herpes zoster in normal persons.

Morbidity and Mortality Associated with Varicella-Zoster Infections in Immunocompromised Patients

Infections with varicella-zoster virus (VZV) are common in immunocompromised patients, however data on the number and complications of such infections are fragmentary. Tables J.11 through J.14 show the disease burden associated with VZV infections in children and young adults with lymphomas and leukemias; and in recipients (children and adults) of renal, cardiac, liver, and allogeneic bone marrow transplants. These groups comprise one of the designated target populations (high-risk individuals) for the vaccine. Other persons at high risk include patients with severe combined immunodeficiency disease, and

TABLE J.5 Estimated Distribution of Deaths Associated With Varicella

Cause of Death	Age (years) Under 1	1–4	5–14	15–24	25–59	60 and Over	All Ages
Encephalitis		2	7	3	1		13
Reye's syndrome		13	43				56
Other complications (e.g., secondary bacterial infections; pneumonia)	12[a,b]		5[b]	73[c]	16[d]	2[d]	108
Total deaths	12	15	55	76	17	2	177

Source: Preblud (1983).

[a]Incidence not calculated; estimated to be seven percent of all deaths (Preblud, 1983).
[b]Calculated as 2.0/100,000 cases of varicella minus deaths due to encephalitis and Reye's syndrome.
[c]Calculated as 50/100,000 cases of varicella minus deaths due to encephalitis.
[d]Calculated as 50/100,000 cases of varicella.

children with kidney disease, juvenile rheumatoid arthritis, lupus or other connective tissue disorders, or asthma, who receive high doses of corticosteroids (Preblud, personal communication, 1983). Data on the numbers of such patients and the frequency of VZV infections in these groups are not available and are not included in the estimates of disease burden.

Table J.15 summarizes the estimated disease burden associated with varicella-zoster in high-risk individuals. In calculations of average duration of hospitalization, all immunocompromised patients who develop clinically apparent VZV infections are assumed to require an additional 14 days of hospitalization. Patients whose infections progress to fatal or non-fatal disseminated disease are assumed to require an additional 7.5 days, for a total of 21.5 days of hospitalization (Feldman et al., 1975). Weighting these durations to reflect the number of immunocompromised patients with uncomplicated VZV infection and the number of patients with disseminated disease gives an estimated duration of 17 additional days of hospitalization for patients under the age of 25 and 16 days for those over 25.

Table J.16 shows the total combined disease burden associated with varicella and herpes zoster in normal and high-risk persons.

Uncertainty in the Disease Burden Estimates

Varicella is notifiable to the CDC only on a voluntary basis and the accuracy of reporting varies widely among states. The CDC estimates that only about 10 percent of cases are reported and that severe cases are more likely to be reported than mild cases. Herpes zoster is not notifiable to the CDC, although some states report the

TABLE J.6 Disease Burden: Varicella—Typicel Case and Ccmplications in Normal Persons

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Typical case	75,767	7	757,667	7	2,765,486	7	151,534	9	34,095	9	3,788	9
C	Requiring hospitalization	Encephalitis, Reye's syndrome, other complications	130	6	3,068	5	2,132	7	293	6	650	6	228	6
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Sequelae of encephalitis and Reye's syndrome			11	n.a.	39	n.a.	4	n.a.	1	n.a.		
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Sequalae of encephalitis and Reye's syndrome			11	n.a.	39	n.a.	4	n.a.	1	n.a.		
F	Total impairment	Sequelae of encephalitis			2	n.a.	8	n.a.	4	n.a.	1	n.a.		
G	Reproductive impairment resulting in infertility													
H	Death		12	n.a.	15	n.a.	55	n.a.	76	n.a.	17	n.a.	2	n.a.

TABLE J.7 Estimated Morbidity and Mortality Due to Herpes Zoster in immunocompetent Persons

	Age (years)					
	Under 1	1–4	5–14	15–24	25–59	60 and Over
Percentage of all cases[a] of H. zoster	0.5	2	5	10.0	38.7	43.5
Number of cases[b]	1,678	6,712	15,582	30,734	118,939	133,692
Cases of disseminated disease (Morbidity Category C)[c]					4,756	17,380
Cases of disseminated disease with chronic sequelae (Morbidity Category D)					642	3,370
Cases of sequelae of encephalitis (Morbidity Category E)					107	121
Fatalities (Morbidity Category H)[d]					62	62

Note: Estimates (except fatalities) based on data reported in Ragozzino et al. (1982) and Dolin et al. (1978). includes initial episodes only.

aPercentage of all cases of H. zoster in the age group 0–14=7.8 percent (23,972 cases). Percentages shown for age groups under 1, 1–4, and 5–14 are based on the assumption that the distribution of cases among these groups is proportional to the age distribution derived from 1984 population projections.

bIncidence=1.3/100,000.

cPercentages based on data reported in Ragozzino et al. (1982). All disseminated cases assumed to occur in persons 25 years or older. For distribution among sequelae see Table J.8.

dFatalities based on average number reported to Centers for Disease Control (1983), 1973–1979 (average 124 per year). Age not reported; all deaths assumed to occur in persons 25 years or older.

TABLE J.8 Distribution of Sequelae of Herpes Zoster Among Age Groups and Disease Categories

	Age Group (years)		Acute Illness			
	25–59	60 and Over	Duration	Morbidity Category	Percentage of Total[a]	Notes on Chronic Illness
Motor Deficits	1,189	1,337	20 days	C	75	All patients in Category C for 365 days enter chronic illness Category D
			365 days	C	25	
Ocular Complications	2,378	2,674	20 days[b]	C	100	
Encephalitis, pneumonia, herpes gangrenosa	1,189	1,337	14 days[c]	C	100	18% enter chronic illness categories D (9%) and E (9%)[d]
Post-herpetic neuralgia[e]		12,032	56 days	C	45	All patients in Category C for 365 days enter chronic illness Category D
			180 days	C	33	
			365 days	C	22[c]	

[a]Based on Dolin et al. (1978).

[b]Average length of treatment for uveitis; keratitis.

[c]Assumed similar to duration of encephalitis/pneumonia in other infectious diseases.

[d]Based on Dolin et al. (1978). Number of fatalities unknown.

[e]Post-herpetic neuralgia reported by Ragozzino et al. to have median age of onset of 67 years, so all cases placed in 60 years and over age group. Percentages of complications/durations based on Ragozzino et al. (1982).

TABLE J.9 Disease Burden: Herpes Zoster—Typical Case and Complications in Norma1 Persons

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Typical case	1,678	14	6,712	14	15,582	14	30,734	14	118,939	14	133,692	14
C	Requiring hospitalization	Motor deficits, ocular complications, encephalitis, pneumonia, post-herpetic neuralgia									4,756	40	17,380	126
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Sequelae of complications in Category C									642	n.a.	3,370	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Sequelae of complications in Category C									107	n.a.	121	n.a.
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death										62	n.a.	62	n.a.

TABLE J.10 Disease Burden: Varicella and Herpes Zoster in Normal Persons

Morbidity Category	Description	Condition[a]	Under 1 Year		1–4 Years		5–14 Years		15–24 Years		25–59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed		77,445	7	764,379	7	2,781,068	7	182,268	10	153,034	13	137,480	14
C	Requiring hospitalization		130	6	3,068	5	2,132	7	293	6	5,406	36	17,608	124
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)				11	n.a.	39	n.a.	4	n.a.	643	n.a.	3,370	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)				11	n.a.	39	n.a.	4	n.a.	108	n.a.	121	n.a.
F	Total impairment				2	n.a.	8	n.a.	4	n.a.	1	n.a.		
G	Reproductive impairment resulting in infertility													
H	Death		12	n.a.	15	n.a.	55	n.a.	76	n.a.	79	n.a.	64	n.a.

[a]see table J.6 and J.9

TABLE J.11 Estimated Morbidity and Mortality Associated With Varicella-Zoster (VZV) Infections in patients with Lymphomas and Leukemias

	Age (years)			
	Under 1	1-4	5-14	15-24
Incidence of lymphomas and leukemias per 100,000 population[a]	7.1	7.1	4.5	3.9
Number of cases of lymphomas and leukemias	265	1,030	1,508	1,579
Number with clinically apparent VZV infection (35% of cases)[b]	93	361	528	553
Number with disseminated disease (30% of clinically apparent VZV infections)[c]	28	108	158	166
Fatalities (7% of clinically apparent VZV infections)[c]	7	25	37	39

[a]Source: National Cancer Institute (1978).
[b]Based on data reported in Reboul (1978).
[c]Based on data reported in Feldman (1975) and Reboul (1978) and estimates provided by Losonsky (personal communication, 1983), Polk (personal communication, 1983), and Preblud (personal communication, 1983).

TABLE J.12 Estimated Morbidity and Mortality Associated with Varicella-Zoster (VZV) Infections in Recipients of Renal Transplants

	Age (years)					
	Under 1	1-4	5-14	15-24	25-59	60 and Over
Number (%) of Transplants[a]			297 (4.75)	297 (4.75)	5,531 (88.5)	125 (2.0)
Number with clinically apparent VZV infection (35% of transplants)[b]			104	104	1,936	44
Number with disseminated disease (15% of clinically apparent VZV infections)[c]			16	16	290	7
Fatalities (7% of clinically apparent VZV infections)[d]			7	7	136	3

[a]Number and age distribution of transplants derived from data provided by the Health Care Financing Administration (1983).
[b,c,d]Risk of VZV infection and death assumed same as that reported for patients with lymphomas and leukemias (see Table J.11). Risk of dissemination estimated to be half that of patients with lymphomas and leukemias.

TABLE J.13 Estimated Morbidity and Mortality Due to Varicella-Zoster (VZV) Infections in Recipients of Cardiac and Liver Transplants

	Age (years)					
	Under 1	1–4	5–14	15–24	25–59	60 and Over
Number of liver transplants[a]		9	21	25	121	
Number of cardiac transplants[a]					100	
Number with clinically apparent VZV infection (35% of transplants)[b]		3	7	9	77	
Number with disseminated VZV disease (20% of clinically apparent VZV infections)[c]		1	1	2	15	
Fatalities (7% of clinically apparent VZV infections)		1	1	1	5	

[a]Number of transplants estimated by Scharschmidt (personal communication, 1984). Age distribution derived from estimates provided by Scharschmidt (personal communication, 1984) and from distribution of projected 1984 U.S. population (Bureau of the Census, 1984); all cardiac transplants assumed to occur in the 25–59 years age group.
[b]Risk of infection and death assumed same as for patients with lymphomas and leukemias see Table J.11).
[c]Risk of dissemination assumed slightly higher than for recipients of renal transplants because of more intense immunosuppressive therapy.

TABLE J.14 Estimated Morbidity and Mortality Associated with Varicella-Zoster (V2V) infections in Recipients of Allogeneic Bone Marrow Transplants

	Age (years)					
	Under 1	1–4	5–14	15–24	25–59	60 and Over
Number of Transplants[a,b]	30	118	490	601	536	74
Number with clinically apparent VZV infection (65% of transplants)[c]	20	77	319	391	348	48
Number with disseminated disease (30% of clinically apparent VZV infections)[d]	6	23	96	117	104	14
Fatalities (8% of clinically apparent VZV infections)[e]	2	6	26	31	28	4

[a]Number of transplants assumed to equal number of transplant recipients. Data on the number of transplants were obtained from the Statistical Center of the International Bone Marrow Transplant Registry (1983). These data have not been reviewed or approved by the Advisory Committee of the IBMTR. Figures have been projected for 1984 at an estimated increase of 52 percent.
[b]Age distribution derived from data reported in Meyers et al. (1982).
[c]From data cited in Weller (1983b).
[d]Averages of percentages reported in Feldman et al. (1975) and Reboul et al. (1978).
[e]From data cited in Weller (1983b).

TABLE J.15 Disease Burden: Varicella and Herpes Zoster Infections in High-Risk Individuals

Morbidity Category	Description	Condition	Under 1 Year		1–4 Years		5–14 Years		15–24 Years		25–59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hospitalization	Lymphomas; leukemias; recipients of organ and bone marrow transplants	113	17	441	17	958	17	1,057	17	2,361	16	92	16
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		9	n.a.	31	n.a.	70	n.a.	78	n.a.	169	n.a.	7	n.a.

Note: Duration are weighted averages.

TABLE J.16 Disease Burden Summary: Varicella and Herpes Zoster in Normal and High-Risk Individuals

Morbidity Category	Description	Condition[a]	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed		77,445	7	764,379	7	2,781,068	7	182,268	10	153,034	13	137,480	14
C	Requiring hospitalization		243	10	3,509	7	3,090	10	1,350	15	7,767	30	17,700	123
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)				11	n.a.	39	n.a.	4	n.a.	643	n.a.	3,370	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)				11	n.a.	39	n.a.	4	n.a.	108	n.a.	121	n.a.
F	Total impairment				2	n.a.	8	n.a.	1	n.a.	1	n.a.		
G	Reproductive impairment resulting in infertility													
H	Death		21	n.a.	46	n.a.	125	n.a.	154	n.a.	248	n.a.	71	n.a.

Notes: For discussion, see text. Durations are weighted averages.

[a] See tables J.10 and J.15.

number of fatalities. Of the complications associated with varicella and herpes zoster, only encephalitis, Reye's syndrome, and death are reportable. The disease burden caused by varicella, herpes zoster, and associated complications was estimated in consultation with experts at the CDC and with the assistance of physicians knowledgeable about the epidemiology and clinical manifestations of varicella. Some published studies, cited in the text, were reviewed but an extensive search of the literature was not undertaken.

As noted above, the calculations on the distribution of causes of hospitalization suggest that complications other than encephalitis and Reye's syndrome (e.g., pneumonia) may cause a greater proportion of hospitalizations than previously thought. There is reasonable confidence that the total number of hospitalizations from Herpesvirus varicellae disease is accurate; however, further investigation of the distribution of causes may be desirable. A more precise definition of the distribution of causes (which affect costs) may not be possible, unless requirements for reporting are strengthened.

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for varicella-zoster are calculated using estimates from Table J.16 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 1,949 (committee median perspective) and 1,332 (age-neutral perspective).

Vaccine Target Population

Two distinct target populations can be identified. The first consists of susceptible individuals who are at high risk, i.e., children and young adults with leukemias and lymphomas and prospective recipients of renal, cardiac, liver, and bone marrow transplants, or individuals who are immunodeficient but may respond to the vaccine. Varicella in susceptible children with congenital immune deficiencies, leukemia, lymphoma, and other immunosuppressive diseases is usually severe, often involves dissemination, and may cause death. Hence, (prospective) immunodeficient susceptible children logically would constitute the highest risk group, and the first group to be immunized when a vaccine becomes available. Immunologic screening to determine susceptibility is available, but on a limited basis. There appear to be no adverse effects associated with giving varicella-zoster vaccine to subjects who are already immune, but evidence on this point is incomplete. Because the vast majority of this high-risk population already are in contact with the health care system, it should not be difficult to obtain adequate access to this target population.

The second target population would include all normal susceptible children, or if one wished to include the first group also, all susceptible children. This target group could be defined as the entire cohort of infants born in the United States each year. Access to this population already has been achieved for the DPT, polio, and MMR vaccines. Perhaps varicella-zoster vaccine could be administered simultaneously with MMR vaccine; studies are underway to evaluate this possibility.

Suitability for Vaccine Control

In many respects, varicella is ideally suited for vaccine control. Candidate vaccines are available, preliminary evidence shows them to be safe and effective, and access to the target population is assured. The major unanswered question involves the nature of the latent state induced by attenuated varicella vaccine virus, and the subsequent severity and frequency, if any, of herpes zoster. Because of the highly transmissible and infectious nature of varicella-zoster virus, universal infection is the rule, and there is little evidence that "herd" immunity is a significant factor in the epidemiology of the disease.

Alternative approaches to prevention or control of varicella do exist, however. Varicella in exposed immunodeficient susceptible children or adults may be modified by the use of varicella-zoster immune globulin. Both vidarabine and, more recently, acyclovir have been shown to be effective in the management of severe or disseminated varicella in immunosuppressed subjects, and in the treatment of herpes zoster in otherwise normal subjects. These alternatives, other than the prophylactic use of varicella-zoster immune globulin, focus on therapy rather than prevention.

In the development of a vaccine program against varicella-zoster, special attention will need to be paid to the risk of disease in older persons who escaped infection in childhood, because primary varicella infections in adults are often quite severe. Infection of these individuals may be delayed (rather than avoided completely) especially if immunization levels are not very high.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the possible reduction in morbidity and mortality that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

Live Attenuated Vaccine for Normal Persons

It is estimated that this vaccine potentially could prevent all cases of varicella and herpes zoster in all age groups. The vaccine probably would be administered to normal children at about one year of age, possibly in combination with the MMR vaccine. Because the likely duration of immunity induced by the vaccine cannot be predicted on the basis of current data, it is possible that a booster may be required at some time in adult life. Adopting this strategy, it is estimated that all cases of varicella and herpes zoster in persons over the age of one potentially could be prevented. Illness occurring in infants less than one would not be prevented, but maternal antibody would provide some degree of protection against serious disease for infants under the age of six months, when the level of maternal antibody declines. Disease in infants between the ages of six months and one year would not be prevented, however. The contribution of the disease burden in this age group to the total disease burden associated with varicella and herpes zoster is small and judged insignificant for the purpose of calculating the potential benefits of the vaccine.

Since the entire disease burden in normal persons is considered potentially preventable, Table J.10, which summarizes disease burden in normal persons, also represents a summary of vaccine preventable illness.

Live Attenuated Vaccine for High-Risk Individuals

It is estimated that with effective (100 percent) immunization of the entire target population this vaccine potentially could prevent all cases of varicella and herpes zoster in this group.

Since the entire disease burden in the high-risk group is considered potentially preventable, Table J.15, which summarizes the disease burden in high-risk individuals, also represents a summary of vaccine preventable illness in this group.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Vaccine preventable illness values for varicella-zoster are calculated using estimates from Tables J.10 and J.15, and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the vaccine preventable illness values are 1,391 for the vaccine for normal persons and 558 for the vaccine for high-risk individuals. Using the age-neutral perspective, the values are 960 and 372, respectively, for these target populations.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by each of the two varicella vaccine candidates, the two vaccine preventable illness values for each vaccine are multiplied by the predicted efficacy of that vaccine. The vaccine for normal persons is predicted to be 95 percent effective in persons under the age of 15 and 67 percent effective in persons over the age of 15. The vaccine for high-risk individuals is predicted to be 90 percent effective in persons under the age of 15 and 50 percent effective in persons over the age of 15. To simplify the calculations, all disease occurring in persons under the age of 15 is assumed to be varicella and all disease occurring in persons over the age of 15 is assumed to be herpes zoster. Adopting this simplification and using vaccine preventable illness values based on a median of committee member perspectives, the potential morbidity and mortality reductions are 1,112 for the vaccine for normal persons and 337 for the vaccine for high-risk individuals. Using the age-neutral perspective, the values are 746 and 231 for the same vaccines.

These values are not adjusted for vaccine adverse effects or anticipated utilization. Use of these values for comparing vaccines is descr ibed in Chapter 7.

Prospects for Vaccine Development

Varicella-zoster vaccines already are well along in their development. The Oka strain vaccine has been evaluated in Japan for the past 10 years by Takahashi et al. (1974), and is being used in trials in the United States in immunodeficient children (Brunell et al., 1982). A similar product has been developed by Merck Sharp and Dohme in the United States, and is now being used in an extensive, double-blind field trial in normal children in the Philadelphia area. During the initial 9 months of this study (involving 914 children, 1 to 14 years of age), no varicella occurred in the vaccinated group, while 39 cases developed in the control group (Weibel et al., 1984).

The probability of success in bringing varicella-zoster vaccine to the point of licensure is considered to be very high, approximately 99 percent for a target population of immunocompromised persons and 95 percent for a target population of normal persons. Because of the low risk-benefit ratio associated with vaccination of immunodeficient children, and the accumulated data from field trials involving these children, the committee estimates that it will take only two years to complete development of a vaccine for this target group, at an estimated cost of $5 million. Field trials in normal susceptible recipients have been initiated more recently, so the committee estimates that it will require two additional years to complete field trials, at an estimated additional cost of $5 million. The protective efficacy of the vaccine against varicella in normal persons is predicted to be about 95 percent; against herpes zoster in normal persons it is expected to be about 67 percent. The duration of vaccine-

induced protection cannot yet be determined. The vaccine appears to be about 90 percent effective against varicella in high-risk individuals and to be about 50 percent effective against herpes zoster in this group (Gershon et al., 1984).

Adverse reactions to the vaccines (detected in short-term follow-up) in field trials have been minor, mostly limited to a mild vesicular transient rash in a small percentage of vaccine recipients (Weibel et al., 1984).

Clinical trials have not posed any unusual logistic, ethical, or legal issues, and none are expected. Comprehensive analysis requires, however, that there be sufficient natural varicella occurring in the control group, against which to measure the protective efficacy in the vaccinated group. Maintenance of long-term surveillance of recipients to assess the frequency and severity of herpes-zoster, if it occurs, may be a problem in the future (McIntosh, 1984).

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to vaccines are displayed together for comparison.

Vaccine for High-Risk Individuals

Lay Acceptance Potential recipients in this target population probably have only a moderate perception of the likelihood of exposure and susceptibility to varicella, but they may be highly apprehensive about the severe consequences of the disease. High-risk recipients are likely to perceive the benefits of the vaccine to be high and the barriers low since it may prevent fatal disease.

Provider Acceptance Providers generally are aware of the risk and of the severity of the disease in this population. They may be somewhat skeptical, however, about the efficacy of the vaccine in this target population; hence, the vaccine received a moderate score for provider perception of vaccination benefits in this group. Perceived barriers to vaccination were judged to be very low, however, since the vaccine may prevent fatal disease in these patients. Overall, scores reflect the committee's belief that the vaccine will be used extensively in high-risk individuals.

Vaccine for Normal Persons

Lay Acceptance It is expected that the vaccine will be used much less frequently in this target population. Although most individuals accept the inevitability of exposure to varicella and the high proba

bility of infection, they believe that the disease is almost always mild. Hence, the motivation to prevent varicella in this target population will be substantially less than in the immunodeficient population, even though lay individuals might believe the vaccine to be highly effective. The moderate cost, estimated at $25 per dose, may act as a modest barrier to extensive vaccine utilization.

Provider Acceptance Physician acceptance of this vaccine for all susceptible normal persons probably will be similar to that of the lay population. In addition, physicians may have lingering concerns about the latent state and the possibility that the vaccine virus might induce more frequent or more severe episodes of herpes zoster.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Total Cost of Disease Burden and Vaccine Preventable Illness Specifically for Varicella

Category A n/a

Category B

# of cases = 3,788,337	
approx. 20% of cases receive 1 phys. visit at $30	= $ 22,730,000
approx. 20% of cases receive medication at $5 [OTC medication]	= $ 3,788,000
TOTAL (B)	= $ 26,518,000

Category C – encephalitis, pneumonia, Reye's syndrome and other hospitalization

# of cases= 6,501	
100% of cases typically receive 3 days of ICU at $600/day	= $ 11,702,000
100% of cases typically receive additional 3 days normal hospitalization at $400/day	= $ 7,801,000
100% of cases typically receive diagnostic testing and treatment (i.e., EEGs, cranial monitoring, CT scans) at rate equivalent to daily inclusive hospital rate	
3 days at $600/day	= $ 11,702,000
3 days at $400/day	= $ 7,801,000

100% of cases typically receive 2 follow-up phys. visits at $30/each = $ 390,000

TOTAL (C) = $ 39,396,000

Category D* - sequelae of encephalitis and Reye's syndrome (assuming normal lifespan)

# of cases = 55
total annual costs for treatment and/or care = $2,000/case; for 60 years duration at 5% discount rate, total present value/case = $40,000 = $ 2,200,000

TOTAL (D) = $ 2,200,000

Category E* - sequelae of encephalitis and Reye's syndrome (assuming lifespan 75% of normal)

# of cases = 55
total annual costs for treatment and/or care = $5,000/case; for 43 years duration at 5% discount rate, total present value/case = $92,000 = $ 5,060,000

TOTAL (E) = $ 5,060,000

Category F* - sequelae of encephalitis (assuming lifespan 50% of normal)

# of cases = 15
total annual costs for treatment and/or care = $20,000/case; for 25 years duration at 5% discount rate, total present value/case = $296,000 = $ 4,440,000

TOTAL (F) = $ 4,440,000

TOTAL (varicella) = $ 77,614,000

Total Cost of Disease Burden and Vaccine Preventable Illness Specifically for Herpes Zoster

Category A n/a

Category B - typical case

# of cases = 307,337

*Expected lifespan duration of 70 years has been reduced by 10 years to reflect the expected peak average age of onset (at 10 years vs. less than 1).

90% of cases typically receive approx. 1.5 phys. visits at $30	= $ 12,447,000
approx. 50% of cases receive medication at $25 [OTC medication]	= $ 3,842,000
TOTAL (B)	= $ 16,289,000

Category C - motor deficits, ocular complications, encephalitis, pneumonia, post-herpetic neuralgia

total # of cases = 22,136

Motor deficits

# of cases = 2,526	
approx. 75% of cases receive 5 days normal hospitalization at $400/day, plus	= $ 3,789,000
15 days outpatient care requiring approx. 4 phys. visits at $30/visit (total 20 days)	= $ 227,000
approx. 25% of cases receive 30 days normal hospitalization at $400/day, plus	= $ 7,578,000
335 days outpatient care requiring approx. 25 phys. visits at $30/visit (total 365 days)	= $ 474,000
100% of cases typically receive additional diagnostic testing/treatment at rate equivalent to daily inclusive hospital rate	
for 75% of cases, 5 days at $400/day	= $ 3,789,000
for 25% of cases, 30 days at $400/day	= $ 7,578,000
TOTAL	= $ 23,435,000

[All patients in Category C for 365 days enter Category D]

Ocular complications

# of cases = 5,052	
100% of cases typically receive 3 days normal hospitalization at $400/day, plus	= $ 6,062,000
17 days outpatient care requiring 2 phys. visits at $30/visit (total 20 days)	= $ 303,000
100% of cases typically receive additional diagnostic testing/treatment at rate equivalent to daily inclusive hospital rate; 3 days at $400/day	= $ 6,062,000
TOTAL	= $ 12,427,000

Encephalitis, pneumonia, herpes gangrenosa

# of cases = 2,526	
100% of cases typically receive 5 days ICU hospitalization at $600/day, plus	= $ 7,578,000
9 days normal hospitalization at $400/day (total 14 days)	= $ 9,094,000

100% of cases typically receive additional diagnostic testing/treatment at rate equivalent to daily inclusive hospital rate;		
5 days at $600/day		= $ 7,578,000
9 days at $400/day		= $ 9,094,000
approx. 100% of cases receive 3 follow-up phys. visit at $30/visit		= $ 227,000
[9% enter Category D; 9% enter Category E]	TOTAL	= $ 33,571,000
Post-herpetic neuralgia		
# of cases = 12,032		
approx. 5% of cases receive 7 days normal hospitalization at $400/day, and additional diagnostic testing/treatment at rate equivalent to daily inclusive hospital rate; 7 days at $400/day		= $ 1,684,000
approx. 45% of cases receive outpatient care requiring approx. 4 phys. visits at $30/visit, and		= $ 650,000
50% of these receive demerol at $5/day for 56 days		= $ 758,000
approx. 33% of cases receive outpatient care requiring approx. 6 phys. visits at $30/visit, and		= $ 715,000
50% of these receive demerol at $5/day for 180 days		= $ 1,787,000
approx. 22% of cases receive outpatient care requiring approx. 12 phys. visits at $30/visit, and		= $ 953,000
50% of these receive demerol at $5/day for 365 days		= $ 2,415,000
[All patients in Category C for 365 days enter Category D]	TOTAL	= $ 10,646,000
	TOTAL (C)	= $ 80,079,000

Category D - sequelae of complications in Category C

total # of cases = 4,012

Motor deficits		
# of cases = 632		
total annual costs for treatment and/or care = $2,000/case; for 10* years duration (normal lifespan) at 5% discount rate, total present value/case = $16,000		= $ 10,112,000
	TOTAL	= $ 10,112,000
Encephalitis, pneumonia, herpes gangrenosa		
# of cases = 228		
for 80% of cases, total annual costs for treatment and/or care = $2,000/case; for 10* years duration (normal lifespan) at 5% discount rate, total present value/case = $16,000		= $ 2,918,000

*Durations based on life expectancy of 70 years and average incidence of disease at age 60 (weighted from disease burden data).

for 20% of cases with expected shortened life-span of 75% of normal (7* years), total annual costs/case = $12,000 = $ 547,000

TOTAL = $ 3,465,000

Post-herpetic neuralgia

# of cases = 2,647

total annual costs for treatment and/or care = $200/case; for 10* years duration (normal lifespan) at 5% discount rate, total present value/case = $2,000 = $ 5,294,000

TOTAL = $ 5,294,000

Unilateral deafness

# of cases = 505

costs for treatment and/or care estimated to be insignificant for the purpose of this calculation

TOTAL (D) = $ 18,871,000

Category E - sequelae of encephalitis

# of cases = 228

total annual costs for treatment and/or care = $5,000/case; for 11† years duration (lifespan 75% of normal) at 5% discount rate, total present value/case = $44,000 = $ 10,032,000

TOTAL (E) = $ 10,032,000

TOTAL (herpes zoster) = $125,271,000

TOTAL (varicella and herpes zoster in normal patients) = $202,885,000

Total Cost of Disease Burden and Vaccine Preventable Illness Specifically for High-Risk Individuals

Categories A & B n/a

*Durations based on life expectancy of 70 years and average incidence of disease at age 60 (weighted from disease burden data).

†Duration based on life expectancy of 70 years and average incidence of disease at age 55 (weighted from disease burden data).

Category C

total # of cases = 5,022

Patients with lymphomas and leukemias		
# of cases = 1,535		
100% of cases typically receive 17 additional days normal hospitalization at $400/day		= $ 10,438,000
100% of cases typically receive additional diagnostic testing/treatment at rate equivalent to daily inclusive hospital rate, 17 days at $400/day [I.V. treatment]		= $ 10,438,000
	TOTAL	= $ 20,876,000
Recipients of renal, cardiac, and liver transplants*		
# of cases = 2,284		
approx. 10% (228) of cases receive 5 additional days ICU hospitalization at $600/day, and		= $ 685,000
12 additional days normal hospitalization at $400/day		= $ 1,096,000
approx. 90% (2,056) of cases receive 16 additional days normal hospitalization at $400/day		= $ 13,156,000
100% of cases typically receive additional diagnostic testing/treatment at rate equivalent to daily inclusive hospital rate,		
for 10%, 5 days at $600/day, and		= $ 685,000
12 days at $400/day		= $ 1,096,000
for 90%, 16 days at $400/day		= $ 13,156,000
	TOTAL	= $ 29,874,000
Recipients of bone marrow transplants		
# of cases = 1,203		
approx. 67% of cases typically receive 5 days additional ICU hospitalization at $600/day, and		= $ 2,418,000
12 additional days normal hospitalization at $400/day		= $ 3,869,000
approx. 33% of cases typically receive 5 days additional ICU hospitalization at $600/day, and		= $ 1,191,000
11 additional days normal hospitalization at $400/day		= $ 1,747,000
100% of cases typically receive additional diagnostic testing/treatment at rate equivalent to daily inclusive hospital rate,		
for 67%, 5 days at $600/day, and		= $ 2,418,000
12 days at $400/day		= $ 3,869,000
for 33%, 5 days at $600/day, and		= $ 1,191,000
11 days at $400/day		= $ 1,747,000
	TOTAL	= $ 18,450,000
	TOTAL (C)	= $ 69,200,000
TOTAL (varicella and herpes zoster in high-risk individuals)		= $ 69,200,000

*Duration of hospitalization and percentage of persons hospitalized for different durations are based on weighted averages. For discussion, see text.

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Appendix

K

PROSPECTS FOR IMMUNIZING AGAINST INFLUENZA VIRUSES A AND B

Influenza infection is a widespread problem in the United states, yet existing influenza vaccines are among the most poorly utilized vaccines available. The need for annual revaccination, misconceptions about the capabilities of the vaccines (some recipients expect them to prevent all respiratory infections during winter months), and unanswered questions about their efficacy in high-risk populations have led many providers to conclude that vaccination against influenza is not worth the effort. Attempts to alter this picture have focused principally on the development of attenuated live virus vaccines to replace the current inactivated virus products. Improvement of subunit vaccines is possible, and other potential approaches (not considered here) include synthetic viral peptides and viral neuraminidase vaccines. It is hoped that vaccines that provide longer lasting immunity will lead to improved utilization; however, antigenic drift and antigenic shift of the viruses, described below, may still necessitate periodic revaccination.

Disease Description

Influenza viruses cause both upper and lower respiratory tract symptoms, including nasal congestion, sore throat, hoarseness, and cough. Systemic symptoms such as fever, muscle aches and pains, and malaise may be the primary symptoms initially, but the respiratory symptoms usually predominate as the disease progresses (Davenport, 1982). Patients often develop a hacking cough with coryza, sore throat, and hoarseness; but some individuals may be asymptomatic or exhibit only mild symptoms. The disease typically runs its course in about a week, but the cough and weakness might last for several weeks, and pneumonia and death can occur.

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An uncommon but devastating condition associated with influenza is Reye's syndrome (Sullivan-Bolyai and Corey, 1981).

The clinical syndromes of influenza A and B often are not distinguishable; however, influenza B is less often associated with the excess morbidity and mortality that may accompany outbreaks of influenza A infections (Davenport, 1982). Characteristically, influenza outbreaks occur during the winter months. They may be limited to small communities or spread to cause epidemics in several states, throughout the nation, or throughout the world (pandemics). During epidemics of influenza A infection, respiratory tract infections in a community tend to be overwhelmed by the presence of influenza and almost all cases of diagnosed viral respiratory tract illness can be associated with influenza virus. This rapid spread presents a significant practical problem for those attempting to design appropriate vaccination programs.

Pathogen Description

Influenza virions are spherical particles containing a nucleocapsid with segmented pieces of single-stranded RNA. The surface membrane contains two major glycoproteins, hemagglutinin and neuraminidase, which are also the antigens important for immunization.

The key problem facing public health authorities in terms of influenza control is that the surface antigens on influenza A viruses change frequently. This is true of both hemagglutinin and neuraminidase. When the antigenic changes are so great that the virus is no longer recognized by antisera raised against earlier strains, the antigens are said to have undergone "shift." This has occurred with influenza A viruses several times in the past few decades (Davenport, 1982). In intervening years, a more limited "drift" has occurred, associated with less striking changes in the amino acid sequences of the surface glycoproteins. Influenza B viruses undergo less frequent changes, which are characterized as "drift" rather than "shift" to antigenically new subtypes (Davenport, 1982). The viruses can be grown easily in embryonated eggs, which have been the source of the inactivated vaccine for the past four decades. Growth of the viruses in several cell culture systems is possible.

The Host immune Response

Infection with influenza viruses induces antibody and cell-mediated immune responses. The exact duration of these responses and the degree of protection they afford following primary infection is not certain, because the viruses change their surface antigens with such great frequency. Repeated infections have been demonstrated even with one subtype (Sigel et al., 1950). Protection against homologous virus challenge can be quite lasting, however (Davenport, 1982). The virus that caused the 1977 "Russian Flu" epidemic was identical to an H1N1 type that circulated first in 1950. Individuals who had experienced infection in the 1950s were resistant against the later challenge

(Beare, 1982; Couch and Kasel, 1983). One caution in interpreting this information as a sign of life-long protection against homologous influenza virus challenge is that the "Russian Flu" virus appeared to cause less morbidity and mortality than is usually associated with influenza A virus infections.

The relationship between the influenza virus and the host immune response is of great scientific interest. Much is known about the influenza hemagglutinin, including its three dimensional structure, its primary amino acid sequence, and the nature of the four antigenic regions or epitopes on the HA1 portion of the molecule. Less is known about the factors that elicit the cellular immune response to influenza infection. The identity of the cross-reactive antigen(s) responsible for stimulating HLA-restricted human lymphocytes to become cytotoxic in individuals who have had a previous influenza infection remains a mystery. This cross-reactive antigen is not recognized in serologic testing of antibodies. The contribution of the cellular immune response to resistance against challenge is not clear, but several laboratory studies suggest that it is an important part of the host response during recovery from influenza pneumonia (Couch and Kasel, 1983).

Magnitude of Disease Burden

Influenza A infections are a predictable cause of excess mortality. Mortality is usually highest when a new strain emerges: in 1957, the Asian strain caused an estimated 70,000 deaths in the United States; the Hong Kong virus that appeared in 1968 caused about 30,000 deaths. Even in years not associated with an antigenic shift, many Americans die as a result of influenza infection, in addition, the days lost from school and work, and the hospitalizations required for complications result in a very high cost of influenza to our society (Office of Technology Assessment, 1981).

Influenza B infections characteristically occur in younger individuals, and are less often associated with excess mortality (Davenport, 1982), but more frequently associated with Reye's syndrome, than the A strain (Luscombe et al., 1980). In recent years, however, mortality has been associated with some well-documented outbreaks of influenza B, especially among high-risk individuals, such as elderly residents of nursing homes.

Despite the importance of influenza infection as a cause of morbidity and mortality, very little data exist from which estimates of the influenza disease burden, in the format used in this study, can be made. The difficulty in developing accurate information arises from a variety of sources: many episodes of illness may not come to medical attention; a specific diagnosis of influenza may not be made; the disease is not reportable; outbreaks and epidemics may occur only in some areas or regions or at different times; and many of the hospitalizations or deaths actually due to influenza infection may be attributed to other causes. Problems with the methods described below

by which estimates were made are further discussed under the Uncertainty in the Disease Burden.

The best source of information on which to base disease burden estimates appears to be the surveillance data developed by Glezen and his associates over the past ten years (Glezen, et al., 1982; Glezen et al., 1984a,b). Descriptions of the methods used in their surveillance program and summaries of their data have been published (Glezen, 1982; Glezen et al., 1982; Glezen et al., 1984b). Certain observations have been constant and are particularly relevant for this report. The peak occurrence of acute respiratory disease (ARD) that causes individuals to seek medical care has coincided with the peak of influenza virus activity in each respiratory disease season. The peak occurrence of ARD hospitalizations of persons five years or older has consistently lagged one week behind the peak of influenza virus activity, and an increase in deaths attributed to pneumonia and/or influenza has peaked each year two weeks after maximum influenza virus activity. These observations have remained constant irrespective of when the influenza outbreak occurred. During the outbreaks, laboratory-confirmed influenza infections were the overwhelming cause of acute respiratory disease.

Age-specific totals for mild illnesses associated with influenza virus infection can be calculated by applying incidence rates derived from the Houston Family Study (1976–1981) to U.S. population figures (Glezen, personal communication, 1984; Glezen et al., 1984a). The results appear in Table K.1. These cases fall into Morbidity Category A; they cause relatively mild acute respiratory disease that lasts for about three days. The total number of illnesses represents an average annual attack rate of about 20 percent.

A rough estimate of influenza-associated illness receiving medical attention can be derived from the rate of visits to a Houston health maintenance organization during an influenza epidemic. The numbers

TABLE K.1 Estimated Annual Number of Illnesses Associated with Influenza virus Infection in the United States, Based on Rates From the Houston Family Study, 1976–1981

Age (years)	U.S. Population Estimates (1984)	Rate/100 Person-Years	Number of Illnesses
Under 1	3,733,808	26.4	985,725
1-4	14,496,682	37.1	5,379,011
5-14	33,514,883	37.5	12,568,081
15-24	40,364,883	21.8	8,799,545
25-59	105,461,505	15.3	16,135,610
60 and over	38,842,615	10.0[a]	3,884,262

[a]Assumed value; no data available from Houston Family Study.

TABLE K.2 Estimated Number of Visits per Year for Medical Care for Acute Respiratory Disease (ARD) in the United States, Based on ARD Visits to an HMO in Houston in 1981–1982

Age (years)	U.S. Population Estimates (1984)	Rate/100 Persons	Number of Visits
Under 1	3,733,808	41.2	1,538,329
1-4	14,498,682	26.8	3,885,647
5-14	33,514,883	12.4	4,155,846
15-24	40,364,883	7.0	2,825,542
25-59	105,461,505	8.7	9,175,151
60 and over	38,842,615	5.0[a]	1,942,131

Note: Visits were made during the period of influenza activity.

[a]Assumed rate; data not available from Houston HMO.

resulting from application of these rates to the U.S. population are shown in Table K.2. The rates shown in Table K.2 were derived during a ten-week influenza epidemic (1981–1982) and hence may be higher than the average for all years; however, some persons may be equally ill without seeking medical contact. The numbers in Table K.2 have been judged, therefore, to be reasonable approximations of the average annual number of cases in Morbidity Category B. The total number of illnesses estimated for Category B represents an average annual attack rate of about 10 percent for illnesses causing moderate restriction of activity.

The number of hospitalizations is estimated on the basis of data from the 1980–1981 epidemic, which had the median rate during the seven years of the study (Glezen et al., 1984a). The survey involved acute general care hospitals with 40 percent of the hospital beds in the study area, and excluded patients who were not residents. The results of the survey are shown in Table K.3; application of the rates to the U.S. population (1984) are shown in Table K.4. Rates in Table K.3 are adjusted to accommodate the one-week lag in hospitalizations mentioned above, and are therefore higher than those reported elsewhere (Glezen et al., 1984b).

Deaths from ARD (pneumonia and influenza: during the influenza virus activity period these are presumed to be due overwhelmingly to influenza) also are shown in Table K.4; they are based on a survey of death certificates (Glezen et al., 1982). It should be noted that about 40 percent of pneumonia and influenza (P-I) deaths occur in nursing homes and other non-hospital settings. The total number of P-I deaths estimated from the Houston study (about 34,500) is many times greater than the average number of estimated excess deaths nationally (about 4,600; Centers for Disease Control, 1982). Detection of excess P-I deaths at the national level depends on the simultaneous occurrence

TABLE K.3 Estimated Rate of Hospitalization of Persons with Acute Respiratory Disease, by Age, During the Influenza A/Bangkok-A/England Epidemic, Harris County, Texas, November 30, 1980—February 21, 1981

Age (years)	Population (4/1/80)	Hospitalized	
		Number	Rate[a]
Under 1	44,947	334	73.4
1-4	157,216	557	35.4
5-10	607,232	311	5.1
20-44	1,056,416	756	7.1
45-54	228,154	302	13.2
55-64	160,501	304	18.0
65 and over	147,081	867	58.9

Source: Glezen et al., 1982; Glezen et al., 1984b.

[a]Per 10,000 persons.

of relatively intense outbreaks in many areas of the country. The rarity of this occurrence and underreporting may account for part of the discrepancy. Ascertainment of P-I as a contributor to death may also have been better in the Houston study. The true number of excess deaths attributable to influenza is estimated to average about 20,000 (Centers for Disease Control, 1982).

Estimates calculated in the upper portion of Table K.4 are shown redistributed among age groups used in this report in the lower portion of the table. The redistribution assumes that hospitalizations and deaths were evenly distributed within each age group in the upper column, e.g., that half of the hospitalizations in the 55 to 64 years age group occurred in individuals 60 to 64. These were added to the number in the 65 years and over group to derive a total for the 60 years and over age group in this report. The number of Reye's syndrome cases arising from prodromal influenza must be added to the hospitalization and death estimates. For this report, the estimated number of cases of Reye's syndrome is assumed to be the midpoint (900) in the range (600–1,200) estimated by the Centers for Disease Control (Hurwitz, 1983, personal communication). All Reye's cases are assumed to occur in age groups under 15 years. Twenty-five percent of Reye's cases can be attributed to prodromal varicella and 65 percent to acute respiratory illness (90 percent of which is influenza); hence, about 58.5 percent of Reye's cases result from prodromal influenza.

TABLE K.4 Estimated Number of Hospitalizations for Acute Respiratory Disease in the U.S. During the Influenza A/Bangkok-A/England Epidemic of 1980–1981, Based on Rates from a Hospital Survey in Houston, Texas

Age (years)	Estimated U.S. Population (1981)	Hospitalization Rate/ 10,000 Persons[a]	Number of Hospitalizations	Number of Deaths[b]
Under 1	3,591,000	73.4	26,358	79
1-4	13,348,000	35.4	47,252	334
5-19	54,665,000	5.1	27,879	300
20-44	86,984,000	7.1	61,759	2,175
45-54	22,529,000	13.2	29,738	4,802
55-64	21,396,000	18.0	39,485	
65 and over	26,255,000	58.9	154,642	26,780
5-14			18,584	200
15-24			21,654	535
25-59			98,993	5,340
60 and over			174,384	27,980

Note: See text for sources.

[a]Age-specific rates found in Houston.
[b]Pneumonia and influenza deaths (Glezen et al., 1982; Glezen et al., 1984b).

The age distribution of Reye's cases following influenza and varicella is assumed to follow the distribution for typical cases of those diseases among the age groups under 15 years (i.e., influenza, under one year, 2.5 percent; 1–4 years, 29 percent; 5–14 years, 68 percent). Irrespective of type of prodromal illness, the case/ fatality ratios for Reye's cases are assumed to be as follows: less than one year, 35 percent; 1–4 years, 25 percent; 5–14 years, 25 percent. All Reye's syndrome cases initially fall into Morbidity Category C.

Adoption of these assumptions yields the following:

Total annual number of Reye's syndrome cases=900

Cases attributable to influenza 900×0.585=527

Cases of Reye's syndrome due to influenza (all cases require hospitalization):

Less than 1 year = 13 (2.5 percent)
1-4 years = 155 (29 percent)
5-14 years = 358 (68 percent)

Deaths attributable to Reye's/Influenza:

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35 percent case fatality rate for less than 1 year =  5
25 percent case fatality rate for 1-4 years        = 39
25 percent case fatality rate for 5-14 years       = 90
```

To derive the total disease burden from influenza (Table K.6), these numbers for Reye's syndrome are added to the totals derived for hospitalizations and deaths (arising from acute respiratory influenza illness, Table K.4) to calculate the numbers of cases of chronic disability. Data reported by Sullivan-Bolyai and Corey (1981) indicate that 48 percent of cases of Reye's syndrome suffer mild to severe chronic neuropsychological problems (e.g., mental retardation, cranial nerve palsies, or motor dysfunction). Half of these cases are judged to fall into Morbidity Category D and half into Morbidity Category E. The numbers of cases of chronic disability resulting from Reye's syndrome are shown in Table K.5.

A summary of the disease burden arising from influenza viruses A and B is shown in Table K.6.

Uncertainty in the Disease Burden Estimates

The problems associated with making reliable estimates of the average annual number of cases of illness due to influenza viruses arise from both the nature of the disease and the paucity of sources of data. Antigenic drift and shift result in new strains, which have different virulence and attack rates in different age groups; this makes averaging problematic. Epidemics may be limited to local communities, so national estimates extrapolated from one data source may be unreliable.

The Houston study was selected from which to derive estimates as the largest continuous data resource. Few if any other sources provide such a long term population based data set (Davenport, 1982). Alternative studies from which estimates of illness in Categories A and B could possibly have been derived (Monto and Kioumehr, 1975) suggest that the rates (and numbers of cases) in these categories may be toward the high end of the observed range. In general, however, numbers of cases estimated from the Houston study are judged reasonable; inaccuracy introduced by the above noted problems in Categories A and B is probably minor because contributions to the total disease burden values by these categories are small. The assumption that all acute respiratory disease during the peak influenza season is caused by influenza virus may not be totally accurate especially for children when respiratory syncytial virus may cause similar symptoms.

The purpose of tabulation of excess deaths is to alert health care providers to the occurrence of epidemic influenza (and not to facilitate estimates of the disease burden in the form needed for this project). Excess death figures by definition do not include normally occurring mortality; also, epidemics may not occur synchronously across the nation.

TABLE K.5 Chronic Disability Resulting From Reye's Syndro

Age Group (years)	Number of Cases	
	Morbidity Category D	Morbidity Category E
Under 1	3	3
1-4	37	37
5-14	86	86
Total	126	126

The estimates included in Table K.6 are considered adequate for the purposes of this comparison, but may differ from true incidence figures for the reasons noted above.

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described in Chapter 4, Total disease burden values (TDBVs) for influenza A and B are calculated using estimates from Table K.1 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. The TDBVs for influenza A and B are 22,373 (committee median perspective) and 36,410 (age-neutral perspective).

Vaccine Target Population

The immunization Practices Advisory Committee of the Centers for Disease Control (CDC) traditionally has recommended the annual administration of inactivated influenza vaccines to individuals whose health status places them at greater than average risk of developing the complications of influenza infection (Centers for Disease Control, 1984). This usually includes all persons over age 65. Targeted vaccination effort is not recommended on a routine basis for healthy children or young adults, except for those in certain occupational groups: for example, health care personnel who have extensive contact with high-risk individuals and military recruits. Children with cystic fibrosis, congenital heart disease, and other chronic diseases are advised to receive the vaccine. It is recommended that physicians should administer vaccine to any person who wishes to reduce their chances of acquiring influenza infection. In this regard it is worth noting that infection of schoolchildren appears to be the most common form of transmission of the influenza virus (Davenport, 1982).

When a significant change in the major surface antigens of an influenza A virus is detected or when a new strain is isolated (such as

TABLE K.6 Disease Burden Sunroary: Influenza Viruses A & B

Morbidity Category	Description	Condition[a]	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities		985,725	3	5,379,011	3	12,568,081	3	8,799,545	3	16,135,810	3	3,884,262	3
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed		1,538,329	5	3,885,647	5	4,155,846	5	2,825,542	5	9,175,151	5	1,942,131	5
C	Requiring hospitalization		26,371	7	67,407	7	18,942	7	21,654	7	98,993	14	174,384	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)		3	n.a.	37	n.a.	86	n.a.						
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)		3	n.a.	37	n.a.	86	n.a.						
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		84	n.a.	373	n.a.	290	n.a.	535	n.a.	5,340	n.a.	27,980	n.a.

Note: n.a.=not applicable.

[a]See text and tables K.1 through K.5.

that causing the "Asian" influenza), the population at large is considered more susceptible than usual to infection. In these cases, vaccination may be recommended for all persons except those who have conditions contraindicating vaccination. High-risk groups continue to have high priority, however.

If reliable evidence is forthcoming that an attenuated live influenza virus might reduce disease transmission within the population then reconsideration of the current high-priority target population may be desirable (to include other groups, e.g. schoolchildren). However, for the purposes of this evaluation, the current target populations have been adopted. This may underestimate the impact of vaccines if broader target populations are ultimately chosen.

Suitability for Vaccine Control

Protection offered by current vaccines is limited in duration and by the antigenic shift and drift that occur in influenza strains. Thus, the vaccine needs to be reformulated and administered annually to match prevalent strains of virus. While antigenic shift and drift complicate vaccine control of influenza, the potential for epidemic spread and the dearth of prophylactic or therapeutic agents for the disease render vaccine prevention a desirable goal, particularly in view of the disease burden and the prospect that live vaccines might offer longer protection.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the benefits that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

The determination of VPI is complicated for influenza by lack of data on what proportion of illness actually falls within the target population. As noted above, the Immunization Practices Advisory Committee (IPAC) of the CDC recommends the administration of influenza vaccine to individuals whose health status places them at high risk (Centers for Disease Control, 1984). All individuals over age 65 are included in this definition, so all illness in that population is considered vaccine preventable, but no data exist on influenza-related illness in high-risk persons under age 65. To overcome this difficulty, the committee adopted figures from Glezen (personal communication, 1984), indicating the proportion of patients hospitalized for ARD whose discharge records describe relevant high-risk conditions listed by IPAC (see Table K.7). Unfortunately, there is no way to determine whether or not these chronic conditions were known to the individuals or their physicians prior to hospitalization.

TABLE K.7 Proportion of Patients Hospitalized for Acute Respiratory Disease Whose Discharge Records Describe High-Risk Conditions Associated With Influenza Complications

Age (years)	Percentage With IPAC High-Risk Conditions
Under 1	20.8
1–4	8.3
5–9	20.2
10–14	18.5
15–19	19.0
20–24	14.1
25–34	14.3
35–44	25.5
45–54	36.1
55–64	55.4
65 and over	60.1

Note: Conditions described by the Immunization Practices Advisory Committee (IPAC) of the Centers for Disease Control as those placing individuals at high risk of influenza complications.

For this report, it is assumed that that half of patients under age 60 whose hospital discharge records describe an IPAC chronic (high-risk) condition would be recognized in advance as needing vaccination. Thus, the following percentages of all influenza hospitalizations (from Table K.6) are considered potentially vaccine preventable: under 1 year, 10 percent; 1–4 years, 4 percent; 5–14 years, 10 percent; 15–24 years, 5 percent; 25–59 years, 11 percent. These proportions also are considered to apply to deaths and episodes falling into Morbidity Categories A and B.

Estimation of the number of cases of vaccine preventable illness in the 60 years and over age group is complex. Part of this group (i.e., those over 65) are automatically included in the vaccine target population; however, for individuals 60–64 years, inclusion in the target population depends on the presence of chronic medical conditions indicative of high risk.

Data published by Glezen and his coworkers (Glezen et al., 1982; Glezen et al., 1984b) indicated the numbers of hospitalizations and deaths that occurred in the 60–64 years portion of the 60 years and over age group, but not the number of illness episodes falling into Morbidity Categories A and B.

Of the 27,980 deaths in the 60 years and over age group, 1,200 (4 percent) occurred in the 60–64 years portion; of the 174,384 hospitalizations, 19,743 (11 percent) occurred in the 60–64 years portion. On the same basis as described above, it was judged that (from Table K.7) 27 percent of the hospitalizations and deaths in the 60–64 years portion and 100 percent of these events occurring in the 65 years and over group were potentially vaccine preventable.

To calculate the proportion of non-hospitalized illnesses in the 60–64 years portion of the 60 years and over age group, a percentage of 7.5 (half way between that for hospitalizations and deaths) was adopted. Use of this percentage yields an estimated 291,320 Category A episodes and 145,000 Category B episodes occurring in the 60–64 years portion of the 60 and over age group. Twenty-seven percent of these episodes are considered vaccine preventable, along with 100 percent of the episodes occurring in individuals 65 and older.

Table K.8 shows the vaccine preventable illness estimates for influenza A and B.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Total vaccine preventable illness values for influenza A and B are calculated using estimates from Table K.6 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the total vaccine preventable illness value for influenza A and B is 10,644; with the age-neutral perspective the value is 28,225.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by the influenza A and B vaccine candidates, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of the vaccine. For both the subunit and live attenuated vaccines, the predicted efficacy is 0.85. The potential reduction in morbidity and mortality for the influenza A and B vaccines is 9,048 using the committee median perspective and 23,991 using the age-neutral perspective.

Prospects for Vaccine Development

Francis et al. (1944), Mawson and Swan (1943), and Salk et al. (1944) were the earliest investigators to report on the production of attenuated influenza virus strains through the use of serial passage. These efforts and the subsequent history of attenuated live influenza virus vaccine research have been reviewed by Stuart-Harris (1980).

TABLE K.8 Vaccine Preventable Illness: Influenza Viruses A & B

Morbidity Category	Description	Condition[a]	Under 1 Year		1–4 Years		5–14 Years		15–24 Years		25–59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities		98,573	3	215,160	3	1,256,808	3	439,977	3	1,774,917	3	3,671,598	3
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed		153,833	5	155,426	5	415,585	5	141,277	5	1,009,267	5	1,835,799	5
C	Requiring hospitalization		2,637	7	1,896	7	1,894	7	1,089	7	10,889	14	159,973	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)		b	n.a.	2	n.a.	9	n.a.						
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)		b	n.a.	2	n.a.	9	n.a.						
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		8	n.a.	15	n.a.	29	n.a.	27	n.a.	587	n.a.	27,104	n.a.

[a]See text and tables K.1 through K.7.
[b]Less than one case, so aggregated with those in 1–4 years age group.

Soviet research on attenuated live virus vaccines began in earnest in the 1950s and has continued; such vaccines are widely used in the U.S.S.R. (Stuart-Harris, 1980).

After the ease with which genetic exchange between influenza viruses (reassortment) could occur was recognized, the use of donor viruses to confer the attenuated phenotype to wild-type viruses was pursued. Host-range mutants, cold-adapted mutants and temperature-sensitive mutants were investigated during the late 1960s and 1970s (Stuart-Harris, 1980).

Some recent work has focused on specific donor-attenuated strains with identifiable genetic lesions that can be transferred to new strains as they emerge. Chanock, at the National institutes of Health, Bethesda, Md., and his associates have been responsible for much of the progress in this area (Stuart-Harris, 1980). One of the major accomplishments has been development of a temperature-sensitive (TS) donor strain that grows in the upper respiratory tract but not in the warmer environment of the lower respiratory tract (Chanock and Murphy, 1979; Stuart-Harris, 1980).

Initial trials of vaccines using this technique were successful in adults but not in children. The vaccine contained live influenza viruses with internal antigens derived from the attenuated parent TS virus and surface hemagglutinin and neuraminidase derived from the wild virus. This combination was antigenic with little reactivity in adults, but when it was given to children and young infants (who had no antibodies to either the hemagglutinin or the neuraminidase of the wild virus) the vaccine viruses underwent limited replication and some TS viruses apparently reverted to the wild (TS^+) phenotype (Chanock and Murphy, 1979; Stuart-Harris, 1980). Most work on $TS^•$ mutants has been conducted with influenza virus A.

A promising variation of this approach has been to use a cold-adapted donor virus initally developed by Maassab et al. (1969). A series of clinical studies have shown that live vaccines developed using the cold-adapted strain as a donor are stable and act appropriately in transferring genetic traits to other influenza A or B viruses (Davenport et al., 1977). In studies of healthy adults and children, bivalent vaccines have protected against subsequent natural challenge (LaMontagne et al., 1983). The current status of this cold-adapted vaccine candidate suggests that it could become available in several years.

An alternative approach is to improve the current inactivated influenza vaccines. The technology is available to prepare a more purified vaccine containing hemagglutinin and neuraminidase (Frank et al., 1981).

Although the side effects from purified preparations theoretically might be fewer than those from the disrupted vaccines that contain materials in addition to hemagglutinin and neuraminidase, it will be very difficult to show any decrease in reactivity. This belief is based on large clinical studies performed in adults and children in 1976 and 1978, when the A/New Jersey and the A/Russian vaccines were used (LaMontagne, 1983; Seal, 1977). In addition, although it may be possible to give much larger doses of hemagglutinin in a more purified,

less reactogenic vaccine, dose response studies suggest that increasing the hemagglutinin content to a much higher level would produce only a small increase in antibody response.

The committee considers the probability that either a more purified hemagglutinin and neuraminidase vaccine or a live attenuated cold-adapted vaccine could be developed successfully to be very high, with a 90 percent probability of success within three to four years. If the vaccines contain the relevant antigens of the (natural) challenge viruses, their efficacy probably will be about 85 percent. Inactivated vaccine will have to be given annually. Until more data have been collected to demonstrate that a live attenuated vaccine protects against drift for periods longer than one year, annual administration probably will be required for this type of vaccine also.

The National Institute of Allergy and infectious Diseases (NIAID) has supported the development of the cold-adapted live attenuated influenza virus up to the point of large scale clinical trials. No similar attempt has been made to develop a more purified hemagglutinin and neuraminidase inactivated preparation. The cost of clinical trials for influenza vaccines is large. Efficacy studies are complicated by the unpredictability of the challenge (circulating) virus. A population might be immunized with an experimental vaccine in a year in which no natural influenza outbreak occurs. This is a generic problem for all natural challenge studies in vaccine recipients, but is more problematic with influenza vaccines than with others.

Another practical problem associated with the live attenuated vaccine is the intranasal route of administration. Clinical researchers also may have difficulty demonstrating that the vaccine is safe and effective for high-risk patients, e.g., those with severe lung disease. One of the primary concerns expressed about current vaccines is the relative lack of data demonstrating their consistent efficacy in high-risk populations. Most efficacy studies have been performed in healthy young adults. If future vaccines are shown to be more effective for high-risk groups than current vaccines, they probably will be accepted more widely by both providers and the lay public.

As summarized above, the major effort to develop new influenza vaccines has been at the NIAID. It appears that the pharmaceutical industry does not anticipate widespread use and acceptability of a live attenuated vaccine in the near future. Members of the committee are not aware of any major commercial efforts in this field.

Predictions on the further development of vaccines for influenza A and B appear in Chapter 5.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, in which scores assigned to various vaccines are displayed together for comparison.

Lay Acceptance

Influenza vaccine is one of the least effectively utilized vaccines, perhaps because the perception of vaccination benefits is low and perceived barriers are numerous. Lay perception of the risk of contracting influenza probably is high because of the tendency to confuse the disease with other acute respiratory diseases. The perception of severity is judged to be only moderate, because most people are not familiar with the disease course in high-risk populations.

There are many perceived barriers, especially among high-risk groups for whom annual vaccination is strongly recommended. Some of the resistance stems from the side effects associated with vaccines that were used widely in the past. Another problem is the mistaken concept that influenza vaccines should prevent all winter respiratory tract illnesses. Any acute illness that is experienced in the winter following receipt of an influenza vaccine may be attributed to vaccine failure. In fact, there are other acute virus infections that cause illness in all members of the community, including those vaccinated against influenza.

One probable barrier specific to the new, live attenuated vaccine would be route of administration. People in this country are not familiar with the use of nasal drops of a live attenuated influenza virus. This concern could become problematic if recipients were to develop unrelated respiratory tract infections after vaccination via the intranasal route. They might attribute the respiratory tract illness to the administration of the vaccine. Although prelicensure clinical studies would reduce the likelihood of this complication to almost zero, recipient and provider fears on this topic might persist.

Provider Acceptance

The major stumbling blocks to lay acceptance of a new influenza vaccine also apply to provider acceptance. Many physicians feel that current vaccines are not worth the effort. The low utilization of vaccine was aggravated at least for a short time by the association of Guillain-Barré syndrome with the A/New Jersey (swine-flu) vaccine. Fortunately, this association has not been found in subsequent years.

Cost of illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden

Category A

\# of cases = 47,752,234

approx. 50% of cases receive medication at $5 [OTC* medication]		= $ 119,381,000
	TOTAL (A)	= $ 119,381,000

Category B

\# of cases = 23,522,646

approx. 33% of cases receive 1 phys. visit at $30	= $ 232,874,000
approx. 20% of cases under 60 years (21,580,515 total) receive diagnostic chest x-ray at $55	= $ 237,386,000
approx. 50% of cases 60 years and above (1,942,131 total) receive diagnostic chest x-ray at $55	= $ 53,409,000
approx. 50% of total cases receive treatment/ medication at $10 [OTC medication]	= $ 117,613,000
approx. 20% of total cases receive 1 additional phys. visit at $30 [bacterial otitis or sinusitis; mild pneumonia]	= $ 141,136,000
TOTAL (B)	= $ 782,418,000

Category C

total # of cases = 387,751

25 and over age groups

\# of cases = 273,377

100% of cases typically receive 14 days of normal hospitalization at $400/day	= $1,530,911,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 14 days at $400	= $1,530,911,000
100% of cases typically receive 1 follow-up phys. visit at $30	= $ 8,201,000
TOTAL	= $3,070,023,000

*Over the counter.

24 years and under age groups		
# of cases = 113,848		
100% of cases typically receive 7 days normal hospitalization at $400/day		= $ 318,774,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 7 days at $400		= $ 318,774,000
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 3,415,000
	TOTAL	= $ 640,963,000
Reye's syndrome		
# of cases = 526		
100% of cases typically receive 3 days ICU at $600/day		= $ 947,000
100% of cases typically receive 3 additional days normal hospitalization at $400/day		= $ 631,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate		
3 days at $600/day		= $ 947,000
3 days at $400/day		= $ 631,000
100% of Reye's cases typically receive 2 follow-up physician visits at $30/each		= $ 32,000
	TOTAL	= $ 3,188,000
	TOTAL (C)	= $3,714,174,000
[approx. 48% of Reye's cases have chronic sequelae and are split between Categories D and E; Sullivan-Bolyai and Corey, 1981]		
Category D - assuming normal lifetime duration		
# of cases = 126		
total annual costs for treatment and/or care = $2,000/case; for 63* years duration total present value/case = $40,000		= $ 5,040,000
	TOTAL (D)	= $ 5,040,000
Category E - assuming lifetime duration 75% of normal		
# of cases = 126		
total annual costs for treatment and/or care = $5,000/case; for 46* years duration total present value/case = $94,000		= $ 11,844,000
	TOTAL (E)	= $ 11,844,000
	TOTAL COST	= $4,632,857,000

*Assuming normal lifetime duration of 70 years and approximate weighted average age of onset at 7 years.

Total Cost of Vaccine Preventable Illness

Category A		
# of cases = 7,457,033		
approx. 50% of cases receive medication at $5 [OTC medication]		= $ 18,643,000
	TOTAL (A)	= $ 18,643,000
Category B		
# of cases = 3,711,187		
approx. 33% of cases receive 1 phys. visit at $30		= $ 36,741,000
approx. 20% of cases under 60 years (1,875,388 total) receive diagnostic chest x-ray at $55		= $ 20,629,000
approx. 50% of cases 60 years and above (1,835,799 total) receive diagnostic chest x-ray at $55		= $ 50,484,000
approx. 50% of total cases receive treatment/ medication at $10 [OTC medication]		= $ 18,556,000
approx. 20% of total cases receive 1 additional phys. visit at $30 [bacterial otitis or sinusitis; mild pneumonia]		= $ 22,267,000
	TOTAL (B)	= $ 148,677,000
Category C		
total # of cases = 178,372		
25 and over age groups		
# of cases = 170,862		
100% of cases typically receive 14 days of normal hospitalization at $400/day		= $ 956,827,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 14 days at $400		= $ 956,827,000
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 5,126,000
	TOTAL	= $1,918,780,000
24 years and under age groups		
# of cases = 7,457		
100% of cases typically receive 7 days normal hospitalization at $400/day		= $ 20,880,000

100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 7 days at $400		= $ 20,880,000
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 224,000
	TOTAL	= $ 41,984,000
Reye's syndrome		
# of cases = 53		
100% of cases typically receive 3 days ICU at $600/day		= $ 95,000
100% of cases typically receive 3 additional days normal hospitalization at $400/day		= $ 64,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate		
3 days at $600/day		= $ 95,000
3 days at $400/day		= $ 64,000
100% of Reye's cases typically receive 2 follow-up physician visits at $30/each		= $ 3,000
	TOTAL	= $ 321,000
	TOTAL (C)	= $1,961,085,000
[approx. 48% of Reye's cases have chronic sequelae and are split between Categories D and E; Sullivan-Bolyai and Corey, 1981]		
Category D - assuming normal lifetime duration		
# of cases = 11		
total annual costs for treatment and/or care = $2,000/case; for 63* years duration total present value/case = $40,000		= $ 440,000
	TOTAL (D)	= $ 440,000
Category E - assuming lifetime duration 75% of normal		
# of cases = 11		
total annual costs for treatment and/or care = $5,000/case; for 46* years duration total present value/case = $94,000		= $ 1,034,000
	TOTAL (E)	= $ 1,034,000
	TOTAL COST	= $2,129,879,000

*Assuming normal lifetime duration of 70 years and approximate weighted average age of onset at 7 years.

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Appendix

L

PROSPECTS FOR IMMUNIZING AGAINST NEISSERIA GONORRHOEAE

Gonorrhea is the most commonly reported infectious disease in the United States. A typical case in males involves urethral discharge and dysuria, but in females the initial infection may be asymptomatic or produce nonspecific symptoms. Women with gonorrhea may develop pelvic inflammatory disease (including salpingitis). This infection of the pelvic organs may result in ectopic pregnancy or infertility. Epididymitis, bacterial endocarditis, disseminated gonococcal infection, septic arthritis, and ophthalmia neonatorum are rarer complications of the disease (Weisner and Thompson, 1982).

The increasing antibiotic resistance of N. gonorrhoeae is a source of growing concern and a consideration in the effort to develop an effective vaccine.

Pathogen Description

Capsule

In the 1970s, several researchers reported the discovery of a gonococcal polysaccharide capsule (Hendley et al., 1977; James and Swanson, 1977; Richardson and Sadoff, 1977). All of these reports were based primarily on morphological criteria, however, and a polysaccharide capsule has yet to be isolated. Most investigators now doubt the existence of a pneumococcal- or meningococcal-like capsule on the gonococcus. It is possible that the much greater severity of meningococcemia as compared to gonococcemia is due to the lack of a capsule on the gonococcus.

Recently, Noegel and Gotschlich (1983) carefully documented the presence of a polyphosphate surface layer on all Neisseria, including gonococci. The pathogenic Neisseria seems to have more abundant

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surface polyphosphate than other Neisseria, but the function and immunogenic potential of this surface polyphosphate are unknown.

Pili

Gonococcal pili (fimbriae) are important in mediating attachment to specific mucosal cells and in resisting ingestion by neutrophils. Polyclonal anti-pilus antibodies raised to whole purified pili block adherence of the homologous (but not heterologous) strain to fallopian tube mucosa (McGee, personal communication, 1984) and erythrocytes (Buchanan and Pearce, 1976), and are opsonic (Siegel et al., 1982). Polyclonal antipilus antibodies also block attachment to human buccal, vaginal, and cervical cells (Tramont, 1977). Unfortunately, gonococcal pili are antigenically heterogeneous in different strains, and in different isolates of a single strain. Brinton found no more than 25 percent shared pilus antigens among 49 of 50 tested clinical isolates (Brinton et al., 1978). Because pilus vaccines have been reported to be effective for certain enteric infections (e.g., E. coli diarrhea in piglets; Brinton et al., 1983), there has been much interest in pili as a gonococcal vaccine candidate. Recent work on pilus vaccines for gonorrhea has been described by Brinton (1984) and Tramont (1984).

Understanding the possible role of pilus antigens in a vaccine requires a more detailed discussion of pilus structure and function. The pilus is made up of repeating units of an approximately 19 Kd subunit. The hydrophilic C-terminal domain (CNBr fragment 3) is chemically and antigenically highly variable, whereas the hydrophobic N-terminal domain (CNBr fragment 1) is common on the small number of stains tested thus far (see Figure L.1) (Schoolnik et al., 1983). The variable C-terminal end is immunodominant: immunization with whole pili results in antibodies directed almost entirely against CNBr3.

Recent studies by several groups have revealed an immunorecessive pilus domain in the middle of the molecule (CNBr fragment 2) that is shared by all those gonococcal pili tested, and that appears to be involved in attachment to red blood cells. Limited data suggest that immunization of animals with isolated CNBr fragment 2 results in antibody that will recognize this common peptide, reducing attachment to red blood cells by all gonococci (Schoolnik et al., 1983). Immunization with whole gonococci or whole pili does not result in antibodies against CNBr2, presumably because CNBr2 is buried within the three-dimensional configuration of the pilus. If a common pilus structure is required to bind to specific mucosal receptors, it clearly would be advantageous for the gonococcus to be able to "hide" this structure, so infection would generate antibodies only against the external variable domain. If this work is substantiated by future efforts, and if the pilus receptor is the same on red blood cells and mucosal cells, it may be possible to utilize CNBr fragment 2 or a related peptide as a broadly effective vaccine.

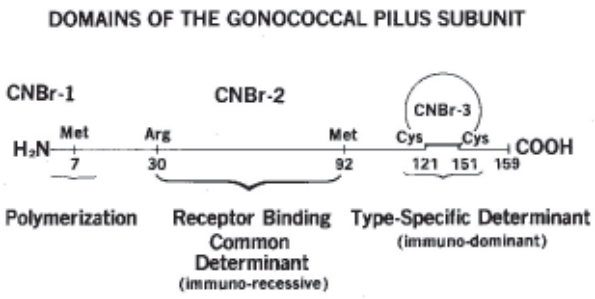

FIGURE L.1 Structure of a repeating unit from the gonococcal pilus. Reprinted with permission from Schoolnik et al., 1983, A pilus peptide vaccine for the prevention of gonorrhea, Prog. Allergy 33:314–331.

Outer Membrane Proteins

Less is known about the role of gonococcal outer membrane proteins in pathogenesis than is known about pili. Several outer membrane proteins are common to all strains, while others are antigenically variable.

Protein I (PI) PI is a 32–36 Kd porin protein that is usually the most numerous of the outer membrane proteins. Peptide mapping studies suggest there are three major families of PI; studies with polyclonal antibodies show that PI can be divided into seven to nine principal serotypes, of which only three to five are common (Buchanan and Hildebrandt, 1981). The role of PI in infection is unclear. Anti-PI antibodies in human convalescent sera are opsonic. Recent preliminary evidence suggests that gonococci may invade eukaryotic cells by inserting PI into the host cell's membrane, possibly triggering endocytosis of gonococci by the host cell (Blake and Gotschlich, 1983; Lynch et al., 1984). Very limited clinical data suggest that anti-PI antibodies may protect against salpingitis: patients with a second episode of gonococcal salpingitis are always infected by a different PI serotype than that observed in the first episode (Buchanan et al., 1980). (Only one study has been reported, however, and the number of patients was small.) PI is considered a possible vaccine candidate.

Protein II (PII) PII consists of a family of related, heat-modifiable outer membrane proteins of 24–30 Kd that appear to be involved in mediating close attachment to mucosal cells. They are interesting because they undergo very high frequency variations of two types: loss-reacquisition ($PII^{\bullet}$ PII^{+}), and antigenic variation (PIIa PIIb PIIe…PIIf).

Gonococci in the PII^{+} phase probably bind better to mucosal cells than $PII^{\bullet}$ gonococci, whereas $PII^{\bullet}$ gonococci apparently are better

able to invade fallopian tubes and the bloodstream. High frequency variations in expression of PII therefore may help the organism by providing a minority population that is well adapted to infection at distant sites. Although many workers are pessimistic about PII as a vaccine candidate because of its antigenic variability, it should not be dismissed until more is known about the structure of its mucosal binding domain.

Protein III (PIII) PIII is a common 30–31 Kd protein (invarient in all strains) of unknown function or vaccine potential.

Protein H.8 (P.H.8) P.H.8, named after monoclonal antibody H.8, is a common heat-modifiable protein of 20–30 Kd found recently on all gonococci and meningococci, but rarely on nonpathogenic Neisseria (Cannon et al., 1984). Earlier studies overlooked this antigen because it stains poorly on SDS-PAGE. Patients convalescing from gonococcal bacteremia or meningococcal meningitis make high titers of anti-P.H.8 (Black and Cannon, personal communication, 1984). The function of P.H.8 in pathogenesis is uncertain. Preliminary data show that vaccination of mice with P.H.8 results in bactericidal anti-gonococcal antibodies and passive transfer of anti-P.H.8 monoclonal antibodies, and protects mice from bacteremia by meningococci of different types (Black and Cannon, personal communication, 1984). There is hope that P.H.8 could be a vaccine candidate, but more information is needed.

Genes for production of pili, PI, and P.H.8 have been cloned in E. coli by recombinant DNA techniques, which could facilitate preparation of vaccine components.

Lipopolysaccharide

Gonococcal lipopolysaccharide (LPS) is a bit unusual because of the apparent absence of a true O-antigenic side chain. Lipopoly-saccharide is the principal toxin for fallopian tubes in tissue culture (Melly et al., 1981). The core polysaccharide probably contains antigenic sites for human bactericidal antibodies. The presence of bactericidal antibodies correlates strongly with protection against gonococcal bacteremia, but apparently does not protect against salpingitis. Lipopolysaccharide or isolated LPS core polysaccharide could be considered a vaccine candidate, but the priority for development of such an antigen will be low unless future work indicates that anti-core polysaecharide might protect against salpingitis.

Other Antigens

IgA1 Protease All gonococci produce one of two types of IgA1 protease that specifically cleave secretory and serum IgA1 at the hinge (Plaut et al., 1975). The role of IgA1 protease in circumvent-

ing mucosal antibody defenses is unclear; the presence of IgA2 and IgG (both resistant to IgA1 protease) in mucosal secretions could overcome the effects of the bacterial IgA1 protease. Lack of a suitable animal model has prevented critical studies of the precise role of IgA1 protease in infection. Antibodies against IgA1 protease conceivably could reduce the effectiveness of this bacterial mechanism for circumventing the host immune system, so IgA1 protease is a possible candidate for inclusion in a multi-component vaccine. IgA1 protease has been cloned into E. coli.

Iron-Repressible Proteins (FeRPs) All gonococci make several new cell surface proteins when grown under conditions of iron starvation (Norqvist et al., 1978). Most studies have ignored these proteins because gonococci have been grown on media with abundant free iron so the proteins were not expressed. In vivo, gonococci probably have to compete with either lactoferrin (on mucosa) or transferrin (in serum) for iron—essentially no free iron is available in humans. One current hypothesis is that FeRPs act as receptors for iron uptake from lactoferrin or transferrin. It is conceivable (but still speculative) that use of FeRPs as antigens in a vaccine could result in antibodies that would block the ability to take up essential iron.

Host Immune Response

Some persons acquire gonococcal infections many times: individuals with repeated episodes of local urogenital infection are not rare. This indicates that gonococci either are not highly antigenic or that they are well equipped by means of antigenic variation or other strategies to circumvent the host response. Evidence that the immune response does have some effect and might prevent reinfection by the homologous isolate comes from the pre-antibiotic era, in which untreated symptomatic infections usually underwent spontaneous cure after an unpleasant period of about two months. However, none of the antibodies found in infected patients have yet been correlated with immunity.

Studies of infection in various animal models have shown that parenteral vaccination with killed whole cells or outer membranes produces an almost 1000-fold increase in protection against homologous rechallenge (Arko et al., 1976). Unfortunately, only one of these models, intraurethral inoculation in chimpanzees, closely resembles the natural infection in humans and it does not display signs and symptoms of the disease. Hence, no satisfactory animal model of disease is available. Most studies have found little evidence of protection against heterologous isolates. The duration of protection in animals is unknown. A single trial of human parenteral vaccination with a killed whole cell vaccine, performed nearly 20 years ago in an Eskimo population, had negative results (Greenberg et al., 1974).

From these observations it appears that a vaccine may be possible, but that its development will depend on a more thorough understanding

of the immunobiology of the organism, including the significance of secretory antibody production (McChesney et al., 1982; Tramont et al., 1980).

Disease Burden

As noted previously, gonorrhea is the most commonly reported infectious disease in the united States. Estimates of the numbers of cases and complications are based on information from Cates (personal communication, 1984), the National Institute of Allergy and infectious Diseases Study Group (1981), and Wiesner and Thompson (1982).

Surveys suggest that physicians report 25 to 50 percent of the gonorrhea cases they treat (Curtis, 1963; Fleming et al., 1970). Thus, the number of cases per year can be calculated as in Table L.1.

The age distribution associated with the estimated 1.7 million infections is assumed to be the same as that found among the reported cases (Table L.2). More than three-quarters of the total number of reported cases (78.4 percent in men and 88.8 percent in women) occur between 15 and 29 years of age.

Add to the 1.7 million cases an estimated 20 percent (335,000) for misdiagnosed infections and the number of new infections becomes about 2.0 million.

Of these new infections, 55 percent are assumed to occur in males and 4.5 percent in females; 95 percent of males and 50 percent of females are assumed to be symptomatic (National Institute of Allergy and infectious Diseases Study Group, 1981). Thus, the number of clinically apparent gonococcal cases per year can be calculated as in Table L.3. Initial symptomatic illness is assumed to fall into Morbidity Category A and last three days; pelvic inflammatory disease (PID) is assumed to fall into Category B and last five days. Morbidity Categories are defined in Table L.4.

Recent reports indicate that about 45 percent of all women with gonorrhea develop PID (Platt et al., 1983). This would result in about 400,000 cases of gonococcal PID (GPID) annually. Studies of the causes of PID (Cates, personal communication, 1984; Falk, 1965; Hedberg and Spetz, 1958; Jacobson and Westrom, 1969; Lip and Burgoyne, 1966; O'Hare

TABLE L.1 Estimated Number of Gonorrhea Infections Annually

Reporting Source	Reported Cases[a]	Underreporting Factor	Treated Cases
Private	238,730	4.0	954,920
Public clinics	721,903		721,903
Total			1,676,823

[a]Cates, personal communication, 1984.

TABLE L.2 Age Distribution of Gonococcal Infections, Gonococcal Pelvic Inflammatory Disease (GPID), and GPID-Hospitalizations

Age (years)	Male	Female
5–14[a]	0.5	2.0
15–24	54.7	73.6
25–59[b]	44.8	24.4

[a]All cases under 15 years are assumed to occur in the 5–15 years age group.
[b]All cases over 25 years are assumed to occur in the 25–59 years age group.

et al., 1980; Rendtorff et al., 1974) suggest that of all PID cases (about 1 million per year), about 40 percent result from gonorrhea. Thus, a similar estimate of GPID (400,000 cases) is obtained using this approach. The rate of complications in non-white women is about twice that found in white women (Blount et al., 1984).

PID causes about 296,000 hospitalizations annually (Washington et al., 1984); 40 percent of these may be assumed to be due to gonorrhea. Thus, the number of hospitalizations for GPID is about 120,000.

One hundred twenty-five deaths from PID were reported to the National Center for Health Statistics in 1978 (1979). Assuming this represents a typical annual rate and that 40 percent are due to GPID, an estimated 50 deaths are due to GPID annually.

It is estimated that about half of women hospitalized for GPID (or 60,000) become infertile. One-fourth of these women are assumed to be between 15 and 24 years of age, and the remaining three-fourths between 25 and 59 years of age. Hospitalization lasts an average of six days (Washington et al., 1984).

In 1981, there were 68,100 fetal deaths due to ectopic pregnancy (Centers for Disease Control, 1982). Of these, half (or 34,050) have been assumed to be due to maternal PID (Curran, 1980). If about 40 percent of PID is gonococcal in origin, then approximately 13,600 GPID-associated fetal deaths occur annually.

The incidences of epididymitis, ophthalmia neonatorum, and disseminated infection caused by N. gonorrhoeae are assumed to be neglible for this disease burden comparison.

Estimates of the disease burden imposed by N. gonorrhoeae, based on the above assumptions, are shown in Table L.4. These estimates should not be taken as a definitive statement on the incidence and distribution of such illness however, because time and resource limitations have necessitated the adoption of certain simplifying assumptions. These have been judged not to compromise the utility of the estimates for the purposes of this study.

TABLE L.3 Clinically Apparent Cases of Gonorrhea by Age and Sex

Sex	Infections	Percentage of Symptomatic Cases	Number of Symptomatic Cases	5–14 Years	15–24 Years
Males	1,100,000	95	1,045,000	5,225	571,615
Females	900,000	50	450,000	9,000	331,200
Total	2,000,000		1,495,000	14,225	902,815

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described and illustrated in Chapter 4. Total disease burden values (TDBVs) for N. gonorrhoeae are calculated using estimates from Table L.4 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 534 (committee median perspective) and 13,814 (age-neutral perspective). The large difference between these two values arises from the use in the age-neutral perspective of an IME value that equates first-trimester fetal deaths (in ectopic pregnancies) with all other deaths. If the IME value for these deaths were changed to 100 (as it is in the committee median perspective), the age-neutral TDBV would become 350.

Target Population

Identification of the target population for a gonococcal vaccine is complicated somewhat by lack of knowledge about the length of protective immunity that could be conferred by any specific vaccine. The most reasonable approach is to assume that the vaccine should be administered as shortly as possible before the age at which the incidence of disease begins to rise—sometime in the late teens. For this report, the target population at steady-state utilization is considered to be all 15-year-old teenagers. (immediately after introduction of an effective vaccine, older individuals probably would receive the vaccine as well.)

Disease incidence rates among military personnel are greater than those for civilians. Thus, this group or others, such as individuals presenting at clinics with sexually transmitted diseases, could be considered as potential high-risk target populations for vaccination.

Suitability for Vaccine Control

Despite the availability of antibiotics, gonorrhea inflicts a considerable burden of illness. In women, its occurrence may not be recognized until after the onset of a pattern of chronic complications.

TABLE L.4 Disease Burden: Neisseria gonorrhoeae

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Urethritis, discharge					14,225	3	902,615	3	577,960	3		
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Pelvic inflammatory disease (PID), initial and recurrent (all in women)					8,000	5	294,400	5	57,600	5		
C	Requiring hospitalization	Severe pelvic inflammatory disease, ectopic pregnancy (all in women)					2,400	6	91,720	6	39,480	6		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility	Infertility following PID							15,000	n.a.	45,000	n.a.		
H	Death	Death from PID; fetal death from ectopic pregnancy	13,600	n.a.			1	n.a.	36	n.a.	12	n.a.		

Note: n.a.=not applicable.

A preventive approach is thus desirable; it also appears to be practicable because an opportunity exists to deliver a vaccine prior to the period of maximum exposure. The growing problem of antibiotic resistant organisms would be obviated by a vaccine.

Success of a vaccination prevention approach is dependent upon development of a suitably protective vaccine. It also may require efforts to change misconceptions about the risk and consequences of the disease, particularly among lay persons.

Vaccine Preventable Illness

Defining the target population is the first step in calculating the possible reduction in morbidity and mortality that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

In calculating the benefits that could result from a gonococcal vaccine, it is assumed that all disease occurring over 15 years of age and all fetal deaths due to ectopic pregnancy are potentially vaccine preventable. None of the disease occurring in the 5–14 years age group is considered vaccine preventable, because children under 15 years of age are not included in the target population. Table L.5 presents a summary of VPI for gonorrhea.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Vaccine preventable illness values for gonorrhea are calculated using estimates from Table L.5 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the vaccine preventable illness value for gonorrhea is 527; with the age-neutral perspective the value is 13,811. If the IME value for first trimester fetal deaths in the age-neutral perspective were changed from 1 to 100 (as it is in the committee median perspective), the age-neutral VPI value would become 347.

Possible Reduction in Morbidity and Mortality (PRMM)

Calculation of the possible reduction in morbidity and mortality (or maximum potential health benefit) that could be achieved with a gonorrhea vaccine is somewhat different than the operation as performed for other vaccines, because in this case the candidate is "one of several promising options" rather than a specific vaccine. The committee believes, however, that a gonorrhea vaccine could achieve licensure

TABLE L.5 Vaccine Preventable Illness: Neisseria gonorrhoeae

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Urethritis, discharge							902,815	3	877,960	3		
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Pelvic inflammatory disease, (initial and recurrent, all in women)							294,400	5	97,600	5		
C	Requiring hospitalization	Severe pelvic inflammatory disease, ectopic pregnancy (all in women)							91,720	6	39,480	6		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility	Infertility following PID							15,000	n.a.	45,000	n.a.		
H	Death	Death from PID, fetal death from ectopic pregnancy	13,600	n.a.					36	n.a.	12	n.a.		

Note: For discussion, see text.

only if it were at least 70 percent effective against mucosal disease and at least 85 percent effective against pelvic inflammatory disease and its consequences. Using these efficacy figures and the vaccine preventable illness values determined above, the PRMM for a gonorrhea vaccine would be 444 using the median of committee member perspectives, and 11,738 using the age-neutral perspective. If the IME value for first trimester fetal deaths in the age-neutral perspective were changed from 1 to 100 (as it is in the committee median perspective), the age-neutral PRMM value would become 294.

Use of these unadjusted potential benefits numbers for comparing vaccines is described in Chapter 7.

Prospects for Vaccine Development

Pili

Injections of purified pili in humans have been studied thoroughly by two groups. Systemic vaccination results in opsonic and antimucosal adherence antibodies in serum and to a lesser (but significant) extent in vaginal secretions (McChesney et al., 1982; Siegel et al., 1982; Tramont et al., 1981). Duration of maintenance of serum antibodies is uncertain; titers start to fall within a few months. Relatively large doses (1–2 mg) are required to achieve uniformly good antibody responses; such doses cause moderate local irritation in some volunteers.

Systemic vaccination (IM) with 1–2 mg doses results in significant protection against intraurethral challenge with an ID_{30-59} of the homologous strain in human male volunteers, but no protection against a single tested heterologous strain expressing a different antigenic type of pilus (Brinton, personal communication, 1984). A recent field trial in Korea of a low dose of a single antigenic type of pilus, given intradermally, resulted in no protection against the multitude of antigenic types of gonococci in that community (Sadoff, personal communication, 1984).

Protein I

Humans apparently tolerate parenteral inoculation with purified PI, either of a single serotype or a mixture of five serotypes, and produce significant serum titers of anti-PI antibodies (Buchanan, personal communication, 1984). No human inoculation studies after PI vaccination have been done, but they are imminent.

Progress in understanding the molecular basis of gonococcal infection has been impressive. Many new concepts have evolved in the past two years. Most structures involved in pathogenesis have not been tested as vaccine candidates, however, primarily because of the lack of readily available and suitable animal

models. Even so, existing animal models and various human organ cultures (fallopian tube, cervix) will allow reasonable testing of vaccine components before extensive human trials are considered. It is too early to speculate on the odds of creating an effective vaccine or when it will be available, but the pace and excellence of the research effort offer significant promise of a vaccine, possibly in five to ten years.

Of the existing vaccine candidates the common binding domain of pili and protein I appear promising. Both deserve human volunteer trials, and possibly field trials. Civilian field trials are expensive and only a few will be possible for financial and other reasons. Trials in military populations are generally less expensive. Choices of antigens for field testing (made difficult by the paucity of animal models for the disease) should be made carefully.

Several of the newly described antigens (P.H.8, possibly FeRPs, and others) could be important. An effective vaccine may be composed of multiple antigens. Decisions concerning major field trials could be delayed until new information on antibody responses to several of the less well characterized antigens is available. This postponement could result in a field trial that demonstrates efficacy of a gonococcal vaccine.

Many of the concepts developed in the past decade of intense research on the gonococcus are relevant to other organisms (e.g., meningococci and Hemophilus influenzae); lessons learned in pursuit of a gonococcal vaccine may have significant impact on efforts to develop other bacterial vaccines.

Predictions on the further development of vaccines for N. gonorrhoeae appear in Chapter 5.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to various vaccines are displayed together to ease comparison.

Lay Acceptance

To judge the likely acceptance of a gonococcal vaccine, it was assumed that parental attitudes would predominate for potential recipients in their mid-teens. Perception of risk of the disease was thought to be low. Severity also was ranked low because most individuals believe that the disease is easy to treat and are ignorant about the consequences of PID. Benefits would be recognized as reasonably high, especially with possible physician cueing about PID, but barriers (cost, parental unwillingness to admit that their children might be sexually active, and number of doses) also would be reasonably high.

Provider Acceptance

Providers probably have a fairly low perception of their patients' risk of gonorrhea, but they probably have a higher perception than lay persons of disease severity (through knowledge of PID). Vaccine benefits would be ranked high because the infertility consequences of PID often are not amenable to remedial treatment. Perceived barriers for physicians would include the necessity of dealing with a topic about which there is some social stigma and the fear of possible accusations of encouraging promiscuity.

Cost of Illness

The scope and purpose of the calculations shown below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden

Category A - urethritis, discharge

# of cases = 1,495,000	
100% of cases typically receive 1 phys. visit at $30	= $ 44,850,000
approx. 50% of cases receive diagnostic workup at $30 [Gram stain, culture and serology]	= $ 22,425,000
100% of cases typically receive treatment at $20 [Penicillin G plus probenecid, ampicillin or tetracycline]	= $ 29,900,000
approx. 25% of cases receive follow-up culture and serology at $30 and 1 follow-up phys. visit at $30	= $ 22,425,000
approx. 5% of cases receive 1 additional phys. visit (due to case of penicillin resistant strain) at $30	= $ 2,242,000
TOTAL (A)	= $121,842,000

Category B - pelvic inflammatory disease (PID: initial and recurrent, all in women)

# of cases = 400,000	
100% of cases typically receive 1 phys. visit at $30	= $ 12,000,000
100% of cases typically receive diagnostic workup at $30/each [Gram stain, culture and serology]	= $ 12,000,000

100% of cases typically receive treatment at $20 = $ 8,000,000
[Penicillin G plus probenecid, ampicillin or tetracycline]
approx. 75% of cases receive follow-up culture and serology at $30 and 1 follow-up phys. visit at $30 = $ 18,000,000
TOTAL (B) = $ 50,000,000

[In many cases, Category B cases may be admitted, becoming Category C.]

Category C

PID
# of cases = 120,000
100% of cases receive an average 6 hospital days at $400/day = $288,000,000
100% of cases receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 6 days at $400/day = $288,000,000
100% of cases typically receive 1 follow-up phys. visit at $30 each and another set of culture and serology at $30 each = $ 7,200,000
5% of cases receive surgical procedure (laparoscopy) at $1,100/procedure = $ 6,600,000
approx. 5% of cases receive gynecological surgery of some sort at $1,000/case, 7 additional routine days of hospital care ($400/day) and diagnostic testing and treatment at $400/day = $ 39,600,000
TOTAL = $629,400,000

Ectopic pregnancies
# of cases = 13,600
approx. 50% (6,800) of cases will be unruptured, and of these,
100% will typically receive preliminary diagnosis (2xBHCG) at $50/case = $ 340,000
100% will typically receive sonogram at $75 = $ 510,000
100% will typically undergo laparoscopy/laparotomy as part of ectopic pregnancy removal. Total surgical costs = $3,000/procedure = $ 20,400,000
approx. 50% (6,800) of cases will be ruptured, and of these, 100% will typically receive surgery at total cost = $2,000/procedure = $ 13,600,000
TOTAL = $ 34,850,000
TOTAL (C) = $664,250,000

Categories D-F n/a

Category G - chronic consequences of infertility following PID

# of cases = 60,000

of the total # of cases, approx. 40,000 will receive further medical/remedial attention, and of these cases,

approx. 33% will receive an initial hysterosalpingogram at $120	= $ 1,584,000
100% will typically eventually undergo a laparoscopy at $1,100	= $ 44,000,000
approx. 25% will undergo remedial surgery entailing 4-5 days inpatient care, at an estimated total cost/case = $5,500	= $ 55,000,000
TOTAL (G)	= $100,584,000
TOTAL COST	= $936,676,000

Cost of Total Vaccine Preventable Illness

Category A - urethritis, discharge

# of cases = 1,480,775

100% of cases typically receive 1 phys. visit at $30	= $ 44,423,000
approx. 50% of cases receive diagnostic workup at $30 [Gram stain, culture and serology]	= $ 22,212,000
100% of cases typically receive treatment at $20 [Penicillin G plus probenecid, ampicillin or tetracycline]	= $ 29,616,000
approx. 25% of cases receive follow-up culture and serology at $30 and 1 follow-up phys. visit at $30	= $ 22,212,000
approx. 5% of cases receive 1 additional phys. visit (due to case of penicillin resistant strain) at $30	= $ 2,221,000
TOTAL (A)	= $120,684,000

Category B - pelvic inflammatory disease (PID: initial and recurrent, all in women)

# of cases = 392,000

100% of cases typically receive 1 phys. visit at $30	= $ 11,760,000
100% of cases typically receive diagnostic workup at $30/each [Gram stain, culture and serology]	= $ 11,760,000
100% of cases typically receive treatment at $20 [Penicillin G plus probenecid, ampicillin or tetracycline]	= $ 7,840,000
approx. 75% of cases receive follow-up culture and serology at $30 and 1 follow-up phys. visit at $30	= $ 17,640,000
TOTAL (B)	= $ 49,000,000

In many cases, Category B cases may be admitted, becoming Category C.]

Category C

PID
# of cases = 117,600
100% of cases receive an average 6 hospital days at $400/day = $282,240,000
100% of cases receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 6 days at $400/day = $282,240,000
100% of cases typically receive 1 follow-up phys. visit at $30 each and another set of culture and serology at $30 each = $ 7,056,000
5% of cases receive surgical procedure (laparoscopy) at $1,100/procedure = $ 6,468,000
approx. 5% of cases receive gynecological surgery of some sort at $1,000/case, 7 additional routine days of hospital care ($400/day) and diagnostic testing and treatment at $400/day = $ 38,808,000
TOTAL = $616,812,000

Ectopic pregnancies
# of cases = 13,600
approx. 50% (6,800) of cases will be unruptured, and of these,
100% will typically receive preliminary diagnosis (2 x BHCG) at $50/case = $ 340,000
100% will typically receive sonogram at $75 = $ 510,000
100% will typically undergo laparoscopy/laparotomy as part of ectopic pregnancy removal. Total surgical costs = $3,000 = $ 20,400,000
approx. 50% (6,800) of cases will be ruptured, and of these, 100% will typically receive surgery at total cost = $2,000 = $ 13,600,000
TOTAL = $ 34,850,000
TOTAL (C) = $651,662,000

Categories D-F n/a

Category G - chronic consequences of infertility following PID

# of cases = 60,000
of the total # of cases, approx. 40,000 will receive further medical/remedial attention, and of these cases,
approx. 33% will receive an initial hysterosalpingogram at $120 = $ 1,584,000

100% will typically eventually undergo a laparoscopy at $1,100	= $ 44,000,000
approx. 25% will undergo remedial surgery entailing 4-5 days inpatient care, at an estimated total cost/case = $5,500	= $ 55,000,000
TOTAL (G)	= $100,584,000
TOTAL COST	= 921,930,000

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Appendix

M

PROSPECTS FOR IMMUNIZING AGAINST PARAINFLUENZA VIRUSES

Disease Description

Prior attempts to make and test vaccines against the parainfluenza viruses (PIV), epidemiologic studies, and new information about the viruses' surface glycoproteins provide the background for new vaccine development. The parainfluenza viruses are somewhat different from one another, so some aspects of their biology must be considered separately. This is particularly true of their epidemiology. PIV-1 and PIV-2 have similar epidemiologic patterns: they tend to be epidemic in the fall and early winter, usually appearing every other year and causing croup in children between one and four years of age. Infections usually do not occur in the first six months of life. PIV-3, on the other hand, behaves epidemiologically more like respiratory syncytial virus (RSV). Infections are common in the first six months of life, and large winter epidemics do not occur; this virus is largely endemic, with periodic epidemicity. Not much is known about PIV-4, but it is thought to be considerably less important than the other three types, and thus will not be considered here.

Pathogen Description

The parainfluenza viruses are species in the Paramyxoviridae family. Considerable information exists about the two surface glycoproteins of paramyxoviruses. One, the HN protein, contains both hemagglutinating and neuraminidase activity (Scheid et al., 1972). These two activities may occupy separate sites on the HN molecule (Portner, 1981). In vitro studies of the other surface glycoprotein have shown that it has the capacity to fuse membranes and is responsible both for the formation of syncytia and for entry of the virus into the cell (Scheid and Choppin, 1974). Antibody to either glyco-

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protein is neutralizing, and antibody to the fusion protein also prevents cell-to-cell spread of the virus (Merz et al., 1980). The fusion proteins of measles and mumps viruses, closely related to paramyxoviruses, are antigenically inactivated by formalin, and it is possible that early measles and parainfluenza vaccines failed for this reason.

Host Immune Response

Reinfections are common with PIV-1, PIV-2, and PIV-3. They appear to be most frequent with PIV-3, another feature of this virus that resembles RSV (Chanock et al., 1963). There is also evidence from volunteer studies in adults that secretory neutralizing antibody correlates better than serum antibody with protection against challenge with PIV-1 (Smith et al., 1966). It is assumed that this rule also holds for PIV-2 and PIV-3, although this has not been proved, and information in children is scanty.

Although there is some cross-reactivity between these three PIV types, cross-protection probably does not occur. There does not appear to be any serologic variation within each type.

Disease Burden

Descriptions and estimates given below are based on reports by Glezen et al. (1982, 1983), and the National Institute of Allergy and Infectious Diseases (in press), and on personal communications from Clyde (1983) and Glezen (1984).

Parainfluenza viruses cause acute respiratory disease in young children, although infection may be asymptomatic. The viruses often produce serious lower respiratory tract illnesses: types 1 and 2 are usually associated with croup, while type 3 may cause bronchiolitis and pneumonia. Infections with type 4 virus are rarely serious and are not considered further. Acute lower respiratory illness from parainfluenza virus infection may eventually contribute to chronic obstructive pulmonary disease (Glezen, in press), however, no attempt has been made here to include such a contribution in chronic morbidity estimates. This aspect of the disease burden of parainfluenza virus infection needs periodic reevaluation. For the disease comparison in this report, all clinically significant cases of parainfluenza infection are assumed to occur in children under five years of age.

It is estimated that 25 percent of children under five years of age experience a clinically significant parainfluenza infection (initial or reinfection) each year (Clyde, personal communication, 1983; Glezen et al., 1982). Applying this percentage to 1984 population projections (18,232,490 children under age 5) produces a total of 4,558,123 cases.

Mild upper respiratory tract parainfluenza illness is judged to fall into Morbidity Category A; an estimated 20 percent subsequently progress to lower tract involvement (Category B). Thirty-one percent of cases (in both categories) are assumed to occur under 1 year of age

and the remaining 69 percent in the 1–4 years age group. The hospitalization rates per 100 children (approximately 0.8 percent of the 3,733,808 projected for the under 1 year age group in 1984, and 0.4 percent of the 14,498,682 projected for the 1–4 years age group) have been calculated from observations by Glezen (1983), and adjusted to reflect the frequency of epidemics caused by certain strains. Overall, these rates represent a case/hospitalization rate of slightly less than 2 percent for children under five.

The durations shown in Table M.1 have been estimated in an attempt to reflect the severity of the type of illness encountered in the respective age groups.

Sporadic case reports are the only source of data on deaths associated with parainfluenza virus infections, so the estimate of 1,000 deaths (Glezen, personal communication, 1984) has a high degree of uncertainty. Deaths that do occur probably are related to parainfluenza type 3 virus infection (mostly pneumonia) in young infants (Glezen et al., 1982), so all are placed in the under 1 year age group.

Estimates of the disease burden for parainfluenza viruses are summarized in Table M.1.

Uncertainty in the Disease Burden Estimates

Estimates of the number of cases shown in Table M.1 have been derived largely from incidence rates of illnesses in the more severe categories, i.e., those requiring hospitalization or physician visits. The distribution of illnesses between the morbidity categories not involving hospitalization have been based on the clinical experience of individuals familiar with parainfluenza virus infections. These figures may need to be revised in light of publications now in press. The estimated number of deaths also represents a judgment by experienced clinicians rather than a calculation from reported data.

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for parainfluenza viruses are calculated using estimates from Table M.1 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 1,167 (committee median perspective) and 1,104 (age-neutral perspective).

Target Population

As noted above, the most severe illnesses caused by parainfluenza virus infections occur in the first years of life. Hence, the target population would be infants at the earliest feasible age. The simplest design for the use of a PIV vaccine would be to administer it during

TABLE M.1 Disease Burden: Parainfluenza Viruses 1, 2, and 3

			Under 1 Year		1–4 Years		5–14 Years		15–24 Years		25–59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Mild respiratory tract disease	1,413,018	4	3,145,105	3								
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Lower respiratory tract disease, bronchiolitis, croup, mild pneumonia	282,604	6	629,021	5								
C	Requiring hospitalization	Severe lower respiratory tract disease, bronchiolitis, croup, pneumonia	29,870	4	57,996	5								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death	Due to pneumonia in infants	1,000	n.a.										

Note: n.a.=not applicable.

the first six months of life. The aim would be to prevent as much PIV-3 disease as possible, and also to reduce PIV-1 and PIV-2 infections, which usually occur later.

High levels of passively acquired maternal antibody appear to play a role in protecting infants against parainfluenza viruses during the first year of life (Glezen et al., in press), so a vaccine administered to pregnant women also might be a possibility, identification of an appropriate PIV vaccine candidate for pregnant women will require more research on the nature of antibodies induced by PIV infection and the extent to which they cross the placenta.

Suitability for vaccine Control

Illness caused by parainfluenza viruses types 1 and 2 occurs predominantly after six months of age, so an opportunity exists to deliver the vaccine prior to the peak of illness. The peak of illness for parainfluenza virus type 3 occurs earlier, however, before the full required number of doses could be delivered. Thus, a lower proportion of these illnesses could be averted. While reinfection does occur, indicating that natural immunity is not fully protective, it is probable that a vaccine could, at a minimum, avert the more severe disease.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the benefit that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

The vaccine envisaged by the committee would require two early doses and probably additional doses to boost or maintain immunity. While the major portion of illness caused by PIV-1 and PIV-2 occurs after six months, the pattern of PIV-3 illness is similar to that of RSV, involving a considerable amount of severe illness under six months of age. The first dose of vaccine probably could be administered at about two months, with a second dose two to three months later. Vaccinees would be only partially protected during this period; hence, only about 80 percent of the cases of illness occurring under one year of age are judged to be vaccine preventable. All cases occurring in older age groups (1–4 years) are judged to be vaccine preventable. Since deaths are thought to be due predominantly to PIV-3 infections in young infants, only about 50 percent of deaths are considered vaccine preventable.

Natural immunity is not fully protective or is short lived so reinfection does occur, although it is milder. Hence, the vaccine is predicted to reduce the severity of illness rather than totally prevent cases of the disease. Reductions in the severity of cases in Category

C could move those cases to Category B: cases initially in Category B could move to Category A. To simplify calculations, however, it is assumed that the vaccine reduces the severity of all cases to negligible levels (less severe than Category A). The error introduced by this assumption is minimized by the fact that residual illness in vaccinees would be in categories that are small contributors to the total disease burden or VPI values.

Table M.2 shows a summary of VPI for parainfluenza viruses.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Total vaccine preventable illness values for parainfluenza are calculated using estimates from Table M.1 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the total vaccine preventable illness value for parainfluenza is 660; with the age-neutral perspective the value is 584.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by the parainfluenza vaccine candidate, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of the vaccine. For the parainfluenza virus vaccine, the predicted efficacy is 0.80. The potential reduction in morbidity and mortality for the parainfluenza virus vaccine is 561 using the committee median perspective and 496 using the age-neutral perspective.

Prospects for Vaccine Development

Prior experience with vaccine development has been limited. Trivalent formalin-inactivated PIV vaccines made in monkey kidney tissue cultures and tested in parallel with the killed RSV vaccine failed to protect against natural infection. Unlike the measles and RSV vaccines (Chanock et al., 1968; Fulginiti et al., 1967), however, the PIV vaccines did not induce paradoxically severe disease due to hypersensitivity (Fulginiti et al., 1969). Thus, there is no evidence that highly antigenic parenterally administered vaccines would be harmful. However, based on the experience with measles virus it would be essential that an immunologically active fusion protein be present in the vaccine.

There is very little ongoing work involving a PIV vaccine. All early attempts were with high-titer inactivated vaccines; mutant attenuated vaccines have not been examined.

TABLE M.2 Vaccine Preventable Illness: Parainfluenza Viruses 1, 2, and 3

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Mild respiratory tract disease	1,130,414	4	3,145,106	3								
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Lower respiratory tract disease, bronchiolitis, croup, mild pneumonia	226,083	6	629,021	5								
C	Requiring hospitalization	Severe lower respiratory tract disease, bronchiolitis, croup, pneumonia	23,896	4	57,995	5								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death	Due to pneumonia in infants	500	n.a.										

Note: For discussion, see text.

Predictions about the chances of success in the development of PIV vaccines are difficult to make. Since reinfections with PIV-1 and PIV-2 appear to be less frequent that those with PIV-3, it may be that these two serotypes will lend themselves more easily to the production of successful vaccines. However, lack of information about reinfections with PIV-1 and PIV-2 may be more a reflection of their epidemic ity at two-year intervals than of their ability to immunize by natural infection. The possibility that serum antibody to these two serotypes may protect against infection (Parrot et al., 1962) gives some hope that a parenteral vaccine of sufficient antigenicity (particularly with regard to the fusion protein) would be protective.

Subunit vaccines may be a rational approach to these problems. It appears likely that these could be developed using either traditional or genetic engineering technology. All three PIV types can be grown in embryonated eggs, and this is a possible source of large quantitites of inexpensive antigen, which could be purified and used in subunit vaccines. There is some information on the antigenicity of these egg-grown viruses when administered by the respiratory route (Wigley et al., 1970). It would be essential to have the F protein present in the antigenically active form in such a vaccine, i.e., not formalin inactivated (Merz et al., 1980).

Clinical Trials

Clinical trials with PIV vaccines will be affected by several problems. The major target is the infant in the first year of life: potential vaccines would have to undergo extensive testing in adults and older children to demonstrate their safety. Attenuated vaccine viruses probably would replicate poorly in older individuals who are likely to be partially immune, so staged trials in progressively younger subjects would be difficult. Subunit vaccines administered parenterally or by the respiratory route might circumvent these problems to some extent, and this may prove to be a promising direction in PIV vaccine research.

Vaccine development will depend on research in several areas. First, vaccines that preserve the antigenicity of the fusion protein need to be tested for their ability to prevent infections by PIV-1 and PIV-2. Second, more information is needed regarding the mechanisms by which small children develop immunity to respiratory viruses (e.g., researchers will need to determine whether vaccines will have to be administered directly to the respiratory mucosa). Third, more emphasis needs to be placed on molecular studies of the three PIV serotypes. The production of cloned cDNA coding for the surface glycoproteins of all three PIV types should be a priority. Finally, detailed information on both the HN and the fusion proteins of all three types should be made available through studies of the glycoproteins themselves, their purification, and their chemistry.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to various vaccines are displayed together for comparison.

Lay Acceptance

Lay perception of the risk of illness from parainfluenza viruses is thought to be low, but the more recognized forms of illness, such as pneumonia, are thought to be perceived as relatively serious. The general belief by parents in pediatric vaccination would result in a moderately high lay score for benefits, while the cost and possible confusion over problems associated with the influenza vaccine probably would present moderate barriers to acceptance.

Provider Acceptance

Provider recognition of the moderate risk of parainfluenza viral illness probably would be reasonably accurate. The perception of the seriousness of the more severe forms of the disease also would be accurate. Physician rating of the benefits of vaccination would be moderate because of the limits on protection against illness. The barriers, while low, might be affected by association with problems related to previous vaccine candidates that involved fusion proteins, such as the RSV vaccine.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for this study. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden

Category A - mild respiratory tract disease

# of cases = 4,558,123		
approx. 25% of cases receive 1 phys. visit at $30		= $ 34,186,000
approx. 10% of cases receive treatment at $5		= $ 2,279,000
	TOTAL (A)	= $ 36,465,000

Category B - lower respiratory tract disease, bronchitis, croup, mild pneumonia

# of cases = 911,625	
approx. 50% of cases receive 1 phys. visit at $30	= $ 13,674,000
approx. 20% of cases receive diagnostic procedure at $55 [chest x-ray]	= $ 10,028,000
approx. 10% of cases receive treatment at $5	= $ 456,000
TOTAL (B)	= $ 24,158,000

Category C - severe lower respiratory tract disease, bronchitis, croup, pneumonia, hospitalization

# of cases = 87,865	
100% of cases typically receive 4 days of normal hosp. at $400/day	= $140,584,000
approx. 1% of cases receive additional 2 days ICU at $600/day [severe pneumonia or croup]	= $ 1,054,000
hospitalized cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate	
for 100% of cases 4 days at $400/day	= $140,584,000
for 1% of cases 2 days at $600/day	= $ 1,054,000
100% of cases typically receive 1 follow-up phys. visit at $30	= $ 2,636,000
TOTAL (C)	= $285,912,000

Categories D - G n/a

TOTAL COST = $346,535,000

Cost of Total Vaccine Preventable Illness

Category A - mild respiratory tract disease

# of cases = 4,275,519	
approx. 25% of cases receive 1 phys. visit at $30	= $ 32,066,000
approx. 10% of cases receive treatment at $5	= $ 2,138,000
TOTAL (A)	= $ 34,204,000

Category B - lower respiratory tract disease, bronchitis, croup, mild pneumonia

# of cases = 855,104	
approx. 50% of cases receive 1 phys. visit at $30	= $ 12,827,000
approx. 20% of cases receive diagnostic procedure at $55 [chest x-ray]	= $ 9,406,000

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    approx. 10% of cases receive treatment at $5                = $    428,000
                                                  TOTAL (B)     = $ 22,661,000

Category C - severe lower respiratory tract disease,
    bronchitis, croup, pneumonia, hospitalization

# of cases = 81,891
    100% of cases typically receive 4 days of normal
      hosp. at $400/day                                         = $131,026,000
    approx. 1% of cases receive additional 2 days
      ICU at $600/day                                           = $    983,000
      [severe pneumonia or croup]
    hospitalized cases typically receive diagnostic
      testing and treatment procedures at rate equivalent
      to daily inclusive hospital rate
      for 100% of cases 4 days at $400/day                      = $131,026,000
      for 1% of cases 2 days at $600/day                        = $    983,000
    100% of cases typically receive 1 follow-up phys.
      visit at $30                                              = $  2,457,000
                                                  TOTAL (C)     = $266,475,000

Categories D - G  n/a

                                                  TOTAL COST    = $323,340,000
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Appendix

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PROSPECTS FOR IMMUNIZING AGAINST RESPIRATORY SYNCYTIAL VIRUS

Disease Description

Respiratory syncytial virus (RSV) is the major cause of lower respiratory tract illness in infants and young children. It is the pathogen most often associated with bronchiolitis and pneumonia, and also causes bronchitis and croup. RSV produces sizable epidemics every two years in large urban centers, resulting in increased hospitalizations and some fatalities (Chanock et al., 1982). The severity of the disease appears to decrease with age and asymptomatic infections can occur.

Pathogen Description

RSV is a lipoprotein-enveloped RNA virus of medium size (120–200 nm). The outer envelope contains glycoprotein. The virus is heat labile, which complicates its isolation and study. RSV is considered by most to be a single serotype, but the evidence for this is not conclusive. Early studies described aberrant strains that were poorly neutralized by post-infectious ferret sera (Coates et al., 1966). Although human convalescent sera did not distinguish these differences, the frequency of such aberrant strains and their contribution to the problem of reinfection has never been entirely explained.

Recent studies of the proteins of RSV have produced new information on the surface structure of the virus and on the antigens that may be important for vaccine development. There are two surface glycoproteins. Neither of them has hemagglutinating or neuraminidase activity; however, one of them is probably responsible for fusion of the viral membrane to infected cells and for fusion of an infected cell to neighboring cells (Walsh and Hruska, 1983). This protein, in an unreduced state, has a molecular weight of 66,000–68,000 (Bernstein and Hruska, 1981).

The advice and assistance of W.P.Glezen in the preparation of this appendix is gratefully acknowledged. The committee assumes full responsibility for any judgments or assumptions.

Monoclonal antibody that imanunoprecipitates this protein neutralizes the virus in vitro, prevents formation of syncytia, and may have some protective effect when administered passively to small animals subsequently inoculated with RSV. The other surface glycoprotein has a molecular weight of 84,000–90,000 and has no known function. Monoclonal antibody to this larger glycoprotein may be neutralizing in the presence of complement. Neither of the glycoproteins has been purified.

Although major portions of DNA complementary to the RSV genome have been cloned (Collins and Wertz, 1983; Venkatesan et al., 1983), it is not entirely clear which of the cloned fragments correspond to the messages for the two surface glycoproteins. Undoubtedly, this information will emerge in the very near future.

Host Immune Response

RSV infection and disease occur in the very young in the presence of maternal IgG, but there is some evidence that infants with high levels of serum antibody are less often infected or severely ill than infants with low levels (Glezen et al., 1981; Parrot et al., 1973). There is also evidence that partial immunity may be conferred by natural infection: adults who have been inoculated with tissue culture grown virus have shown subsequent resistance to reinfection by the same route (Mills et al., 1971).

Most studies suggest, however, that RSV infection recurs at yearly or biennial intervals under natural conditions (Beem, 1967; Henderson et al., 1979). Reinfections are frequently less severe than first infections, but this appears to be a function of increasing age more than immunity (Henderson et al., 1979). Reinfections in the same RSV epidemic probably are rare, however. It seems likely that secretory immunity is more important in protection against reinfection than systemic, although this point cannot be made with certainty.

Disease Burden Estimates

The descriptions and estimates supplied below are based largely on information in Chanock et al. (1982), Denny and Clyde (1983), and Tyeryar (1983), and on advice from Glezen based on his unpublished and published observations (personal communication, 1983; Glezen, 1983; Glezen et al., 1983).

Conditions produced by RSV range from asymptomatic infections to severe life-threatening lower respiratory tract illnesses, such as bronchiolitis and pneumonia. The peak of severe illness is under six months of age, and by two years of age nearly 100 percent of children have been infected. Reinfection occurs with somewhat decreasing severity in older children (Chanock et al., 1982).

For this disease comparison, all clinically significant illness has been assumed to occur in infants and children less than five years of age. The following attack rates, assumed on the basis of advice from

Glezen (personal communication, 1983), have been applied to 1984 population projections (18,232,490 children under 5 years of age) to calculate the disease burden: risk of hospitalization from pneumonia and bronchiolitis, 0.5 percent; risk of moderate to severe lower respiratory tract illness falling into Morbidity Category B, 5.0 percent; risk of acute respiratory illness falling into Category A, 15 percent. While infection and reinfection after infancy are generally milder, some RSV infections are quite severe in the 1–4 years age group (e.g., croup). The assumed distribution of cases, hospitalizations, and deaths (60 percent, under 1 year; 40 percent, 1–4 years) reflects this situation.

The estimates of number of deaths is based on the report of MacDonald et al. (1982) that about 5 percent of hospitalized cases die.

Table N.1 shows estimates derived using these assumptions.

Uncertainty in the Disease Burden Estimates

Estimates shown in Table N.1 are derived from rates estimated on the basis of observations in relatively small areas and then extrapolated to generate figures for national incidence. This procedure could lead to some errors in the estimates if rates vary regionally. Additionally, the distribution of cases between Categories A and B and between age groups was made on the basis of subjective clinical experience rather than from reported data, because RSV produces such a wide spectrum of respiratory tract diseases. No data are available from which to estimate deaths in non-hospitalized cases.

Whether acute lower respiratory tract illness from respiratory syncytial virus infections eventually contributes to chronic obstructive pulmonary disease remains speculative (Glezen, in press). No attempt has been made to estimate possible chronic morbidity associated with RSV infection.

Calculation of Total Disease Burden Values

The method used to compare morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for RSV are calculated using estimates from Table N.1 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 4,759 (committee median perspective) and 4,707 (age-neutral perspective).

Vaccine Target Population

Normal infants would be the principal target population for an RSV vaccine, because the most severe disease caused by the virus occurs early in the first year of life, between six weeks and about four

TABLE N.1 Disease Burden: Respiratory syncytial virus

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Mild respiratory tract illness	1,640,924	4	1,093,930	4								
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Moderate to severe lower respiratory tract illness	546,970	6	364,650	6								
C	Requiring hospitalization	Pneumonia, bronchiolitis	54,697	8	36,465	8								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		2,736	n.a.	1,832	n.a.								

months of age. Other possible target populations include the elderly (Garvie and Gray, 1980), and older children with chronic cardiopulmonary disease (e.g., congenital heart disease, bronchopulmonary dysplasia, and asthma). RSV could be severe or fatal for children in this latter group at any age (MacDonald et al., 1982). Delivery of vaccine to pregnant or soon-to-be pregnant women may offer an alternative approach to immunizing young infants if the latter proves not to be practicable.

A vaccine conferring temporary immunity might be acceptable for the major target population because the period of highest vulnerability is so brief (the first year of life). This vaccine could be administered in the autumn in temperate climates where the disease is epidemic.

Suitability for Vaccine Control

Severe RSV illness occurs in young infants, so vaccine prevention or amelioration of RSV illness will depend on the ability to develop a vaccine that can stimulate immunity at a very early age. Estimates below and predictions in Chapter 5 are predicated upon the assumption that this will be possible. A vaccine that produces immunity of relatively short duration may be acceptable for the reasons discussed above.

The feasibility of the alternative strategy—immunizing pregnant women—also needs to be investigated, especially if producing a vaccine immunogenic in young infants proves to be impossible.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the possible reduction in morbidity and mortality that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

A large proportion of RSV illness in the first year of life occurs below the age of six months. Even assuming the development of a vaccine that is immunogenic in young infants, the vaccine would have to be delivered at a very early age, and in the case of the glycoprotein vaccine, only partial protection would be achieved before subsequent doses were administered. Because of these considerations, it is judged that only two-thirds of the burden of RSV in the first year of life would be vaccine preventable—even with the envisaged vaccines. All RSV illness in individuals 1–4 years of age is considered vaccine preventable.

Table N.2 shows a summary of the VPI for RSV.

TABLE N.2 Vaccine Preventable Illness: Respiratory syncytial virus

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities	Mild respiratory tract illness	1,093,950	4	1,093,950	4								
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Moderate lower respiratory tract illness	364,647	6	364,650	6								
C	Requiring hospitalization	Pneumonia, bronchiolitis	36,465	8	36,465	8								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		1,832	n.a.	1,832	n.a.								

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Total vaccine preventable illness values for RSV are calculated using estimates from Table N.2 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the total vaccine preventable illness value for RSV is 3,828; with the age-neutral perspective the value is 3,775.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by the RSV vaccine candidate, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of the vaccine. For RSV, the predicted efficacy is 0.80. The potential reduction in morbidity and mortality for both vaccines is 3,062 using the committee median perspective and 3,020 using the age-neutral perspective.

Prospects for Vaccine Development

History

Early investigators attempted to prevent RSV infection by inoculating susceptible children with a formalin-inactivated, concentrated, adjuvant-enhanced vaccine. The results of these trials are well known. Vaccinees developed high levels of neutralizing and complement-fixing antibody, but on subsequent exposure to wild RSV they developed infections that were more severe than those seen in parallel control children (Chin et al., 1969; Fulginiti et al., 1969; Kapikian et al., 1969; Kim et al., 1969). This hyper-reactivity has never been satisfactorily explained. The disease was similar to that seen in normal children, but it occurred at an older age and was somewhat more severe.

Attempts to make live attenuated vaccines also have met with little success. Early cold-adapted vaccines were too pathogenic for use in young children. Temperature-sensitive mutants, while less pathogenic than cold-adapted variants, still produced significant upper and very mild lower respiratory symptoms in vaccinees encountering the virus for the first time (Kim et al., 1973). Moreover, there was evidence that these vaccines did not protect completely (Wright et al., 1976).

There is reasonable hope that a subunit vaccine can be developed. This is particularly true if the glycoproteins responsible for protection can be identified and can be made by introducing cloned DNA fragments into appropriate cellular hosts. Clearly, in light of the experience noted above and that with measles virus, further work is

needed to understand the response of the immune system to administration of such antigens by various routes.

Current Vaccine Development

Recent vaccine development has focused primarily on two areas: live vaccines administered parenterally and live attenuated vaccines administered in the respiratory tract. A vaccine grown in tissue culture and designed for subcutaneous administration was recently tested in a large number of young children (Belshe et al., 1982). This vaccine failed to protect, although it weakly stimulated antibody to RSV.

Attenuated vaccines administered in the respiratory tract have been examined more extensively. The most promising candidates have been members of the temperature-sensitive mutant group developed by Chanock and his associates at the National Institutes of Health (Gharpure et al., 1969). The ts-1 vaccine, while considerably less pathogenic than earlier strains, still induced symptomatic illness, including otitis media and mild bronchitis, in unprimed infants. Attempts have been made to further mutagenize this strain and also to test the more attenuated ts-2 mutant. These attempts have not yet been successful.

The prospects for developing vaccines from genetically engineered live strains also are reasonably promising. Most of the genome of RSV has been sequenced, as noted above.

Clinical Trials

The major problem anticipated in clinical trials of RSV vaccines stems from the necessity to examine infants in the first year of life. Live attenuated vaccines that are of sufficiently low pathogenicity to be safe in this group are likely to be poorly infectious in partially immune adult or older pediatric patients. Subunit vaccines administered to the respiratory mucosa may be easier to test, but they hold the definite, albeit small, risk of producing severe atypical disease on subsequent exposure to wild virus. However, as knowledge of the natural illness and natural immunity grows, the likelihood of repeating the experience with the killed parenteral vaccine diminishes.

Other difficulties to be encountered involve the problems of growing this virus in large quantities and also of purifying it or its proteins. RSV tends to grow only to modest titers in tissue culture, and it has been difficult to purify the whole virus or its glycoproteins.

Vaccine Development

Successful development of new RSV vaccines will depend on investigations in several areas. Researchers must learn more about natural immunity to RSV infection in infants and adults, and about the possible role of antigenic variants in recurrent RSV infections.

Attempts to purify antigens from viruses grown in tissue culture and to produce intact antigens from cloned DNA fragments should be encouraged.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to various vaccines are displayed together to facilitate comparison.

Lay Acceptance

Parents' perceptions of RSV illness as a threat to their children have been judged to be moderate to low. In contrast, a high score has been assigned for severity, because the disease often occurs in very young infants. The benefits probably would be viewed as only moderate, because the vaccine may ameliorate but not totally prevent illness. Barriers also would be moderate, and may be somewhat higher for a glycoprotein vaccine if several doses are necessary, as expected.

Provider Acceptance

Provider recognition of RSV as a risk to children is probably higher than that of the public, and accompanied by the realization that the disease is quite severe. Providers are likely to view the benefits (possible amelioration rather than prevention of serious disease) more favorably than parents. Barriers would be moderately high, however, predominantly because of apprehension over administering the vaccines (or any agent) to very young children.

Costs of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. The calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden

Category A - mild respiratory tract disease

# of cases = 2,734,874	
approx. 25% of cases receive 1 phys. visit at $30	= $ 20,512,000
approx. 10% of cases receive treatment at $5	= $ 1,367,000
TOTAL (A)	= $ 21,879,000

Category B - lower respiratory tract disease, bronchitis, croup, mild pneumonia

# of cases = 911,620	
approx. 50% of cases receive 1 phys. visit at $30	= $ 13,674,000
approx. 20% of cases receive diagnostic procedure at $55 [chest x-ray]	= $ 10,028,000
approx. 10% of cases receive treatment at $5	= $ 456,000
TOTAL (B)	= $ 24,158,000

Category C - severe lower respiratory tract disease, bronchitis, croup, pneumonia, hospitalization

# of cases = 91,162	
100% of cases typically receive 4 days of normal hosp. at $400/day	= $145,859,000
approx. 1% of cases receive additional 2 days ICU at $600/day [severe pneumonia or croup]	= $ 1,094,000
hospitalized cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate	
for 100% of cases 4 days at $400/day	= $145,859,000
for 1% of cases 2 days at $600/day	= $ 1,094,000
100% of cases typically receive 1 follow-up phys. visit at $30	= $ 2,735,000
TOTAL (C)	= $296,641,000

Categories D - G n/a

TOTAL COST = $342,678,000

Cost of Total Vaccine Preventable Illness

Category A - mild respiratory tract disease		
# of cases = 2,187,900		
approx. 25% of cases receive 1 phys. visit at $30		= $ 16,409,000
approx. 10% of cases receive treatment at $5		= $ 1,094,000
	TOTAL (A)	= $ 17,503,000
Category B - lower respiratory tract disease, bronchitis, croup, mild pneumonia		
# of cases = 729,297		
approx. 50% of cases receive 1 phys. visit at $30		= $ 10,939,000
approx. 20% of cases receive diagnostic procedure at $55 [chest x-ray]		= $ 8,022,000
approx. 10% of cases receive treatment at $5		= $ 365,000
	TOTAL (B)	= $ 19,326,000
Category C - severe lower respiratory tract disease, bronchitis, croup, pneumonia, hospitalization		
# of cases = 72,930		
100% of cases typically receive 4 days of normal hosp. at $400/day		= $116,688,000
approx. 1% of cases receive additional 2 days ICU at $600/day [severe pneumonia or croup]		= $ 875,000
hospitalized cases typically receive diagnostic testing and treatment procedures at rate equivalent to daily inclusive hospital rate		
for 100% of cases 4 days at $400/day		= $116,688,000
for 1% of cases 2 days at $600/day		= $ 875,000
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 2,188,000
	TOTAL (C)	= $237,314,000
Categories D - G n/a		
	TOTAL COST	= $274,143,000

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Appendix

O

PROSPECTS FOR IMMUNIZING AGAINST ROTAVIRUS

Disease Description

Rotavirus infection causes an acute diarrheal disease. In developed countries it is usually of mild to moderate severity and self-limited within a week (rotavirus illness in technologically less developed countries will be considered separately in the second phase of this study). Typical clinical features have been determined primarily by observing patients affected severely enough to require admission to the hospital; most cases are so mild that medical attention is either not obtained or is handled on an outpatient basis.

In young infants, the illness often begins with vomiting, followed by an explosive, watery diarrhea. Diarrhea usually lasts twice as long as the vomiting, and may be severe enough to result in isotonic dehydration. The stools contain a relatively low concentration of sodium and may be mucoid in 20 to 25 percent of cases, but usually are devoid of blood or pus (Kapikian et al., 1982). Temperature elevations are present in about half of hospitalized patients, and generally are low grade. Concurrent clinical signs of pharyngitis, otitis media, or bronchitis (ronchi or wheezing) may occur in 10 to 25 percent of infants (Gurwith et al., 1981).

Mortality is unusual, but may occur in patients with severe dehydration if adequate fluid replacement is delayed. This situation is more frequent in developing countries. Community studies in developing nations also suggest that both symptomatic and asymptomatic infections result in growth retardation, which may have a significant impact on nutritional status (Mata et al., 1983). Neonatal infection may be frequent in certain hospital nurseries, but is usually either clinically asymptomatic or mild.

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Parents are often infected when their young children develop rotavirus diarrhea, but the parents usually are asymptomatic. Nevertheless, travelers diarrhea due to rotavirus has been described in adults (Ryder et al., 1981).

Pathogen Description

Rotavirus is a double-stranded RNA virus in the Reoviridae family, with a distinctive genome of 11 segments. Serological classification is somewhat confusing. Recent work finally has permitted separation of distinct serotypes based on outer capsid antigens detected by neutralization with hyperimmune sera (Wyatt et al., 1982). Four human serotypes have been described, and at least three additional distinct animal serotypes have been identified. Epidemiological studies are in progress to determine the prevalence of these serotypes in different parts of the world. The present data indicate that serotypes 1 and 2 are present worldwide and that serotype 3 may be less prevalent; serotype 4 has been found in only one or two outbreaks in Europe (Kapikian, personal communication, 1984). Some heterologous cross-reactivity has been reported between animal and human serotypes. The number and cross-reactivity of serotypes is obviously important for vaccine development.

Rotavirus subgroups exist in addition to serotypes. These involve inner capsid antigens detected by complement fixation, ELISA, or immune adherence assays (Kapikian, et al., 1981). Two well-defined subgroups, 1 and 2, also may be identified by differences in RNA patterns detected by electrophoresis in polyacrylamide-agarose gels (Kalica et al., 1981). A third subgroup may exist as well (Kapikian, personal communication, 1984). Serotype and subgroup determinations are controlled by different segments of the virus genome.

In vitro cultivation of human rotaviruses has been difficult. Strain Wa, the prototype serotype 1 rotavirus, originally was propagated in African green monkey kidney cells following 11 passages in newborn, germ-free piglets (Wyatt et al., 1980). Other strains, such as DS-1 (prototype of serotype 2), have been grown in vitro following rescue by genetic reassortment with readily grown bovine rotaviruses (Greenberg et al., 1981). Recently, many rotaviruses (up to 75 percent of stool isolates) have been cultivated in MA 104 cells, a primary embryonic cynomolgus monkey kidney line, following pretreatment of virus by trypsinization and low speed centrifugation (Sato et al., 1981; Urasawa et al., 1981).

Protective antigens have not been well defined. There is evidence of cross-protection between animal and human viruses, but the responsible determinants have not been identified (Wyatt et al., 1979).

Host Immune Response

Experimental studies in animals have demonstrated that feeding colostrum containing antibody to rotavirus during challenge is

protective. The colostrum is not protective if given prior to challenge, however. Epidemiological studies in humans suggest that breast-fed infants are similarly protected, supporting the role of intestinal antibody in the response to rotavirus.

Disease due to rotavirus occurs primarily in the 6–24 months age group, and by the third year of life over 90 percent of individuals have serologic evidence of prior infection. Limited data from experimental infections in human adults indicate that homologous protection from clinical manifestations persists for at least 19 months (Kapikian et al., 1983). Both heterotypic and heterosubgroup serologic responses also have been found (Kapikian et al., 1983). Prechallenge serum neutralizing antibody titer is associated with a lower frequency of symptomatic infection and virus shedding following virus challenge. A similar association appears to exist between disease and level of intestinal antibody, but the evidence is less clear-cut.

Asymptomatic, naturally acquired, neonatal rotavirus infection has been shown to reduce the severity of subsequent episodes, but not to confer immunity against reinfection (Bishop et al., 1983). Recent studies employing a live oral bovine rotavirus vaccine (RIT 4237) indicate that heterologous protection against symptomatic illness also occurs (Vesikari et al., 1983). Significant protection in immunized compared to non-immunized infants was observed during a natural outbreak of virus following immunogenicity and safety trials of this vaccine in Finland (Vesikari et al., 1984).

There are no longitudinal data available with which to address the question of the duration of protection. The period of vulnerability to symptomatic rotavirus infection is largely restricted to the first two to three years of life, however, indicating that immunity is acquired and may last for decades.

Disease Burden Estimates

Estimates of the disease burden imposed by rotavirus are based primarily on information from Kapikian et al. (1982), Klish (personal communication, 1983), Rodriguez (personal communication, 1984), and other sources cited below.

Although the frequency with which infection produces clinical illness drops precipitously after age three, infection and illness do occur in adults (Monto et al., 1983). Disease episodes in adults are generally quite mild, however, so they are not included in these estimates.

Only a small number of studies conducted in the United States could be found from which estimates of the burden of rotavirus illness could be made in a form suitable for this disease comparison. Most of these were done in relatively restricted areas.

In a family study in northern Virginia, Rodriguez and his colleagues (personal communication, 1984) have observed incidence rates for human rotavirus (HRV) gastroenteritis. Application of these rates to 1984 U.S. population projections results in the number of cases shown in Table O.1. Estimates derived from the observations of Koopman

TABLE O.1 Estimated Annual Incidence of Human Rotavitus Gastroenteritis

Age Group	Projected 1984 Population	Incidence Rate[a] (percent)	Predicted Number of Cases
Under 12 months	3,733,808	11	410,718
12-23 months	3,684,199	40	1,473,680
24-35 months	3,646,058	13	473,988
35-60 months	7,168,425	8	573,474
1-4 years			2,521,142
5-14 years	33,514,883	5	1,675,744

[a]From Rodriguez (personal communication, 1984). See discussion of uncertainty in the disease burden.

et al. (1984) on HRV gastroenteritis involving contact with a physician are shown in Table O.2.

Predictions made on the basis of data from Rodriguez (personal communication, 1984) are considered more likely to reflect the true incidence of rotavirus infections, because the study design includes a more active search for cases, some of which do not involve physician contact. The discrepancy between the estimates shown in Tables O.1 and O.2 is small for the under one year age group. The larger discrepancy in the 1–4 years age group could be explained by generally less severe symptoms and by a disinclination on the part of parents to seek medical care for minor illnesses in older children.

Limited information is available on which to base a distribution of the severity of non-hospitalized rotavirus illness between Morbidity

TABLE O.2 Estimated Predicted Annual Incidence of Human Rotavirus Gastroenteritis involving a Physician Contact

Age Group	Projected 1984 Population	Incidence Rate[a] (percent)	Predicted Number of Cases
Under 12 months	3,733,808	15	560,075
12-23 months	3,684,199	5	184,210
24-35 months	3,646,058	2	72,921
35-60 months	7,168,425	2	143,369
1-4 years			400,500

[a]From Koopman et al. (1984).

Categories A and B. The disease incidence peaks around 12 to 18 months (Klish, personal communication, 1983), declining dramatically after 3 years of age. Additionally, young infants by virtue of their size are more likely to experience more severe consequences (resulting from dehydration). In light of the above factors, it is assumed arbitrarily that 60 percent of cases under one year and 60 percent of cases in children one to two years of age will fall into Category B, and that no child older than two years of age will be sick enough to be placed in Category B.

Estimates of the numbers of non-hospitalized cases in various categories are shown in Table O.3. The typical duration of illness falling into Category A is estimated to be three days, and that falling into Category B to be five days.

The number of cases of rotavirus GE requiring hospitalization also can be estimated from the studies of Rodriguez et al. (1980). Hospitalizations average four days.

Koopman et al. (1984) reported a hospitalization rate of 11 percent for cases of rotavirus GE in children under 2 years; the majority of these (11 of 13) were under 1 year of age, as were the cases. Application of the 11 percent hospitalization rate to the number of cases predicted from the same researchers' incidence rates under 2 years of age yields a predicted 81,871 hospitalizations for rotavirus GE—a figure about three times higher than the estimate (21,919) derived from the data of Rodriguez et al. (1980), as shown in Table O.4.

The rates in the study by Rodriguez et al. (1980) are based on a significantly larger population and number of hospitalizations. It is possible that the discrepancy in the two predictions of hospitalized cases arises from an unusually high rate of hospitalizations in the clinical setting (i.e., private practice) associated with the rate reported by Koopman et al. For these reasons, predictions based on the Rodriguez et al. (1980) study are used for Category C in this disease comparison, although they are the lower figures.

No information, other than reports of occasional cases, is available from which to estimate deaths due to rotavirus in the U.S.

TABLE O.3 Distribution of Non-Hospitalized Cases of Human Rotavirus Gastrcenteritis

Age Group	Total Number of Cases	Category A	Category B
Under 12 months	410,718	164,287	246,431
12-23 months	1,473,680	589,472	884,208
24-60 months	1,047,462	1,047,462	
1-4 years	2,521,142	1,636,934	884,208
5-14 years	1,675,744	1,675,744	

Note: See text for basis of distribution.

TABLE O.4 Annual Incidence of Human Rotavirus Gastroenteritis Requiring Hospitalization

Age Group	Projected 1984 Population	Hospitalizations per 1,000 Population[a]	Predicted Number of Hospitalizations
Under 12 months	3,733,808	3.66	13,740
12-23 months	3,684,199	2.22	8,179
24-60 months	10,814,483	0.18	1,947
5-14 years		0	

[a]From Rodriguez et al. (1980).

(Kapikian et al., 1982). Carlson et al. (1978) reported an average of about four deaths from rotavirus in infants and young children in metropolitan Toronto, Canada, over a five-year period. The population of metropolitan Toronto at the mid-point of the years studied (1974) was 2,741,000 (United Nations, 1977). Extrapolation from the rate observed in Toronto yields a predicted 345 deaths in the U.S. population for 1984. A figure of this magnitude was considered somewhat high by the committee based on individual experience in a wide range of clinical settings. The authors of the Toronto study noted that language difficulties leading to poor communication between parents and physicians may have contributed to deaths in about half of the cases. This is considered to be a less likely occurrence in most of the U.S. Hence, a figure of 150 deaths from rotavirus is assumed, divided equally between the under one year and the 1–4 years age groups.

Estimates of the disease burden imposed by rotavirus, derived as described above, are shown in Table O.5. These estimates should not be taken as a definitive statement on the incidence and distribution of rotavirus illness, however, because time and resource limitations have necessitated the adoption of certain simplifying assumptions.

Uncertainty in the Disease Burden Estimates

Data on which to base estimates of the incidence of rotavirus illness, complications, and deaths are severely limited. The estimates of non-hospitalized rotavirus illness are based largely on incidence rates observed by Rodriguez and his colleagues (personal communication, 1984). The estimate of deaths from rotavirus illness is derived from a small study in Toronto, modified to reflect U.S. clinical experience: the presence of language barriers leading to poor communication between parents and physicians, noted by Carlson et al. (1978), may be a more serious problem in their study population than it is in the U.S.

Recent information (Rodriguez, personal communication, 1984) indicates that the incidence rate of unhospitalized rotavirus gastroen-

teritis may be slightly higher than that used in the above calculation (i.e., 6 percent vs. 5 percent).

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described and illustrated in Chapter 4. Total disease burden values (TDBVs) for rotavirus are calculated using estimates from Table O.5 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 281 (committee median perspective) and 227 (age-neutral perspective).

Vaccine Target Population

The principal target for a rotavirus vaccine is the young infant in the first few months of life. Vaccination at this stage could reduce the morbidity associated with rotavirus infection in the early years. A secondary target might be women of childbearing age. This would induce protection during the nursing period by stimulating higher titers of antibody in breast milk. The advantages of this approach to passive protection are reduced by the generally mild or asymptomatic nature of neonatal infection and by the small protection it offers against future symptomatic infection.

Suitability for Vaccine Control

Rotavirus appears to be ideally suited to vaccine control. There are a limited number of serotypes involved in human disease. Heterotypic responses occur during natural infection and would simplify the task of type representation in a vaccine. The immune response to natural infection occurs early in life, including the neonatal period, and significantly reduces the morbidity associated with later infection. This protection may be lifelong. The vaccine undoubtedly would be given orally, thus facilitating administration, although it might be found necessary to boost the immune response with parenteral vaccine. The target population is readily identified and vaccination could be combined with the current DPT and MMR programs in the United States, or with the World Health Organization Expanded Program on Immunization schemes for developing countries.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the benefit that could be produced by a vaccine candidate. This knowledge

TABLE O.5 Disease Burden Summary: Rotavirus

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localised pain, mild systemic reaction, or impairment requiring minor change in normal activities	Mild diarrhea	164,287	3	1,636,934	3	1,675,744	3						
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Severe diarrhea	246,431	5	884,208	5								
C	Requiring hospitalization	Dehydration	13,740	4	10,126	4								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)													
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)													
F	Total impairment													
G	Reproductive impairment resulting in infertility													
H	Death		75	n.a.	75	n.a.								

Note: n.a.=not applicable.

can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

Vaccine would be administered to the young infant well before the peak of illness. It is assumed, therefore, that all disease occurring in infants and children is potentially vaccine preventable. Thus, the numbers of cases of vaccine preventable rotavirus illness are the same as the numbers of cases in the disease burden (Table O.5).

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Total vaccine preventable illness values for rotavirus are calculated using estimates from Table O.5 and the two sets of IME values employed throughout this report. Using IME values based on a median of committee member perspectives, the total vaccine preventable illness value for rotavirus is 281; with the age-neutral perspective the value is 227.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the reduction in morbidity and mortality that could be produced by the rotavirus vaccine candidates, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of each vaccine. For both rotavirus vaccines, the predicted efficacy is 0.90. The potential reduction in morbidity and mortality for both rotavirus vaccines is 253 using the committee median perspective and 204 using the age-neutral perspective.

Prospects for Vaccine Development

The protective antigens for rotavirus have not been clearly identified or purified. The one experimental model available to study them is somewhat cumbersome, involving in utero immunization of susceptible animals with candidate vaccines, followed by challenge in the first week of life (Wyatt et al., 1979; Zissis et al., 1983). Experimental human challenge has been accomplished in adults (Kapikian et al., 1983). The most useful studies separate volunteers with high and low titers of pre-existing antibody, because it is difficult to find adults without some level of immunity. Safety, immunogenicity, and efficacy trials ultimately will have to be conducted in children and infants. This imposes important ethical and logistical constraints on vaccine development.

Several vaccine types can be developed (Kapikian et al., 1980). One approach uses a bovine rotavirus that grows well in tissue culture for induction of protection to cross-related human viruses. The

Nebraska calf diarrhea virus, strain RIT 4237, already has been tested in adults and young children (Vesikari et al., 1983). Although the first few passages of this isolate are not well documented, subsequent passage in primary cell culture is known, and the vaccine appears to be safe, attenuated, and protective. The extent of protection provided against different serotypes is not yet clear.

Human rotavirus grown in cell culture is a second vaccine candidate. Techniques using trypsin-treated virus grown in MA 104 cells or reassortment virus obtained by co-cultivation with bovine rotavirus presumably will permit culture of all major serotypes and subgroups of clinical importance. Attenuation may be achieved by a variety of methods, such as prolonged passage, temperature mutations, reassortment, or direct mutagenesis. Virulence of these strains can be studied in animal models (gnotobiotic newborn piglets) or in human adult volunteers with absent or low-titer serum antibody, however, work of this type is laborious and slow.

Predictions on the development of the two vaccine types described above are included in Chapter 5.

A third potential vaccine type would involve the use of recombinant DNA techniques to clone rotavirus genes for insertion into plasmid vectors. Production of rotavirus antigens in vitro could be employed as a source of purified antigen vaccines. This work is in its infancy and will require considerably more basic research before it reaches fruition; therefore, predictions for this vaccine are not included in Chapter 5.

A fourth vaccine type would be a synthetic peptide vaccine consisting of the peptide portions of key protective protein or glycoprotein antigens. These must be identified and synthesized before their protective efficacy can be demonstrated. It is uncertain how large these molecules will be or how difficult they will be to synthesize in quantity. Depending on size, they may or may not be immunogenic without inclusion of suitable adjuvants. Although some work is now being done in this area, this approach probably will be the slowest to yield a useful product; again, predictions for this vaccine are not included in Chapter 5.

Because the target population will be young infants on whom it will not be possible to perform controlled challenge studies, field studies will need to be designed to take advantage of the natural disease occurrence of rotavirus infection following immunization. This will necessitate a large population in a highly endemic region and prolonged follow-up. Such trials will require extensive field epidemiology and laboratory backup and undoubtedly will be expensive.

Major points at which the National Institutes of Health could have significant leverage include characterization of the virulence factors and relevant protective antigens, efforts to produce and test human cultivated rotavirus vaccine strains in experimental animals and human volunteers, and efforts to mount field tests of ready vaccines. This work could be incorporated into both the intramural and the extramural research programs of the National Institute of Allergy and Infectious Diseases.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to various vaccines are displayed together for comparison.

Lay Acceptance

Lay identification of rotavirus as a cause of diarrheal illness probably is fairly low, so a low score has been assigned in this category. The apparent severity of diarrheal illness, especially in young children, and its disruptive consequences result in a moderate lay score in this category. The lay perception of benefits probably would be only moderate, especially with physician cueing that the vaccine would not be for all causes of diarrhea. The barriers would be fairly low and relate primarily to anxiety over administration of a live virus to small children.

Provider Acceptance

Provider perceptions of the risk of illness and the severity both have been assumed to be moderately low. Assuming reasonable proof of efficacy for licensing, it is anticipated that providers would favor preventing a diarrheal illness and hence rank benefits fairly high. For physicians, a licensed live viral vaccine would pose few barriers, hence, a low score has been assigned to this category.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this disease comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Costs of Total Disease Burden and Vaccine Preventable Illness

Category A

# of cases = 3,476,965		
5% of cases typically receive 1 phys. visit at $30	= $	5,215,000
10% of cases typically receive treatment/medication at $10 [OTC medication]	= $	3,477,000
TOTAL (A)	= $	8,692,000

Category B

# of cases = 1,130,639		
50% of cases typically receive 1 phys. visit at $30		= $ 16,960,000
25% of cases typically receive diagnostic procedure at $25 [stool culture]		= $ 7,066,000
25% of cases typically receive treatment/medication at $25 [electrolyte replacement solution]	TOTAL (B)	= $ 7,066,000 = $ 31,092,000

Category C

# of cases = 23,866		
100% of cases typically receive 4 days of normal hospitalization at $400/day		= $ 38,186,000
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 716,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 4 days at $400/day		= $ 38,186,000
	TOTAL (C)	= $ 77,088,000
	TOTAL COST	= $116,872,000

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Appendix

P

PROSPECTS FOR IMMUNIZING AGAINST STREPTOCOCCUS GROUP B

Disease Description

Streptococcus group B (GBS) is almost exclusively a perinatal pathogen (Baker, 1977). While infections have been reported outside the perinatal period, primarily in individuals with impaired immune function, the major concern is with pregnant women and newborn infants. GBS is a common cause of urinary tract infection, amnionitis, and endometritis during pregnancy and is the principal cause of serious bacterial infection in the newborn. Early-onset disease occurs within the first few days of life, often resulting from intrauterine infection. Clinical manifestations range from respiratory distress and apnea to septic shock. Late-onset disease may occur from the end of the first week of life to three or four months of age. The usual clinical presentation is meningitis, with or without bacteremia.

GBS meningitis is followed by the usual sequelae: mental retardation, neurologic disease, seizure disorders, or deafness occur in about one-fourth of survivors. Epidemiologic studies have demonstrated that early-onset GBS disease is associated with several risk factors, including maternal amnionitis, prolonged rupture of placental membranes, deficiency of antibody to the type-specific polysaccharide antigen (Ia, Ib, II, and III), and prematurity (Boyer et al., 1983). Although the incidence of GBS is higher in premature infants than in term births, the number of term births is much higher, so term infants may account for more than 50 percent of clinically significant GBS infections, in some of these cases there are no identifiable maternal risk factors (Cochi and Feldman, 1983).

For early onset disease, a potential maternal source for the organism is an identified risk factor for GBS infection (Pass et al., 1979), but it is difficult to predict which infants born to carrier mothers are at greatest risk of disease. Degree of exposure (presumably inoculum size) appears to affect development of disease (Boyer, 1983; Pass et al., 1979; Pyati et al., 1983).

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Pathogen Description

Group B streptococci are subdivided into five serotypes (Baker, 1977), but have four protective polysaccharide antigens (Ia, Ib, II, and III). Serotype Ic shares type Ia polysaccharide and contains Ibc protein. Serotype III is responsible for about two-thirds of all invasive infections, and is found in 95 percent of isolates from infections occurring beyond the first week of life. Animal protection studies and clinical data indicate that antibodies to the sialated (complete) type-specific antigens are protective, variability in both lethal dose and susceptibility to opsonization has been reported among GBS strains.

Host Immune Response

Adults have been immunized with GBS polysaccharides from serotypes Ia, II, and III (Baker et al., 1978; DeCueninck et al., 1982; Eisenstein, et al., 1983; Fischer et al., 1983). The sialated polysaccharide vaccines induce an immune response, defined as an increase in antibody concentration of more than 1 g/ml, in 65 to 100 percent of recipients, depending on serotype and pre-immunization levels. GBS II vaccine is the best immunogen and GBS Ia the worst, based on preliminary reports (Fischer et al., 1983). The antibody isotypes produced in response to GBS vaccines and their persistence are not yet clear, but might be predicted from work with other polysaccharide vaccines. The extent to which antibodies to GBS will cross the placenta is an important consideration because fetal protection will depend on this mechanism. The protective level of antibody in human sera is difficult to estimate because most pregnant women have very low levels of antibody to GBS and still have low risk of infection, and because the attack rate in colonized infants is only 1 to 2 percent. Estimates of the level of antibody required for protection have been generated from animal models (Klegerman et al., 1983), and antibody concentrations measured in infected infants or their mothers always have been below the protective levels estimated from the animal models. However, a variety of factors (inoculum size, site, clinical complications) may affect the level required for protection (Gray and Dillon, 1984; Wilkinson, 1978).

Disease Burden Estimates

For these disease burden calculations, estimates of morbidity and mortality are confined to neonatal and maternal disease.

Neonatal Disease

Early-onset disease incidence rates have been estimated by hospitals with large perinatal centers and high proportions of premature and

high-risk newborns. Attack rates of early-onset disease range nationally from 1.35 to 5.4 cases per 1,000 live births (Baker and Barrett, 1973; Boyer et al., 1983; Franciosi et al., 1973; Pass et al., 1979). The Centers for Disease Control (CDC) has developed estimates of the national incidence of GBS early-onset disease by adjusting these local incidence rates for birthweight and applying them to national birth statistics. The national incidence of early-onset GBS disease using birthweight stratification is estimated to be between 1.6 and 2.1 per 1,000 live births, or about 7,198 cases per year (Cochi and Feldman, 1983).

The most common clinical manifestations of disease are septicemia (35 percent), pneumonia (35 percent), and meningitis (30 percent). The case fatality rate is approximately 27.5 percent (Baker and Edwards, 1983). Permanent neurological sequelae of varying severity (e.g., cortical blindness, deafness, severe developmental retardation, seizure disorders, spasticity, and hypothalamic dysfunction) may occur in up to 50 percent of survivors of meningitis (Baker, personal communication, 1984; Edwards et al., 1984; Wald et al., 1984). One study of young GBS survivors reported lower rates (30 percent) of CNS damage (Chin and Fitzhardinge, 1984). Table P.1 shows estimated morbidity and mortality associated with early-onset disease.

Late-onset disease Since late-onset disease does not appear to be affected by birthweight, no correction is needed to estimate incidence. The CDC estimates that late-onset disease accounts for about 35 percent of all cases of neonatal GBS disease (Cochi, personal communication, 1984). Thus, the number of cases of late-onset disease is estimated to be about 3,876 per year, or about 1 per 1,000 live births.

Manifestations of infection range from transient asymptomatic bacteremia to fulminant meningitis, which can be fatal within a few hours. The most common clinical manifestation is meningitis (85 percent of cases) (Baker and Edwards, 1983). The case fatality rate for meningitis is approximately 25 percent (Baker, personal communication, 1984). Approximately 50 percent of survivors of meningitis have permanent neurological sequelae, similar to those seen in early-onset disease (see above) (Baker, personal communication, 1984). Other common clinical manifestations are bacteremia, pneumonia, arthritis, and cellulitis. It is estimated that about 15 percent of cases will have bacteremia, and that the case fatality ratio will be 1 to 2 percent (Gotoff, personal communication, 1984). Table P.2 shows estimated morbidity and mortality associated with late-onset disease.

For the disease burden summary (Table P.4), neonatal meningitis, bacteremia, pneumonia, and septicemia are classified as Morbidity Category C; the average duration (16 days) has been calculated by weighting the duration of each of the component diseases to reflect the proportion of total cases each represents.

TABLE P.1 Morbidity and Mortality Associated With Early-Onset Disease

Number of cases of disease (Morbidity Category C)[a] (1.9/1,000 live births)	7,198
Septicemia (35%) (duration 10 days)	2,519
Pneumonia (35%) (duration 14 days)	2,519
Meningitis (30%) (duration 21 days)	2,159
Fatalities (27.5% of all cases)	1,979
Survivors of meningitis	1,566
Distribution of sequelae of meningitis (783 cases)	
Morbidity Category D (20%)	157
Morbidity Category E (60%)	470
Morbidity Category F (20%)	157

[a]Assumes no overlap among manifestations in Category C.

Maternal Disease

Postpartum patients are the single largest group of adult patients with proven GBS infection (Baker and Edwards, 1983). Clinical symptoms include fever, malaise, and uterine tenderness. It is estimated that GBS is the second most common cause of bacteremia following caesarean section, accounting for 20 percent of all cases (Losonsky, personal communication, 1983; Polk, personal communication, 1983). About 16 percent of women delivering by caesarean section develop endometritis/ parametritis, and GBS accounts for approximately 20 percent of these infections. In vaginal deliveries, approximately 4 percent of women develop endometritis and 20 percent of these cases are assumed to be caused by GBS. Some infections may result in infertility; however, data on this point are not available. Cases of endometritis and bacteremia are assumed to prolong hospitalization (Morbidity Category C) by seven days. Morbidity due to GBS in postpartum patients is summarized in Table P.3. Estimates for GBS bacteremia shown in Table P.3 are in general agreement with rates reported by Pass et al. (1982) and Gray and Dillon (in press). These studies also support the role of caesarean section as a risk factor for maternal disease.

Table P.4 summarizes the disease burden associated with neonatal and maternal GBS infection. The distribution of births between age groups, used to calculate the numbers for maternal GBS infections, is based on information from the National Family Planning and Reproductive Health Association (1983).

TABLE P.2 Morbidity and Mortality Associated With Late-Onset Disease

Number of cases of disease (Morbidity Category C)[a]	3,876
Meningitis (85%) (duration 21 days)	3,295
Bacteremia (15%) (duration 10 days)	581
Fatalities	
25% of cases of meningitis	824
1-2% of cases of bacteremia	9
Survivors of meningitis	2,471
Distribution of sequelae of meningitis (1,235 cases)	
Morbidity Category D (20%)	247
Morbidity Category E (60%)	741
Morbidity Category F (20%)	247

[a]Estimated to be 35 percent of all cases of neonatal GBS disease (Cochi, personal communication, 1984). Assumes no overlap among manifestations in Category C.

Uncertainty in the Disease Burden Estimates

GBS is not notifiable to the Centers for Disease Control (CDC), however, 27 states voluntarily report cases of GBS meningitis. National data on the incidence of GBS, associated complications or sequelae, and fatalities are not available in the literature and are not collected by any reporting agency. The disease burden was estimated in consultation with experts at the CDC and with the assistance of physicians knowledgeable about the epidemiology and clinical manifestations of GBS. Some published studies (cited in the text) also were reviewed.

Calculation of Comparative Total Disease Burden Values

The method used in this study to compare morbidity and mortality resulting from various diseases is described in Chapter 4. Total disease burden values (TDBVs) for streptococcus group B are calculated using estimates from Table P.4 and infant mortality equivalence values based on a median of committee member perspectives or on an age-neutral perspective. TDBVs thus obtained are 3,957 (committee median perspective) and 3,915 (age-neutral perspective).

TABLE P.3 Maternal GBS Infections

	Vaginal Deliveries	Caesarean Sections
Total number (%) of deliveries estimated for 1984	3,182,203 (84%)	606,134 (16%)
Number of cases of endometritis/ parametritis	127,288[a]	96,981[b]
Number caused by GBS (20%)	25,458	19,396
Number of cases of bacteremia		15,153[c]
Number caused by GBS (20%)		3,031

[a]Estimated to be 4 percent of vaginal deliveries.
[b]Estimated to be 16 percent of caesarean sections.
[c]Estimated to be 2 to 3 percent of caesarean sections.

Vaccine Target Population

The target population for protection is the newborn infant. The target population for active immunization would be pregnant women, although immunization might take place prior to pregnancy. Conjugation of the polysaccharide antigen with a protein carrier might increase the antigenicity of a streptococcus group B vaccine. The native polysaccharide antigens already have been shown to be immunogenic in nonpregnant adults. The incidence of reactions is relatively low, less than that associated with the pneumococcal vaccine, in addition, Hemophilus influenzae type b polysaccharide vaccine has been used in pregnant women without significant complications (Hill, 1983). However, a foreseeable problem in vaccinating such a target population would be the usual hesitancy to expose pregnant women to exogenous substances.

Suitability for Vaccine Control

Theoretically, a program of active immunization aimed at pregnant women would have the best prospects of controlling early-onset and late-onset GBS disease. Successful vaccine control by this approach, will require elicitation of antibodies capable of crossing the placenta to protect the fetus. Alternative strategies include passive immunization of the newborn, which would not prevent early-onset disease that develops in utero, and various forms of chemoprophylaxis, which would be unlikely to prevent late-onset disease (Fischer et al., 1983). Chemoprophylaxis has been studied during pregnancy, labor, and the

TABLE P.4 Disease Burden Sumnary: Streptococcus Group B

Morbidity Category	Description	Condition	Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hospitalization	Meningitis; bacteremia pneumonia; septicemia; postpartum bacteremia/ endometritis	11,083	16					24,305	7	23,560	7		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Sequelae of meningitis	404	n.a.										
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Sequelae of meningitis	1,211	n.a.										
F	Total impairment	Sequelae of meningitis	404	n.a.										
G	Reproductive impairment resulting in infertility													
H	Death		2,812	n.a.										

Note: Durations are weighted averages.
n.a.=not applicable.

postpartum period: the advantages and limitations of the different forms of chemoprophylaxis have been discussed elsewhere (Fischer et al., 1983). In general, chemoprophylaxis does not appear to be as practicable as vaccine control because of its complex logistical requirements for serological screening, culturing, and antibiotic administration.

Vaccine Preventable Illness Estimates

Defining the target population is the first step in calculating the possible reduction in morbidity and mortality that could be produced by a vaccine candidate. This knowledge can be translated into an estimate for vaccine preventable illness (VPI). VPI is defined as the number of cases, complications, sequelae, and deaths that could be prevented by immunization of the entire target population with a hypothetical vaccine that is 100 percent effective.

Over 50 percent of clinically significant neonatal GBS disease occurs in term infants. It is assumed that maternal immunization would provide passive immunity in the term neonate of sufficient duration to protect against both early- and late-onset disease. In the premature infant, however, even high levels of the appropriate (IgG) maternal antibody might not result in sufficient placental transport to confer protection. Therefore, only 90 percent of neonatal GBS disease is assumed in this exercise to be potentially preventable by maternal immunization. Theoretically, it also should be possible to prevent 100 percent of maternal disease caused by GBS with an ideal vaccine that decreased or eliminated carriage of GBS. Table P.5 shows a summary of VPI for GBS.

Vaccine Preventable Illness Values

The concept of "infant mortality equivalence value" is used to standardize vaccine preventable illness scores, just as it is used to standardize disease burden values (see Chapter 4). Vaccine preventable illness values for GBS are calculated using estimates from Table P.5 and the two sets of IME values employed throughout this report, using IME values based on a median of committee member perspectives, the total vaccine preventable illness value for GBS is 3,570; with the age-neutral perspective the value is 3,528.

Possible Reduction in Morbidity and Mortality (PRMM)

To calculate the possible reduction in morbidity and mortality (the maximum potential health benefits) that could be produced by the GBS vaccine candidate, the total vaccine preventable illness value for each IME perspective is multiplied by the predicted efficacy of the

TABLE P.5 Vaccine Preventable Illness: Streptococcus Group B

			Under 1 Year		1-4 Years		5-14 Years		15-24 Years		25-59 Years		60 Years and Over	
Morbidity Category	Description	Condition	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain, mild systemic reaction, or impairment requiring minor change in normal activities													
B	Moderate pain or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed													
C	Requiring hospitalization	Meningitis; bacteremia pneumonia; septicemia; postpartum bacteremia/ endometritis	9,966	16					24,305	7	23,580	7		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity)	Sequelae of meningitis	364	n.a.										
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity)	Sequelae of meningitis	1,090	n.a.										
F	Total impairment	Sequelae of meningitis	364	n.a.										
G	Reproductive impairment resulting in infertility													
H	Death		2,531	n.a.										

vaccine. For the GBS vaccine candidate, the predicted efficacy is 0.80. Thus, the potential reduction in morbidity and mortality for the GBS vaccine is 2,856 using the committee median perspective and 2,823 using the age-neutral perspective. These values are not adjusted for vaccine adverse effects or anticipated utilization. Use of PRMM values for comparing vaccines is described in Chapter 7.

Prospects for Vaccine Development

The type-specific polysaccharide antigens were identified as the protective antigens many years ago by Lancefield (1972). More recently, the sialated polysaccharide antigens have been purified and characterized by Jennings et al. (1980, 1983a, 1983b). Because the polysaccharide antigens may vary somewhat in molecular size, it may be possible to develop more immunogenic antigens consisting of conjugates or other larger polymers. The purified sialated polysaccharide antigens have been utilized in clinical trials to demonstrate their immunogenicity. A pilot study of GBS III vaccine in pregnant women recently began in Houston and is expected to be completed in late 1984 (Baker, personal communication, 1984). Success of maternal immunization is dependent on the production of the IgG isotype of antibodies that cross the placenta rather than IgM. Hence, candidate vaccines should be assessed for the classes of antibody they produce as well as for maternal immunogenicity.

Active immunization of the neonate probably would not be beneficial because the majority of cases of early-onset disease result from infection prior to delivery. Also, very young infants do not respond predictably to polysaccharide antigens, even when they are conjugated.

If active immunization of the mother is not possible, then passive immunization of the newborn could be carried out using an immunoglobulin reagent with known quantities of antibody to the GBS serotypes, prepared from immunized or immune donors (Santos et al., 1981; Vogel et al., 1980). If the studies in Houston referred to above confirm that immunization in pregnant women is effective and without significant side effects, then clinical trials could be carried out to demonstrate efficacy in prevention of neonatal early- and late-onset GBS disease. These clinical trials would require very large populations because of the relatively low incidence of the disease. Hence, they may require the collaboration of a number of centers or groups.

Anticipated Vaccine Utilization

The health belief model parameters (perceptions of risk of illness, severity, vaccination benefits, and barriers) used to predict vaccine utilization are described in Chapter 6, where scores assigned to the vaccines are displayed together for comparison.

Lay Acceptance

Lay perceptions of the risk and severity of illness have been judged to be moderately low, primarily because the public is thought to be relatively unfamiliar with GBS disease. The potential benefits of the vaccine probably would be perceived as high because of physician cueing. Many women are reluctant to be vaccinated when pregnant, however, so the barriers to vaccination may be high.

Provider Acceptance

Overall, provider perception of the risk of illness is expected to be moderate (the high perception of risk in some areas will be balanced by a very low perception of risk among providers for populations in which the disease is rare). The perceived severity of disease is likely to be high. Even though the predicted efficacy of the vaccine is relatively low, when it is efficacious it will prevent very severe disease; thus, perceived benefits are likely to be high. Liability concerns arising from immunization of pregnant women may act as a barrier to vaccination; these concerns may be somewhat less than those associated with a live preparation. Provider acceptance also may depend, in part, on the availability of alternative strategies such as chemoprophylaxis.

Cost of Illness

The scope and purpose of the calculations included below are described in Chapters 4 and 7. These calculations are based on certain simplifying procedures and assumptions that have been judged not to compromise their utility for the purposes of this disease comparison. The total costs should be taken only as an approximation of the direct cost of this disease.

Cost of Total Disease Burden

Category A & B n/a

Category C

Early and late onset disease - meningitis, bacteremia, pneumonia, septicemia
# of cases = 11,083
100% of cases typically receive 7 days neonatal ICU hospitalization at $800/day = $ 62,009,000
100% of cases typically receive additional 14 days of normal hospitalization at $400/day = $ 62,009,000

100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate		
7 days at $800/day		= $ 62,009,000
14 days at $400/day		= $ 62,009,000
100% of cases typically require 1 follow-up phys. visit at $30		= $ 332,000
	TOTAL	= $248,368,000
Maternal disease - postpartum bacteremia/ endometritis		
# of cases = 47,885		
100% of cases typically have hospital stay prolonged by 7 days at $400/day		= $134,078,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 7 days at $400/day		= $134,078,000
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 1,437,000
	TOTAL	= $269,593,000
	TOTAL (C)	= $517,961,000
Category D - sequelae of meningitis; assuming 20 year duration		
# of cases = 404		
total annual costs for treatment and/or care = $2,000/case; for 20 years at 5% discount rate, total present value/case = $26,000		= $ 10,504,000
	TOTAL (D)	= $ 10,504,000
Category E - sequelae of meningitis; assuming 20 year duration		
# of cases = 1,211		
total annual costs for treatment and/or care = $5,000/case; for 20 years at 5% discount rate, total present value/case = $65,000		= $ 78,715,000
	TOTAL (E)	= $ 78,715,000
Category F - sequelae of meningitis; assuming lifetime approx. 25 years		
# of cases = 404		
total annual costs for treatment and/or care = $20,000/case; for 25 years at 5% discount rate, total present value/case = $296,000		= $119,584,000
	TOTAL (F)	= $119,584,000
Category G n/a		
	TOTAL COST	= $726,764,000

Cost of Total Vaccine Preventable Illness

Category A & B n/a

Category C

Early and late onset disease - meningitis, bacteremia, pneumonia, septicemia

# of cases = 9,966		
100% of cases typically receive 7 days neonatal ICU hospitalization at $800/day		= $ 55,810,000
100% of cases typically receive additional 14 days of normal hospitalization at $400/day		= $ 55,810,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate		
7 days at $800/day		= $ 55,810,000
14 days at $400/day		= $ 55,810,000
100% of cases typically require 1 follow-up phys. visit at $30		= $ 299,000
	TOTAL	= $223,539,000

Maternal disease - postpartum bacteremia/ endometritis

# of cases = 47,885		
100% of cases typically have hospital stay prolonged by 7 days at $400/day		= $134,078,000
100% of cases typically receive diagnostic testing and treatment at rate equivalent to daily inclusive hospital rate, 7 days at $400/day		= $134,078,000
100% of cases typically receive 1 follow-up phys. visit at $30		= $ 1,437,000
	TOTAL	= $269,593,000
	TOTAL (C)	= $493,132,000

Category D - sequelae of meningitis; assuming 20 year duration

# of cases = 364		
total annual costs for treatment and/or care = $2,000/case; for 20 years at 5% discount rate, total present value/case = $26,000		= $ 9,464,000
	TOTAL (D)	= $ 9,464,000

Category E - sequelae of meningitis; assuming 20 year duration

# of cases = 1,090		
total annual costs for treatment and/or care = $5,000/case; for 20 years at 5% discount rate, total present value/case = $65,000		= $ 70,850,000
	TOTAL (E)	= $ 70,850,000

Category F - sequelae of meningitis; assuming lifetime approx. 25 years

of cases = 364

total annual costs for treatment and/or care = $20,000/case; for 25 years at 5% discount rate, total present value/case = $296,000 = $107,744,000

TOTAL (F) = $107,744,000

Category G n/a

TOTAL COST = $681,190,000

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Appendix

Q

QUESTIONNAIRE FOR ASSESSING MORBIDITY-MORTALITY TRADE-OFFS

Attachment 1 lists eight generic categories of clinical consequences that may be associated with each disease and vaccine that we are considering. From the CDC and other sources we are compiling estimates, for each disease, of the annual number of days of morbidity in Categories A through C and of the annual number of events in Categories D through H. In order to develop a composite measure of the health impact of the various diseases, it is necessary to gauge the relative importance, or disutility, of the various categories of morbidity and mortality at different ages.

Each member of the committee is being asked to prepare a personal assessment of the relative weights to be assigned to each of the eight categories. Because the relative values may depend upon the age of the afflicted population, we will be attempting an assessment for morbidity in each of six age groups: (1) infants under 1 year of age; (2) children from 1–4 years old; (3) children from 5–14 years old; (4) adolescents and young adults from 15–24 years old; (5) adults from 25–59 years old; and (6) adults 60 years of age or older.

There are a number of different ways we could approach this problem of assessing relative values. For the sake of consistency, we ask that each committee member try to work through the thought exercise in the same way as described below.

Attachment 2 is the recording form to be filled out.

Instructions for Completing the Recording Form

To understand how to complete the form consider column 1 of Attachment 2 which refers to episodes of illness or of the consequences of illness occurring in infants under 1 year of age. The unit measure for morbidity in Categories A through C is a day of morbidity in a patient, in Categories D through G, the unit measure is (usually) a lifelong episode. Category H means death in the near term.

Your task will be to estimate the number of units in each morbidity category that you consider to carry the same disutility as one death. For example, consider morbidity state E, moderate to severe chronic disability. You might think such a disability would be dreadful for an infant of under 1 year to incur, nearly as bad as dying. In this case

Attachment 1

Morbidity Categories

A. Moderate localized pain and/or mild systemic reaction or impairment requiring minor change in normal activities.

B. Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., house-bound or in bed.

C. Severe pain, severe short-term impairment, or hospitalization.

D. Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity).

E. Moderate to severe chronic disability (requiring hospitalization, special care or other major limitation of normal activity).

F. Total impairment.

G. Reproductive impairment resulting in infertility.

H. Death.

you might judge that two cases of moderate to severe disability are equivalent (in how bad they seem to you) to one death. If so, you would enter the number "2" in the space next to Category E in column 1 on Attachment 2. Alternatively, you might believe that people, especially children, can adapt reasonably well to severe disability, and therefore you would be willing to accept a larger number of cases in lieu of one death, if you were willing to balance 25 cases of severe disability against one death, you would enter the number "25" in the space next of Category E in column 1. At the other extreme, you might consider severe disability to be worse than death, and be willing to balance only 0.5 cases of moderate to severe lifelong disability starting under 1 year of age against one death. You would then enter 0.5. Bear in mind that Category E refers to "moderate to severe chronic disability" that requires continuing hospitalization or special care. While the specific nature and severity of a "moderate to severe chronic disability" would naturally influence your rating, we are aiming here to get an overall sense of your disutility across the range of moderate to severe chronic disabilities.

As another example, let's consider one of the acute morbidity categories measured in days, say A, moderate localized pain and/or mild systemic reaction requiring minor change in normal activities. Again, we want to assess units of the morbidity category that would just

Attachment 2

Age Related Morbidity and Mortality "Trade-offs"

Category	Unit	Column 1 Under 1 Year	Column 2 1-4 Years	Column 3 5-14 Years	Column 4 15-24 Years	Column 5 25-59 Years	Column 6 60 Years and Over
A. Moderate localized pain and/or mild systemic reaction or impairment requiring minor change in normal activities.	Days						
B. Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed	Days						
C. Severe pain, severe short term impairment, or hospitalization	Days						
D. Mild chronic disability (not requiring hospitalization, institutionalization or other major limitation of normal activity)	Cases						
E. Moderate to severe chronic disability (requiring hospitalization, special care or other major limitation of normal activity)	Cases						
F. Total impairment	Cases						
G. Reproductive impairment resulting in infertility	Cases						
H. Death	Cases	1	1	1	1	1	1
Deaths		1					

balance the disutility of one death in the age group being assessed. We expect that these units will be very large because we are measuring relatively mild consequences in terms of days spent experiencing them, you might find it helpful to bear in mind that a child under 5 years has a life expectancy of more than 25,000 days. If a day in the morbidity state is equivalent to the loss of a modest fraction of a day of life, then the number of days in the morbidity state judged to be

equivalent to one death could be many multiples of 25,000. For example, you might think that 150,000 days of moderate localized pain for an infant (under 1 year) (morbidity state A) would be equivalent to a single death in the same age category, and you would enter this number on Attachment 2 opposite Category A in column 1. Of course, your estimate might be higher or lower, in any of these estimates there is no universally "right" answer, only what seems to you to be the most balanced trade-off.

After you have completed your trade-off judgments for infants under 1 year of age (column 1, Attachment 2), carry out the analogous exercise for the other age categories (i.e., columns 2–6).

You may find it helpful to imagine yourself as a typical member of the population at risk for each of these morbidity categories. Thus, in a population of 100,000, one annual death would represent a 1/100,000 annual risk of death for you. 100,000 days of moderate, generalized (Category B) morbidity would represent an average of one morbidity day for you. An equivalence between one death and 100,000 days of morbidity Category B, then, would reflect an equivalence between 1/100,000 risk of death and one day of moderate morbidity.

In assessing these trade-offs, also bear in mind that these are intended to reflect the relative values you would attach to the health consequences (including physical and psychosocial aspects) of these outcomes, and not the direct economic consequences (i.e., treatment costs). The latter are being analyzed separately based on cost data being supplied by CDC and other sources. In other words, if you imagine yourself as a typical person at risk for these consequences, you should respond as though you were fully covered by health insurance in trading off the risks.

Instructions for Estimating Mortality Trade-off Across Age Groups

The lowest row on Attachment 2 asks you to indicate the relative trade-off among deaths in each age group. Here comparisons are against a single death in an infant under 1 year of age. The question is how many deaths in each of the other age groups would just balance one death in an infant. You might feel all deaths are equivalent, and mark a "1" in all the spaces for each age group. You might feel a death in an adult (25–59 years) is even worse than a death in an infant and assign a number smaller than 1.0 to such adult deaths (column 5). You might be willing to balance 10 deaths in the elderly (column 6) against one early death. Again, any trade-offs are legitimate so long as they reflect your best personal judgment.

Consider also the value you would assign to a first-trimester fetal loss compared to the death of one infant (up to one year of age). In other words, if you valued the loss of one fetus as severely as the death of an infant, your relative valuation would be 1.0. If you would be willing to accept 100 first-trimester fetal deaths as balancing one infant death, your relative valuation would be 100. If it would take even more fetal loss to balance one infant death, then your relative valuation would be higher. Of course, it could in principle be lower as well.

Appendix

R

TECHNICAL NOTES

The calculations described in Chapters 4, 7, and 9 were conducted using the MULTIPLAN© spread sheet program, Version 1 (Microsoft Corporation, 10700 Northup Way, Bellevue, WA 98004), run on an IBM Personal Computer (International Business Machines, Boca Raton, FL 33432). The program requires 64K of memory.

Inquiries regarding templates for these calculations for use with the MULTIPLAN© program should be directed to:

Director
Division of Health Promotion and Disease Prevention
Institute of Medicine
National Academy of Sciences
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Use of the MULTIPLAN© program or the IBM Personal Computer do not constitute endorsement by the Institute of Medicine or the National Academy of Sciences.

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Appendix

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BIOGRAPHICAL NOTES ON COMMITTEE MEMBERS

SAMUEL L.KATZ is the Wilburt C.Davison Professor of Pediatrics and chairman of the Department of Pediatrics at Duke University, a position he has held since 1968. His research has focused on human virology, infectious diseases, and immunization. He has served on a variety of scientific advisory boards, committees and consultative groups, and editorial boards relating to problems in infectious diseases and immunization. He received his M.D. degree from Harvard University and his B.A. degree from Dartmouth College.

JOHN (A.J.) BEALE has been director of research for Wellcome Biotechnology Limited in the United Kingdom since the formation of that company in 1982. Before that he was director of biological products at The Wellcome Foundation Limited for ten years. He studied medicine at Guy's Hospital and specialized in infectious disease and microbiology. He spent two years in the mid-fifties as a research fellow in virology at the Hospital for Sick Children in Toronto.

MARSHALL H.BECKER is professor and chairman in the Department of Health Behavior, School of Public Health, and professor in the Department of Pediatrics, School of Medicine, at the University of Michigan in Ann Arbor. From 1974 to 1977 he was associate professor in the departments of Pediatrics, Behavioral Sciences, and Social Relations at Johns Hopkins University. He has published extensively on such topics as beliefs and attitudes as determinants of individuals' health-related behaviors, patient compliance with prescribed regimens, diffusion of innovations among health professionals, drug-prescribing patterns, and different approaches to organizing the delivery of medical care. He is a medical sociologist and holds M.P.H. and Ph.D. degrees from the University of Michigan.

JAMES CHIN is chief of the Infectious Disease Section of the California Department of Health Services. His specialization in the epidemiology and control of infectious diseases began with the Hooper Foundation in San Francisco, and with the Institute for Medical Research in Kuala Lumpur, Malaysia. Dr. Chin has served on many national committees related to infectious disease control, including the American Public Health Association Committee on Infectious

Diseases, the National Advisory Committee on immunization Practices, and the Armed Forces Epidemiology Board. He received a B.S. in 1954 from the University of Michigan, an M.D. in 1958 from the State University of New York, Downstate, and an M.P.H. in 1961 from the University of California, School of Public Health, Berkeley.

PURNELL W.CHOPPIN is Leon Hess Professor of Virology and vice president for academic programs at The Rockefeller University. He has been at that university since 1957, where he began as a postdoctoral fellow. He became a professor in 1970. His research has been on the structure, replication, and mechanisms of pathogenesis of myxoviruses and paramyxoviruses; the structure and function of viral membranes; and viral-cell membrane interactions. He received an M.D. degree from Louisiana State University, and his residency training in internal medicine at Barnes Hospital, Washington University, St. Louis.

THEODORE C.EICKHOFF has been director of internal Medicine at Presbyterian St. Luke's Medical Center and professor of medicine at the University of Colorado School of Medicine, Denver, since 1981. From 1968 to 1981 he was head of the Division of Infectious Disease at the University of Colorado School of Medicine. He has participated in a number of vaccine development and evaluation studies, and is a member of the American College of Physicians' Immunization Advisory Committee. Presently, he is chairman of the Vaccines and Related Biological Products Advisory Committee, National Center for Drugs and Biologics, Food and Drug Administration, and is president of the Infectious Diseases Society of America. He received his M.D. degree from Case Western Reserve University School of Medicine, and conducted his internal medicine residency and infectious disease fellowship training at the Harvard Medical Unit, Boston City Hospital.

FRANCIS A.ENNIS has been a professor of medicine and of molecular genetics and microbiology at the University of Massachusetts Medical School since 1982. From 1973 to 1981 he was director of the Division of Virology at the Bureau of Biologics in the Food and Drug Administration, and from 1970 to 1973 was co-director of the Division of Infectious Diseases at Boston University Medical School. His research interests concern immune responses to virus infections and vaccines. He has an A.B. degree from Boston College and an M.D. degree from Tufts University.

HARVEY V.FINEBERG became dean at the Harvard School of public Health in 1984 and had been a faculty member there since 1973. His research interests include the innovation and diffusion of new medical technology, the evaluation of medical practices, the application of decision sciences to health care, and the interface between medical science and public policy. He holds A.B., M.D., and Ph.D. degrees from Harvard.

MAURICE R.HILLEMAN is director, Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, where he also has

held the positions of senior vice president and director of virus and cell biology research. From 1948 to 1958 he was chief of viral respiratory disease research at the Walter Reed Army Institute of Research; prior to that, he was chief of viral diseases at E.R.Squibb & Sons. He holds an adjunct professorship in pediatrics in the School of Medicine at the University of Pennsylvania and had prior appointments at the University of Maryland and Rutgers University. Dr. Hilleman has had a long career in academia, government, and industry and has engaged in a wide variety of basic and applied research activities in virology, immunology, epidemiology, vaccine development, and clinical evaluation. He has served as a long-term advisor to the U.S. government and the World Health Organization. He holds a Ph.D. degree from the University of Chicago in Microbiology and Virology.

GERALD T.KEUSCH has been professor of medicine and chief of the Division of Geographic Medicine, Department of Medicine, at Tufts University School of Medicine, Boston, since 1979. Prior to that, he was assistant and then associate professor of medicine at Mount Sinai School of Medicine in New York. He has been interested in the pathogenesis of diarrheal diseases and in the interaction of malnutrition and infection, and has worked in both the laboratory and the field in developing countries. He has an M.D. degree from Harvard Medical School and an A.B. from Columbia College.

RICHARD F.KINGHAM is a partner in the Washington, D.C., law firm of Covington & Burling. Since joining the firm in 1973, he has specialized in federal regulation of foods, drugs, and related products. He was involved in contract negotiations and legislative drafting in connection with the 1976 swine flu immunization program and subsequently participated in a number of proceedings relating to federal regulation of vaccines and proposals for vaccine injury compensation systems. He has served as a lecturer at the University of Virginia Law School since 1977, most recently teaching seminars in food and drug law and administrative law. He holds a J.D. degree from the University of Virginia and a B.A. degree from George Washington University.

BERNARD ROIZMAN is the Joseph Regenstein Distinguished Service Professor in the Department of Molecular Genetics and Cell Biology and chairman of the Committee on Virology at the University of Chicago, where he has been on the faculty since 1965. Prior to that he was on the faculty of Johns Hopkins University. His scientific interests center on the molecular biology of herpesviruses. He has been on the editorial board of numerous scientific journals and served as a member or chairman of advisory and review panels for the American Cancer Society, the National Science Foundation, the National institutes of Health, the Leukemia Research Foundation, the International Committee for Taxonomy of Viruses, the International Microbial Commission, Emory University, Northwestern University, Showa University, the Sloan Kettering Institute, the Goodwin Institute for Cancer Research, the Institute Merieux, and others. He is a member of the National Academy of Sciences and holds a Sc.D. from Johns Hopkins University.

HENRY R.SHINEFIELD is chief of pediatrics at the Kaiser Permanente Medical Center in San Francisco and clinical professor of pediatrics at the university of California School of Medicine in San Francisco. He has served as a member or chairman of many committees on infectious disease, anti-infective agents, and vaccines for the National institutes of Health and the Food and Drug Administration. He is a member of national and regional medical, pediatric, and infectious diseases societies, and has served as a consultant or as a member of the editorial boards of pediatric and infectious diseases journals.

JANE E.SISK is a project director in the Health Program of the Congressional Office of Technology Assessment (OTA), a position she has held since 1981. She has recently completed a project on the medical devices industry and previously worked on studies of federal vaccine policies and on cost-effectiveness analyses of influenza and pneumococcal vaccines. From 1978 to 1981, she was a Veterans Administration scholar based at the National Center for Health Services Research, where she examined the use of medical technologies under different financing and organizational arrangements. She received a Ph.D. in economics from McGill University and a B.A. in international relations from Brown University.

CLADD E.STEVENS became head of the Laboratory of Epidemiology of The New York Blood Center in 1981. For the preceding seven years, she had worked in that laboratory with the late Wolf Szmuness, following two years in Taiwan as a post-doctoral fellow. Her research on the epidemiology of viral hepatitis has included extensive experience in efficacy trials of hepatitis B vaccine. She has an M.D. degree from Baylor College of Medicine and an M.P.H. degree from the University of Washington.

LEROY WALTERS has been director of the Center for Bioethics at the Kennedy Institute of Ethics, Georgetown University, since 1971. He is also an associate professor of philosophy at Georgetown and has served on numerous national committees and advisory panels, including the Recombinant DNA Advisory Committee, National Institutes of Health, and the National Council on Health Care Technology, Department of Health and Human Services. He is editor of the Bibliography of Bioethics (Vol. 1–9), co-editor of Contemporary Issues in Bioethics, and the author of many articles on ethical issues in biomedical research. He is also a member of the editorial boards of the Journal of Medicine and Philosophy, IVF: The Journal of In Vitro Fertilization and Embryo Transfer, and the American Journal of Reproductive Immunology. He has a M. Phil, degree and a Ph.D. in Religious Studies (Ethics) from Yale University.

MILTON C.WEINSTEIN is professor of policy and decision sciences at the Harvard School of Public Health, a position he has held since 1980. He teaches decision analysis, health economics, and quantitative methods to students of medicine, health policy and management, and biostatistics. His research activities center around methods for

evaluation of medical practices and technologies, and for resource allocation in health care and health science research. He is principal author of two books, Hypertension; A Policy Perspective, and Clinical Decision Analysis. He is president of the Society for Medical Decision Making for 1984–85. He holds A.B. and A.M. degrees in applied mathematics from Harvard University, and M.P.P and Ph.D. degrees in public policy analysis from the John F.Kennedy School of Government.

Appendix

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ADDITIONAL SOURCES OF ADVICE TO THE COMMITTEE

Charles A.Alford, The University of Alabama in Birmingham.
William P.Allen, National Institutes of Health, Bethesda, Md.
Miriam J.Alter, The Centers for Disease Control, Atlanta, Ga.
Larry J.Anderson, The Centers for Disease Control, Atlanta, Ga.
Porter W.Anderson, The university of Rochester Medical Center
Bascom Anthony, Harbor-UCLA Medical Center, Torrance, Calif.
Carol J.Baker, Baylor College of Medicine, Houston, Tex.
William H.Bancroft, Walter Reed Army Medical Center, Wash., D.C.
John G.Bartlett, The Johns Hopkins University School of Medicine, Baltimore, Md.
Joel B.Baseman, The University of Texas Health Science Center at San Antonio.
Edwin H.Beachey, Veterans Administration Medical Center, Memphis, Tenn.
Alan L.Bisno, University of Tennessee Center for the Health Sciences, Memphis.
Edward W.Brink, The Centers for Disease Control, Atlanta, Ga.
Charles Brinton, University of Pittsburgh, Pa.
Claire V.Broome, The Centers for Disease Control, Atlanta, Ga.
Philip A.Brunell, The University of Texas Health Science Center at San Antonio.
Yvonne J.Bryson, UCLA School of Medicine, Torrance.
Thomas M.Buchanan, Seattle Public Health Hospital, Wash.
James P.Carlos, National Institutes of Health, Bethesda, Md.
Willard Cates, Jr., The Centers for Disease Control, Atlanta, Ga.
James D.Cherry, University of California at Los Angeles School of Medicine.
Wallace A.Clyde, Jr., The University of North Carolina at Chapel Hill.
Stephen L.Cochi, The Centers for Disease Control, Atlanta, Ga.
Michael F.Cole, National Institutes of Health, Bethesda, Md.
Lawrence Corey, University of Washington, Seattle.
Rebecca A.Cox, San Antonio State Chest Hospital, Tex.
Floyd W.Denny, The University of North Carolina at Chapel Hill.
Jules L.Dienstag, Harvard Medical School, Boston, Mass.
Hugh C.Dillon, Jr., The University of Alabama in Birmingham.
R.Gordon Douglas, Jr., The New York Hospital-Cornell Medical Center, N.Y.

Walter R.Dowdle, The Centers for Disease Control, Atlanta, Ga.
Gordon R.Dreesman, Baylor College of Medicine, Houston, Tex.
David J.Drutz, University of Texas Health Sciences Center, San Antonio.
Robert Edelman, National Institutes of Health, Bethesda, Md.
Paul Eggers, Health Care Financing Administration, Baltimore, Md.
Roger W.Evans, Battelle Human Affairs Research Centers, Seattle, Wash.
Stanley Falkow, Stanford University, Calif.
Patricia Ferrieri, University of Minnesota, Minneapolis.
Samuel B.Formal, Walter Reed Army Medical Center, Wash., D.C.
Hjordis M.Foy, University of Washington, Seattle.
Donald P.Francis, The Centers for Disease Control, Atlanta, Ga.
Carl E.Frasch, Food and Drug Administration, Bethesda, Md.
Vincent A.Fulginiti, University of Arizona College of Medicine, Tuscon.
Robert J.Gerety, Food and Drug Administration, Bethesda, Md.
Anne A.Gershon, New York University Medical School, N.Y.
Janet R.Gilsdorf, C.S.Mott Children's Hospital, Ann Arbor, Mich.
W.Paul Glezen, Baylor College of Medicine, Houston, Tex.
Sherwood L.Gorbach, Tufts University, Boston, Mass.
Lance K.Gordon, Connaught Research Institute, Ontario, Canada.
Samuel P.Gotoff, University of Chicago, 111.
Emil C.Gotschlich, The Rockefeller University, New York, N.Y.
Dan M.Granoff, Washington University in St. Louis, Mo.
Darrel D.Gwinn, National Institutes of Health, Bethesda, Md.
James Barry Hanshaw, University of Massachusetts Medical School, Worcester.
M.Carolyn Hardegree, Food and Drug Administration, Bethesda, Md.
George R.Healy, The Centers for Disease Control, Atlanta, Ga.
James C.Hill, National Institutes of Health, Bethesda, Md.
King K.Holmes, Seattle Public Health Hospital, Wash.
Frederick B.Hollinger, Baylor College of Medicine, Houston, Tex.
Eugene S.Hurwitz, The Centers for Disease Control, Atlanta, Ga.
Robert E.Johnson, The Centers for Disease Control, Atlanta, Ga.
Albert Z.Kapikian, National Institutes of Health, Bethesda, Md.
Karl Kappus, The Centers for Disease Control, Atlanta, Ga.
Stanislav V.Kasl, Yale University School of Medicine, New Haven, Conn.
Dennis L.Kasper, Harvard Medical School, Boston, Mass.
Edward H.Kass, Harvard Medical School, Boston, Mass.
Alan P.Kendal, The Centers for Disease Control, Atlanta, Ga.
Edwin D.Kilbourne, Mount Sinai Medical Center, New York, N.Y.
David L.Klein, National institutes of Health, Bethesda, Md.
Jerome O.Klein, Boston City Hospital, Mass.
William J.Klish, Baylor College of Medicine, Boston, Tex.
Saul Krugman, New York University School of Medicine, N.Y.
John R.La Montagne, National Institutes of Health, Bethesda, Md.
Martha L.Lepow, Albany Medical College, N.Y.
Richard A.Lerner, Scripps Clinic and Research Foundation, La Jolla, Calif.
Sol Levine, Boston University, Mass.

Charles R.Manclark, Food and Drug Administration, Bethesda, Md.
James E.Maynard, The Centers for Disease Control, Phoenix, Ariz.
William M.McCormack, Harvard Medical School, Boston, Mass.
Kenneth McIntosh, The Children's Hospital, Boston, Mass.
Donald N.Medearis, Harvard Medical School, Boston, Mass.
Gerald Medoff, Washington University in St. Louis, Mo.
Peter J.Middleton, The Hospital for Sick Children, Toronto, Canada.
James N.Miller, The University of California at Los Angeles.
Edward A.Mortimer, Jr., Case Western Reserve University, Cleveland, Ohio.
Jeanne C.Mowe, American Association of Tissue Banks, Rockville, Md.
Andre J.Nahmias, Emory University School of Medicine, Atlanta, Ga.
Abner L.Notkins, National Institutes of Health, Bethesda, Md.
June E.Osborn, University of Michigan, Ann Arbor.
Joseph Pagano, University of North Carolina, Chapel Hill.
Demosthenes Pappagianis, university of California, Davis.
Stanley A.Plotkin, The Children's Hospital of Philadelphia, Pa.
Stephen Preblud, The Centers for Disease Control, Atlanta, Ga.
Robert H.Purcell, National Institutes of Health, Bethesda, Md.
Milton Puziss, National Institutes of Health, Bethesda, Md.
Fred Rapp, The Pennsylvania State University, Hershey.
Arthur L.Reingold, The Centers for Disease Control, Atlanta, Ga.
Judith Rodin, Yale University, New Haven, Conn.
William J.Rodriguez, Children's Hospital, Washington, D.C.
Frederick L.Ruben, University of Pittsburgh School of Medicine, Pa.
Bruce F.Scharschmidt, University of California, San Francisco.
Gary C Schatz, The Centers for Disease Control, Atlanta, Ga.
Gary Schoolnik, Stanford University Medical Center, Calif.
Sarah H.Sell, Tennessee Department of Public Health, Nashville.
P.Frederick Sparling, University of North Carolina at Chapel Hill.
Sergio Stagno, The University of Alabama in Birmingham.
John Stewart, The Centers for Disease Control, Atlanta, Ga.
Richard L.Sweet, Veterans Administration, San Francisco, Calif.
Franklin J.Tyeryar, National Institutes of Health, Bethesda, Md.
Joel I.Ward, UCLA School of Medicine, Torrance.
Thomas H.Weller, Harvard School of Public Health, Boston, Mass.
Richard J.Whitley, The University of Alabama in Birmingham.
Emanuel Wolinsky, Cleveland Metropolitan General Hosptial, Ohio.
Richard G.Wyatt, National Institutes of Health, Bethesda, Md.
Sandra Zachary, Health Care Financing Administration, Baltimore, Md.
Arie J.Zuckerman, London School of Hygiene and Tropical Medicine, United Kingdom.

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