New Vaccine Development: Establishing Priorities: Volume II, Diseases of Importance in Developing Countries

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

ISBN: 0-309-56820-X, 432 pages, 8 1/2 x 11, (1986)

New Vaccine Development
Establishing Priorities

VOLUME II

Diseases of Importance in Developing Countries

Part Two of a Two-Part Study by the
Committee on Issues and Priorities for New Vaccine Development
Division of Health Promotion and Disease Prevention
and
Division of International Health
INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C. 1986

NATIONAL ACADEMY PRESS 2101 CONSTITUTION AVE., NW WASHINGTON, DC 20418

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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The work on which this publication is based was initiated and funded by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, under contract No. NO1-AI-22678. The U.S. Agency for International Development, through the Public Health Service's Vaccine Development and Health Research Participating Agency Services Agreement No. 000001-04-S5, also provided valuable financial support.

Library of Congress Cataloging-in-Publication Data
(Revised for vol. 2)
New vaccine development.
Prepared for the National Institute of Allergy and Infectious Diseases.
Includes bibliographies and index.
Contents: v. 1. Diseases of importance in the United States—v. 2. Diseases of importance in developing countries.
1. Vaccines—Research—Government policy. 2. Communicable diseases—United States—Preventive inoculation. 3. Communicable diseases—Developing countries—Preventive inoculation. I. Institute of Medicine (U.S.). Committee on Issues and Priorities for New Vaccine Development. II. National Institute of Allergy and Infectious Diseases (U.S.)
RA638.N49 1985 614.4'7'0973 84–62037

ISBN 0-309-03494-9 (pbk.: v. 1)
ISBN 0-309-03679-8 (v. 2)

Printed in the United States of America

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Acknowledgements

This report could not have been prepared without the assistance of many individuals who willingly gave their valuable time to provide information and advice, and to prepare or comment on draft sections of the final document. A list of those to whom the committee is particularly indebted appears as Appendix H. It is possible that some individuals may have been omitted from this list by oversight. If this has happened, the committee offers its sincere apologies.

Preface

This volume is the second report from the Institute of Medicine's Committee on Issues and Priorities for New Vaccine Development. The first report dealt with vaccines for diseases of importance in the United States. The purpose of this volume is to help in setting priorities for the accelerated development of vaccines against diseases prevalent in developing countries. The background of the study and the committee's approach were outlined in the preface to Volume I, which is reprinted in Appendix J. The project was initiated by the National Institute of Allergy and Infectious Diseases, which provided major funding for the overall effort. For the second phase of the project on diseases of importance in developing countries, valuable financial support was also provided by the U.S. Agency for International Development.

In the second phase of the study, the committee made particular efforts to draw on the expertise and opinions of individuals who have worked extensively in public health fields in developing countries. Consultants from several parts of the world attended a meeting of the committee in August 1984, and many others contributed views by mail or telephone.

Any group assessing vaccine development—whether for disease afflicting the United States population or mankind in general—would be sorely remiss if it omitted consideration of acquired immune deficiency syndrome (AIDS). As the committee was completing its first analysis, reports identifying the probable etiologic agent of AIDS were emerging, scarcely three to four years after the recognition of the syndrome. At that time, the committee believed that comparison of AIDS vaccine prospects with those of other advanced candidates for accelerated vaccine development would have been premature.

In the ensuing year remarkable progress has been made, largely because of the powerful molecular and cellular biotechnologies that have emerged from basic biomedical research. Yet, significant questions remain before the prospects for vaccine development can be assessed clearly or its priority relative to other diseases evaluated. Uncertainty and apprehension as to the increasing magnitude of the problem (both domestic and global) is but one reason why this disease may merit separate consideration.

The state of knowledge in this area is now approaching that where consideration can be given to the question of accelerated AIDS vaccine development. However, the Committee on Issues and Priorities for New Vaccine Development elected to forgo the option of including AIDS in this volume, because of the fact that at the time this volume was nearing completion the Institute of Medicine and the National Academy of Sciences, in consortium, had embarked on an intensive assessment of research needs and opportunities and treatment and health care issues related to AIDS. That exercise, scheduled for completion in the fall of 1986, includes consideration of vaccine prospects.

The committee gratefully acknowledges the assistance provided by its consultants (listed above) and other advisers listed in Appendix H. It also wishes to take particular note of the continued excellent support of the Institute of Medicine staff headed by Roy Widdus. The assistance and advice of the National Institute of Allergy and Infectious Diseases project officer, C.David Wise, is also gratefully acknowledged, as is that provided by George T.Curlin, of the Public Health Service, on behalf of the Agency for International Development.

Samuel L.Katz
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Abstract

This report describes a method designed to aid government decision makers in establishing priorities for accelerated development of vaccines against diseases of importance in developing countries. The method is based on a quantitative model in which vaccine candidates are ranked according to their potential health benefits (reduction of morbidity and mortality). The model also provides the capacity to utilize "affordability" (willingness to pay for benefit) as a supplementary criterion.

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, gaps must be filled by estimates or judgments by experts. Commentary is included in Chapter 1 to explain the advantages of the system and to prevent 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 nonquantifiable 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 or intent 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 certain other nonquantifiable factors relating to the diseases and alternative control approaches.

The method was applied to 29 vaccine candidates for 19 diseases of importance in the developing world where new or improved vaccines were judged technically feasible within the next decade. (A prior assessment considered vaccines for diseases of importance in the United States). Costs and benefits are viewed from a perspective for the developing world as a whole. 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 assumed that vaccine utilization within target populations would be uniform because delivery was likely to be through the World Health Organization Expanded Program on Immunization. However, techniques are described for incorporating differential utilization, if desired. A new technique 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 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. The perspective used to illustrate application of the method was

the median of responses from a number of health professionals in a range of developing countries. (The committee, however, does not endorse this or any other specific perspective for policy formulation in this area.)

A comprehensive assessment of the net expected costs (possibly savings) associated with each vaccine candidate would include the cost of vaccine development, the likely cost of the vaccination program, the expected cost savings from treatment averted, and the cost of adverse reactions. Procedures to perform these calculations (conducted for the domestic U.S. analysis) are described in the report. For this analysis the committee judged it was not practical or realistic to attempt to estimate, for the entire developing world, the typical treatments for various disease conditions and their average costs. Thus, the cost components in this analysis relate to expenditures necessary to achieve the vaccine benefits, that is, the cost of development and the cost of vaccine for the immunization programs. (Delivery and administration costs, like utilization, are assumed to be uniform.) No "indirect" economic measures of health outcome were used.

Implementing the method requires substantial amounts of information about diseases and vaccine characteristics. Data having the desired degree of reliability are 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 results from several sensitivity analyses indicate that the rank order of candidates remains fairly stable for the issues tested, which include different discount rates, probabilities of success, and various levels of financial resource constraint. Additional analyses are suggested to provide further information on the key elements that affect decisions and to indicate where new information is most needed.

The table on page xi shows the categories into which the assessed vaccine candidates fall under a fairly wide range of assumptions and resource availabilities. Because certain candidates may enter different categories if other plausible assumptions are adopted, the assignments in the table should not be regarded as definitive.

The committee recommends use of the method to government decision makers. The capacity to make rational choices on vaccine development priorities and vaccine formulation would be enhanced by better information on disease incidence and the pathogen serotypes prevalent in particular regions. Therefore, NIAID and other national and international agencies should consider means of improving the epidemiologic information on infectious diseases.

After the committee achieved consensus on vaccine development predictions (late summer 1985), preliminary unpublished results from certain ongoing studies came to their attention. These results, if confirmed, may slightly alter the predictions on some vaccine candidates, particularly on candidates targeted against the same pathogen relative to each other, e.g., as for cholera and rotavirus. The committee did not conduct calculations based on the preliminary information but believes it would not significantly alter the overall conclusions described above; it recommends early reappraisal of candidate ranking as data from ongoing studies are publicly reported.

An improved vaccine for hepatitis B virus (a polypeptide produced by recombinant DNA technology), predicted by the committee to be licensed in 1 year or less, was in fact licensed on July 24, 1986.

Summary of Findings: Rankings of Various Vaccine Candidates Based on Their Potential Health Benefits Under a Variety of Assumptions and Resource Constraints

High	Intermediate	Low
S.pneumoniae	Hepatitis B virus	Hepatitis A (either candidate)
Plasmodium spp. (malaria; both monovalent and circumsporozoite protein-based approaches)	*H.influenzae* type b	*N.meningitidis*
	E.coli (either candidate)	Yellow fever virus
	Streptococcus group A	Dengue
Rotavirus (all three candidates)	*S.typhi* (an aromatic amino acid-requiring strain)	Rabies (live vector virus)
S.typhi (Ty21a)	*M.leprae*	Japanese encephalitis virus
Shigella spp.	*V.cholerae* (either candidate)	
	Respiratory syncytial virus (either candidate)	
	Parainfluenza	
	Rabies (vero cell derived or glycoprotein)	

NOTE: Because certain vaccine candidates may enter different categories if other plausible assumptions are adopted, these assignments should not be regarded as definitive.

Contents

New Vaccine Development Establishing Priorities

Summary

Establishing priorities for the development of vaccines against diseases prevalent in developing countries is complicated by large variations in the morbidity and mortality arising from such diseases, in their geographic distribution, in the extent of knowledge about relevant pathogens and host responses, in the resources and time required for vaccine development, and in anticipated vaccine efficacy and extent of use. This report presents a comprehensive method designed to help government decision makers set priorities for accelerated development of vaccines against important diseases in the developing world. The method can be used to assess new vaccine candidates or to reassess current contenders as additional information becomes available. The primary utilization of many of these vaccines would be for reducing morbidity and mortality in developing countries. Other uses would be for U.S. travelers to such countries, for military and other personnel stationed in them, and for response to the importation of these diseases (e.g., dengue fever) and their transmission in the United States.

The decision-making approach suggested uses similar kinds of information about the occurrence and importance of events that theoretically could be used in other methods of decision making. Because information is incomplete and because the method entails, in some instances, predicting the future, gaps must be filled by estimates or judgments by experts.

The procedures described in this report bear many similarities to those in the committee's first report on vaccines for diseases of importance in the United States. However, the reader is cautioned that there are certain significant differences in the approach adopted for this assessment. In the former analysis, the calculations were aimed at estimating real, expected benefits and net costs associated with the vaccine candidates. In this analysis, benefit values represent potential benefits, and potential expenditures on vaccines are the only cost component evaluated (cost savings from treatment averted are not assessed). One consequence of these differences is that any attempt to compare values between reports is not valid.

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 such 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 available data and estimates. The committee believes that the system would improve the decision-making process by making it more accessible to evaluation and reconstruction by other decision makers and by facilitating examination of the effect of alternative assumptions or estimates. However, some cautions and comments are needed to prevent misinterpretation of the power and precision of the method.

To identify the components on which quantitative information is desirable (though not necessarily available), the system (more than others) exposes areas of ignorance and uncertainty in which expert judgment, by necessity, must be used. The proposed approach uses equations to define 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 way that intuitive integration of such components does not. This is expressed in the sensitivity analyses reported in the study.

All processes in which diseases are ranked by importance involve value judgments on disease conditions; 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 is one means of isolating these differences of opinion (which are often incorporated into decision making in an ill-defined way) and determining if they affect the ultimate priorities.

The committee considered these problems, resolved differences of opinion, and sought agreement on the approach it would follow in this complex area. When information was incomplete or quantitative prediction was complicated by many unresolved issues, it chose what it believed 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 made. Because of the uncertain data and estimates used in the calculation of health benefits and costs, the final numerical rankings are useful as they relate to each other rather than because of their absolute precision. That is, the system facilitates comparison of vaccine projects in a way that is open to revision if different estimates or assumptions seem appropriate and as new data become available.

The proposed model is based on comparison of the relative potential health benefits calculated for each vaccine candidate. Calculations of potential expenditures on vaccines to achieve these benefits— representing "affordability" —are also made and can be incorporated into the decision process, if desired. This approach combines elements of decision analysis and cost-effectiveness analysis. The approach was selected by the committee because it identifies each logical component contributing to vaccine benefits and costs* without placing a monetary value on human life or suffering. The approach requires substantial amounts of information about diseases and vaccine candidates. 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 and 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 merely providing a single list of priorities, the committee also demonstrated with sensitivity analyses how different rankings could result from the adoption of various viewpoints on the affordability of benefits, on the undesirability of illness or death in specific age groups, or from assumptions about disease incidence, the possible effect of new treatments, and other factors that cannot be predicted with certainty.

Several other nonquantifiable issues, all of which concern the policymaker, also must be incorporated into the final judgment on vaccine priorities. These include:

- goals of the responsible agency and its schedule for achieving them
- ethical questions on the distribution of benefits between socioeconomic or age groups, countries, or regions
- most appropriate time at which the agency can exert influence and the opportunity and need for such influence
- extent of private sector activities
- the desired balance of the development portfolio (e.g., pediatric versus adult vaccines, global versus regional diseases)
- arguments that can be made for treating certain vaccine development projects as unique because of their potential for facilitating immunization programs in general (e.g., by eliminating constraints on delivery, such as poor stability) or by improving public confidence (e.g., by reducing adverse reactions)
- the prospect that a particular project may serve as a useful model for a number of other desired vaccines
- disease related factors, such as epidemiologic and clinical characteristics likely to overwhelm medical services, and the

*In this application of the method not all direct cost components are included, but procedures are outlined whereby they could be, if so desired.

availability of alternative control strategies or safe and effective therapy
- possible synergistic interaction with other diseases
- the immediate U.S. interest in diseases that may be imported into the United States, that threaten travelers or personnel stationed overseas, or that are existing problems in the United States

The committee sought to develop a flexible system that could be updated as necessary. This required identifying explicitly all assumptions, estimates, and predictions incorporated in each calculation. Numerical 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 that uncertainty surrounds other factors, for example, probable vaccine efficacy and disease incidence. 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 concepts and basic assumptions that are used throughout the study. For example, if a candidate vaccine is omitted from the full analysis, no conclusions should be drawn regarding its position relative to the assessed contenders. The assessment is conducted from an aggregate perspective for the developing world as a whole, and each development project is treated as an independent investment decision. Effects of morbidity and mortality are expressed in nonmonetary terms.

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.

SELECTION OF CANDIDATES

The committee defined 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 A.

The diseases and vaccine candidates chosen for assessment are shown in Table 1.1. Detailed information about individual candidates is presented in Appendixes D-1 through D-19. The committee and its advisers reviewed the prospects for immunizing against a number of major diseases for which accelerated vaccine development was ultimately judged not to be feasible or appropriate at this time. That information will be included in a supplement to this volume (see Appendix I). The supplement also will briefly describe some newer techniques that are likely to be increasingly applied to vaccine

TABLE 1.1 Candidates for Accelerated Vaccine Development: Diseases of Importance in Developing Countries

Pathogen	Vaccine Envisaged	Target Population[a]
Dengue virus	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	Infants and children in endemic areas; travelers to endemic areas
Escherichia coli (enterotoxigenic)	A combination of purified colonization factor antigens and possibly other antigens	Infants<6 months
	Genetically engineered attenuated strains	Infants<6 months
Hemophilus influenzae type b	Conjugated polysaccharide	Infants
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages; routine for preschool children
	Polypeptide recombinant vaccine produced in yeast	Susceptibles of all ages; routine for preschool children
Hepatitis B virus	Polypeptide produced by recombinant DNA technology	Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations, at earliest possible age
Japanese encephalitis virus	Inactivated virus produced in cell culture	Children in epidemic and endemic areas; foreign visitors to epidemic regions
Mycobacterium leprae	Armadillo-derived M.leprae	Immuno-prophylactic: all children in endemic areas. Immuno-therapeutic: all recently infected persons
Neisseria meningitidis	Conjugated capsular polysaccharides, Groups A,C,Y, and W135	Infants, 3 to 6 months
Parainfluenza viruses	Trivalent, subunit vaccine (which must contain fusion proteins)	Infants
Plasmodium spp.	Plasmodium falciparum, synthetic or recombinant sporozoite antigen preparation	All infants at risk, military personnel, travelers
	Multivalent synthetic or recombinant sporozoite antigen preparation (P.falciparum, P.vivax, P.ovale, P.malariae)	All infants at risk, military personnel, travelers
Rabies virus	Vero cell derived vaccine	Persons at high risk, plus post-exposure prophylaxis
	Glycoprotein produced by rDNA technology in mammalian cells	Persons at high risk, plus post-exposure prophylaxis
	Attenuated live vector virus containing gene for protective glycoprotein antigen	Birth cohort in areas of high risk

development in the coming decade. The vaccine-disease combinations to be described in the supplement should be regularly reviewed for possible inclusion in future applications of the model.

Pathogen	Vaccine Envisaged	Target Population[a]
Respiratory syncytial virus	Polypeptides produced by recombinant DNA technology	Infants at earliest possible age
	Attenuated live virus	Infants at earliest possible age
Rotavirus	Attenuated high passage bovine RV	Infants at earliest possible age (preferably with oral polio vaccine)
	Attenuated low passage bovine RV	Infants at earliest possible age (preferably with oral polio vaccine)
	Rhesus monkey RV	Infants at earliest possible age (preferably with oral polio vaccine)
Salmonella typhi	Attenuated ga1E mutant S. typhi strain TY21a	Children; young adults at risk; travelers from developed countries to endemic areas
	Aromatic amino acid dependent strains of S. typhi	Children; young adults at risk; travelers from developed countries to endemic areas
Shigella spp.	Probably plasmid mediated outer membrane protein invasion determinant (there are a small number of promising options needing investigation to determine best approach)	Infants at birth or earliest possible age; elderly for epidemic strains
Streptococcus A	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	Children, <3–4 yrs
Streptococcus pneumoniae	Conjugated polysaccharides, polyvalent	Infants
Vibrio cholera	Genetically defined live mutant V. cholerae (A−B+ or A−B−) with respect to toxin subunit synthesis	Children, esp. <2 yrs
	Inactivated antigens	Children, esp. <2 yrs
Yellow fever virus	Attenuated live virus produced in cell culture	Young children

[a]Calculations of benefits are conducted assuming delivery at ages consistent with schedules of vaccinations recommended by the World Health Organization Expanded Program on Immunization (see Chapters 6 and 7).

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 illness episodes and their durations, with additional data on related complications, sequelae, and deaths. (For chronic disability, the system incorporates the annual increment to the pool of individuals affected.) It also incorporates value judgments on the undesirability (disutility) of various conditions occurring in various age groups.

Disease Burden Estimates

Whenever possible, global or regional information from the World Health Organization or other knowledgeable sources was used as the starting point for the disease burden estimates needed in this analysis. For many conditions, however, information needed to estimate disease burdens was not available or was not of the desired reliability; 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 of disease consequences to any level desired and to observe the effect of this change on the rankings of candidates. The undesirability of conditions for morbidity category/ age group combinations are expressed as infant mortality equivalence (IME) values, that is, the number of acute morbidity days or chronic cases considered to be equal in undesirability to an infant death. The perspective used as an example throughout this report reflects the median of responses from public health professionals in a variety of developing countries (elicited by means of a questionnaire—see Appendix E). The median values are shown in Table 1.3. Other perspectives could be used, for example, an "age-neutral" perspective. The effect on rankings of using other perspectives is discussed. The committee, however, does not endorse any particular perspective for policy formulation in this area. Different rankings may result from the adoption of different viewpoints on the undesirability of illness and death at different stages of life.

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

TABLE 1.2 An Example of the Format Used to Compile Information on the Burden of Illness Arising from Infectious Diseases in Developing Countries: Hepatitis A Virus[a]

Morbidity Category	Description	Condition	<5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration (days)	Number of Cases	Duration (days)	Number of Cases	Duration (days)	Number of Cases	Duration (days)
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity									
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Jaundice, including convalescence from category C (total)	139,843	7	635,651	7	2,256,561	7	149,378	7
C	Severe pain, severe short-term impairment, or hospitalization	Severe hepatitis	31,735	14	158,675	14	1,221,794	14	206,277	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death	Death following fulminant hepatitis		n.a.	1,144	n.a.	5,146	n.a.	8,005	n.a.

[a]See Appendix D-4 for derivation.

TABLE 1.3 Infant Mortality Equivalence Valuesa: The Medians of Values from Health Professionals in Developing Countries

	Age Group			
Morbidity Category[b]	Under 5 Years	5–14 Years	15–59 Years	60 Years and Over
A	40,000	32,500	8,750	50,000
B	23,713	17,500	5,650	25,000
C	2,000	2,244	2,000	5,000
D	75	62.5	30	550
E	5.5	5.5	2.75	23.125
F	1	0.4	0.309	5
G	100	22.5	16.5	300
H	1	0.5	0.4	5

[a]Infant mortality equivalence is 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.
[b]Morbidity categories are defined in Table 1.2.

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 an infant death (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. This process permits the comparison of diseases having different consequences and can be used as described in Chapter 7 to compare vaccine benefits.

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

- time after licensure to adoption in immunization programs 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

These factors have been incorporated into the calculations of potential health benefits and expenditures on vaccines. Chapter 5 presents in tabular form the specific estimates for each of the vaccine candidates, which are discussed in Appendixes D-1 through D-19.

Definition of Probable Vaccine Target Population

The determination of a probable vaccine target population for each vaccine was based on the age and geographic distributions of the relevant disease and the relative risk of illness. Whenever possible, the target population was matched with one already employed by the World Health Organization's Expanded Program on Immunization (WHO-EPI) , for reasons discussed below.

Treatment of Vaccine Utilization

The benefits derived from a vaccine depend, in part, on the proportion of the target population that actually receives it, which may vary among vaccines. However, for the analysis described in this report, the committee assumed that the utilization rates would be uniform across target populations, because delivery would probably be achieved through the WHO-EPI. Its vaccination schedule recommendations are intended to be adapted to local conditions and constraints. WHO-EPI flexibility in this regard may establish new opportunities for optimizing the delivery of vaccines considered in this analysis (see Chapter 6). Actual decisions to incorporate specific vaccines into EPI should be based on local assessments of disease burden, resources, and other considerations. The methods used in the committee's previous report (Institute of Medicine, 1985) can be adapted to situations in which utilization is likely to differ between vaccines. In this report, however, utilization is not used to differentiate among vaccine candidates.

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

Various vaccines require various amounts of time for development to licensure, and after licensure before wide incorporation into general

immunization efforts (i.e., adoption). In addition, the health benefits from vaccines are realized at different times after vaccination.

These factors affect the time interval before the health benefits associated with a vaccine and certain cost outlays (such as vaccine purchase for immunization programs) will reach a steady state and are used to determine the annualized "present value" of results that will be achieved at various times in the future.

The process by which benefits and costs that are delayed for some years are converted to their current equivalent value is termed "discounting." This procedure enhances the relative importance of effects realized after a short delay as compared with a long one. 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 portion of the disease burden that is preventable by delivery to the entire target population, at the anticipated age of administration, of a hypothetical vaccine that is 100 percent effective.

Calculation of Potential Health Benefits for Each Vaccine

Chapter 7 describes the integration of the components outlined above to derive the annualized present value of the potential health benefits for each vaccine candidate. Figure 1.1 summarizes the basic steps used in the analysis. (When it is believed that vaccines may have different utilization rates within their respective target populations, predicted rates can be used as an adjustment in this calculation process and the values derived would represent expected, rather than potential, health benefits.)

Cost Calculations

A comprehensive assessment of the expected net costs associated with the use of vaccine candidates would require the calculation of the cost of vaccine development, the cost of the immunization program including vaccine administration, the cost savings from treatment averted, and the cost of adverse reactions. Procedures to perform these calculations are outlined in this report and in more detail in the committee's first report (Institute of Medicine, 1985).

For this analysis, however, the committee judged that it was not practical to attempt to estimate the costs associated with treating disease or the potential savings from treatment averted by vaccines. The committee believed that it would be extremely difficult and probably unrealistic to estimate for the developing world as a whole the proportion of cases, complications, and sequelae that receives treatments, the nature of those treatments, and their average costs.

Additionally, the committee assumed that utilization of vaccines would be through the WHO-EPI and at a uniform rate. Hence, the cost of delivery and administration would not be a factor in differentiating among vaccines.

These judgments lead to simplification of the cost components of this analysis: the cost of vaccine development and the cost of vaccine for immunization programs (see Figure 1.2). These "expenditures on vaccine" can, if desired, be included as a criterion in the decision process, representing the composite "affordability" of disease control efforts.

However, these estimated expenditures are only relative, not absolute, because they exclude elements assumed to be uniform, that is, administration and utilization. Further, the omission of cost savings, which may vary between diseases, means that the estimates do not indicate the net cost of the total effort to control a given disease by immunization. Net costs may in fact be negative; that is, a vaccine can be cost saving.

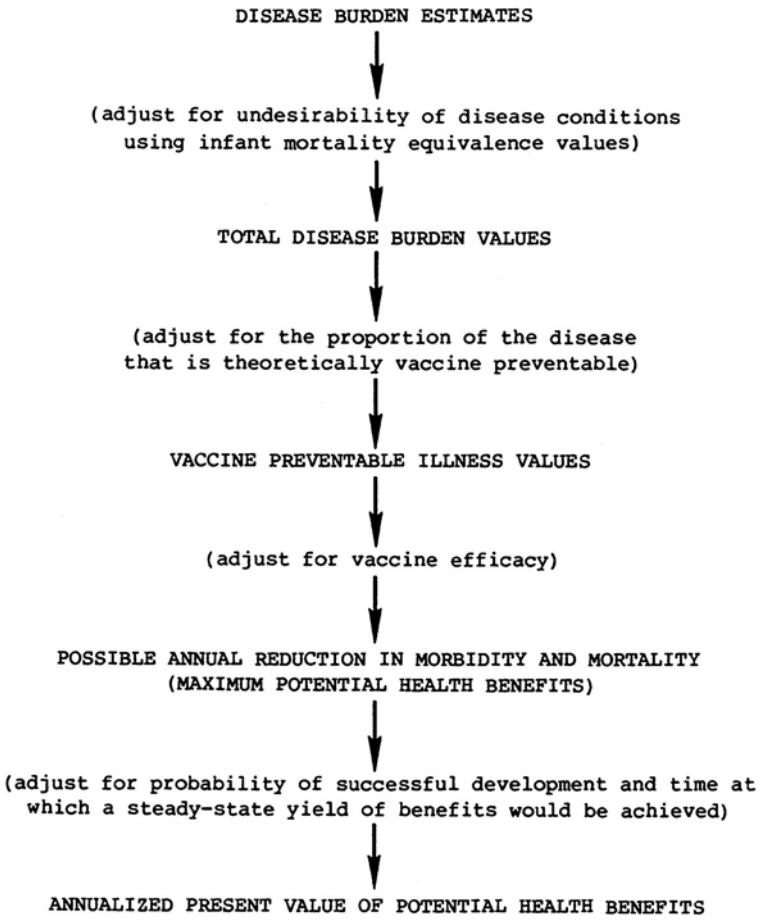

FIGURE 1.1 Calculation of potential health benefits.

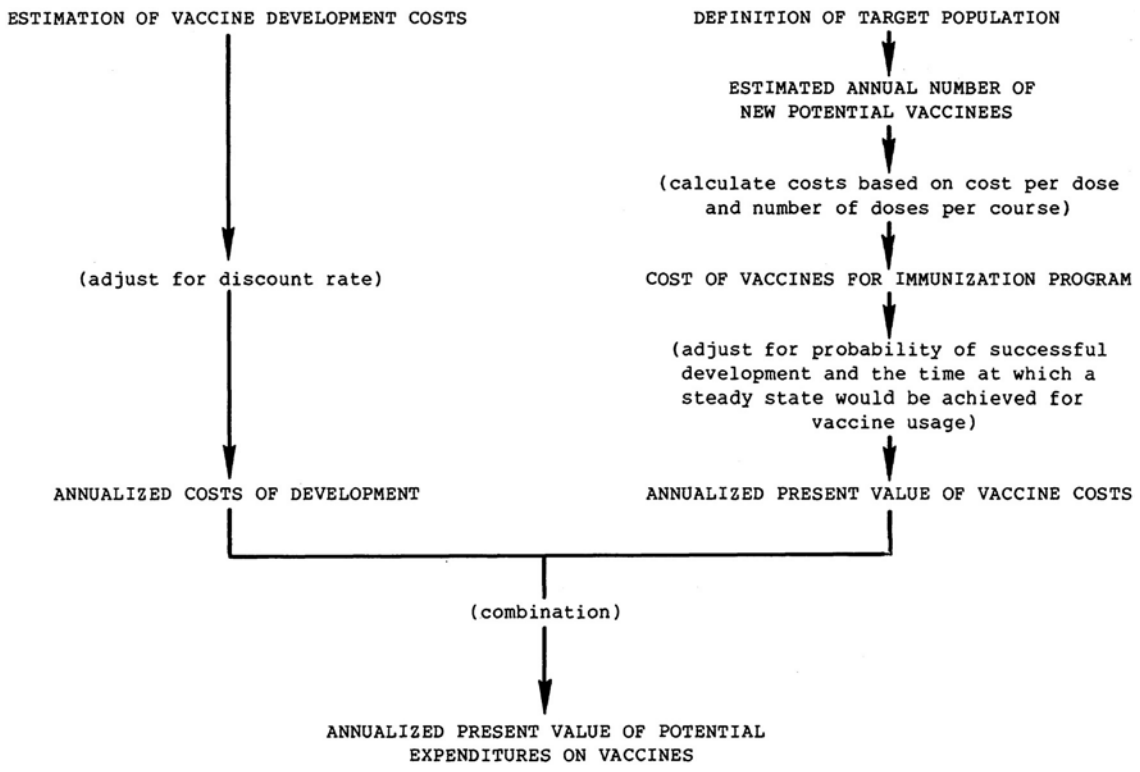

FIGURE 1.2 Calculations of expenditures on vaccines.

INTERPRETATION OF RESULTS

The process of ranking vaccines in order of desirability by using the health benefit, expenditure, and other information developed with this method depends on the ultimate goals of the exercise and constraints that limit the number of candidates that may be selected. The committee proposes that the potential global health benefit of a vaccine take precedence in determining its initial ranking for accelerated development priority. The affordability of benefits, represented by the relevant expenditures on vaccine, can also be introduced into the decision process, if desired. This is illustrated in Chapter 9 where the effect on the health benefit rankings of various levels of constraint on financial resources is examined.

Chapter 3 provides a detailed description of the procedures that can sometimes be used to establish priority rankings if two equally important selection criteria are used. These are based on the concept of dominance: if a vaccine candidate is more desirable than another on one dimension (either potential health benefits or expenditures on vaccine—lower is preferable) and at least as good on the second dimension, then it dominates the other candidate.

Chapter 8 identifies some additional issues that should be considered in the final selection of priorities for accelerated vaccine development. These include the distribution of benefits from new

vaccines among geographic or other population subgroups; various disease characteristics, such as susceptibility to control by other available means, ease and cost of treatment, synergistic interaction with other diseases, and epidemic potential; and the need and opportunity for intervention to accelerate development. The last of these will be influenced by the extent of interest from commercial companies and the possibilities for development via collaborative efforts with industry, other countries, or international organizations.

FINDINGS, CONCLUSIONS, RECOMMENDATIONS

Table 1.4, drawn from Chapter 4, shows a ranking of the burdens of illness resulting from the diseases for which vaccine candidates are assessed.

Chapter 9 presents the committee's findings on the potential benefits and expenditures associated with the development of specific vaccines and the implications of some sensitivity analyses.* The resulting priority list is not meant to dictate the actions of government decision makers or groups (e.g., in other countries) who may be examining priorities from other perspectives. The principal focus of the committee's efforts was to provide a flexible, reproducible technique for the assessment of vaccine development projects.

The analyses indicate that of the 29 projects considered, vaccines for S. pneumoniae, Plasmodium spp. (malaria; both monovalent and multivalent circumsporozoite protein-based approaches), rotavirus (all three candidates), S. typhi (Ty21a), and shigella consistently rank among the top 10 positions in priority lists based on potential health benefits under a wide range of assumptions and resource availabilities (Table 1.5 and Chapter 9). As willingness to pay to obtain health benefits drops to $1,000 or below per IME prevented, the rankings change more significantly.

Vaccines for hepatitis B and H. influenzae type b rank in the top 10 in the central analysis but are dislodged under certain assumptions. Vaccines for E. coli (either candidate) or the alternative candidate for S. typhi (an aromatic amino acid-requiring strain) move into the top 10 under certain assumptions.

A fairly consistent “middle-tier” is present in the potential health benefit ranking under a variety of assumptions. in addition to the candidates that will contend for higher ranking under certain assumptions, this group includes vaccines for Streptococcus group A, M. leprae, V. cholerae, respiratory syncytial virus, parainfluenza, and rabies (Vero cell derived or glycoprotein).

Table 1.6 shows the findings for a wide range of assumptions and resource availabilities. Because certain vaccines may enter other

*Expenditures represent the cost of vaccine development and cost of vaccine (but not delivery, which is assumed uniform) for the vaccination program (see Chapters 4 and 6).

categories if different, plausible assumptions are adopted, the assignments in Table 1.6 should not be regarded as definitive.

TABLE 1.4 Ranking of Diseases by Total Disease Burden Values

Disease	Total Disease Burden Value (IME units)[a]
Streptococcus pneumoniae	6,612,261
Hepatitis B virus	2,394,256
Plasmodium spp.	2,111,795
Salmonella typhi	1,308,121
Escherichia coli	978,248
Rotavirus	925,042
Shigella spp.	828,068
Streptococcus Group A	811,477
Mycobacterium leprae	657,349
(Escherichia coli)	(550,248)[b]
(Rotavirus)	(488,542)[b]
Hemophilus influenzae type b	471,336
Vibrio cholera	229,217
Respiratory syncytial virus	183,326
Parainfluenza virus	145,954
Neisseria meningitidis	68,252
Rabies virus	67,821
Dengue virus	34,365
Yellow fever virus	32,887
Hepatitis A virus	30,229
Japanese encephalitis virus	18,075

[a]Infant mortality equivalence units.
[b]Values represent the anticipated disease burden from certain diarrheal pathogens if a plausible increase in oral rehydration therapy is assumed (see Appendix C) .

Most of the vaccines that consistently rank low (as compared with the other candidates in this assessment) would prevent diseases that, although often serious, are found in relatively small regions of the developing world. In such areas they may have considerable benefit relative to the more widespread diseases that rank higher when the developing world is considered as a whole.

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 in Chapters 8 and 9.

Scientific opinion differs on some of the judgments incorporated into the proposed method, and uncertainty surrounds certain data (e.g., on disease incidence) or the predictions (e.g., of 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 that 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 populations also are desirable.

TABLE 1.5 The Effect of Resource Constraints on the Ranking of Various Vaccine Candidates

	Rank Based on Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Costs[a]				
	Willingness to Pay (dollars) per IME Averted				
Vaccine	Unrestricted	100,000	10,000	1,000	500
S. pneumoniae	1	1	1	5	–[b]
Rotavirus (HPBRV)	2	2	2	–	–
Malaria (monovalent)	3	3	6	–	–
Rotavirus (LPBRV)	4	4	4	–	–
Rotavirus (RMRV)	5	5	5	–	–
S. typhi (Ty21a)	6	6	3	3	–
Malaria (multivalent)	7	7	7	–	–
Shigella	8	8	8	1	2
Hepatitis B	9	13	–	–	–
H. influenzae b	10	9	10	–	–
S. typhi (aa-strain)	11	10	9	6	–
Streptococcus group A	12	11	12	–	–
E. coli (attenuated live)	13	12	11	2	3
E. coli (purified antigens)	14	14	16	–	–
V. cholera (attenuated live)	15	15	13	4	1
M. leprae	16	16	14	–	–
V. cholera (inactivated)	17	17	15	7	–
RSV (attenuated live virus)	18	18	–	–	–
RSV (glycoprotein)	19	21	–	–	–
Parainfluenza viruses	20	22	–	–	–
Rabies (Vero cell derived)	21	19	17	–	–
Rabies (glycoprotein)	22	20	18	–	–
Hepatitis A (attenuated live virus)	23	27	–	–	–
Hepatitis A (polypeptide)	24	–	–	–	–
N. meningitidis	25	26	–	–	–
Yellow fever virus	26	23	20	–	–
Dengue virus	27	25	–	–	–
Rabies (live vector virus)	28	24	19	–	–
Japanese encephalitis virus	29	–	–	–	–

[a] Rankings are based on values shown in Table 9.3.
[b] – denotes not affordable at indicated willingness to pay.

Data needed for disease comparisons are lacking in some areas and are of variable quality in others. Additionally, data on the pathogen serotypes prevalent in particular regions may be lacking. Better data bases in these matters would facilitate rational choices on vaccine development priorities and vaccine formulations. Therefore, NIAID and

TABLE 1.6 Summary of Findings: Rankings of Various Vaccine Candidates Based on Their Potential Health Benefits Under a Variety of Assumptions and Resource Constraints

High	Intermediate	Low
S. pneumoniae	Hepatitis B virus	Hepatitis A (either candidate)
Plasmodium spp. (malaria; both monovalent and circumsporozoite protein-based approaches)	H. influenzae type b	N. meningitidis
	E. coli (either candidate)	Yellow fever virus
Rotavirus (all three candidates)	Streptococcus group A	Dengue
S. typhi (Ty21a)	S. typhi (an aromatic amino acid-requiring strain)	Rabies (live vector virus)
Shigella spp.	M. leprae	Japanese encephalitis virus
	V. cholerae (either candidate)	
	Respiratory syncytial virus (either candidate)	
	Parainfluenza	
	Rabies (vero cell derived or glycoprotein)	

NOTE: Because certain vaccine candidates may enter different categories if other plausible assumptions are adopted, these assignments should not be regarded as definitive.

other national and international organizations should consider means to improve available epidemiological data on infectious diseases.

As a group, the vaccines assessed in this report are generally further from licensure than those evaluated in the first volume of the committee's report (Institute of Medicine, 1985). Additionally, for most there appears to be less commercial interest in their development (although this is sometimes difficult to ascertain). The committee therefore recommends to NIAID and other federal agencies the careful examination of opportunities to accelerate the development and availability of vaccines identified here as meriting high priority. Although this report nominally addresses vaccines for the developing world, many of those assessed (e.g., S. pneumoniae) would considerably benefit the population in the United States.

The committee believes that a major strength of this analysis is that it encourages those using it to examine all judgments and assumptions in the decision process. The committee recommends use of the proposed system by government decision makers. New candidates should be assessed as they become technically feasible and new data should be incorporated as they become available.

After the committee achieved consensus on vaccine development predictions (late summer 1985) preliminary unpublished results from certain ongoing studies came to their attention. These results, if confirmed, may slightly alter the predictions on some vaccine candidates, particularly on candidates targeted against the same pathogen relative to each other, e.g., as for cholera and rotavirus. The committee did not conduct calculations based on the preliminary information but believes it would not significantly alter the overall conclusions described above; it recommends early reappraisal of candidate ranking as data from ongoing studies is publicly reported.

An improved vaccine for hepatitis B virus (a polypeptide produced by recombinant DNA technology), predicted by the committee to be licensed in 1 year or less, was in fact licensed on July 24, 1986.

REFERENCE

Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume I. Diseases of Importance in the United States. 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 cleanup. The methods themselves draw from techniques in systems analysis, decision analysis, and cost-benefit analysis.

METHODS FOR PROJECT RANKING AND SELECTION

The five methods considered for use in ranking vaccine candidates were (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 system developed by the committee, presented in Chapter 3, was designed primarily to assist in planning efforts of the U.S. National Institute of Allergy and Infectious Diseases (NIAID). It combines essential features of cost-effectiveness analysis and decision analysis. Other organizations may find that modifications of the system discussed below may be better suited to their needs; however, the adoption of any method or combination of methods for setting vaccine development priorities must include recognition of two basic issues.

Major portions of this chapter were prepared originally for Volume I of the report of the Committee on Issues and Priorities for New Vaccine Development (National Academy Press, 1985). They are reprinted here to assist those who wish to use Volume II as an independent document.

First, the availability of data on morbidity and mortality, pathogenicity, host responses to infection, the resources and time required for vaccine development, and potential vaccine utilization varies tremendously for various diseases and national settings. Because this information is incomplete and because the features of vaccines not yet available, their development, and the behavior of health care providers and vaccine recipients cannot be predicted with certainty, any effort to set priorities must incorporate estimates or judgments.

Second, the selection of a structural framework in which to combine these expert opinions with available data does not in itself improve the quality of the data. Although equations may be employed to define how various elements should be organized, their use does not imply that the factors or the results have the accuracy sometimes associated with formal mathematical calculations.

The formal analytical methods described below and the system proposed by the committee in Chapter 3 can improve the quality of the decision-making process. They require identification of each factor contributing to a decision, which makes later reconstruction of the priority-setting process and examination of the effects of changing assumptions easier and more accurate.

The last part of this chapter considers some general issues in implementing any method of ranking, 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 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, that is, 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.

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.

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

Multiattribute scoring and decision analysis with multiple objectives (see below) may incorporate implicit (subjective) judgments about expected outcomes. The committee believes that every effort should be made to use available data in an explicit fashion and to clearly identify and define areas in which personal values may influence the choices.

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.

TABLE 2.2 A Hypothetical Example of Multiattribute Scoring[a]

	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)[b]	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

[a]Scores and subscores are normalized to 100.
[b]Reduction in expected frequency of disease among vaccinees.

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 number of lives saved	=	potential number of lives saved	×	vaccine efficacy	×	vaccine coverage	×	probability of vaccine 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 might 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 number of lives saved	=	(10,000)	×	(0.75)	×	(0.80)	×	(0.70)
	=	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, 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 effectiveness 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.

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.

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 (noneconomic) 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 $(C_i+PC_i-MC_i)/E_i$ 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.

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 nonhealth outcomes. (As noted above, multiattribute scoring and decision analysis with multiple objectives often use this kind of judgment implicitly.) Measures of economic productivity, such as earnings, often are used to monetize health improvements, but any such method has serious problems. 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, although its value as a prescriptive tool is recognized even by some critics of its ethical standing (Office of Technology Assessment, 1980; Swartzman et al., 1982).

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, the methods did not permit identification of all subjective elements included in the analysis.

From the committee's perspective, the benefit-cost approach also had two major drawbacks. 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.

After lengthy consideration, a decision analysis approach that focuses on the potential health benefits of vaccine candidates but also identifies cost considerations was selected 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 proposed approach is no exception. It is important to note that some factors cannot be quantified and incorporated into such an analysis. Chapter 8 deals with issues of this kind 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 such formal procedures as the Delphi method (Dalkey, 1969). These are described further in Volume 1 of the committee's report (Institute of Medicine, 1985).

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 is very large.

Interdependence Among Projects

The methods described above assume, in general, that the consequences of implementing one project 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, tetanus, pertussis 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 list of alternatives before the optimal group 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 of higher priority than vaccine N. However, if K, L, and M all benefit populations in one region (e.g., Africa), while N benefits the population of another region (e.g., South America), 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.

Several different criteria could be used to compile portfolios in establishing vaccine priorities for important diseases in developing countries. As the example illustrates, one criterion might be the geographic boundaries of the target population. Another might be the level of development. The needs of the world's poorer nations may be quite different from those of developing countries that have progressed further. A third criterion might be the age range of the principal target population; diseases that affect young children may be considered separately from those that attack adults in certain occupations (e.g., in some parts of the world, young men who work in forested areas have a high risk of yellow fever).

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. The proposed method is described in Chapter 3.

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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 most reliable 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 estimates should be made explicit or left implicit. The committee chose to identify and quantify pertinent estimates 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 calculations.

Several assumptions, discussed below, underlie the analysis, and certain issues are best clarified at the outset of any discussion of the methods employed. 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 (described in Appendix A) was based on expert views of the current state of knowledge about each disease pathogen and the corresponding host response. The supplement to this volume summarizes the committee's conclusions about some disease problems for which vaccine prospects are

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

unclear or for which more basic research is required before targeted vaccine development will be realistic (see Appendix I). If a candidate vaccine is omitted from the full analysis, it obviously will not appear in the rank order, and no conclusions should be drawn regarding its position relative to the assessed contenders.

Differences between the assessments of vaccine candidates for diseases of importance in the United States (Institute of Medicine, 1985) and in the developing world (this volume) mean that values for (or relative rankings based on) benefits and costs should not be compared between analyses. In the first exercise an effort was made to calculate absolute likely benefits that would accrue from vaccine development and the actual net costs (including costs of treatment averted) associated with their use. Because real values were calculated, the incremental cost per unit of benefits could legitimately be used to differentiate between vaccine candidates in the interpretation of rankings on these criteria.

In the present analysis, the committee treated certain factors affecting actual vaccine benefits and net costs differently than in the first report. Vaccine utilization is not incorporated into the calculation of benefits (for reasons discussed in Chapter 6), hence benefits are potential rather than expected. Utilization is also not included in cost calculations, and disease treatment costs are also not included (see Chapter 4).

These differences in methods have important consequences. The values derived for the health benefits and the expenditures on vaccines to achieve them should be viewed as representing relative vaccine attributes and not their absolute magnitude. Thus, as noted above, it is not appropriate to compare health benefit or cost calculations between the assessments presented in this volume and its companion (Institute of Medicine, 1985).

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. 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.

2. The analysis views costs and benefits from a perspective of the developing world as a whole: 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, in the light of their knowledge of other efforts within and outside the United States.
3. The analysis recognizes only those primary economic impacts of new vaccines that were judged likely to differentiate between vaccine candidates, that is, the costs of vaccine development and the expenditures on vaccine for the immunization programs. while the cost

(price) of the vaccine for the immunization program (Cv in Figure 3.2) is included, the cost of vaccine administration is a primary economic impact that is not included in the analysis. As discussed in Chapter 6, it was assumed for the purposes of this analysis that all vaccines would be delivered through the World Health Organization's Expanded Program on Immunization (WHO-EPI). All vaccine candidates could then reach the level of utilization achieved by that program, and differences in utilization need not be incorporated as a factor in the analysis. Similarly, the cost of vaccine administration is assumed not to be significantly different between vaccine candidates if all are delivered through the EPI (although there may be some differences in cost, e.g., between injected and oral vaccines).

The first volume of the committee's report (Institute of Medicine, 1985) presents a method that can be used to estimate the net costs associated with vaccine use, where the cost of treatment averted and differential vaccine utilization are incorporated into the calculations of costs and health benefits. This more detailed approach may be possible where these factors can be reliably estimated, for example, within a specific country.

Secondary impacts of vaccines 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.”) For the reasons discussed in Chapter 4, it was judged impractical to attempt to estimate global averages for treatment costs for the conditions resulting from the target diseases. The tertiary impacts, which are also not considered in this analysis, involve changes in the costs of care for other diseases that the patient may get because the vaccine has prevented death due to the target disease.

4. This analysis covers vaccine priorities for the population of the developing world as a whole. It aggregates vaccine benefits and costs irrespective of the local, national, or regional groupings affected by particular diseases. Chapter 4 contains the working definition of the developing world adopted for this analysis.
5. The analysis treats each potential vaccine as an independent investment decision. For example, the analysis, for reasons discussed in Chapters 4 and 8, does not attempt to incorporate quantitatively the synergism that exists between some diseases, resulting in mortality or more severe morbidity (e.g., measles and diarrhea). Thus, some vaccines may in practice avert a disease burden greater than that nominally attributable to the pathogens against which they protect. Additionally, the analysis does not take into account other interactions, such as the effect of an improved pertussis vaccine on the long-term acceptance of immunization in general or the benefits of an improved polio vaccine on the ease of delivery of other childhood vaccines (see Chapter 8).
6. The method of estimating disease burdens used in this analysis treats diseases as noninteracting phenomena, although possible interactions are recognized as a factor for consideration in the final choice of priorities for accelerated development. If it becomes possible to better quantitate known or suspected interactions, for example, between measles and diarrhea or between viral and bacterial

respiratory infections, then future applications of this method might formally account for them in disease estimates.

The purpose of the committee's effort was to provide U.S. government decision makers with a tool to help guide their investments in accelerated development of vaccines for use in developing countries. The approach adopted in this analysis is not necessarily the correct approach for other purposes (see Chapter 8, Table 8.1). It is hoped, however, that the methods outlined in this report and its companion volume (Institute of Medicine, 1985) may be useful to other groups, such as regional organizations or specific countries, in their efforts to establish priorities.

METHOD

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

The net expected health system expenditures and the net expected health benefits are “annualized” and discounted to their present values. Annualized means that all benefits and expenditures 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.

Calculation Procedures

A comprehensive approach to comparing costs associated with achieving the health benefits from a vaccine would entail calculating the present value of the annualized equivalent of the net expected health system costs. This would include 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

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

(1)

where

r	=	discount rate;
C_{Dev}	=	cost of vaccine development;
P_{Dev}	=	probability of vaccine development;
C_{VP}	=	annual cost of the vaccination program (which includes the the cost [price] of the vaccine C_V for the program and the cost of its administration program, C_p);
T_{Use}	=	time until steady-state vaccine use, that is, 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, that is, the delay of vaccination benefits; and
C_{SE}	=	annual medical costs from side effects.

Because of the decision that for a global analysis the estimation of average treatment cost was impractical and because of the judgment (discussed in Chapters 5 and 9) that side effects were likely to be negligible, the above formulation simplifies. The expenditures on vaccines to achieve the anticipated benefits can be expressed as

$$rC_{Dev} + \frac{P_{Dev}C_V}{(1+r)^{T_{Use}}},$$

(2)

where

rC_{Dev}	=	amortized cost of vaccine development; and

$$\frac{P_{Dev}C_V}{(1+r)^{T_{Use}}} = \text{annualized present value of the cost of vaccine for the immunization program.}$$

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. The annualized equivalent may be expressed as

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

(3)

where symbols are defined as in Equation 1 and

B	=	expected annual steady-state benefits from vaccine, adjusted for efficacy (E) and differential utilization (U), if necessary; and
SE	=	expected annual incidence of vaccine side effects.

In this analysis, it is assumed that differential utilization will not be a factor in determining the potential health benefits achievable with vaccine candidates (all are assumed delivered through WHO-EPI) and, as discussed in Chapter 7, side effects are judged to be negligible. Thus, in this analysis the expression for relative benefits simplifies to

$$\frac{P_{Dev} B'}{(1+r)^{T_{Use}+T_{Lag}}}, \quad (4)$$

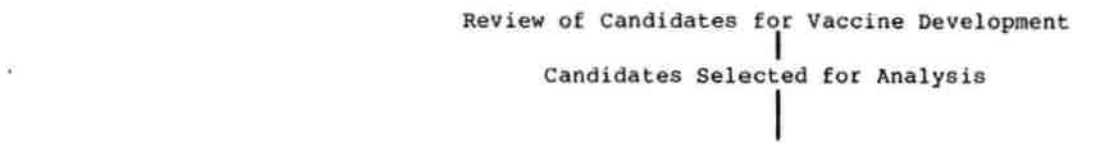
where

B'	=	expected annual steady-state benefits from vaccine, adjusted for efficacy but not adjusted for utilization (it thus represents relative potential benefits).

Figure 3.1 summarizes the hierarchy of components that would make up a comprehensive analysis of the expected health benefits and expected costs for each prospective vaccine. Figure 3.2 shows the components assessed in the simplified analysis judged appropriate for the purposes of the exercise described in this report. Each element of benefit and of cost is based on estimates related to the target disease or to the subject vaccine. Implementation of the comprehensive approach shown in Figure 3.1 for vaccines for diseases of importance in the United States is described in the committee's first report (Institute of Medicine, 1985). Chapter 7 of this report describes the implementation of the comparison scheme shown in Figure 3.2. The scheme integrates the components of benefit and cost separately, adjusts each for the probability that it will occur and for the expected delay until realization, and presents the conclusions of a central analysis.

INTERPRETATION OF RESULTS

The interpretation of results from implementation of the comprehensive approach to the analysis (Figure 3.1) —which develops annualized net expected costs and annualized expected health benefits for each candidate vaccine—is discussed in the committee's first report (Chapter 3, Institute of Medicine, 1985). The description below illustrates procedures for the interpretation of the results of the simplified analysis shown in Figure 3.2.



Symbol in Equation	Component of Benefit	Component of Cost	Symbol in Equation
B	Expected annual benefit (reduction in morbidity and mortality in target population brought about by vaccine) [Chapter 4; appendixes]	Annual cost of medical treatment averted [Chapter 4; appendixes]	C_{Tr}
E	Expected vaccine efficacy [Chapter 5; appendixes]		
U	Expected utilization of vaccine [Chapter 6; appendixes]	Annual production, storage, distribution, and administration costs of vaccine [Chapters 5 and 7]	C_{VP}
SE	Expected annual incidence of vaccine side effects [Chapters 5 and 7]	Annual medical costs from side effects [Chapters 4, 5, and 7]	C_{SE}
P_{Dev}	Probability of vaccine development [Chapter 5]	Probability of vaccine development [Chapter 5]	P_{Dev}
		Research, development, and field testing up to the time of licensure [Chapter 5]	C_{Dev}

FIGURE 3.1 Summary of comprehensive analytic strategy.

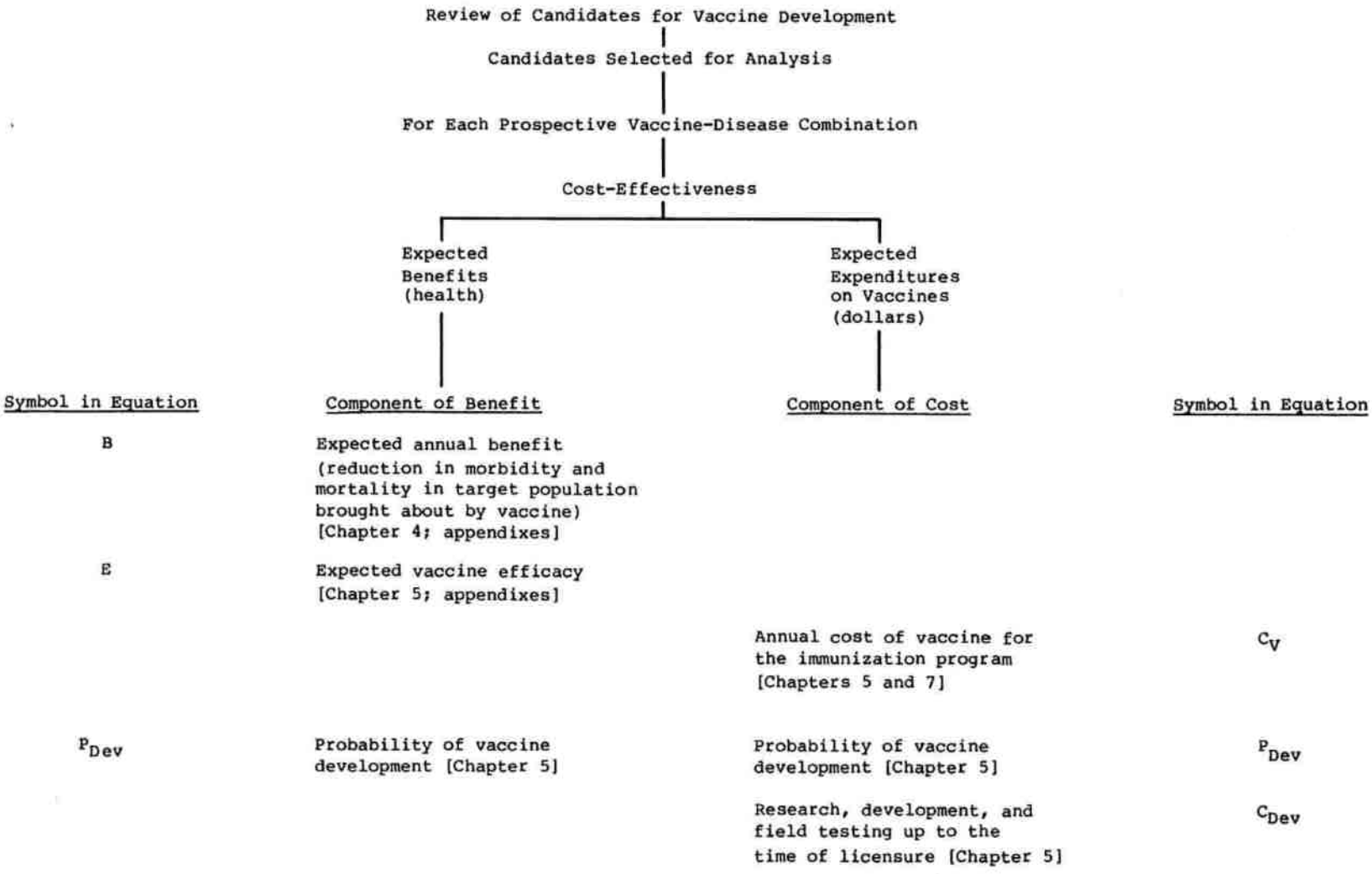


FIGURE 3.2 Summary of analytic strategy adopted for comparison of vaccine candidates for developing countries.

TABLE 3.1 Sample Array of Hypothetical Benefits and Expenditures for Various Vaccines

Vaccine	Annualized Present Value of Potential Health Benefits	Annualized Present Value of Potential Expenditures on Vaccines ($ millions)
A	250	10
B	200	20
C	200	40
D	100	80
E	150	100
F	100	200
G	125	300
H	105	400
I	150	500
J	80	1,000

NOTE: Health benefits may be expressed in any unit as long as it is used consistently for all diseases or vaccines.

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

Table 3.1 summarizes results for 10 vaccine candidates, A through J. Each project is associated with a potential expenditure and a potential benefit, both adjusted to their present values to make results with different time horizons comparable to one another, and converted to annualized equivalents. The figures take into account many (but not all) uncertainties that apply to the development, use, and consequences of each vaccine. However, some factors (e.g., utilization) are assumed not to differentiate between vaccine projects, and some costs or possible savings (e.g., treatment cost savings), which may differentiate between projects, are not included in the calculations. Hence, the values are not real or absolute. Within a category they should only be regarded as relative. That is, differences between benefits of vaccine candidates or differences between costs are meaningful, but comparisons of benefits and costs for a particular vaccine are not.

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. The expected number of lives saved per year is 1,000 in both cases.

In Table 3.1 a potential expenditure necessary to achieve the potential health benefit is listed for each project. In reality the net costs associated with a vaccine may be negative (i.e., a savings might be realized) if the treatment costs averted by its use (not included in the expenditure estimates) outweigh the expenditures on vaccines and their administration.

The committee proposes that the potential global health benefit of a vaccine take precedence in determining its initial ranking for accelerated development priority. The affordability of the benefit, represented by the relevant expenditures on vaccines, can also be entered into the decision process if desired, along with a variety of further nonquantifiable considerations (discussed in Chapter 8). Since the expenditures on vaccines do not represent net costs, the committee favors using the information provided by the ranking on this criterion as a secondary input into the decision-making process.

The priority ranking of vaccine candidates for accelerated development on the basis of potential health benefits is a straightforward process. The spacing of the numerical values may permit grouping of vaccines into clear categories. Depending on the degree of confidence decision makers have in estimates incorporated into the calculations for vaccine candidates that achieve nearly equivalent health benefit values, it may be necessary to resort to other criteria, for example, affordability or availability of other control measures to inform choices. In either case, decision makers should examine the nonquantifiable considerations outlined in Chapter 8 to guide the final selection of priorities. The calculation procedures outlined in this report are an aid to—not a substitute for—the final process of informed decision making.

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 account for the anticipated investment required from NIAID for each candidate vaccine. This might influence the number of accelerated development projects pursued, the particular projects pursued, or both. These are issues best decided by NIAID policymakers; the proposed method merely informs the decision process.

"Affordability" or willingness to pay to achieve benefit can be incorporated into the decision process in one of two ways. First, adjustments can be made to the health benefit values to reflect the effect of various levels of financial resource constraints; this may affect the rankings. This procedure is illustrated in Chapter 9. Second, costs may be considered as equal in importance to benefits.

If decision makers wish to incorporate the costs of vaccine development and use into the ranking process as a decision criterion equally important to the potential health benefit, then rankings can sometimes be developed based on the concept of dominance of one investment over another. If vaccine x is better on one dimension

(either benefits or affordability) 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 y. The first step in this procedure is to rank vaccine candidates on the basis of health benefit (greater is preferable) and on expenditure (lower is preferable). For the vaccines A through J listed in Table 3.1, the rankings are shown in Table 3.2.

TABLE 3.2 Rankings of Various Hypothetical Vaccinesa

Annualized Present Value of Potential Health Benefits		Annualized Present Value of Potential Expenditures on Vaccines ($ millions)	
A	250	A	10
B, C	150	B	20
E, I	150	C	40
G	125	D	80
H	105	E	100
D, F	100	F	200
J	80	G	300
		H	400
		I	500
		J	1,000

[a]Greater benefits and lower expenditures are preferred.

GUIDELINES

Applying the test for dominance noted above to these candidate vaccines produces the results shown in Table 3.3 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 (as judged by these criteria) are vaccines A, B, and C, and the least attractive of the listed vaccines 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. The procedures for further selections are outlined below.

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) of other vaccines.

In the example, there are 10 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 far right column of Table 3.2, these are each dominated by at least four other vaccines.

This leaves two remaining candidates for the fourth vaccine, D and E. In the system employed in this assessment the choice between vaccines D and E requires consideration of the other factors listed in Chapter 8. It may also require judgments about considerations omitted from the cost calculations, such as the potential savings from treatment averted for some vaccines. (In the more comprehensive form of the assessment where "real" costs can be related to "real benefits," the incremental cost-effectiveness (C/E) ratio can be used to differentiate between contenders. This process requires value judgments about society's willingness to forgo resource savings or to incur costs in

TABLE 3.3 Vaccine Dominance

	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	

NOTE: Column dominates row; see text for explanation.

order to realize health benefits. These procedures are described and illustrated in the first volume of the committee's report [Institute of Medicine, 1985].)

SUMMARY

The approach described in this report is recommended by the committee for the selection of priorities for accelerated development of vaccines against diseases prevalent in developing countries because it separately identifies each logical component of potential benefits and potential expenditures associated with individual vaccine contenders. The analysis distinguishes quantifiable consequences from the probability they will occur and also incorporates information on when the consequences are likely to occur. In addition, the approach requires that an effort be made to state the sources and reasons for all assumptions and estimates. The committee suggests that the potential global health benefits of a vaccine take precedence in determining its initial ranking for accelerated development. The affordability of the benefits, as represented by the relevant expenditures on vaccines, should also be considered along with other nonquantifiable considerations (discussed in Chapter 8) in the final selection of priority projects.

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.

The approach adopts a perspective for the developing world as a whole on health benefits and expenditures. This does not imply that the priorities that emerge from this analysis are necessarily those that should be adopted in all circumstances. The methods used in this analysis (and additional procedures used to estimate differences in vaccine utilization and cost savings from treatment averted) can be applied by others for determining priorities for specific countries or regions.

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 expenditures and the annualized potential health benefits have been determined for each vaccine candidate, the results must be interpreted based on the type of constraints that limit the number of candidates that may be selected. Specific procedures exist for incorporating affordability (willingness to pay) into the rankings based on health benefits or for using expenditures as a decision criterion equal to health benefits. If ranking or dominance considerations alone do not provide a complete slate of candidates, decision makers must make judgments on the basis of various other

nonquantifiable considerations, such as the availability of alternative control measures.

REFERENCE

Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume I. Diseases of Importance in the United States. Washington, D.C.: National Academy Press.

4

Comparison of Disease Burdens

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 the vaccine is intended to benefit 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 diseases that afflict populations in developing countries.

The classification of developing countries used in this study is in accordance with that used by the United Nations. Table 4.1 shows the regions, their populations, and other population features. Table 4.2 further defines the population estimates for the developing regions. Population estimates used throughout this volume were adapted from the 1984 World Population Data Sheet (Population Reference Bureau, Inc., 1984). Population estimates by age group were derived with the assistance of the Population Reference Bureau.

In the proposed system for comparing diseases, information on morbidity and mortality are combined with value judgments on the undesirability of various generic conditions into a single numerical score for each disease.* The same principles have been used in the comparisons of potential health benefits anticipated from individual vaccine candidates in Chapter 7. It is possible to use the same system to compare diseases identified in Appendix A that are candidates for long-term rather than accelerated vaccine development.

For the first phase of this study, setting vaccine priorities for the United States, the committee developed a method to calculate and compare the costs associated with various diseases. This method is described briefly in the latter portion of this chapter. For the reasons explained below, no attempt is made in this analysis to compare total treatment costs for diseases or the potential cost savings from

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

TABLE 4.1 World Population Data

Region or Country	Population as of Mid-1984 (millions)	Crude Birth Rate (per 1,000 population)	Infant Mortality Rate (per 1,000 live births)	Percent Population Under Age 15	Percent Population Over Age 64	Urban Population (percent)
World[a]	4,762	28	84	35	6	40
Less developed	3,596	32	94	38	4	32
Africa	531	45	119	45	3	29
Asia[b]	2,662	30	91	38	4	25
Latin America[c]	397	31	65	39	4	65
Oceania[d]	5	41	89	43	3	18
More developed	1,116	16	19	23	12	71
Europe	491	14	15	22	13	72
North America[e]	262	15	11	22	12	74
USSR	274	20	32	25	10	64
Australia, New Zealand	19	16	11	25	10	85
Japan	120	13	7	23	9	76

[a]Error in total population due to rounding.
[b]Japan is excluded. China is included.
[c]Mexico, Central America, and South America are included.
[d]Australia and New Zealand are not included.
[e]Canada and the United States are included.
SOURCE: Population Reference Bureau, Inc. (1984).

treatment averted by vaccine candidates in the developing world. This does not mean that these techniques cannot be applied in developing regions. Individuals setting priorities for a single country or region who have access to information (or reliable estimates) necessary to calculate treatment costs and potential cost savings from vaccines could employ the methods presented in Volume I (Institute of Medicine, 1985).

TABLE 4.2 Estimated 1984 Population by Age Groups for Regions in Which Developing Countries Predominate (thousands)

	Age Group (years)						
Region	Under 1	1–4	Under 5	5–14	15–59	60 and Over	Total
Latin America	12,736	44,499	57,235	100,220	214,415	25,130	397,000
Africa	23,040	73,762	96,802	141,459	265,451	27,288	531,000
Asia	73,400	270,300	343,700	666,402	1,472,242	179,656	2,662,000
Oceania	187	635	822	1,285	2,620	273	5,000
Total	109,363	389,196	498,559	909,366	1,954,728	232,347	3,595,000
(Percentage)	(3)	(11)	(14)	(25)	(54)	(6)	

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 various 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.

A format was devised with generic categories for estimates of the annual number of cases, complications, sequelae, and deaths associated with each disease. The scheme was designed to cover all major conditions that result from infectious diseases. 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 four age groups. An example of the matrix used to compile these estimates is shown in Table 4.3; the methods used to determine the entries are described below. Data on individual diseases are presented in Appendixes D-1 through D-19.

TABLE 4.3 Examples of the Format Used to Compile Information on the Burden of Illness Arising from Infectious Diseases: Hepatitis A Virus[a]

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration (days)	Number of Cases	Duration (days)	Number of Cases	Duration (days)	Number of Cases	Duration (days)
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity									
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work		139,843	7	635,651	7	2,256,561	7	149,378	7
C	Severe pain, severe short-term impairment, or hospitalization	Jaundice, nausea, malaise	31,735	14	158,675	14	1,221,794	14	206,277	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	Severe jaundice, fulminant hepatitis		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death			n.a.	1,144	n.a.	5,146	n.a.	8,005	n.a.

[a]See Appendix D-4 for derivation.

Trade-Off Values

Individual value judgments (trade-off values)* on the undesirability of particular disease states were elicited through a questionnaire (see Appendix E) completed by a range of health professionals in developing countries. 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 1 day for each state of acute illness and 1 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 4.4. The morbidity/ mortality and age categories in the questionnaire were the same as those used to develop estimates of disease incidence.

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 with the death of a child under 5 years of age (for an example derived from Table 4.4, see Table 4.5).

Expression of Morbidity and Mortality Burdens

Specific infant mortality equivalence values can be combined with disease burden estimates, such as those given in Appendixes D-1 through D-19, to generate scores that express the seriousness of a disease relative to others as viewed by the individual making the trade-off decisions.

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

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

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

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

TABLE 4.4 Example of an Individual Scheme of Trade-off Values

Morbidity Category	Description	Unit	Trade-Off Values			
			Under 5 Years	5-14 Years	15-59 Years	60 Years and Over
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Days	20,000	15,000	10,000	5,000
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Days	10,000	10,000	5,000	500
C	Severe pain, severe short-term impairment, or hospitalization	Days	1,000	500	200	100
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	Cases	100	100	200	200
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Cases	5	5	10	2
F	Total impairment	Cases	1	1	1	2
G	Reproductive impairment resulting in infertility	Cases	5	5	2	100
H	Death	Cases	1	1	1	1
		Deaths adjusted for age group	1	0.5	0.3	3

The total score or total disease burden value (TDBV) is then a summation of the subtotals. A sample calculation sheet is shown in Table 4.6.

The views of various 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 presenting the results of the disease burden comparison performed by this committee, some discussion of the method is desirable.

TABLE 4.5 Example of an Individual Scheme of Infant Mortality Equivalence Values

Morbidity Category	Description	Unit	Infant Mortality Equivalence Values			
			Under 5 Years	5-14 Years	15-59 Years	60 Years and Over
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Days	20,000	7,500	3,000	15,000
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Days	10,000	5,000	1,500	1,500
C	Severe pain, severe short-term impairment, or hospitalization	Days	1,000	250	60	300
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	Cases	100	50	60	600
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Cases	5	2.5	3	6
F	Total impairment	Cases	1	0.5	0.3	6
G	Reproductive impairment resulting in infertility	Cases	5	2.5	0.6	300
H	Death	Cases	1	0.5	0.3	3

Procedures Used in Deriving Disease Estimates

The committee solicited information that would enable estimates to be made in the format shown in Table 4.3 from individuals knowledgeable about particular diseases. If the disease was not one for which the World Health Organization collects information, the committee used other sources. 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 D-1 through D-19. For some of the diseases included in this comparison, only limited data exist on their incidence in developing countries. Estimates sometimes had to be made on the basis of reports from a few

developing countries and the assumption that extrapolation to the entire developing world was reasonably valid.

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; convalescence or protracted initial illness (even possibly leading to death) from which the individual eventually might recover was not considered chronic disability.
- To simplify implementation of the scheme, acute episodes of illness usually were assigned entirely to the morbidity category representing the most severe signs and symptoms present, although the episode might include periods of recovery at less severe levels.
- Category C was interpreted as morbidity for which hospitalization was desirable, even if probably not accessible.
- For diseases in which the pathogen produces a broad spectrum of illness severity rather than 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 epidemiologic surveys of the disease; in other cases previously reported incidence rates were applied to 1984 population figures (Population Reference Bureau, Inc., 1984).
- It was judged that trends in the patterns of diseases under consideration (see Appendixes D-1 through D-19) were generally not of sufficient magnitude to obscure differences among diseases, that is, that the relative impact of diseases when vaccines were likely to become available would be similar to that in 1984. This is amenable to verification. The effect of trends in population numbers and disease incidence on future vaccine benefits is discussed in Chapter 7. The impact of certain diarrheal diseases (especially mortality) probably will be decreased by the increased use of oral rehydration therapy. Two scenarios are therefore included in the calculations of disease burdens and vaccine benefits for these pathogens; they are described in Appendix C.
- For epidemic diseases, the approximate average annual incidence was calculated using epidemic incidence and the average length of the inter-epidemic period.

Limitations of the Current Estimates

Limitations on the accuracy of estimates included in Appendixes D-1 through D-19 need to be recognized. The extent to which the estimates represent true disease patterns varies among diseases for the following reasons.

- The quality and availability of data on specific diseases vary.
- The types of data from which estimates were made vary. (For some diseases, infection rates for certain populations could be coupled

with estimates of the proportion of clinically symptomatic infections to yield numbers of cases displaying symptoms. For other diseases, estimates were based on surveillance data, on prospective or retrospective studies in certain populations, or on reported disease incidence.) The reliability of data from such disparate sources varies considerably, even within countries.

- It is almost universally accepted that, with few exceptions, reliable surveillance data from developing countries are unavailable. (Underreporting or overreporting may occur for many reasons, and it is

TABLE 4.6 Example of Total Disease Burden Value Calculations: Hepatitis A Virus

		Age Group							
		Under 5 Years				5-14 Years			
Morbidity Category	Description	Cases	Duration (days)	Infant Mortality Equivalence Value	Subtotal	Cases	Duration (days)	Infant Mortality Equivalence Value	Subtotal
A	Moderate localized pain and/or mild systemic reaction or impairment requiring minor change in normal activities, and associated with some restriction of work activity			40,000	0			32,500	0
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	139,843	7	23,713	41	635,651	7	17,500	254
C	Severe pain, severe short-term impairment, or hospitalization	31,735	14	2,000	222	158,675	14	2,244	990
D	Mild chronic disability (not requiring hospitalization, institutionalization or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.	75	0		n.a.	62.5	0
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity and seriously restricting ability to work)		n.a.	5.5	0		n.a.	5.5	0
F	Total impairment		n.a.	1	0		n.a.	0.4	0
G	Reproductive impairment resulting in infertility		n.a.	100	0		n.a.	22.5	0
H	Death	0	n.a.	1	0	1,144	n.a.	0.5	2,288
TOTALS					263				3,532

[a]Infant mortality equivalence values represent the median of responses from individuals in developing countries.

generally not practical to determine the extent of the error. Therefore, raw data on reported disease incidence were rarely used as a sole basis for disease estimates.)

- Conditions affecting disease incidence are not uniform. Therefore, the exceptionally broad scope of the attempted estimates and the occasional need to extrapolate data from very few countries or studies to the entire developing world led to numerical estimates of uncertain validity.
- For certain conditions, the estimates (both absolute numbers

15-59 Years				60 Years and Over				
Cases	Duration (days)	Infant Mortality Equivalence Value	Subtotal	Cases	Duration (days)	Infant Mortality Equivalence Value	Subtotal	Subtotal by Category
		8,750	0			50,000	0	0
2,256,561	7	5,650	2,796	149,378	7	25,000	42	3,133
1,221,794	14	2,000	8,553	206,277	14	5,000	578	10,342
	n.a.	30	0		n.a.	550	0	0
	n.a.	2.75	0		n.a.	23.125	0	0
	n.a.	0.309	0		n.a.	5	0	0
	n.a.	16.5	0		n.a.	300	0	0
5,146	n.a.	0.4	12,865	8,005	n.a.	5	1,601	16,754
			24,213				2,220	30,229

and distributions) were based on individuals' clinical and epidemiological experience and judgment, for which no means of verification existed.
- The resources and time available to generate estimates were limited.

As noted above, many of the estimates used in this report are highly uncertain. However, the data-based approach presented here can be refined as epidemiological information increases. The committee believes that its method ensures the optimal use of available information and is preferable to qualitative measures (e.g., high, intermediate, or low) or scaling methods (e.g., assigning scores to incidence on a scale of 1 to 10).

The committee cautions that while the current estimates have been judged sufficient for the purposes of this report, efforts to collect additional data on relative disease burdens and to refine estimates from available data would be highly desirable. Discussions of the uncertainty of each disease's estimates appear in Appendixes D-1 through D-19.

VALUE JUDGMENTS IN QUANTIFYING MORBIDITY AND MORTALITY

The use of infant mortality equivalence (IME) values in quantifying disease burdens (as in Table 4.6) 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 trade-off or IME 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 expected from vaccines.

The intent of selecting priorities for accelerated vaccine development is to benefit health—in the case of this report, the health of the populations in developing countries. Hence, the perspectives of medical or public health experts in those countries are of interest. Perspectives of the population at large, the intended beneficiaries, also are important.

If a representative sample from each group (health practitioners or the general populations in developing countries) 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 group members might consider an adult death (15–59 years) more undesirable than an infant death, a fairly large minority might believe just the opposite. Acute morbidity of severity sufficient to interfere with producing food or earning a living might also be relatively highly ranked for undesirability in

developing countries. In comparison, the economic impact of illness on the individual in developed countries is usually less immediate. The aggregation of these preferences is a complex issue both methodologically and ethically and needs careful consideration.

To help set IME values for this report, the committee polled a wide range of public health professionals and medical researchers from regions where developing countries predominate. Time and resource constraints did not permit polling representatives of the general population. The committee recognized that the responses obtained probably did not include the full range of perspectives required by an analysis of this type. However, the composite perspective described below was adopted to illustrate application of the system and to describe the qualitative effects of using different perspectives.

IME Perspective Used in This Study

For IME values in its calculations, the committee used a median of IME perspectives derived from the responses of health professionals in developing countries. Trade-off values elicited from these individuals were distributed over a considerable range.

The median IMEs, shown in Table 4.7, are used here and in Chapter 7 solely to illustrate the operation of the system, not to suggest the most appropriate or correct IME values. Choosing IME values 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 in adults, hospitalizations (at any age), or infertility is relatively more undesirable than expressed by the median perspective. Adopting this perspective would cause diseases inflicting or vaccines preventing a particularly disfavored morbidity or mortality to 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.

The committee's first report on vaccine priorities for important diseases in the United States (Institute of Medicine, 1985) compared the effect of adopting the median of committee member perspectives with an age-neutral perspective. In the former perspective, death in the 25–59* years age group was most disfavored (and in the over 60 years age group, the least disfavored), while in the latter perspective, deaths at any age were judged equally undesirable. For the diseases in this study, the ranking was generally similar, but influenza (which causes many deaths in the over 60 years age group) ranked relatively

higher in the age-neutral perspective. When fetal deaths from ectopic pregnancy were considered equal in undesirability to all other deaths/ gonorrhea also ranked relatively higher in the age-neutral perspective.

TABLE 4.7 The Median Infant Mortality Equivalence Values for Respondents from Developing Countries

Morbidity Category	Description	Unit	Infant Mortality Equivalents			
			Under 5 Years	5-14 Years	15-59 Years	60 Years and Over
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Days	40,000	32,500	8,750	50,000
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Days	23,713	17,500	5,650	25,000
C	Severe pain, severe short-term impairment, or hospitalization	Days	2,000	2,244	2,000	5,000
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	Cases	75	62.5	30	550
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Cases	5.5	5.5	2.75	23.125
F	Total impairment	Cases	1	0.4	0.309	5
G	Reproductive impairment resulting in infertility	Cases	100	22.5	16.5	n.a.
H	Death	Cases	1	0.5	0.4	5

The committee derived a second set of IME values for this study based on trade-off questionnaires (see Appendix E) completed by individuals in the United States who are involved in improving health in developing countries. Table 4.8 presents these values. (The committee recognizes that the medians shown in Tables 4.7 and 4.8 were not drawn from statistically valid samples.) Adopting the perspective represented in Table 4.8 rather than Table 4.7 would lower the relative rankings for diseases that primarily cause mild acute morbidity, but would raise the rankings of diseases that cause very severe (total) chronic disability.

Adopting particular IME perspectives is comparable in some ways to ranking diseases or vaccines for particular age groups in the population. For example, an IME perspective that highly disfavors diseases affecting children would emphasize the relative ranking of pediatric

vaccines. Chapter 8 presents further discussion of the grouping of vaccine candidates.

COMPARISON OF COSTS ASSOCIATED WITH DISEASES

Another way to compare candidates for accelerated vaccine development would be to compare the extent to which they would render unnecessary expenditures for treating diseases or avert other disease-related economic losses, for example, lost work productivity, and their cost-effectiveness in doing so. To make such comparisons it is necessary to know (or to obtain reliable estimates on) the costs associated with each disease. The costs incurred in vaccine development and in vaccination programs are discussed in Chapters 5 and 7, respectively.

TABLE 4.8 The Median Infant Mortality Equivalence Values for Respondents from the United States

			Infant Mortality Equivalents			
Morbidity	Category Description	Unit	Under 5 Years	5–14 Years	15–59 Years	60 Years and Over
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Days	300,000	140,000	50,000	10,000,000
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Days	80,000	10,000	4,000	100,000
C	Severe pain, severe short-term impairment, or hospitalization	Days	8,000	1,000	500	10,000
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	Cases	500	80	25	5,000
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Cases	5	1	0.6	50
F	Total impairment	Cases	0.2	0.05	0.025	1
G	Reproductive impairment resulting in infertility	Cases	300	150	50	n.a.
H	Death	Cases	1	0.5	0.1	10

Estimating Aggregate Direct Costs of Diseases in the Developing World

The committee did not attempt to predict the cost associated with treating diseases included in this analysis. It would be extremely difficult and probably unrealistic to estimate, for the developing world as a whole, the proportion of cases, complications, and sequelae that receive treatment; the nature of those treatments; and their average costs. No data exist on these questions, and the committee judged that convening a group sufficiently large to develop reliable estimates of these costs would not be practical.

Estimating Costs for Diseases in Specific Countries or Regions

Although it was not feasible to include disease cost comparisons in this analysis, it might be possible to compare the costs of treating various diseases in a particular region or country in the developing world. The procedures used by the committee to estimate the direct costs (mostly treatment-related) associated with important diseases in the United States can be adopted for this purpose. Those procedures are described fully in the first volume of the committee's report (Institute of Medicine, 1985). Excluded from those calculations are costs resulting from loss of work, loss of future earnings, and public health measures to prevent further spread of illness (e.g., contact tracing for sexually transmitted diseases).

Indirect Costs

How best to calculate indirect costs associated with disease, such as loss of work time or loss of future earnings, is quite controversial. For its analysis of vaccine priorities for the United States, the committee did not believe 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 IMB 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; these could be addressed in future applications of the model. These considerations are also pertinent to the assessment described in this report.

FINDINGS

Application of the procedures described above to derive burden estimates for the diseases that are candidates for accelerated vaccine

development is described in Appendixes D-1 through D-19. Various assumptions were entailed in deriving such estimates. Table 4.9 shows the total disease burden values calculated for each disease (using disease burden estimates and the median of perspectives from public health professionals in developing countries). Use of these total disease burden values to rank the diseases is demonstrated in Table 4.10.

TABLE 4.9 Morbidity and Mortality Burdens Resulting from Various Diseases

Disease	Total Disease Burden Value[a] (IME units)[b]	Normalized (percent)
Dengue virus	34,365	0.52
Escherichia coli	978,248	14.79
	(550,248)[c]	(8.32)
Hemophilus influenzae type b	471,336	7.13
Hepatitis A virus	30,229	0.46
Hepatitis B virus	2,394,256	36.21
Japanese encephalitis virus	18,075	0.27
Mycobacterium leprae	657,349	9.94
Neisseria meningitidis	68,252	1.03
Parainfluenza virus	145,954	2.21
Plasmodium spp.	2,111,795	31.94
Rabies virus	67,821	1.03
Respiratory syncytial virus	183,326	2.77
Rotavirus	925,042	13.99
	(488,542)[c]	(7.39)
Salmonella typhi	1,308,121	19.78
Shigella spp.	828,068	12.52
Streptococcus Group A	811,477	12.27
Streptococcus pneumoniae	6,612,261	100.00
Vibrio cholera	229,217	3.47
Yellow fever virus	32,887	0.50

[a]See Appendixes D-1 through D-19 for derivations of disease burden estimates used to calculate TDBVs.
[b]Infant mortality equivalence units.
[c]Values in parentheses represent the anticipated disease burden from certain diarrheal pathogens if a plausible increase in oral rehydration therapy is assumed (see Appendix C).

Chapter 7 describes application of the disease comparison system to the calculation of potential health benefits from candidate vaccines.

LIMITATIONS OF THE PROPOSED SYSTEM

The proposed system assesses the most obvious feature of infectious diseases, morbidity, and mortality. The aggregate nature of the total

disease burden value for each disease may be regarded by some as obscuring important differences among disease consequences. Although they are assigned to the same generic morbidity category, some disease conditions may be regarded as more severe (more undesirable) than those of another disease. This problem exists with any category system; to assign trade-off (or IME) values to the whole spectrum of conditions arising from all diseases would be too complex and unmanageable.

TABLE 4.10 Ranking of Diseases by Total Disease Burden Values

Disease	Total Disease Burden Value (IME units)[a]
Streptococcus pneumoniae	6,612,261
Hepatitis B virus	2,394,256
Plasmodium spp.	2,111,795
Salmonella typhi	1,308,121
Escherichia coli	978,248
Rotavirus	925,042
Shigella spp.	828,068
Streptococcus Group A	811,477
Mycobacterium leprae	657,349
(Escherichia coli)	(550,248)[b]
(Rotavirus)	(488, 542)[b]
Hemophilus influenzae type b	471,336
Vibrio cholera	229,217
Respiratory syncytial virus	183,326
Parainfluenza virus	145,954
Neisseria meningitidis	68,252
Rabies virus	67,821
Dengue virus	34,365
Yellow fever virus	32,887
Hepatitis A virus	30,229
Japanese encephalitis virus	18,075

[a]Infant mortality equivalence units.
[b]Values represent the anticipated disease burden from certain diarrheal pathogens if a plausible increase in oral rehydration therapy is assumed (see Appendix C) .

Additionally, the system does not, as presently conceived, permit differentiation of diseases on the basis of episode duration. That is, it does not indicate 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.

Other disease characteristics not recognized by the proposed system include the following:

- The epidemic potential of the disease: the average annual incidence is used for comparative purposes, but certain epidemic

diseases may overwhelm available medical services and engender particular concern in the at-risk populations.

- The potential for synergistic interaction with other diseases: the committee evaluated the possibility of incorporating into the disease burden estimates of the effects of known synergism, such as between diarrheal disease and measles. The committee concluded that current knowledge of these phenomena did not permit reliable quantification of their consequences, but that they should be recognized in the ultimate selection of priorities.

These issues are discussed further in Chapter 8.

Problems in obtaining accurate estimates of disease incidence and difficulties in deciding which IME perspectives to adopt also limit the usefulness of the system. Nevertheless, 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 undesirability of various disease consequences.

To illustrate use of the proposed system, diseases that are candidates for accelerated vaccine development have been ranked according to a median of trade-off perspectives elicited from public health experts in developing countries. The effects of adopting alternative perspectives are also discussed. Considerable uncertainty surrounds some of the estimates of disease burdens because data of the desired reliability are not available.

No attempt has been made to calculate the costs of treating diseases in the developing world as a whole because of the many uncertainties involved in such aggregate estimates. However, the committee believes that estimates of total direct costs for certain diseases could be used to help set vaccine priorities in specific countries or regions of the developing world.

RECOMMENDATIONS

The capacity to make rational choices of vaccine development priorities and vaccine formulation would be enhanced by better information on disease incidence and the pathogen serotypes prevalent in particular regions. Therefore, the National Institute of Allergy and Infectious Diseases and other national and international agencies should consider ways to improve the epidemiologic information on infectious diseases.

REFERENCES

Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume I. Diseases of Importance in the United States. Washington, D.C.: National Academy Press.

Population Reference Bureau. 1984. World Population Data Sheet. Washington, D.C.: Population Reference Bureau.

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 health benefits expected from each new vaccine and the associated costs. The characteristics of a vaccine (e.g., live attenuated virus versus subunit) may affect its efficacy, and the complexity of the development process determines the costs associated with producing health benefits and the time at which they would be achieved.

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

SELECTION OF CANDIDATES

The committee defined candidates for accelerated development as those vaccines for which 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 A.)

The diseases and vaccine candidates chosen for the ranking process are shown in Tables 5.1 and 5.2 and described in detail in Appendixes D-1 through D-19. Some marginal candidates were excluded (because of

Much of the material in this chapter is from New Vaccine Development: Establishing Priorities, Volume I (Institute of Medicine, 1985). However, some sections, like the one on predictions of vaccine efficacy, have been changed to reflect the special requirements of health care delivery in developing countries.

TABLE 5.1 Predictions Table—Primary

Pathogen (Target Population)	Type of Vaccine	Cost of Development ($ millions)	Probability of Successful Development
Dengue virus (Infants and children in endemic areas; travelers to endemic areas)	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	25	0.75
Escherichia coli (enterotoxigenic) (Infants<6 months)	A combination of purified colonization factor antigens and possibly other antigens	25	0.50
	Genetically engineered attenuated strains	25–50	0.70
Hemophilus influenzae type b (Infants)	Conjugated polysaccharide	15	0.90
Hepatitis A virus (Susceptibles of all ages; routine for preschool children)	Attenuated live virus	15	0.95
	Polypeptide recombinant vaccine produced in yeast	25	0.95
Hepatitis B virus (Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations, at earliest possible age)	Polypeptide produced by recombinant DNA technology	5	0.99
Japanese encephalitis virus (Children in epidemic and endemic areas; foreign visitors to epidemic regions)	Inactivated virus produced in cell culture	50	0.50
Mycobacterium leprae (Immunoprophylactic: all children in endemic areas. Immunotherapeutic: all recently infected individuals)	Armadillo-derived M. leprae	25	0.50
Neisseria meningitidis (Infants, 3 to 6 months)	Conjugated capsular polysaccharides. Groups A,C,Y, and W135	30	0.50 (dependent upon success in developing conjugation procedures with other vaccines)
Parainfluenza viruses (Infants)	Trivalent, subunit vaccine (which must contain fusion proteins)	25	0.80
Plasmodium spp. (All infants at risk, military personnel, travelers)	Plasmodium falciparum, synthetic or recombinant sporozoite antigen preparation	25	0.50
	Multivalent synthetic or recombinant sporozoite antigen preparation (P. falciparum, P. vivax, P. ovale, P. malariae)	35	0.50

Time to Licensure (years)	Time to Adoption (years)	Efficacy	Number of doses	Cost per dose (dollars)
10	2	0.85	1	12
10	2	0.75 (against strains in vaccine)	Approx. 3	5–10
10	2	0.80 (against strains in vaccine)	1–2	1–2
3	5	0.90	2 (with DTP)	5–10
4	5 (as part of combination)	0.90	1	15
5	5	0.90	3	20
1	2 (dependent on price)	0.90	3	30
6–8	2–3	0.80	2 (boosters required with all current; none gives life-long immunity)	10–20
10	5	0.75	1	25
4–6	5 (in moderate to high risk areas)	0.80	2	10
5	5	0.80 (against severe disease in young children)	2+boosters	15
5–8	2	0.80 (assuming immunity is long-lasting)	3	10–15
8–10	2	0.80 (assuming immunity is long-lasting)	3	10–15

Pathogen (Target Population)	Type of Vaccine	Cost of Development ($ millions)	Probability of Successful Development
Rabies virus (Individuals at high risk, plus post-exposure prophylaxis)	Vero cell	5	0.90
(Same)	Glycoprotein produced by rDNA technology in mammalian cells	3–5	0.85
(Birth cohort in areas of high risk)	Attenuated live vector virus containing gene for protective glycoprotein antigen	10–20	0.50
Respiratory syncytial virus (Infants at earliest possible age)	Polypeptides produced by recombinant DNA technology	25	0.80
	Attenuated live virus	25	0.80
Rotavirus (Infants at earliest possible age, preferably with oral polio vaccine)	Attenuated high passage bovine rotavirus	10	0.90
	Attenuated low passage bovine rotavirus	30	0.80
	Rhesus monkey rotavirus	30	0.80
Salmonella typhi (Children; young adults at risk; travelers from developed countries to endemic areas)	Attenuated ga1E mutant S. typhi strain TY21a	2	0.90
	Aromatic amino acid dependent strains of S. typhi	2	0.50
Shigella spp. (Infants at birth or earliest possible age; elderly for epidemic strains)	Probably plasmid mediated outer membrane protein invasion determinant (small number of promising options need investigation to determine best approach)	25–50	0.70 for polyvalent vaccine (0.85 for targeted S. dysenteriae and S. flexneri strains)
Streptococcus A (Children,<3 to 4 years)	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	50	0.80
Streptococcus pneumoniae (Infants)	Conjugated polysaccharides, polyvalent	30	0.80
Vibrio cholera (Children, especially <2 years)	Genetically defined live mutant V. cholerae (A−B+ or A−B− with respect to toxin subunit synthesis	25	0.75
	Inactivated antigens	10	0.65
Yellow fever virus (Young children)	Attenuated live virus produced in cell culture	15	0.95

Time to Licensure (years)	Time to Adoption (years)	Efficacy	Number of doses	Cost per dose (dollars)
3	2–5 (dependent on price)	0.99	3–5	10
3	2–5 (dependent on price)	0.95	3–5	10
3	2	0.95	1	1
5	2	0.80 (against severe disease in young children)	2+booster	15
5	2	0.80 (against severe disease in young children)	1–2	15
2	2	0.80 (against severe disease in young children)	1	10
5	2	0.90 (against severe disease in young children)	1	10
5	2	0.90 (against severe disease in young children)	1	10
1	2 (endemic areas)	0.80	2–3	2
5–8		0.80–0.90	2–3	2
approx. 10	2	0.80–0.90 (for a multivalent vaccine)	1–2	2
6–8	2–5	0.80 (depends on adjuvant or carrier development)	2	5
5	2	0.80	1–2	20
5–7	2	0.90	1–2	2
3–5	2	0.65	2–3	2
2–4	2 (endemic areas)	0.90	1	5

TABLE 5.2 Predictions Table—Secondary

Pathogen (Target Population)	Type of Vaccine	Clinical Trial Difficulty
Dengue virus (Infants and children in endemic areas; travelers to endemic areas)	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	Phase I trials must be in adults, in nonendemic areas. Some apprehension over possible enhancement effects for dengue and with new approach
Escherichia coli (enterotoxigenic) (Infants < 6 months)	A combination of purified colonization factor antigens and possibly other antigens	Moderate. High attack rate in children and travelers makes evaluation possible in relatively small population. But may need to evaluate protection against certain serotypes or CFA types
	Genetically engineered attenuated strains	Needs careful monitoring for reversion to virulence
Hemophilus influenzae type b (Infants)	Conjugated polysaccharide	Need to be carried out in very young children
Hepatitis A virus (Susceptibles of all ages; routine for preschool children)	Attenuated live virus	Large number of subjects needed. Initial trials in adults may give false concepts of immunogenicity and reactogenicity for children
	Polypeptide recombinant vaccine produced in yeast	Large number of subjects needed
Hepatitis B virus (Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations, at earliest possible age)	Polypeptide produced by recombinant DNA technology	Relatively simple
Japanese encephalitis virus (Children in epidemic and endemic areas; foreign visitors to epidemic regions)	Inactivated virus produced in cell culture	Difficult. Low clinical attack rate requires very large number of subjects.
Mycobacterium leprae (Immunoprophylactic: all children in endemic areas. Immuno therapeutic: all recently infected individuals)	Armadillo-derived M. leprae	Low incidence and long incubation period requires many subjects and long time for trials
Neisseria meningitidis (Infants, 3 to 6 months)	Conjugated capsular polysaccharides, Groups A,C,Y, and W135	Difficult because epidemic disease is unpredictable
Parainfluenza viruses (Infants)	Trivalent, subunit vaccine (which must contain fusion proteins)	
Plasmodium spp. (All infants at risk, military personnel, travelers)	Plasmodium falciparum, synthetic or recombinant sporozoite antigen preparation	Mosquito challenge to volunteers
	Multivalent synthetic or recombinant sporozoite antigen preparation (P. falciparum, P. vivax, P. ovale, P. malariae)	Mosquito challenge to volunteers

Route of Administration	Adverse Reactions	Delivery Requirements	Incorporation into EPI
Intradermal	Low grade fever, soreness, muscle aches	Cold chain required; possible freeze-drying in future	Yes
Oral	None	Adjuvant use may reduce number of doses	Yes
Oral	Possibly mild diarrhea in 20%	Cold chain for lyophilized bacteria; adjuvant may be needed	Yes
Intramuscular	5% local	Refrigeration	If in a polyvalent vaccine
Parenteral, subcutaneous, or intramuscular	Minimal	Refrigeration of lyophilized preparation	As a combination with IPV and other antigens
Subcutaneous or intramuscular	Minimal	Refrigeration	Might be combined with other nonliving vaccines
Intramuscular or subcutaneous	Negligible	Refrigeration	Could be incorporated at present; efficacy much improved if delivery possible at birth, i.e., with modified EPI schedules
Subcutaneous	Some possibility of life-threatening effects associated with current vaccines: allergic encephalomyelitis; acute viral encephalitis	Nothing unusual	Yes
			Feasible
Intramuscular	Minor local	Refrigeration	Feasible
Subcutaneous	None	Nothing unusual	
Subcutaneous or intramuscular	No data—unknown	Adjuvant required, probably alum	Probably
Subcutaneous or intramuscular	No data—unknown	Nothing unusual	Probably

Pathogen (Target Population)	Type of Vaccine	Clinical Trial Difficulty
Rabies virus (Individuals at high risk, plus post-exposure prophylaxis)	Vero cell	Little; depends on antibody response
(Same)	Glycoprotein produced by rDNA technology in mammalian cells	Fatal natural disease and current availability of effective vaccine require rigorous proof of likely efficacy prior to field trials
(Birth cohort in areas of high risk)	Attenuated live vector virus containing gene for protective glycoprotein antigen	Some possible apprehension over new approach
Respiratory syncytial virus (Infants)	Polypeptides produced by recombinant DNA technology	Difficult. Needed very early in life; need rapid response. Vaccines won't take in persons with antibodies
	Attenuated live virus	
Rotavirus (Infants, 0–6 months)	Attenuated high passage bovine rotavirus	Relatively easy. Pathogen present everywhere in world. Can do trial in children<1 year
	Attenuated low passage bovine rotavirus	
	Rhesus monkey rotavirus	
Salmonella typhi (Children; young adults at risk; travelers from developed countries to endemic areas)	Attenuated ga1E mutant S. typhi strain TY21a	Trials largely completed; further work needed to optimize vaccine
	Aromatic amino acid dependent strains of S. typhi	
Shigella spp. (Infants at birth or earliest possible age; elderly for epidemic strains)	Probably plasmid mediated outer membrane protein invasion determinant (small number of promising options need investigation to determine best approach)	Moderate to difficult
Streptococcus A (Children,<3 to 4 years)	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	Moderate to very difficult
Streptococcus pneumoniae (Infants)	Conjugated polysaccharides, polyvalent	Requires high degree of patient and physician cooperation. Multitude of bacterial types creates problems of accurately determining vaccine efficacy
Vibrio cholera (Children, especially <2 years)	Genetically defined live mutant V. cholerae (A−B+ or A−B−) with respect to toxin subunit synthesis	Difficult. Need large populations in hyperendemic areas. Screening possible in volunteers
	Inactivated antigens	Difficult. Same problems as live
Yellow fever virus (Young children)	Attenuated live virus produced in cell culture	Ethical problems in field testing an improved vaccine when an effective one already exists

Route of Administration	Adverse Reactions	Delivery Requirements	Incorporation into EPI
Intramuscular or subcutaneous	Slight/none	Refrigeration	Probably not warranted. Duration of immunity not certain and post-exposure prophylaxis strategy preferred
Same as at present (with alum adjuvant)	Fewer reactions than current vaccine	Nothing unusual	Same
Probably intradermal	Unknown	Probably nothing unusual	Probably, depending on duration of immunity
Subcutaneous	None	Nothing unusual	Feasible
Intranasal	None	Nothing unusual	Feasible
Oral	Minimal or none	Refrigeration and must be administered with food or milk	Yes
Oral (an alternative to enteric-coated capsules, i.e., a liquid vaccine formula, may be needed for infants and young children)	None seen None	Refrigeration and moisture control for enteric-coated capsules	Feasible (if new vaccine formulation is developed)
Oral	None	Probably lyophilization; possibly enteric-coated capsules	Feasible
Intramuscular			Readily incorporated
Parenteral	Local soreness, low grade fever	Refrigeration (4 C)	Feasible, dependent on cost
Oral	Present prototypes cause mild diarrhea in 20%	Cold chain for lyophilized bacteria	Feasible
Oral	None expected	Lyophilized probably will withstand moderate ambient temperatures	Probably promptly in endemic areas
Subcutaneous	Minimal	Refrigeration	Feasible

staff resource constraints), and the prospects for their development are discussed briefly in the supplement to this volume (see Appendix I). This supplement also includes information on pathogens that cause major global disease problems but that were considered unsuitable for accelerated vaccine development at this time.

VACCINE CANDIDATES AND TARGET POPULATIONS

One or more vaccine candidates for accelerated development have been identified for each disease. Vaccine descriptions usually are based on current research in specific areas. in some cases, however, the number of vaccine possibilities led the committee to base predictions on a combination of research findings and general knowledge about probable requirements for licensure.

To identify an appropriate vaccine target population, the committee considered the age distribution of the disease consequences (particularly of those conditions considered most desirable to avoid); the relative risk of illness in various geographic population groups; and accessibility to the health care system. For reasons described in the next chapter, the committee assumed that most of the vaccine candidates would be delivered through the World Health Organization Expanded Program on Immunization (WHO-EPI). The effects of this assumption on determinations of vaccine efficacy are outlined below.

PREDICTIONS ON VACCINE DEVELOPMENT

Predictions on vaccine development are an attempt to foresee events from 1985 until 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 developmental resources.

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. The committee assumed that vaccine candidates would have to comply with safety and efficacy standards similar to those required by U.S. licensing regulations and the WHO.

Cost of Development

The estimate for the cost of development includes all future costs needed to bring the vaccine to licensure, irrespective of the funding source. 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, and possible difficulties in conducting clinical trials or in establishing efficacy and safety in the target population.

Time to Licensure

The time to licensure is defined as the shortest time in which a vaccine could be licensed, if all developmental stages are completed without major delays. Factors considered in determining this time were similar to those for estimating the cost of development.

The committee also considered interrelationships among 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 its predictions on the characteristics of individual vaccines primarily on known characteristics of existing vaccines of similar type, for example, 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 and is given by

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

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.

Vaccine efficacy predictions also incorporate the assumption that vaccines will be administered at ages compatible with delivery through EPI (see Appendixes D-1 through D-19 for specific details). unfortunately, the EPI delivery schedule may not be ideal for some

candidates. Efficacy would be affected if recipients were unable to respond fully or to maintain immunity for a sufficient length of time.

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 vaccine acceptance. Predictions about side effects are based on the nature of the new vaccine and its purity, and on observations of similar existing vaccines. To facilitate calculations, predictions concerning the incidence of adverse reactions are best expressed “per dose” rather than “per vaccinee.”

In this analysis, anticipated adverse reactions were judged, for the vaccines considered, to be negligible for the purposes of calculating potential vaccine benefits (see Chapter 7). For new contenders the likely reactions and their frequency should be evaluated to determine if an adjustment of the potential health benefits, which accounts for adverse reactions, is warranted.

Production Technology, Delivery Requirements, and Cost per Dose

The technical difficulty of producing a vaccine and the delivery (storage) requirements affect vaccine cost. The committee based its 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 a vaccine's predicted protective efficacy and the route of administration also may affect the ease of integrating the vaccine into existing immunization programs. Predictions of these characteristics are based largely on the nature (including the probable antigenicity) of each vaccine candidate.

CONCLUSIONS

The predictions in Tables 5.1 and 5.2 resulted from extensive deliberations by the full committee on estimates made by a subgroup, with suggested revisions by many outside consultants. The predictions were designed to reflect relative differences in vaccine candidates' prospects for development; they are not intended to be precise descriptions of future events. Predicting vaccine development is complicated by many factors, including the rapid pace of new advances in biotechnology. Some candidates excluded from the current analysis

(but discussed in the supplement to this volume) may soon need to be reassessed.

Although the outcome of scientific investigations cannot be predicted, the committee believes that the estimates and probabilities in Tables 5.1 and 5.2 are reasonable because they are based more on developmental than basic research investigations. 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 flexibility of the model described in this report makes it easy to substitute alternative or updated predictions as they become available.

REFERENCE

Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume I. Diseases of Importance in the United States. Washington, D.C.: National Academy Press.

6

Assessing the Likely Utilization of New Vaccines

The expected health benefits from a vaccine development project depend not only on the number of potential recipients of the vaccine (the target population), but also on the proportion of the target population that will actually receive it.* However, predicting future utilization rates of vaccine candidates is difficult, even for a relatively homogeneous population, because vaccine utilization depends on many interrelated and complex factors. These factors include:

- vaccine availability
- the capacity of the health care system to deliver the vaccine to potential recipients
- the effects of statutory interventions, such as the U.S. school immunization requirements (including the extent to which they are enforced)
- 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 that affect patient acceptance (number of doses, route of administration, adverse reactions, 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, and

*High utilization rates are also desirable because for many diseases they reduce disease transmission and the probability of exposure to the disease.

by the influence of media coverage (e.g., pertussis vaccine acceptance in the United Kingdom)

These factors affect each other in ways that are not fully understood or quantifiable. In its report on vaccine priorities for important diseases in the United States, this committee considered the issues of vaccine availability and utilization separately (Institute of Medicine, 1985a). A similar approach has been adopted for this project because factors affecting availability and utilization in the developing world are different. In addition, for some vaccines considered in this assessment, there may not be a need for universal availability or utilization.

VACCINE AVAILABILITY

Availability of a licensed vaccine depends on the willingness of a pharmaceutical company or other entity to manufacture it and on the company's ability to produce the vaccine in sufficient quantities to meet 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 (e.g., ability to pay), public health initiatives, patentability or status as sole supplier, and provider and lay acceptance
- legal concerns, particularly costs associated with vaccine injury compensation liability, which is a major issue in the United States
- technical difficulty of production and of distribution (in a manner that ensures potency) in target areas
- humanitarian and public relations issues

Probably some of the vaccine candidates considered in this analysis will not be commercially attractive to manufacturers in the United States or other industrialized countries, and they eventually will be made locally in developing countries. The committee had insufficient information to predict the availability of new vaccines,* so it assumed that any vaccine that met reasonable safety and efficacy standards (e.g., U.S. licensing standards or World Health Organization [WHO] guidelines) would be available in quantities sufficient to meet the demand. Such a scenario would probably require the transfer of vaccine

*The Committee on Public-Private Sector Relations in Vaccine Innovation, Institute of Medicine, recently made recommendations designed to encourage public-private sector collaboration in the development and manufacture of vaccines, particularly those of low commercial potential (Institute of Medicine, 1985b).

production technology to developing countries, most likely under the guidance and assistance of such international agencies as the WHO.

VACCINE UTILIZATION

Prediction of Utilization in Defined Populations

To develop a theoretical basis for predicting vaccine utilization in the United States, the committee adapted basic concepts of the "health belief model" (HBM), a social-psychological model of health-related decision making developed by U.S. Public Health Service psychologists in the early 1950s (Becker, 1974; Janz and Becker, 1984). Questions exist concerning the validity of the HBM as a predictive tool, but it offers an appropriate conceptual framework for studying public immunization behavior within a defined, relatively homogeneous population. A brief review of the health belief model and a description of the methods used by the committee to predict vaccine utilization in the United States appear in Volume I of the committee's report (Institute of Medicine, 1985a).

To estimate probable utilization, each vaccine candidate was assigned scores to reflect lay (target population) and provider perceptions of risk of illness, severity of disease, vaccine benefits, and barriers to vaccination. These scores were then combined into overall vaccine acceptance scores for each candidate. The combined scores were used to estimate vaccine utilization in situations in which individuals could freely choose their health behavior, and in which other factors, for example, the efficiency of the health care system, did not otherwise limit utilization. (Mandatory immunization requirements, e.g., for school admission, if enforced, tend to override the influence of these other factors in determining acceptance.)

Little research has been conducted to determine whether the health belief model as formulated for the U.S. population is applicable to other societies. Several studies of voluntary vaccine utilization in developing countries suggest that the factors determining relevant health decisions in the developing world are similar to those postulated in the HBM (Adeniyi, 1972; Azurin and Alvero, 1971; Hingson, 1974; Hingson and Lin, 1972; Hsu, 1955; Lin et al., 1971; Ogionowo, 1973; Ristori, 1969). It is important to recognize, however, that local perceptions of disease and health care are molded by social, educational, and economic conditions radically different from those in the United States. Accurate assessment of these perceptions requires input from individuals familiar with the cultures involved.

The committee believes that its general approach to estimate U.S. vaccine utilization probably could be adapted to any defined population, for example, a specific country, where the range of HBM perceptions can be estimated with reasonable confidence.

Utilization of Vaccines in the Developing World

A committee subgroup evaluated the feasibility of making utilization predictions for vaccine candidates in the entire developing world. The subgroup determined that because of the diversity of health care systems and populations involved, it would be unrealistic to attempt to combine predictions for countries or regions. Also, in many areas, health care systems cannot routinely reach large portions of the target population. In some countries, successful periodic mass immunization campaigns have been conducted, utilizing the mass media and personnel with minimal health training. For most of the developing world, however, the only consistent method for delivering vaccines is through the WHO-supported Expanded Program on Immunization (EPI), which generally provides DTP (diphtheria and tetanus toxoids and pertussis vaccine), polio, BCG (Bacillus Calmette-Guerin), and measles vaccines to infants and children, and tetanus toxoid to susceptible women (including those who possibly are pregnant). All of the vaccine candidates considered in this analysis could be adapted to conform to the current EPI schedule of administration (see Appendixes D-1 through D-19). Its vaccination schedule recommendations are intended to be adapted to local conditions and constraints. WHO-EPI flexibility in this regard (World Health Organization, 1985) may establish new opportunities for optimizing the delivery of vaccines discussed in this report.*

Because of these constraints, the committee assumed that utilization rates of vaccine candidates would be uniform in target populations in the developing world, and that these rates would be identical to those achieved through EPI. Thus, potential utilization is not used to differentiate among vaccine candidates in this analysis.

This assumption is not a recommendation that all or any of these vaccine candidates should be incorporated into EPI worldwide or in a particular country. Such decisions should be based on local assessments of disease burdens, resources, and other considerations. The committee

*In some cases, delivery of a vaccine considered in this assessment at the ages when EPI vaccines are presently administered may not provide optimal protection against that disease. In these cases, predictions of vaccine efficacy and estimates of the proportion of the disease burdens that are vaccine preventable have been adjusted accordingly (see Chapter 5 and specific appendixes). While rabies immunization could be added to the EPI, this strategy is probably not practical for some vaccine candidates, and an alternative scenario has been analyzed for them, namely post-exposure prophylaxis. Although delivery in accordance with EPI schedules is assumed in this analysis, the epidemiologic features of certain diseases suggest that strategies for vaccine delivery shortly after birth (for hepatitis B vaccine) or before school entry (for epidemic meningococcal meningitis) deserve consideration in some regions. WHO-EPI presently encourages giving oral poliomyelitis vaccine beginning at birth in countries where polio remains endemic (Henderson, personal communication, 1985) .

also recognizes that various technical problems could interfere with the addition of these vaccines to the EPI. For example, antagonisms could exist between potential vaccine candidates and those already included in the WHO program. Moreover, changes may be made in the basic EPI as new and better vaccines are developed or as information on current vaccine use is refined. Further research will be needed to investigate the feasibility and desirability of substantially increasing the number of antigens administered at any one time.

SUMMARY

The expected health benefits from a vaccine depend, in part, on the proportion of the target population that actually receives it (which, in turn, affects the probability of acquiring the disease). Predicting utilization rates is complicated by various factors, including availability, cost, the health system capacity to deliver vaccine, statutory interventions, the target population, and provider and recipient acceptance.

Because delivery of vaccines would probably be achieved through the WHO-EPI, the committee assumed for the analysis that utilization rates of vaccine candidates would be uniform across target populations. (Actual decisions about whether to incorporate specific vaccines into EPI should be based on local assessments of disease burdens, resources, and other considerations.) Thus, utilization is not used to differentiate among vaccine candidates in this analysis. Methods described in the committee's previous report can be adapted if utilization is expected to differ among vaccines.

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7

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

This chapter presents the method used to calculate and compare the reductions in morbidity and mortality that could result from the vaccine candidates evaluated in this report. The proposed method has two principal components: (1) calculation of values for the annual health benefits that would occur at a time when such benefits have reached a steady state, and (2) adjustment of these values to reflect the probability of their occurring and the times at which they may occur. Procedures are also presented whereby expenditures associated with the purchase of vaccines for immunization programs may be calculated and combined with the annualized cost of development.

This chapter presents a central analysis; Chapter 9 discusses sensitivity analyses involving some of the factors used in the base case.

PROCEDURES

The steps for calculating potential health benefits from the vaccine candidates are listed below and illustrated in Figure 7.1.

1. Calculate the total disease burden values (TDBVs) for each candidate disease. These values incorporate both disease burden estimates and a factor expressing the undesirability of the conditions. Infant mortality equivalence (IME) values, described in Chapter 4, quantify these value judgments. The set of IME values used throughout this analysis is the median of perspectives derived from a poll of public health experts in developing countries: it is for illustrative purposes only. Adopting alternative perspectives in these calculations would have effects similar to those described in Chapter 4. Derivations of disease burden estimates for the various diseases are described in Appendixes D-1 through D-19.
2. Estimate the proportion of the total disease burden that is vaccine preventable. This is defined as that portion that could theoretically be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective against the strains/types included in it. This factor is influenced by the distribution of the disease in

relation to the age of anticipated vaccination, by whether any disease falls outside the target population, and by the ability to formulate a vaccine effective against all strains/types causing disease. Factors influencing the estimate of the proportion of vaccine preventable illness are discussed in relevant sections of Appendixes D-1 through D-19.

3. Calculate vaccine preventable illness (VPI) values for each disease/vaccine combination. In this analysis, VPI values are calculated from TDBVs using the estimate of the proportion of the disease burden that is potentially preventable. A more exacting approach is to estimate for each disease in each age group/morbidity category combination, the number of cases, complications, sequelae, or deaths that could theoretically be prevented annually (in a steady state of vaccine use) and then use IME values to calculate VPI values in a manner similar to that for deriving TDBVs as described in Chapter 4.
4. Calculate 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

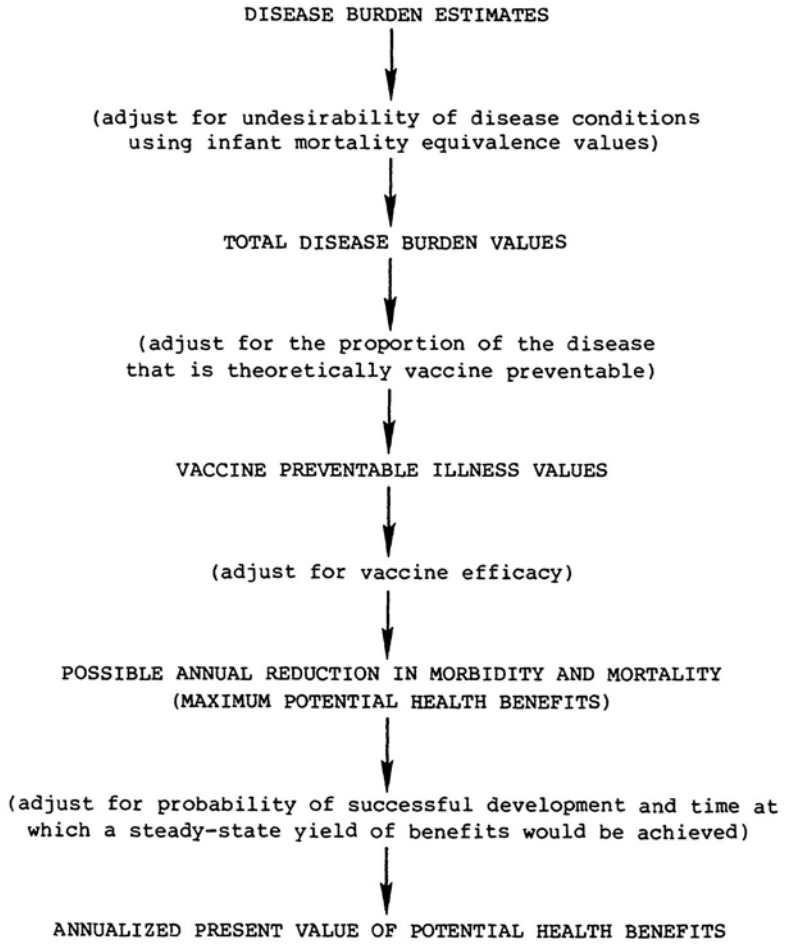

FIGURE 7.1 Calculation of potential health benefits.

diseases in which vaccine efficacy is expected to be the same for all conditions, calculation of PRMM simply entails multiplying the vaccine preventable illness values (one for each IME perspective) by the efficacy. If the vaccine is expected to have different efficacies for various conditions, the calculations are more complex. PRMM values must be calculated separately for each morbidity category/age group combination and then added together.

5. Calculate the annualized present value of potential health benefits. These values represent an adjustment of the possible reductions in morbidity and mortality values to account for the probability of a vaccine's successful development and the time at which a steady-state yield of benefits would be achieved. As discussed in Chapter 6, it is assumed for this analysis that there are no differences in the utilization of vaccine candidates.
6. Calculate the vaccine expenditures necessary to achieve the possible reductions in morbidity and mortality, as illustrated in Figure 7.2.

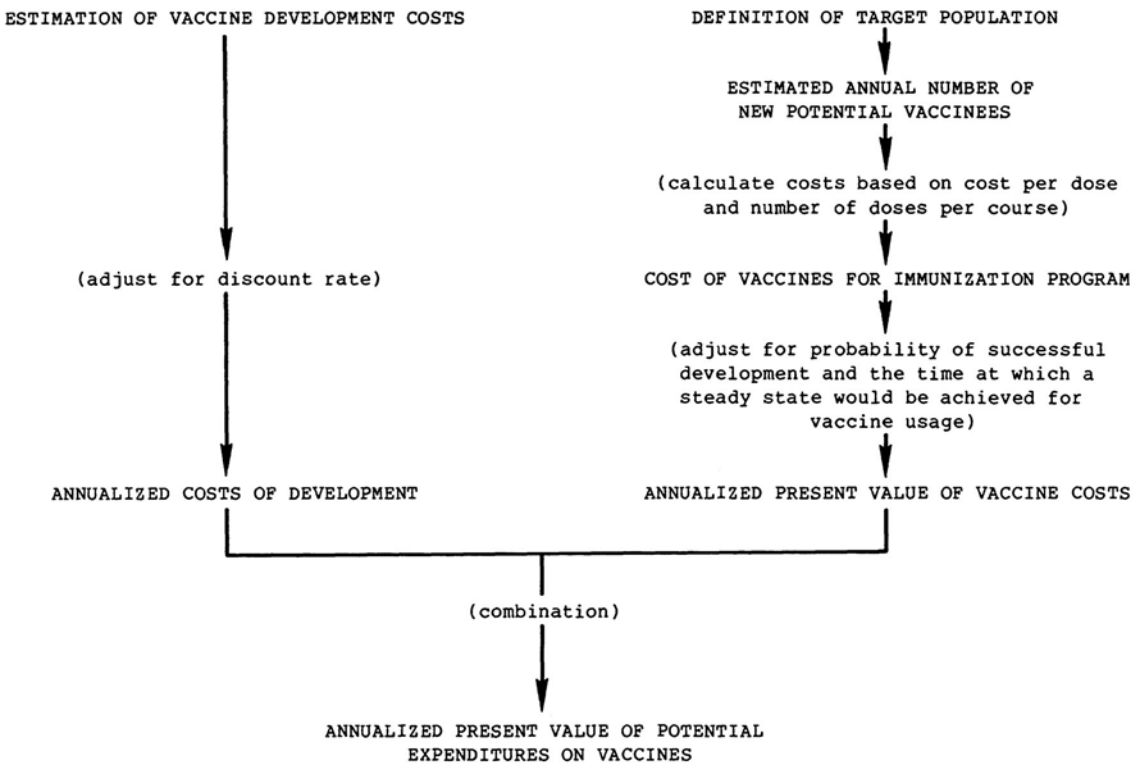

FIGURE 7.2 Calculations of expenditures on vaccines.

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

Vaccine Characteristics

The vaccine characteristics used in this comparison are described in Chapter 5, Tables 5.1. and 5.2. Detailed information on specific vaccines is included in Appendixes D-1 through D-19.

Target Population

Target populations for the vaccines are described in the relevant appendixes and briefly outlined in Table 7.1. The number of new potential vaccine recipients entering the target population each year must be determined to calculate the vaccine costs for each immunization program. These calculations are based on the envisaged target population and the 1984 population projections (see Chapter 4). The basis for the calculation of the number of new potential recipients of each vaccine is shown in Table 7.1 and described more fully in relevant appendixes.

In addition to indigenous populations at risk from the various diseases in developing countries discussed here, it is likely that travelers and personnel from developed countries who are stationed overseas would also be given some vaccines. Relative to the indigenous target populations, the number of such potential vaccinees is judged to be insignificant. However, decision makers may wish to consider the size of these groups and the benefits that would result from their protection when making ultimate choices on vaccine priorities.

Vaccine Preventable Illness

For each disease, an estimate of the potential vaccine preventable illness is needed. This can be expressed either as a proportion of the total burden of illness, or developed as estimates of the numbers of cases, complications, sequelae, and deaths that result from each disease. These estimates are derived from the distribution of the disease burden; the envisaged target population; the characteristics of the vaccine (e.g., the number of doses necessary to achieve full protection) and the likely age(s) for vaccine delivery; and for some diseases, where appropriate, the proportion of the disease affecting an identified high-risk group or target population.

In this analysis, VPI was expressed as a proportion of the total disease burden. The factors used for each vaccine/disease combination to estimate VPI are discussed in Appendixes D-1 through D-19.

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 reexamined. Because of the trend in most developing countries toward greater relative numbers of individuals in the younger 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

Because no vaccine in this analysis is predicted to have serious side effects, the current calculations omit adverse reactions, if desired, estimation of each vaccination program's adverse effects can be incorporated into the benefit calculations. The predicted incidence of adverse reactions, the annual number of potential new vaccinees, and the IME values for the types of adverse conditions predicted can be used to calculate values representing the vaccine-induced morbidity and mortality (if any). These values for adverse effects may be used as a correction to PRMM figures. In the analysis of vaccine priorities for the United States, it was calculated that anticipated occurrence of adverse reactions necessitated only a very small adjustment of PRMM (i.e., less than 1 percent of PRMM).

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

The Times for Occurrence of Vaccine-Associated Health Benefits and Cost Savings

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

Time to Licensure

Factors affecting the predictions of the time 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.

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

Pathogen (Target Population)	Type of Vaccine	Individuals Entering Target Population[a]	Delay in Vaccination Benefits
Dengue virus (Infants and children in endemic areas; travelers to endemic areas)	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	Birth cohort in endemic areas: 48 million	Probable age of vaccination (<1 year) to peak of DHF/DSS[b] (6 years), i.e., approx. 5 years Vaccinate to peak age of dengue fever (adolescents and adults)
Escherichia coli (enterotoxigenic) (Infants<6 months)	A combination of purified colonization factor antigens and possibly other antigens Genetically engineered attenuated strains	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to peak age of disease (1–2 years), i.e., approx. 1 year
Hemophilus influenzae type b (Infants)	Conjugated polysaccharide	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to peak of serious disease (2–3 years), i.e., approx. 2 years
Hepatitis A virus (Susceptibles of all ages; routine for preschool children)	Attenuated live virus Polypeptide recombinant vaccine produced in yeast	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to peak age of disease in LTDCs (2–4), i.e., approx. 2 years
Hepatitis B virus (Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations, at earliest possible age)	Polypeptide produced by recombinant DNA technology	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to mid-point between peak of acute disease (10 years) and serious chronic illness (35– 40 years), i.e., approx. 30 years
Japanese encephalitis virus (Children in epidemic and endemic areas; foreign visitors to epidemic regions)	Inactivated virus produced in cell culture	Birth cohort in endemic/ epidemic areas: 64.8 million	Probable age of vaccination (<1 year) to peak age of disease (approx. age 8), i.e. approx. 7 years
Mycobacterium leprae (Immunoprophylactic: all children in endemic areas. Immunotherapeutic: all recently infected individuals)	Armadillo-derived M. leprae	Immunoprophylactic—birth cohort in endemic areas: 44.8 million Immunotherapeutic—incidence approx. 1.5 million	6 years, based on estimated incubation period

Pathogen (Target Population)	Type of Vaccine	Individuals Entering Target Population[a]	Delay in Vaccination Benefits
Neisseria meningitidis (Infants, 3 to 6 months)	Conjugated capsular polysaccharides, Groups A,C,Y, and W135	Endemic—birth cohort: 115.1 million Epidemic—birth cohort in areas subject to epidemics: 13.1 million	Endemic—probable age of vaccination (<1 year) to peak of disease (2 years), i.e., approx. 1 year. Epidemic—probable age of vacc. to peak of disease (approx. 11 years), i.e., approx. 6 years
Parainfluenza viruses (Infants)	Trivalent, subunit vaccine (which must contain fusion proteins)	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to peak of illness (2 years), i.e., approx. 1 year
Plasmodium spp. (All infants at risk, military personnel, travelers)	Plasmodium falciparum, synthetic or recombinant sporozoite antigen preparation Multivalent synthetic or recombinant sporozoite antigen preparation (P. falciparum, P. vivax, P. ovale, P. malariae)	Birth cohort in major areas of occurrence: 78 million	Probable age of vaccination (<1 year) to peak of most severe consequences (i.e., death in young children 2–5 years) i.e., approx. 3 years
Rabies virus (Individuals at high risk, plus post-exposure prophylaxis)	Vero cell	Yearly number of individuals requiring post-exposure prophylaxis as estimated by WHO: 5.6 million	Less than 1 year
(As above)	Glycoprotein produced by rDNA technology in mammalian cells	Yearly number of individuals requiring post-exposure prophylaxis as estimated by WHO: 5.6 million	Less than 1 year
(Birth cohort in areas of high risk)	Attenuated live vector virus containing gene for protective glycoprotein antigen	Birth cohort in high risk areas: approximately 53 million	Probable age of vaccination 2–4 years Highest risk group is assumed to be teenagers; delay in benefits is assumed to be 10 years
Respiratory syncytial virus (Infants at earliest possible age)	Polypeptides produced by recombinant DNA technology Attenuated live virus	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to peak of illness (2 years), i.e., approx. 1 year

Rotavirus (Infants at earliest possible age, preferably with oral polio vaccine)	Attenuated high passage bovine rotavirus Attenuated low passage bovine rotavirus Rhesus monkey rotavirus	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to peak of disease (6–24 months) , i.e., approx. 1 year
Salmonella typhi (Children; young adults at risk; travelers from developed countries to endemic areas)	Attenuated ga1E mutant S. typhi strain TY21a Aromatic amino acid dependent strains of S. typhi	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to midpoint of peak range of disease (approx. 14 yrs.), i.e., approx. 13 years
Shigella spp. (Infants at birth or earliest possible age; elderly for epidemic strains)	Probably plasmid mediated outer membrane protein invasion determinant (there are a small number of promising options needing investigation to determine best approach)	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to peak of disease (6–24 months), i.e., approx. 1 year
Streptococcus A (Children,<3 to 4 years)	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	Birth cohort: 115.1 million	Probable age of vaccination (<1 year) to peak of severe disease and complications (10 years), i.e., approx. 9 years
Streptococcus pneumoniae (Infants)	Conjugated polysaccharides, polyvalent	Birth cohort: 115.1 million	Frobable age of vaccination (<1 year) to peak of disease (3 years?), i.e., approx. 2 years
Vibrio cholera (Children, especially <2 years)	Genetically defined live mutant V. cholerae (A−B+ or A−B−) with respect to toxin subunit synthesis Inactivated antigens	Birth cohort in endemic areas: 22.2 million	Probable age of vaccination (<1 year) to peak incidence of disease in endemic areas (2–4 years), i.e., approx. 2 years
Yellow fever virus (Young children)	Attenuated live virus produced in cell culture	Birth cohort in endemic areas: 24.8 million	Probable age of vaccination (<1 year) to peak of disease (approx. 15, depending on area), i.e., approx. 14 years

[a]See appropriate appendix for derivation.
[b]Dengue hemorrhagic fever/dengue shock syndrome.

Time to Adoption and Steady-State Yield of Benefits

After licensure, the utilization of a vaccine increases until it reaches a steady state. Vaccination program costs also increase to a steady state (as would the numbers of adverse effects, if applicable). The rate at which a vaccine is adopted depends on provider and target population attitudes toward the new vaccine and other issues discussed in Chapter 6.

Predictions of the time to adoption for the various candidate vaccines are shown in Table 7.2. The major factor considered in estimating these times was the perception in the developing world of the seriousness of the disease threat. The times may be affected by such factors as governmental or donor purchase programs, or by the combination of new vaccines with vaccines currently delivered via the World Health Organization Expanded Program on Immunization (WHO-EPI). These factors were not considered in arriving at the times in Table 7.2, but the effects of adopting alternative values could be evaluated easily (see Appendix F).

The time between the probable age of vaccine administration and the probable age of disease occurrence without vaccination is termed the delay of vaccination benefits. This time must be determined separately for each vaccine (consider the difference between the vaccines for Hemophilus influenzae type b and hepatitis B virus) and 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 presented later in this chapter, the present values of vaccine costs are calculated on the assumption that costs are incurred from the time at which steady-state vaccine use is achieved. The present values of health benefits and expected reduction in morbidity costs are calculated on the assumption that the benefits and reduced costs occur at the time of steady-state yield of vaccine benefits. Equations for deriving present values are given in Chapter 3.*

If desired, a more exact procedure can be used for these calculations—one that accounts for 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

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

where T is the time to adoption or the time from licensure to steadystate yield of benefits, and r is the discount rate, in this analysis, the discount rate adopted is 0.05, so

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

TABLE 7.2 Times Associated with Vaccine Use and Benefits

Pathogen (Target Population)	Type of Vaccine	Time to Licensure (years)	Time After Licensure to Adoption (years)	Total Time to Steady State of Vaccine Use (years)	Delay of Vaccination Benefits (years)	Total Time to Steady-State Yield of Benefits (years)
Dengue virus (Infants and children in endemic areas; travelers to endemic areas)	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	10	2	12	5	17
Escherichia coli (enterotoxigenic) (Infants < 6 months)	A combination of purified colonization factor antigens and possibly other antigens	10	2	12	1	13
	Genetically engineered attenuated strains	10	2	12	1	13
Hemophilus influenzae type b (Infants)	Conjugated polysaccharide	3	5	8	2	10
Hepatitis A virus (Susceptibles of all ages; routine for preschool children)	Attenuated live virus	4	5	9	2	11
	Polypeptide recombinant vaccine produced in yeast	5	5	10	2	12
Hepatitis B virus (Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations, at earliest possible age)	Polypeptide produced by recombinant DNA technology	1	2	3	30	33
Japanese encephalitis virus (Children in epidemic and endemic areas; foreign visitors to epidemic regions)	Inactivated virus produced in cell culture	7	2.5	9.5	7	16.5

Pathogen (Target Population)	Type of Vaccine	Time to Licensure (years)	Time After Licensure to Adoption (years)	Total Time to Steady State of Vaccine Use (years)	Delay of Vaccination Benefits (years)	Total Time to Steady-State Yield of Benefits (years)
Mycobacterium leprae (Immunoprophylactic: all children in endemic areas. Immuno therapeutic: all recently infected individuals)	Armadillo-derived M. leprae	10	5	15	6	21
Neisseria meningitidis (Infants, 3 to 6 months)	Conjugated capsular polysaccharides, Groups A,C,Y, and W135	5	5	10	3	13
Parainfluenza viruses (Infants)	Trivalent, subunit vaccine (which must contain fusion proteins)	5	5	10	1	11
Plasmodium spp. (All infants at risk, military personnel, travelers)	Plasmodium falciparum, synthetic or recombinant sporozoite antigen preparation	6.5	2	8.5	3	11.5
	Multivalent synthetic or recombinant sporozoite antigen preparation (P. falciparum, P. vivax, P. ovale, P. malariae)	9	2	11	3	14
Rabies virus (Individuals at high risk, plus post-exposure prophylaxis) (As above)	Vero cell	3	3.5	6.5	1	7.5
	Glycoprotein produced by rDNA technology in mammalian cells	3	3.5	6.5	1	7.5
(Birth cohort in areas of high risk)	Attenuated live vector virus containing gene for protective glycoprotein antigen	10	2	12	10	22

Respiratory syncytial virus (Infants at earliest possible age)	Polypeptides produced by recombinant DNA technology	5	2	7	1	8
	Attenuated live virus	5	2	7	1	8
Rotavirus (Infants at earliest possible age. preferably with oral polio vaccine)	Attenuated high passage bovine rotavirus	2	2	4	1	5
	Attenuated low passage bovine rotavirus	5	2	7	1	8
	Rhesus monkey rotavirus	5	2	7	1	8
Salmonella typhi (Children; young adults at risk; travelers from developed countries to endemic areas)	Attenuated ga1E mutant S. typhi strain TY21a	1	2	3	13	16
	Aromatic amino acid dependent strains of S. typhi	6.5	2	8.5	13	21.5
Shigella spp. (Infants at birth or earliest possible age; elderly for epidemic strains)	Probably plasmid mediated outer membrane protein invasion determinant (a small number of options need investigation to determine best approach)	10	2	12	1	13
Streptococcus A (Children, < 3 to 4 years)	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	7	3.5	10.5	9	19.5
Streptococcus pneumoniae (Infants)	Conjugated polysaccharides, polyvalent	5	2	7	2	9
Vibrio cholera (Children, especially < 2 years)	Genetically defined live mutant V. cholerae (A−B+ or A−B−) with respect to toxin subunit synthesis	6	2	8	2	10
	Inactivated antigens	4	2	6	2	8
Yellow fever virus (Young children)	Attenuated live virus produced in cell culture	3	2	5	14	19

Costs

Ideally, calculation of the annual costs associated with each of the vaccine candidates would include three major components: (1) the reduction in morbidity costs, (2) the vaccination program costs, and (3) the vaccine development costs. The costs of adverse reactions also should be calculated, if applicable. Such a comprehensive calculation can be attempted where reliable estimates of treatment costs can be made. However, as discussed in Chapter 4, the committee judged that attempting to incorporate the average cost of disease treatment(s) in the developing world into the calculations would be unrealistic. Additionally, the committee assumed that all vaccine candidates would, if developed, be delivered through the WHO-EPI; hence, possible differential utilization or delivery costs would not be a factor in the priority selection of vaccine candidates.

Because of these judgments, the cost comparisons in this analysis are somewhat simplified, including only those expenditures on the candidate vaccines necessary to achieve the potential health benefits. Table 7.3 shows these expenditures: vaccine development costs and vaccine costs for the immunization programs. The annual number of new potential vaccinees is derived as shown in Table 7.1, and Table 5.1 indicates the predicted cost per dose (price) for each vaccine and the number of doses required.

THE TREATMENT OF VACCINE IMPROVEMENT PROJECTS

Some clarification of the assumptions underlying vaccine improvement projects may be useful. In these cases, the incremental benefit should be used in comparisons.

For all diseases, the TDBV represents the burden of illness presently occurring with the current vaccine usage. However, in some cases (cholera, yellow fever, Japanese encephalitis, N. meningitidis), the current vaccine use may not be as widespread or, because of vaccination timing or efficacy, as likely to prevent as large a proportion of the disease as would the universal pediatric approach with the improved vaccine assumed in this analysis. Hence, the current disease burden reasonably represents the disease amenable to further control.

For other diseases (H. influenzae type b) the currently available (PRP) vaccine may not be used widely in developing countries either because most disease occurs in age groups (under 2 years) for which the vaccine is ineffective or because the vaccine is relatively new. Hepatitis B vaccine is also not yet widely used in developing countries, probably because it is relatively new and expensive. For these diseases, the present total disease burden is a reasonable starting point for calculations.

Developing an improved vaccine for Streptococcus pneumoniae represents a situation where the assumptions may greatly affect the potential health benefit calculations. The current vaccine is not widely used in the developing world, probably because it is immunogenic

in children 2 years of age or older, but not in infants. It could be argued that the health benefits of an improved pneumococcal vaccine are simply the incremental benefit that could be obtained from extending protection to the child population under 2 years of age who would respond to the conjugated improved vaccine. However, a more reasonable assumption is that the current vaccine would not be used in the developing world for the reason stated above and because the delivery requirement (children 2 years and older) could not conveniently be added to existing vaccination schedules. Additionally, it is doubtful the existing vaccine would be used if the improved version becomes available. Hence, the potential benefits of an improved vaccine are calculated using the entire existing disease burden as a starting point. The proportion of the TDBV that is vaccine preventable is discussed in Appendix D-17.

This analysis does not include calculation of the potential benefits of improving any vaccine that is in widespread use in the developing world. For such calculations it is necessary to estimate the incremental benefits (e.g., in efficacy, disease proportion amenable to vaccine prevention by virtue of effectiveness at younger ages, etc.) or costs associated with its use as compared to the existing vaccine. The analyses of potential benefits for improved influenza and pertussis vaccines presented in the committee's first report illustrate the approach needed in such calculations (Institute of Medicine, 1985).

RESULTS

The results of the central analysis, presented below, are based on the following assumptions:

- the probability of successful development and other vaccine characteristics, e.g., efficacy, described in Chapter 5
- the times to licensure and adoption, and the delay of vaccination benefits, as shown in Tables 5.1 and 7.2
- a discount rate of 0.05
- the IME perspective representing the median of values derived from public health professionals in various developing countries (as described in Chapter 4)
- the uniformity of utilization rates across target populations (Chapter 6)

Health Benefits

Table 7.4 shows values representing the possible health benefits resulting from the development of each vaccine candidate. Total disease burden values represent the burden of illness resulting from the pathogen(s) against which the vaccine is directed.

Vaccine preventable illness values represent the burden of illness that could be averted by delivering a hypothetical vaccine that is 100

TABLE 7.3 Expenditures to Achieve Health Benefits for Various Vaccines

Pathogen (Target Population)	Type of Vaccine	Probability of Successful Development	Cost of Development (dollars)	Minimum Time to Steady State of Vaccine Use
Dengue virus (Infants and children in endemic areas; travelers to endemic areas)	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	0.75	25,000,000	12
Escherichia coli (enterotoxigenic) (Infants < 6 months)	A combination of purified colonization factor antigens and possibly other antigens	0.50	25,000,000	12
	Genetically engineered attenuated strains	0.70	37,500,000	12
Hemophilus influenzae type b (Infants)	Conjugated polysaccharide	0.90	15,000,000	8
Hepatitis A virus (Susceptibles of all ages; routine for preschool children)	Attenuated live virus	0.95	15,000,000	9
	Polypeptide recombinant vaccine produced in yeast	0.95	25,000,000	10
Hepatitis B virus (Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations)	Polypeptide produced by recombinant DNA technology	0.99	5,000,000	3
Japanese encephalitis virus (Children in epidemic and endemic areas; foreign visitors to epidemic regions)	Inactivated virus produced in cell culture	0.50	50,000,000	9.5
Mycobacterium leprae (Immunoprophylactic: all children in endemic areas. Immunotherapeutic: all recently infected individuals)	Armadillo-derived M. leprae	0.50	25,000,000	15
Neisseria meningitidis (Infants, 3 to 6 months)	Conjugated capsular polysaccharides. Groups A,C,Y, and W135	0.50	30,000,000	10
Parainfluenza viruses (Infants)	Trivalent, subunit vaccine (which must contain fusion proteins)	0.80	25,000,000	10
Plasmodium spp. (All infants at risk, military personnel, travelers)	Plasmodium falciparum, synthetic or recombinant sporozoite antigen preparation	0.50	25,000,000	8.5
	Multivalent synthetic or recombinant sporozoite antigen preparation (P. falciparum, P. vivax, P. ovale, P. malariae)	0.50	35,000,000	11

Annual Number of New Potential Vaccinees	Doses/ Course	Cost/Dose (dollars)	Cost/ Course (dollars)	Expected Annual Cost of Vaccination Programs (dollars)	Annualized Present Value of Vaccination Program Costs (dollars)	Annualized Present Value of Total Expenditures to Achieve Health Benefits (dollars)
48,000,000	1	12.00	12.00	576,000,000	240,553,765	241,803,765
115,100,000	3	7.50	22.50	2,589,750,000	721,034,852	722,284,852
115,100,000	1	1.50	1.50	172,650,000	67,296,586	69,171,586
115,100,000	1	7.50	7.50	863,250,000	525,853,421	526,603,421
115,100,000	1	15.00	15.00	1,726,500,000	1,057,271,429	1,058,021,429
115,100,000	3	20.00	60.00	6,906,000,000	4,027,700,683	4,028,950,683
115,100,000	3	30.00	90.00	10,359,000,000	8,859,008,746	8,859,258,746
64,800,000	2	15.00	30.00	1,944,000,000	611,459,820	613,959,820
44,800,000	1	25.00	25.00	1,120,000,000	269,369,575	270,619,575
115,100,000	2	10.00	20.00	2,302,000,000		
115,100,000	2	15.00	30.00	3,453,000,000		
78,000,000	3	12.50	37.50	2,925,000,000		
78,000,000	3	12.50	37.50	2,925,000,000		

Pathogen (Target Population)	Type of Vaccine	Probability of Successful Development	Cost of Development (dollars)	Minimum Time to Steady State of Vaccine Use
Rabies virus (Individuals at high risk, plus post-exposure prophylaxis) (As above)	Vero cell	0.90	5,000,000	6.5
	Glycoprotein produced by rDNA technology in mammalian cells	0.85	4,000,000	6.5
(Birth cohort in areas of high risk)	Attenuated live vector virus containing gene for protective glycoprotein antigen	0.50	15,000,000	12
Respiratory syncytial virus (Infants)	Polypeptides produced by recombinant DNA technology	0.80	25,000,000	7
	Attenuated live virus	0.80	25,000,000	7
Rotavirus (Infants, 0 to 6 months)	Attenuated high passage bovine rotavirus	0.90	10,000,000	4
	Attenuated low passage bovine rotavirus	0.80	20,000,000	7
	Rhesus monkey rotavirus	0.80	30,000,000	7
Salmonella typhi (Children 5 to 18; young adults; travelers from developed countries to endemic areas)	Attenuated ga1E mutant S. typhi strain TY21a	0.90	2,000,000	3
	Aromatic amino acid dependent strains of S. typhi	0.50	2,000,000	8.5
Shigella spp. (Infants at birth; elderly for epidemic strains)	Probably plasmid mediated outer membrane protein invasion determinant (a number of promising options need investigation to determine best approach)	0.70	37,500,000	12
Streptococcus A (Children, < 3 to 4 years)	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	0.80	50,000,000	10.5
Streptococcus pneumoniae (Infants)	Conjugated polysaccharides, polyvalent	0.80	30,000,000	7
Vibrio cholera (Children, especially < 2 years)	Genetically defined live mutant V. cholerae (A−B+ or A−B−) with respect to toxin subunit synthesis	0.75	25,000,000	8
	Inactivated antigens	0.65	10,000,000	6
Yellow fever virus (Young children)	Attenuated live virus produced in cell culture	0.95	15,000,000	5

Annual Number of New Potential Vaccinees	Doses/ Course	Cost/Dose (dollars)	Cost/ Course (dollars)	Expected Annual Cost of Vaccination Programs (dollars)	Annualized Present Value of Vaccination Program Costs (dollars)	Annualized Present Value of Total Expenditures to Achieve Health Benefits (dollars)
5,600,000	4	10.00	40.00	224,000,000		
5,600,000	4	10.00	40.00	224,000,000		
53,000,000	1	1.00	1.00	53,000,000		
115,100,000	2	15.00	30.00	3,453,000,000		
115,100,000	1	15.00	15.00	1,726,500,000		
115,100,000	1	10.00	10.00	1,151,000,000		
1,15,100,000	1	10.00	10.00	1,151,000,000		
115,100,000	1	10.00	10.00	1,151,000,000		
115,100,000	2	2.00	4.00	460,400,000	357,939,747	358,039,747
115,100,000	2	2.00	4.00	460,400,000	152,053,450	152,153,450
115,100,000	1	2.00	2.00	230,200,000	89,728,782	91,603,782
115,100,000	2	5.00	10.00	1,151,000,000	551,667,844	554,167,844
115,100,000	1	20.00	20.00	2,302,000,000	1,308,790,738	1,310,290,738
22,200,000	1	2.00	2.00	44,400,000	22,538,751	23,788,751
22,200,000	2	2.00	4.00	88,800,000	43,071,553	43,571,553
24,800,000	1	5.00	5.00	124,000,000	92,299,382	93,049,382

TABLE 7.4 Health Benefits Associated with Various Vaccines

Pathogen (Target Population)	Type of Vaccine	Probability of Successful Development	Time to Steady-State Yield of Vaccine Benefits	Total Disease Burden Value
Dengue virus (Infants and children in endemic areas; travelers to endemic areas)	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	0.75	17	34,365
Escherichia coli (enterotozigenic) (Infants < 6 months)	A combination of purified colonization factor antigens and possibly other antigens	0.50	13	978,248
	Genetically engineered attenuated strains	0.70	13	978,248
Hemophilus influenzae type b (Infants)	Conjugated polysaccharide	0.90	10	471,336
Hepatitis A virus (Susceptibles of all ages; routine for preschool children)	Attenuated live virus	0.95	11	30,229
	Polypeptide recombinant vaccine produced in yeast	0.95	12	30,229
Hepatitis B virus (Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations)	Polypeptide produced by recombinant DNA technology	0.99	33	2,394,256
Japanese encephalitis virus (Children in epidemic and and endemic areas; foreign visitors to epidemic regions)	Inactivated virus produced in cell culture	0.50	16.5	18,075
Mycobacterium leprae (Immunoprophylactic: all children in endemic areas. Immunotherapeutic: all recently infected individuals)	Armadillo-derived M. leprae	0.50	21	657,349
Neisseria meningitidis (Infants, 3 to 6 months)	Conjugated capsular polysaccharides. Groups A,C,Y, and W135	0.50	13	68,252
Parainfluenza viruses (Infants)	Trivalent, subunit vaccine (which must contain fusion proteins)	0.80	11	145,954
Plasmodium spp. (All infants at risk, military personnel, travelers)	Plasmodium faleiparum, synthetic or recombinant sporozoite antigen preparation	0.50	11.5	2,111,795
	Multivalent synthetic or recombinant sporozoite antigen preparation (P.falciparum, P.vivax, P.ovale, P.malariae)	0.50	14	2,111,795

Proportion of Disease that is Vaccine Preventable	Vaccine Preventable Illness Value	Predicted Vaccine Efficacy	Possible Reduction in Morbidity and Mortality	Annualized Present Value of Health Benefits
1.00	34,365	0.85	29,210	9,558
0.65	635,861	0.75	476,896	126,454
0.50	489,124	0.80	391,299	145,260
0.90	424,202	0.90	381,782	210,943
1.00	30,229	0.90	27,206	15,112
1.00	30,229	0.90	27,206	14,392
0.50	1,197,128	0.90	1,077,415	213,192
1.00	18,075	0.80	14,460	3,232
1.00	657,349	0.75	493,012	88,481
0.95	64,839	0.80	51,872	13,754
0.80	116,763	0.80	93,411	43,692
0.99	2,082,019	0.80	1,665,615	475,190
1.00	2,111,795	0.80	1,689,436	426,640

Pathogen (Target Population)	Type of Vaccine	Probability of Successful Development	Time to Steady-State Yield of Vaccine Benefits	Total Disease Burden Value
Rabies virus (Individuals at high risk, plus post-exposure prophylaxis) (as above)	Vero cell	0.90	7.5	67,821
	Glycoprotein produced by rDNA technology in mammalian cells	0.85	7.5	67,821
(Birth cohort in areas of high risk)	Attenuated live vector virus containing gene for protective glycoprotein antigen	0.50	22	67,821
Respiratory syncytial virus (Infants)	Polypeptides produced by recombinant DNA technology	0.80	8	183,326
	Attenuated live virus	0.80	8	183,326
Rotavirus (Infants, 0 to 6 months)	Attenuated high passage bovine rotavirus	0.90	5	925,042
	Attenuated low passage bovine rotavirus	0.80	8	925,042
	Rhesus monkey rotavirus	0.80	8	925,042
Salmonella typhi (Children; young adults at risk; travelers from developed countries to endemic areas)	Attenuated ga1E mutant S. typhi strain TY21a	0.90	16	1,308,121
	Aromatic amino acid dependent strains of S. typhi	0.50	21.5	1,308,121
Shigella spp. (Infants at birth; elderly for epidemic strains)	Probably plasmid mediated outer membrane protein invasion determinant (a small number of promising options need investigation to determine best approach)	0.70	13	828,068
Streptococcus A (Children, < 3 to 4 years)	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	0.80	19.5	811,477
Streptococcus pneumoniae (Infants)	Conjugated polysaccharides, polyvalent	0.80	9	6,612,261
Vibrio cholera (Children, especially < 2 years)	Genetically defined live mutant V. cholerae (A−B + or A−B−) with respect to toxin subunit synthesis	0.75	10	229,217
	Inactivated antigens	0.65	8	229,217
Yellow fever virus (Young children)	Attenuated live virus produced in cell culture	0.95	19	32,887

Proportion of Disease that is Vaccine Preventable	Vaccine Preventable Illness Value	Predicted Vaccine Efficacy	Possible Reduction in Morbidity and Mortality	Annualized Present Value of Health Benefits
1.00	67,821	0.99	67,143	41,910
1.00	67,821	0.95	64,430	37,983
0.75	50,866	0.95	48,322	8,260
0.66	120,995	0.80	96,796	52,412
0.75	137,495	0.80	109,996	59,559
1.00	925,042	0.80	740,034	521,852
1.00	925,042	0.90	832,538	450,795
1.00	925,042	0.90	832,538	450,795
1.00	1,308,121	0.80	1,046,497	431,471
1.00	1,308,121	0.85	1,111,903	194,745
0.85	703,858	0.85	598,279	222,096
0.90	730,329	0.80	584,263	180,513
0.50	3,306,131	0.80	2,644,904	1,363,943
1.00	229,217	0.90	206,295	94,986
1.00	229,217	0.65	148,991	65,548
1.00	32,887	0.90	29,598	11,127

percent effective to the entire target population, at the time envisaged for immunization. The values for the possible reduction in morbidity and mortality take into account the vaccine's predicted efficacy.

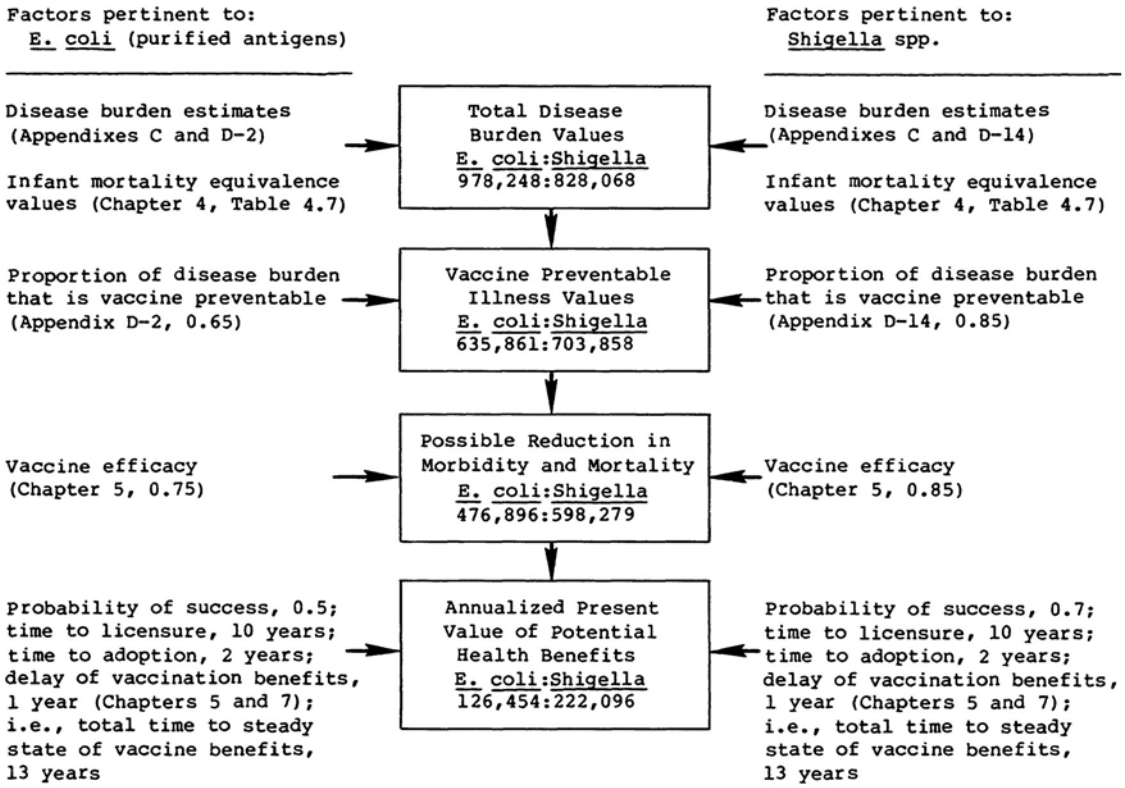

FIGURE 7.3 The sequence of calculations for comparing the potential health benefits of two vaccine candidates.

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 7.3 illustrates the sequence of calculations in the proposed method for comparing the health benefits expected from two vaccine candidates. Chapter 3 and the foregoing text describe the specific computations involved at each stage.

Costs

The vaccine expenditures associated with achieving each vaccine candidate's benefits are shown in Table 7.3.

The annualized present value of vaccine costs incorporates the annual number of potential new vaccines; the cost per dose; and the number of doses required, adjusted for the probability of successful vaccine development and the time at which steady-state vaccine use would be achieved. The annualized present value of vaccine expenditures incorporates the vaccine cost for the immunization program and the annualized vaccine development cost (i.e., the discount rate multiplied by the cost of development).

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

The health benefit values and the vaccine expenditures necessary to achieve these benefits do not incorporate adjustments for utilization, which was judged to be uniform in this analysis. Thus, values represent potential benefits and expenditures.

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8

Additional Issues in the Selection of Priorities for Accelerated Vaccine Development

The final selection of candidates for accelerated vaccine development requires consideration of several factors in addition to the potential benefits described in previous chapters. As noted in Chapters 3 and 7, affordability (as represented by vaccine expenditures) can be included in the decision process as a second decision criterion, if desired. Various nonquantifiable factors also need evaluation. These include ethical issues, questions about industry activities on certain vaccines, the relative benefits of immunization versus other methods of disease control or treatment (if available), and the epidemic potential of the disease and interaction between diseases. Nonquantifiable factors could also include questions relating to the geographic (or geopolitical) distribution of benefits and the degree to which some of the evaluated diseases pose an immediate threat to U.S. travelers, personnel, and, by possible importation, to the general U.S. population.

EQUITY CONSIDERATIONS IN CALCULATING DISEASE BURDENS AND VACCINE BENEFITS

Age-Related Weights

The methods for comparing disease burdens (Chapter 4) and vaccine benefits (Chapter 7) allow different weights in the infant mortality equivalence scale to be placed on events that occur at various ages. These weights directly affect both disease burden values and calculations of the possible health benefits of vaccine candidates. For example, if the death of one child under age 5 is considered equivalent to the deaths of 10 persons over age 60, then a disease that kills 1,000 infants annually would be viewed as imposing the same disease burden as another disease that kills 10,000 elderly persons annually.

The model allows decision makers to assess the impact of various infant mortality equivalence trade-offs. The report on vaccines for important diseases in the United States (Institute of Medicine, 1985a) compared rankings calculated by using a median of committee members' perspectives with those obtained by using an age-neutral perspective, in which lives at various ages had equal value. The rankings resulting from the two perspectives were almost identical for the diseases

studied. For this reason and because of limited resources, this report does not include such comparisons. However, those making decisions about vaccine priorities for developing countries might wish to explore the effects of various trade-offs in the ranking process.

Effect of Infant Mortality on Fertility Control

One example of a value judgment that could affect vaccine programs for developing countries is the belief that reducing infant and child mortality has a lower priority than alleviating adult morbidity, because the former simply perpetuates population growth and increases pressure on resources. At its extreme, this view suggests that rapid early death from infectious disease is preferable to slow starvation. Because population growth is a concern in many parts of the developing world, the committee addressed this concept directly.

Reductions in infant mortality may result in a short-term decrease in fertility because breast-feeding a surviving child (if practiced) lengthens the time of postpartum reduced fertility (Bongaarts and Menken, 1983). The death of a child may influence its parents toward further births to "replace" the lost child. Lower infant and child mortality reduces the impact of any such "make-up behavior." Analyses of parental behavior by Cochrane and Zachariah (1983) indicate that, in the short term, preventing an infant/child death averts an average of about 0.5 births. Thus, the reduction in mortality is not fully offset by a reduction in fertility, and some population growth will occur. The study by Cochrane and Zachariah (1983) did not address longer term trends that may result from changes in general community attitudes.

Reduced child mortality is likely to reduce fertility because fewer births are required to meet family size preferences. This decrease is likely to lag behind the decrease in mortality, however, because changes in child survival may not be recognized immediately in the community, resulting in a delay that precedes widespread change in population behavior (Heer, 1983). The magnitude of population growth before the adjustment to lower fertility rates cannot be predicted with any certainty. However, it appears that mortality reduction is an essential prerequisite for fertility reduction (Gwatkin, 1984) .

That some population growth will occur as mortality declines highlights the need for integration of agricultural and health program planning to avoid food shortages.

The model proposed in this study allows the incorporation of various views on the weight that should be assigned to averting morbidity and mortality at various ages. Opinions were solicited from a range of public health professionals in developing countries; presumably, they are generally aware of the interactions between mortality reduction and fertility discussed above. None of the individual responses could be interpreted as highly favoring adult versus infant/child mortality reduction.

Lives Versus Cases Versus Days

The infant mortality equivalence scheme allows decision makers to vary trade-off values within age groups as well as among them. It would be possible to construct a perspective in which all deaths were considered equal, but morbidity was weighted differently for various age groups. For example, days of hospitalization in adult life might be weighted more heavily than days of hospitalization in childhood. Analyses with such perspectives would be valuable in evaluating the stability of the final rankings under various assumptions.

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 sex, race, ethnic origin, socioeconomic class, place of residence, occupation, or life-style. However, diseases occur more frequently in some regions than in others, and within countries the incidence or prevalence of diseases varies across population groups.

This analysis uses an aggregate "global" perspective in its ranking methodology. The committee does not imply that this is the only feasible approach; other organizations might find alternative perspectives better suited to their needs.

One method for going beyond a single, global burden-of-illness comparison is to construct individual disease burden profiles for specific regions, countries, or other groupings, for example:

- major regions, such as Latin America, Africa, or Southeast Asia
- specific countries
- major regions within countries
- the poorest nations or groups
- middle-income developing nations
- women

These multiple burden-of-illness profiles might not lead directly to new public policy recommendations, but they would serve as a reminder that the global profile developed here is an aggregate that obscures differential effects in definable regions, countries, or population groups. The multiple profiles also could help decision makers decide whether to devote special attention to the needs of specific regions or the more vulnerable groups, however those groups were defined. Table 8.1 shows that many of the diseases under consideration are not globally or uniformly distributed.

Another method to meet the needs of specific groups might involve the portfolio approach described below.

TABLE 8.1 Examples of Pathogens Disproportionately Affecting Certain Regions

Patnogen	Region of Highest Prevalence	Other Regions Affected
Dengue virus	Endemic in south Asia, southeast Asia, west Africa, north Australia	Isolated epidemics in Caribbean 1963, 1969; Central America 1977; Polynesia and Micronesia 1963, 1979
E. coli (enterotoxigenic)	Worldwide	
H. influenzae type b	Worldwide	
Hepatitis A virus	Worldwide	
Hepatitis B virus	Worldwide, though higher prevalence in developing countries than developed world. High chronic carriage rates in southeast Asia, and sub-Saharan Africa	
Japanese encephalitis virus	Endemic in tropical Asia, Australia, and New Guinea	
Mycobacterium leprae	Tropical areas of India, southeast Asia, Pacific Islands, and Latin America	
Neisseria meningitidis	Meningitis belt across sub-Saharan Africa, Nile River valley	Worldwide
Parainfluenza viruses	Worldwide	
Plasmodium spp.	Sub-Saharan Africa, south and southeast Asia, tropical Central and South America, Pacific Islands, and New Guinea	
Rabies virus	Developing countries	Industrialized countries
Respiratory syncytial virus	Worldwide	
Rotavirus	Worldwide	
Salmonella typhi	Developing countries	Industrialized countries
Shigella spp.	Developing countries	Industrialized countries
Streptococcus Group A	Worldwide	
Streptococcus pneumoniae	Worldwide	
Vibrio cholera	Endemic in south and southeast Asia, Africa	Occasional epidemics in southern Europe and the Middle East
Yellow fever virus	Tropical South America, sub-Saharan Africa	

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 the United States and for developing countries; also, as noted above, vaccines could be ranked by potential benefits for major regions of the world or for specific countries. Other groupings of vaccines also should be considered. Possible classification categories include the following:

1. Stage of vaccine development*

a. improvement of existing or available vaccines (e.g., cholera and yellow fever)
b. vaccines at an advanced stage of development that are already in, ready for, or almost ready for clinical and/or field trials (e.g., Hemophilus influenzae type b, rotavirus, and Streptococcus pneumonia)
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 routine pediatric care
b. vaccines primarily for adults
c. vaccines for the entire population
d. vaccines for specific high-risk groups
e. vaccines for pregnant or pregnable women to protect neonates

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

The rationale for developing some kind 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

*The committee has partially adopted this concept in choosing 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 1c above is foreseeable (see Appendix A).

might depend on technological advances that are not expected for several years. Although 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).

However, development of an improved vaccine might score quite low by objective measures, while policy considerations indicate that this vaccine should receive high priority (see below for discussion of pertussis vaccine). Limited selected use vaccines, the "orphan vaccines," will probably have to be ranked in a separate grouping if any of them is to receive developmental support.

INTERDEPENDENCE OF VACCINE DEVELOPMENT EFFORTS

The proposed system for ranking candidate vaccines treats the development process for each vaccine as independent of efforts in other areas. It does not attempt to assess the extent to which research and development for one project leads to procedures or techniques applicable to and accelerating the availability of other vaccines.

This possibility needs to be evaluated in the final establishment of priorities. (In regard to the current analysis, research on the incorporation of genes for protective antigens into virus vectors, and the development of simple, safe techniques for the conjugation of polysaccharide antigens to proteins pursued for particular projects, may serve as models for a number of other vaccines.) Such projects may therefore be worthy of special consideration.

INTERDEPENDENCE OF IMMUNIZATION EFFORTS

Similarly, the proposed system treats the benefits of each project independently and does not incorporate the possibility that certain vaccines, once available, might benefit immunization efforts as a whole. Two examples suggest that consideration of these wider benefits might be warranted in some cases.

The analysis of important diseases in the U.S. population indicated that the health benefits resulting from an improved pertussis vaccine would not compare favorably with those produced by a range of new vaccines (for diseases that are not now vaccine preventable). The committee concluded, however, that development of a less reaction-producing, possibly safer, pertussis vaccine deserves special treatment because of its potential for restoring U.S. public confidence in immunization programs. Although the fear of adverse effects from the pertussis vaccine may be less in the developing world, in part because of the greater threat represented by the disease, it is likely that such effects cause concern and may lead to failure to complete recommended immunization schedules. Hence, an improved vaccine would benefit immunization efforts as a whole.

Immunization programs will be logistically constrained by their most sensitive agents. Hence, improving the temperature stability of the most labile vaccines would contribute to immunization efforts generally. The committee evaluated the situation for the two vaccines presently perceived to be the most in need of improved temperature stability, namely poliomyelitis vaccine and measles vaccine. The committee judged that the prospects for substantial improvements in either of the vaccines in the near future were not promising. Therefore, they are not included in this analysis. it is, however, noteworthy that presently feasible adjustments to the formulation of poliomyelitis vaccine can improve its temperature stability but that these modifications are not universally utilized. Magnesium chloride stabilized vaccine—as produced in the United Kingdom, France, Belgium, and a number of other countries but not in the United States—retains potency in the field without refrigeration for 2 weeks with daytime temperatures sometimes reaching 42°C during this period (Peetermans et al., 1976). Utilization of this modification should obviously be evaluated for all situations where it might be beneficial.

The difficulty in quantifying interactions between different vaccines within the general immunization effort led the committee to analyze each vaccine development project independently. However, the overall impact of a potential vaccine candidate should be considered by those who ultimately set the priorities.

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 selection of candidates for accelerated development. The charge did not differentiate between U.S. and foreign companies. Presumably, potential profitability is the major motivating force for private sector activity in vaccine development throughout the world. The potential profitability of a vaccine for developing countries may depend, in part, on whether or not the vaccine also can be used in developed countries. If the disease is absent or of low prevalence in developed countries, companies may be unable to recoup research and development costs. In addition, manufacturers may be less willing to invest in a vaccine if the target population required for clinical trials is distant or difficult to identify.

In the United States, one of the major deterrents to vaccine development is potential liability resulting from clinical trials or widespread use. The impact of this factor on the availability of vaccines for developing countries is difficult to predict; probably, it is less important than concerns about sales revenues.

Industry's willingness to manufacture vaccines that are licensed and to invest in research and development of new vaccines is addressed in the report, Vaccine Supply and Innovation, by the Institute of Medicine's Committee on Public-Private Sector Relations in Vaccine Innovation (Institute of Medicine, 1985b). That study's recommendations

may lead to changes in the factors that govern industry's interest in vaccine innovation. The level of industry's interest in specific vaccines also may change over time as new development techniques are refined.

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

The committee suggests, however, that decisions on implementation of an accelerated vaccine development program should incorporate a review of relevant activities in the private sector. This review should focus on (1) identifying projects for which mutual collaboration might facilitate industrial development of a needed vaccine and (2) identifying high-priority vaccines for which obvious disincentives exist (e.g., special liability issues or limited sales potential, resulting from small market size or particularly severe restrictions on the ability of potential recipients to pay for vaccines). Government funding of the development of such vaccines might make them more attractive to manufacturers.

Periodic reassessment, preferably biennially, of this aspect of the program is particularly desirable because of rapid changes in the technology of producing new vaccines.

INTEREST IN OTHER COUNTRIES OR INTERNATIONAL ORGANIZATIONS

Opportunities for acceleration of vaccine development by U.S. collaboration with other countries and international organizations may also influence the final choices of vaccines for development. The committee recommends that government decision makers consider such opportunities in selecting projects to be pursued.

OTHER DIEASE CHARACTERSTICS RELEVANT TO ESTABLISHING PRIORITIES

Alternative Disease Control Measures

The method devised ranks vaccine candidates on the basis of their potential health benefits. It does not address the relative benefits of disease prevention, control, or treatment by approaches other than immunization.

In some situations, the availability of effective alternatives to immunization might be an important consideration in setting priorities for vaccine development projects. For example, if two vaccine candidates ranked similarly on potential health benefits and costs, vaccine development might be considered more urgent for the candidate for which alternative prevention, control, or treatment measures were less satisfactory.

Table 8.2 provides a summary of the current prevention, control, and treatment measures for diseases in this analysis. More complete information on many of these diseases is presented in Warren and Mahmoud (1984) and in a series of monographs on selective primary health care that will be published shortly by Walsh and Warren (in press).

Some caution is warranted in assuming that vaccine development is less urgent if alternative prevention, treatment, or control measures are available. The history of vector control (with pesticides) and drug therapy for a wide range of diseases indicates that even with continued efforts, these measures may become less effective (or completely ineffective) because of increasing vector or pathogen resistance.

For example, certain strains of Mycobacterium leprae recently have become resistant to dapsone, the principal drug used to treat leprosy for the past 20 years. The prevalence of drug resistance has increased in some areas from 1 to 2 cases per thousand in 1966 to as high as 100 per thousand in 1981 (Bloom, personal communication, 1985). Resistance to dapsone, compounded by the considerable expense of rifampicin and the generally unacceptable side effects (skin coloration) of clofazimine, necessitates the pursuit of preventive immunization strategies.

It was not within the charge of this committee to address the relative merits of immunization versus other means of controlling diseases. It should be noted, however, that immunization generally has been shown to be one of the most cost-effective measures for improving health and that it is relatively free of the resistance problems afflicting vector control and drug therapy. Papers by Feachem and colleagues demonstrate the use of cost-effectiveness analysis in comparing alternative approaches to combatting particular diseases (Ashworth and Feachem, 1985; de Zoysa and Feachem, in press; Feachem, 1983, 1984; Feachem and Koblinsky, 1983, 1984; Feachem et al., 1983).

For rabies, immunization of the major vector, domesticated or semi-domesticated dogs, could be part of an overall strategy of disease prevention. Although cheaper human-use vaccines with fewer side effects would provide considerable benefit, developing animal vaccines that are inexpensive and easily administered (e.g., through baits) may offer the major hope for reducing the incidence of rabies in many countries. This analysis addresses only the potential benefits of vaccines for human use.

Epidemiologic and Clinical Features

The proposed system for calculating a vaccine's potential health benefits uses average annual incidence rates to develop disease burden estimates. This process might understate the importance of certain diseases that occur in epidemic form and produce severe clinical symptoms. A large epidemic of such a disease could overwhelm health care services in developing countries. Because of limited resources, these countries are often barely able to provide appropriate care under normal circumstances. The potential for widespread epidemics also might exacerbate public anxiety about such diseases. Table 8.3 summarizes

the potential impact of the candidate diseases on health care systems in developing countries.

Potential for Disease Eradication

The possibility that a disease might be eradicated has not been incorporated into the calculation of potential benefits, but it could be considered in the ultimate selection of priorities for vaccine development. Early investment in the attack on a theoretically eradicable disease might speed its ultimate elimination and hasten future savings. However, because the current prospects for global eradication of the candidate diseases are remote, this issue probably should not be a major component in the selection of priorities in the near future.

Interaction with Other Diseases

A further consideration in establishing vaccine development priorities is the extent to which particular disease consequences exacerbate (or are exacerbated by) other illness.

The interaction between diarrheal disease and measles is probably the most significant example (Feachem and Koblinsky, 1983). Other interactions are suspected, for example, between viral respiratory infections and bacterial pneumonia, and between various diseases and malaria. In addition, all diarrheas pose the threat of nutritional debilitation, with exacerbation of other illnesses as a consequence.

Because the committee judged that knowledge of these phenomena would not permit reliable quantification of their consequences, no adjustments were made of disease estimates. The phenomena should, however, be recognized and the strength of the evidence considered in the ultimate selection of priorities.

FINDINGS, CONCLUSIONS, AND RECOMMENDATIONS

Various legitimate perspectives exist of the relative undesirability of death and morbidity in different age groups. The method proposed for calculating expected benefits from various vaccines allows decision makers to observe the effects on the final rankings of adopting various perspectives. The determination of which weights to use is inherently a political or public policy decision, not a scientific one.

Scientific evidence can be valuable, however, in assessing certain value judgments. For example, epidemiologic and demographic studies suggest that mortality reduction may be a prerequisite for fertility reduction in developing countries. If a long-term view is taken, this finding contradicts the suggestion that programs to reduce infant and child mortality should receive low priority because they contribute to undesirable population growth and increase pressure on scarce resources (although some growth may occur in the delay between mortality and

TABLE 8.2 Alternatives to Candidate Vaccines

Pathogen	Prevention or Control Measures	Treatment
Dengue virus	Vector control,[a] personal protection[b]	Supportive care
E. coli (enter otoxigenic)	Potable water supply, improve sanitation, educational and behavioral change,[c] improve socioeconomic status	Oral rehydration therapy, antibacterial agents for severe cases
H. influenzae type b	Improve crowded living conditions, increase air circulation, early antibacterials for severe acute respiratory illness	Antibacterial agents (some problems with resistance), bronchodilators
Hepatitis A virus	Potable water supply, improve sanitation, education and behavioral change,[c] passive immunization of travelers	Supportive care
Hepatitis B virus	Improve crowded living conditions, improve socioeconomic status, personal hygiene, vaccine for high-risk groups (expensive)	Supportive care
Japanese encephalitis virus	Vector control,[a] control of nonhuman hosts, vaccine (slow antibody response)	Supportive care
Mycobacterium leprae	Active case finding in endemic areas; rapid, appropriate treatment of cases; chemoprophylaxis; personal sanitation; and isolation of cases (all ineffective)	Anti-mycobacterial agents (problems with development of resistance), patient education to prevent complications
Neisseria meningitidis	Respiratory isolation of cases, chemoprophylaxis of exposed persons, vaccine (limited serotype coverage), improve crowding and ventilation	Antibacterial agents, supportive care
Parainfluenza viruses	Improve crowded living conditions, increase air circulation	Supportive care, early antibacterial agents for secondary bacterial pneumonia
Plasmodium spp.	Vector control,[a] personal protection,[b] chemoprophylaxis for children and pregnant women to prevent falciparum malaria	Anti-malarials (some problem with resistance), supportive care

Rabies virus	Animal control, post-exposure prophylaxis, vaccine (expensive, multiple doses), education to lessen risk of exposure	Supportive care (disease usually fatal)
Respiratory syncytial virus	Improve crowded living conditions, increase air circulation	Supportive care, early antibacterial agents for secondary bacterial pneumonia
Rotavirus	Potable water supply, improve sanitation, education and behavior change,[c] improve socioeconomic status	Oral rehydration therapy
Salmonella typhi	Potable water supply, improve sanitation, case finding for carriers, education and behavioral change[c]	Antibacterial agents (some problems with resistance), oral rehydration therapy for gastroenteritis
Shigella spp.	Potable water supply, improve sanitation, education and behavioral change[c]	Antibacterial agents (resistance is becoming a problem)
Streptococcus Group A	Treatment of cases, improve crowded living conditions	Antibacterial agents
Streptococcus pneumoniae	Improve crowded living conditions, increase air circulation, vaccine (limited effectiveness in highest risk group, under 2 yrs) early antibacterial agent treatment for acute respiratory infections	Antibacterial agents
Vibrio cholera	Potable water supply, improve sanitation, education and behavioral change,[c] vaccine (limited efficacy)	Oral rehydration therapy
Yellow fever virus	Vector control,[a] personal protection,[b] vaccine (expensive)	Supportive care

[a]Vector control includes insecticide and larvicide spraying, standing water control.
[b]Personal protection includes vector avoidance and screening of buildings.
[c]Education and behavioral change includes personal hygiene, prolonged breast feeding, hygienic food preparation.

TABLE 8.3 Impact of Epidemic Disease on Health Care Services

Pathogen	Epidemic Potential	Burden on Health Care Services
Dengue virus	High	High patient burden in epidemics of dengue fever, high burden per patient in dengue hemorrhagic fever epidemic, may be disruptive to medical services
E. coli (enterotoxigenic)	Moderate to high, poor water and hygiene, disaster/mass migration settings	High burden in terms of patients during epidemic
H. influenzae type b	Low	Low (individual patients may be a burden in terms of resources required)
Hepatitis A virus	Low in populations of low socioeconomic status (all persons exposed in early childhood), moderate to high in higher socioeconomic populations, food borne outbreaks	Low
Hepatitis B virus	Low in most settings, higher in disaster/ mass migration settings (high risk populations: drug abusers, homosexual men, dialysis patients)	Moderate (cases may be severe and may have chronic sequelae)
Japanese encephalitis	High	High in terms of number of patients during virus epidemic, severe and chronic cases may be disruptive to medical services
Mycobacterium leprae	Low	Low
Neisseria meningitidis	High (especially in “meningitis belt” in Africa)	High
Parainfluenza viruses	Probably high	Moderate
Plasraodium spp.	High in areas of seasonal transmission, low in holoendemic areas, disaster/mass migration situations; epidemic potential in situations where (now chemical, but potentially vaccine) prophylaxis might be interrupted or ceased	High during epidemic
Rabies virus	Low	Low
Respiratory syncytial virus	High	Moderate to high
Rotavirus	High, disaster/mass migration situations, populations of low socioeconomic status	High
Salmonella typhi	High, disaster/mass migration situations, mostly water borne	High
Shigella spp.	High, low socioeconomic areas, endemic in tropical areas	High
Streptococcus Group A	Pharyngitis: high; others: low, except under conditions of crowding	Low
Streptococcus pneumoniae	Moderate	Moderate
Vibrio cholera	High in areas where protected water supplies not available, disaster/mass migration situations	High, may be disruptive to medical services
Yellow fever virus	High	High

fertility reduction). That some population growth will result from infant and child mortality reduction highlights the need for integration of agricultural and health planning to avoid food shortages.

The method of ranking in this report uses an aggregate or global perspective, but the actual benefits from new vaccines will not be distributed evenly among regions, countries, socioeconomic groups, ethnic groups, age groups, or other population subsets. The committee's method can provide useful information about the distribution of potential benefits, but the committee recommends that relevant equity issues should be addressed in a broader political/public policy forum. The portfolio approach could help focus the decision-making process.

The proposed system treats each vaccine development project independently, but some projects may have a wider impact. For example, a pertussis vaccine that caused fewer reactions might help increase public confidence in immunization programs in general and decrease failure to complete recommended schedules. Specific diseases may also interact synergistically in causing mortality. These interactions are difficult to quantify, but they should be considered by those setting vaccine priorities.

Other nonquantifiable factors that might affect project rankings include the availability of alternative measures of disease control or treatment, the potential impact of epidemic disease on health care facilities, and the opportunity for complete eradication of a particular disease.

In implementing the program of accelerated vaccine development, decision makers periodically should review activity in the private sector to identify projects for which public-private collaboration might expedite development, and to identify industry-scientific disincentives to the development of high-priority vaccines. Additional governmental funding for these vaccines (e.g., for clinical trials) might make them attractive to commercial manufacturers.

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 nonquantifiable considerations discussed here.

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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. Potential health benefits and potential vaccine expenditures have been calculated for each of the 29 vaccine projects.* The committee suggests that the potential global health benefit of a vaccine takes precedence in determining its initial ranking for accelerated development priority. The "affordability" of benefits, represented by the potential expenditures on vaccines, can be entered into the decision process, if desired, and the techniques for doing so are illustrated with the central analysis. The first rankings presented 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 various discount rates and of alternative assumptions about the probability of successful development. The effect on the rankings of adopting alternative assumptions on the disease burden derivations is also examined for selected vaccines. The effect of adopting perspectives on the undesirability of morbidity and death different from the median set of values used in the central analysis is discussed. In addition, approaches for incorporating differential utilization into the rankings are explained.

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 examination of all judgments and assumptions involved in the decision process. New data should be incorporated as they become available.

*The analysis covers 29 vaccine projects directed against 19 diseases. In some cases, there may be more than one promising approach; also, various vaccine candidates for a particular disease may not have the same anticipated target population.

This model was developed to assist the National Institute of Allergy and Infectious Diseases (NIAID) and the U.S. Agency for International Development (AID) in their decision making. The priorities identified by this model are not appropriate for all circumstances, but it is hoped that the model or some modification of it may be useful to other groups, both in the United States and elsewhere, that are faced with similar resource allocation problems.

The Central Analysis

The central analysis described below incorporates the following:

vaccine and development characteristics described in Chapter 5, including predictions on the target population, efficacy, and vaccine cost

- estimates of the burden of each disease, derived as described in Appendixes B, C, and D-1 through D-19
- the assumption that utilization rates would not differ among vaccine candidates (because delivery of vaccines would probably be through the World Health Organization Expanded Program on Immunization [WHO-EPI])
- estimates of the number of new entrants to the respective target populations, as described in Appendixes D-1 through D-19 and summarized in Chapter 7, Table 7.1
- times to licensure and adoption, delay of vaccination benefits presented in Chapter 7, Table 7.2

  calculations of each vaccine candidate's potential health benefits and associated expenditures as described in Chapters 4 and 7
- a 5 percent discount rate for future health benefits and costs
- a perspective, for illustrative purposes only, on the undesirability of various morbidity conditions and mortality, derived from the median values of responses from a range of health professionals in developing countries
- independent consideration of each disease and the development of each vaccine candidate (for each target population)
- expression of health benefits in units considered equivalent in undesirability to the death of an infant (i.e., infant mortality equivalents, see Chapter 4)

FINDINGS

The results of the central analysis (Chapter 7) are shown in Tables 9.1 and 9.2.

The range of potential benefits from the various vaccine candidates, viewed as present-day investment options, is considerable,

spanning over two orders of magnitude, as does the range of potential expenditures.*

The expenditures listed in Tables 9.1 and 9.2 do not represent the net costs of using a vaccine (which may be a cost saving if averted treatment costs outweigh development and vaccination program costs). Hence, they cannot be used in formal cost-benefit or cost-effectiveness analyses. However, they can be used to illustrate how priority rankings may differ if financial resources (mostly needed in the countries of use) become a concern.

The ranking based on health benefits in Table 9.2 would be the initial priority assignment if resource constraints were not a concern. As financial constraints become a concern, the potential health benefit values can be adjusted to reflect the expenditures that might be considered feasible to gain a unit of benefit—in this analysis an infant mortality equivalence unit (IME). At each level of "willingness to pay," this adjustment represents the health benefit (IME units prevented) that could be obtained by spending an amount of money equivalent to the expenditures on a particular vaccine in a different manner, for example, on another vaccine. This is termed the net opportunity cost of resources. Specifically,

$$\begin{array}{l}\text{Annualized present value of potential health benefit adjusted for opportunity cost}\end{array} = \begin{array}{l}\text{annualized present value of potential health benefit}\end{array} - \frac{\text{annualized present value of potential expenditures}}{\text{\$ willingness to pay per IME averted}}\,.$$

Table 9.3 shows, for the various vaccine candidates, the annualized present values of potential health benefits adjusted for opportunity costs at various levels of willingness to pay per IME averted. Positive values reflect the relative size of benefits for vaccines that are "affordable" at that level of willingness to pay. Negative values apply to vaccines that are not affordable at that level of willingness to pay, that is, the cost of obtaining a unit of health benefit with that particular vaccine exceeds the resources or willingness to pay. It must be emphasized that the values in Table 9.3 reflect the use of expenditures as a measure of affordability rather than net costs, as discussed above. Expenditures on some vaccines may return net cost savings.

Rankings developed from these adjusted values reflect, for each level of willingness to pay, both the size of the potential benefit and its affordability. Table 9.4 shows the rankings of vaccine candidates at various levels of willingness to pay.

If desired, expenditures on vaccine development and use may be incorporated into the ranking process as a decision criterion

*Expenditures represent vaccine development cost and vaccine cost (but not delivery, which is assumed uniform) for the vaccination program (see Chapter 4).

TABLE 9.1 Health Benefits and Expenditures Associated with Various Vaccine Candidates: Central Analysis

Pathogen (Target Population)	Vaccine Envisaged	Annualized Present Value of Potential Health Benefits (IME Units)	Annualized Present Value of Expenditures on Vaccines Necessary to Achieve Potential Health Benefits ($ millions)
Dengue virus (Infants and children in endemic areas; travelers to endemic areas)	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	9,558	242
Escherichia coli (enterotoxigenic) (Infants < 6 months)	A combination of purified colonization factor antigens and possibly other antigens	126,454	722
	Genetically engineered attenuated strains	145,260	69
Hemophilus influenzae type b (Infants)	Conjugated polysaccharide	210,943	527
Hepatitis A virus (Susceptibles of all ages; routine for preschool children)	Attenuated live virus	15,112	1,058
	Polypeptide recombinant vaccine produced in yeast	14,392	4,029
Hepatitis B virus (Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations)	Polypeptide produced by recombinant DNA technology	213,192	8,859
Japanese encephalitis virus (Children in epidemic and and endemic areas; foreign visitors to epidemic regions)	Inactivated virus produced in cell culture	3,232	614

Mycobacterium leprae (Immuno-prophylactic: all children in endemic areas. Immuno-therapeutic: all recently infected individuals)	Armadillo-derived M. leprae	88,481	271
Neisseria meningitidis (Infants, 3–6 months)	Conjugated capsular polysaccharides, groups A,C,Y, and W135	13,754	708
Parainfluenza viruses (Infants)	Trivalent, subunit vaccine (which must contain fusion proteins)	43,692	1,697
Plasmodium spp. (All infants at risk, military personnel, travelers)	Plasmodium falciparum, synthetic or recombinant sporozoite antigen preparation	475,205	967
	Multivalent synthetic or recombinant sporozoite antigen preparation (P. falciparum, P. vivax, P. ovale, P. malariae)	426,640	857
Rabies virus (Individuals at high risk, plus post-exposure prophylaxis) (As above)	Vero cell	41,910	147
	Glycoprotein produced by rDNA technology in mammalian cells	37,983	139
(Birth cohort in areas of high risk)	Attenuated live vector virus containing gene for protective glycoprotein antigen	8,260	16
Respiratory syncytial virus (Infants)	Polypeptides produced by recombinant DNA technology	52,412	1,964
	Attenuated live virus	59,559	983

Pathogen (Target Population)	Vaccine Envisaged	Annualized Present Value of Potential Health Benefits (IME Units)	Annualized Present Value of Expenditures on Vaccines Necessary to Achieve Potential Health Benefits ($ millions)
Rotavirue (Infants, 0–6 months)	Attenuated high passage bovine rotavirus	521,852	853
	Attenuated low passage bovine rotavirus	450,795	655
	Rhesus monkey rotavirus	450,795	656
Salmonella typhi (Children; young adults at risk; travelers from developed countries to endemic areas)	Attenuated ga1E mutant S. typhi strain TY21a	431,471	358
	Aromatic amino acid dependent strains of S. typhi	194,745	152
Shigella spp. (Infants at birth; elderly for epidemic strains)	Probably plasmid mediated outer membrane protein invasion determinant (there are a small number of promising options needing investigation to determine best approach)	222,096	92
Streptococcus A (Children, < 3–4 years)	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	180,513	554
Streptococcus pneumoniae (Infants)	Conjugated polysaccharides, polyvalent	1,363,943	1,310
Vibrio cholera (Children, especially < 2 years)	Genetically defined live mutant V. cholerae (A−B+ or A−B−) with respect to toxin subunit synthesis	94,986	24
	Inactivated antigens	65,548	44
Yellow fever virus (Young children)	Attenuated live virus produced in cell culture	11,127	93

TABLE 9.2 Benefits and Affordability of Various Vaccine Candidates

Vaccine	Annualized Present Value of Potential Health Benefits (IME units)	Vaccine	Annualized Present Value of Potential Expenditures ($ millions)
S. pneumoniae	1,363,943	Rabies (live vector virus)	15.5
Rotavirus (HPBRV)	521,852	*V. cholera* (attenuated live)	23.8
Malaria (monovalent)	475,205	*V. cholera* (inactivated)	43.6
Rotavirus (LPBRV)	450,795	*E. coli* (attenuated live)	69.2
Rotavirus (RMRV)	450,795	Shigella	91.6
S. typhi (Ty21a)	431,471	Yellow fever	93.0
Malaria (multivalent)	426,640	Rabies (glycoprotein)	138.7
Shigella	222,096	Rabies (Vero cell derived)	146.8
Hepatitis B	213,192	*S. typhi* (aa-strain)	152.2
H. influenzae b	210,943	Dengue	241.8
S. typhi (aa-strain)	194,745	*M. leprae*	270.6
Streptococcus group A	180,513	*S. typhi* (Ty21a)	358.0
E. coli (attenuated live)	145,260	*H. influenzae* b	526.6
E. coli (purified antigens)	126,454	Streptococcus group A	554.2
V. cholera (attenuated live)	94,986	Japanese encephalitis	614.0
M. leprae	88,481	Rotavirus (LPBVR)	655.4
V. cholera (inactivated)	65,548	Rotavirus (RMRV)	655.9
RSV (attenuated live virus)	59,559	*N. meningitidis*	708.1
RSV (glycoprotein)	52,412	*E. coli* (purified antigens)	722.3
Parainfluenza viruses	43,692	Rotavirus (HPBRV)	852.7
Rabies (Vero cell derived)	41,910	Malaria (multivalent)	856.8
Rabies (glycoprotein)	37,983	Malaria (monovalent)	967.3
Hepatitis A (attenuated live virus)	15,112	RSV (attenuated live)	982.8
Hepatitis A (polypeptide)	14,392	Hepatitis A (attenuated live)	1,058.0
N. meningitidis	13,754	*Streptococcus pneumoniae*	1,310.3
Yellow fever virus	11,127	Parainfluenza	1,697.1
Dengue virus	9,558	RSV (glycoprotein)	1,964.4
Rabies (live vector virus)	8,260	Hepatitis A (polypeptide)	4,029.0
Japanese encephalitis virus	3,232	Hepatitis B	8,859.3

Health benefits are expressed in units equivalent in undesirability to the death of an infant (IMEs) and are calculated using the median of IME perspectives from responding health professionals in developing countries.

TABLE 9.3 Some Relationships Between Expenditures and Health Benefitsa

Pathogen (Target Population)	Vaccine Envisaged	Annualized Present Value of Potential Health Benefits (IME Units)	Annualized Present Value of Expenditures on Vaccines Necessary to Achieve Potential Health Benefits (dollars)
Dengue virus (Infants and children in endemic areas; travelers to endemic areas)	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	9,558	241,803,765
Escherichia coli (enterotoxigenic) (Infants < 6 months)	A combination of purified colonization factor antigens and possibly other antigens	126,454	722,284,852
	Genetically engineered attenuated strains	145,260	69,171,586
Hemophilus influenzae type b (Infants)	Conjugated polysaccharide	210,943	526,603,421
Hepatitis A virus (Susceptibles of all ages; children)	Attenuated live virus	15,112	1,058,021,429
	Polypeptide recombinant vaccine produced in yeast	14,392	4,028,950,683
Hepatitis B virus (Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations)	Polypeptide produced by recombinant DNA technology	213,192	8,859,258,746
Japanese encephalitis virus (Children in epidemic and and endemic areas; foreign visitors to epidemic regions)	Inactivated virus produced in cell culture	3,232	613,959,820
Mycobacterium leprae (Immuno-prophylactic: all children in endemic areas. Immuno-therapeutic: all recently infected individuals)	Armadillo-derived M. leprae	88,481	270,619,575
Neisseria meningitidis (Infants, 3–6 months)	Conjugated capsular polysaccharides, groups A,C,Y, and W135	13,754	708,114,155
Parainfluenza viruses (Infants)	Trivalent, subunit vaccine (which must contain fusion proteins)	43,692	1,697,123,972
Plasmodium spp. (All infants at risk, military personnel, travelers)	Plasmodium falciparum, synthetic or recombinant sporozoite antigen preparation	475,205	967,271,590
	Multivalent synthetic or recombinant sporozoite antigen preparation (P. falciparum, P. vivax, P. ovale, P. malariae)	426,640	856,843,460

Expenditure per IME Prevented	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $100,000/IME	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $10,000/ IME	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $1,000/ IME	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $500/ IME	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $100/ IME
25,298	7,140	–14,622	–232,246	–474,049	–2,408,479
5,712	119,231	54,226	–595,831	–1,318,116	–7,096,394
476	144,568	138,343	76,088	6,917	–546,456
2,496	205,677	158,283	–315,660	–842,264	–5,055,091
70,014	4,531	–90,691	–1,042,910	–2,100,931	–10,565,103
279,946	–25,898	–388,503	–4,014,559	–8,043,509	–40,275,115
41,555	124,600	–672,734	–8,646,066	–17,505,325	–88,379,395
189,944	–2,907	–58,164	–610,727	–1,224,687	–6,136,366
3,058	85,775	61,419	–182,138	–452,758	–2,617,714
51,483	6,673	–57,057	–694,360	–1,402,474	–7,067,387
38,843	26,721	–126,020	–1,653,432	–3,350,556	–16,927,548
2,035	465,532	378,478	–492,066	–1,459,338	–9,197,511
2,008	418,072	340,956	–430,203	–1,287,047	–8,141,795

Pathogen (Target Population)	Vaccine Envisaged	Annualized Present Value of Potential Health Benefits (IME Units)	Annualized Present Value of Expenditures on Vaccines Necessary to Achieve Potential Health Benefits (dollars)
Rabies virus (Individuals at high risk, plus post-exposure prophylaxis) (As above)	Vero cell	41,910	146,811,503
	Glycoprotein produced by rDNA technology in mammalian cells	37,983	138,655,304
(Birth cohort in areas of high risk)	Attenuated live vector virus containing gene for protective glycoprotein antigen	8,260	15,506,192
Respiratory syncytial virus (Infants)	Polypeptides produced by recombinant DNA technology	52,412	1,964,436,106
	Attenuated live virus	59,559	982,843,053
Rotavirus (Infants, 0–6 months)	Attenuated high passage bovine rotavirus	521,852	852,737,494
	Attenuated low passage bovine rotavirus	450,795	655,395,369
	Rhesus monkey rotavirus	450,795	655,895,369
Salmonella typhi (Children; young adults at risk; travelers from developed countries to endemic areas)	Attenuated ga1E mutant S. typhi strain TY21a	431,471	358,039,747
	Aromatic amino acid dependent strains of S. typbi	194,745	152,153,450
Shigella spp. (Infants at birth; elderly for epidemic strains)	Probably plasmid mediated outer membrane protein invasion determinant (a small number of promising options need to be investigated to determine best approach)	222,096	91,603,782
Streptococcus A (Children, < 3–4 years)	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	180,513	554,167,844
Streptococcus pneumoniae (Infants)	Conjugated polysaccharides, polyvalent	1,363,943	1,310,290,738
Vibrio cholera (Children, especially <2 years)	Genetically defined live mutant V. cholerae (A−B+ or A−B−) with respect to toxin subunit synthesis	94,986	23,788,751
	Inactivated antigens	65,548	43,571,553
Yellow fever virus (Young children)	Attenuated live virus produced in cell culture	11,127	93,049,382

[a]Unadjusted annualized present values of potential health benefits represent a situation where resource constraints are not a concern: no vaccine candidate is affordable if the willingness to pay per IME averted is $100 or less.

Expenditure per IME Prevented	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $100,000/IME	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $10,000/ IME	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $1,000/ IME	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $500/ IME	Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Cost at $100/ IME
3,503	40,442	27,229	−104,901	–251,713	–1,426,205
3,650	36,596	24,117	–100,673	–239,328	–1,348,570
1,877	8,105	6,709	–7,246	–22,752	–146,802
37,480	32,768	–144,031	–1,912,024	–3,876,460	–19,591,949
16,502	49,731	–38,725	–923,284	–1,906,127	–9,768,871
1,634	513,325	436,578	–330,885	–1,183,623	–8,005,523
1,454	444,242	385,256	–204,600	–859,995	–6,103,158
1,455	444,237	385,206	–205,100	–860,995	–6,108,158
830	427,891	395,667	73,431	–284,608	–3,148,926
781	193,224	179,530	42,592	–109,562	–1,326,789
412	221,180	212,936	130,492	38,889	–693,942
3,070	174,971	125,096	–373,655	–927,823	–5,361,165
961	1,350,840	1,232,914	53,652	–1,256,638	–11,738,964
250	94,748	92,607	71,197	47,408	–142,902
665	65,112	61,191	21,976	–21,595	–370,168
8,362	10,197	1,822	–81,922	–174,971	–919,366

equivalent to potential health benefits. In this case the principle of dominance applies: vaccines yielding greater potential benefits and lower expenditures are preferred. Procedures are discussed in Chapter 3. However, because the expenditures do not reflect overall net costs, the committee believes that initial rankings of candidates should be based on their potential health benefits.

TABLE 9.4 The Effect of Resource Constraints on the Ranking of Various Vaccine Candidates

	Rank Based on Annualized Present Value of Potential Health Benefits Adjusted for Opportunity Costs[a]				
	Willingness to Pay (dollars) per IME Averted				
Vaccine	Unrestricted	100,000	10,000	1,000	500
S. pneumoniae	1	1	1	5	-[b]
Rotavirus (HPBRV)	2	2	2	-	-
Malaria (monovalent)	3	3	6	-	-
Rotavirus (LPBRV)	4	4	4	-	-
Rotavirus (RMRV)	5	5	5	-	-
S. typhi (Ty21a)	6	6	3	3	-
Malaria (multivalent)	7	7	7	-	-
Shigella	8	8	8	1	2
Hepatitis B	9	13	-	-	-
H. influenzae b	10	9	10	-	-
S. typhi (aa-strain)	11	10	9	6	-
Streptococcus group A	12	11	12	-	-
E. coli (attenuated live)	13	12	11	2	3
E. coli (purified antigens)	14	14	16	-	-
V. cholera (attenuated live)	15	15	13	4	1
M. leprae	16	16	14	-	-
V. cholera (inactivated)	17	17	15	7	-
RSV (attenuated live virus)	18	18	-	-	-
RSV (glycoprotein)	19	21	-	-	-
Parainfluenza viruses	20	22	-	-	-
Rabies (Vero cell derived)	21	19	17	-	-
Rabies (glycoprotein)	22	20	18	-	-
Hepatitis A (attenuated live virus)	23	27	-	-	-
Hepatitis A (polypeptide)	24	-	-	-	-
N. meningitidis	25	26	-	-	-
Yellow fever virus	26	23	20	-	-
Dengue virus	27	25	-	-	-
Rabies (live vector virus)	28	24	19	-	-
Japanese encephalitis virus	29	-	-	-	-

[a]Rankings are based on values shown in Table 9.3.
[b]- denotes not affordable at indicated willingness to pay.

Disease Burden Assumptions

A major factor in determining the ultimate ranking of a vaccine candidate is the total disease burden value (TDBV) used as the starting point in the calculations of potential benefit. The central analysis rankings reflect the committee's best efforts, within its resources and the reliability and quantity of available data, to generate disease

burden estimates. Some of the estimates rest on uncertain assumptions or extrapolations from limited data. Some specific examples may help demonstrate how the overall method differentiates between vaccine candidates even when the starting points are somewhat uncertain.

For the top-ranked vaccine candidate, S. pneumoniae, the total disease burden in the central analysis represents a set of assumptions, including some use of antibiotics (see Appendix D-17). A "preantibiotic" TDBV twice that used in the central analysis could have been used in calculations, but would have merely served to further separate S. pneumoniae vaccine from the runners-up. Using a different starting point for the derivation of the disease burden estimates (see Appendixes B and D-17)* yields a somewhat lower estimate of pneumococcal pneumonia, the major contributor to the S. pneumoniae disease burden. Ignoring bacteremia and otitis media, the approach in Appendix B yields estimates for the under 15 years age group that results in a disease burden value of 1,921,300 (versus 6,612,261 in the central analysis which derives from the estimates developed in Appendix D-17). Because the lower value represents the partial disease burden for the under 15 years age group, it is assumed that all of the disease is potentially preventable (i.e., VPI=1.0; see Appendix D-17). Using the lower DBV of 1,921,300 as the starting point in the analysis results in a value for the annualized present value of potential health benefits (APVPHB) of 713,367. This value still results in the candidate S. pneumoniae vaccine having highest priority. The effect of adopting alternative assumptions on the probability of success for this candidate is discussed below.

For certain diarrheal pathogens it can be argued that by the time the new vaccines are available, the disease burden will have been significantly reduced by the adoption of oral rehydration therapy (ORT), which averts dehydration deaths. For those pathogens where this scenario was plausible (E. coli and rotavirus), TDBVs were calculated from disease burden estimates which assumed that by the time of vaccine availability, ORT had reduced deaths by 50 percent. The effect of adopting these TDBVs in the analysis was examined. Even with the assumption that the disease amenable to reduction by these vaccines is reduced substantially (by about 50 percent), the degree of spacing between the other candidates resulted in these vaccines shifting only slightly in the rankings. The three rotavirus candidates dropped in the central analysis from positions 2, 4, and 5 to positions 5, 6, and 7 (total candidates = 29). The two E. coli candidates dropped from positions 13 and 14 to positions 15 and 16.

*The approach in Appendix B starts from reports on overall acute respiratory infections in developing countries; these reports probably underestimate the actual incidence of disease. The approach in Appendix D-17 starts from the assumption that pneumococcal pneumonia incidence in developing countries is likely to be similar to that in developed countries in the 1920s; such rates are reasonably well documented.

Individuals wishing to evaluate the effect on the ultimate rankings of adopting different assumptions on the magnitude of the disease burden can do so in crude fashion by adjusting the final APVPHB in accordance with their beliefs. For example, if they believe that the overall disease incidence is twice that used in the central analysis (but that rates for complications, sequelae, case-fatality rates, etc., are reasonable) the central analysis APVPHB value should be doubled. The rank of the new APVPHB value can then be determined. More complex disagreements with disease burden determination (e.g., favoring a different frequency of complications) requires recalculation of the disease burden estimates and the TDBV.

Target Population and Assumptions on Vaccine Preventable Illness

The bases for the various disease burden proportions that are judged to be vaccine preventable are described in Appendixes D-1 through D-19. The effect of alternative assumptions can easily be examined by substituting a new value in the calculation process shown in Table 7.4. Assumptions different from those in the central analysis may alter the ranking of vaccines. For example, 50 percent of the disease burden for hepatitis B vaccine is estimated to be preventable by delivering the vaccine at the usual WHO-EPI scheduled times. If vaccines were delivered universally at birth, some higher proportion would be preventable and the potential benefits would be raised proportionally.

The targeted population may markedly affect the potential expenditures. For example, delivery of the N. meningitidis vaccine to the entire birth cohort in the developing world (115.1 million births) would cost about $708 million. Focusing vaccine delivery on births in the African meningitis belt (13.1 million births) would reduce the cost by about 90 percent to $82 million. (Because this strategy would not protect against endemic or rare epidemic disease in other parts of the world, potential health benefits would also be less; see Appendix D-8).

Similarly, immunotherapeutic use of a vaccine for M. leprae—to curtail progressive disease in all recognized new cases—would cost $10.3 million as contrasted to immunoprophylactic use in the birth cohort at risk, which would cost $270 million. These strategies are, however, significantly different, and this commentary does not suggest that immunotherapy would be more “cost-effective.” To be useful, such a strategy would require substantially increased efforts at early case detection.

Discount Rate

The committee believes that incorporating a discounting procedure for future health benefits and expenditures 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 more or less weight on

achieving early benefits was examined by selecting discount rates higher (0.10) and lower (0.02) than in the central analysis. Results from analyses using these discount rates are compared to results from the central analysis in Tables 9.5 and 9.6.

In general, using discount rates of 10 percent or 2 percent would not substantially affect the structure of the ranking, although some vaccines are shifted slightly in position. Notable among these is hepatitis B, which drops from position 9 on health benefits to position 15 if a 10 percent discount rate is adopted. Although the development of this second generation vaccine is relatively advanced, it drops in position when a high discount rate is adopted (i.e., one that favors shorter term realization of benefits) because the delay of vaccination benefits for hepatitis B immunization is long.

Alternative Development Scenario: Probability of Success

The central analysis uses 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 a time period for likely time to licensure. Tables 9.7 and 9.8 show the results. Such an assumption would not substantially affect the overall rankings, but some vaccines shift slightly in position. Some vaccines with lower probabilities of success (e.g., malaria at 0.5) rise in the rankings relative to those whose probability of success was already closer to 1.0. The spacing of benefit values is such that, for certain vaccines (e.g., M. leprae) with a lower probability of success, the more optimistic assumption (p=1.0) raises the potential benefit value but does not change the ranking.

The committee performed another sensitivity analysis, by way of example, to show the effects of lowering the probability of successful development for a single, highly ranked, vaccine—S. pneumoniae (Table9.9). The original estimate, shown in Tables 9.1 and 9.2, was 80 percent. Elimination of this vaccine from the top half of the ranking on potential health benefits (Table 9.2) required assuming a probability of success less than 5 percent. Assuming a probability of success less than about 12 percent is required to eliminate it from the top five positions.

Assessing the Effect of Differential Utilization

Table 9.2 shows annualized present values of potential health benefits (APVPHBs) unadjusted for utilization because the committee assumed this factor would not differ among vaccines. If future applications of this or similar systems (e.g., for specific countries) must account for differential utilization, then the appropriate values for the annualized present values of expected health benefits can be obtained simply by multiplying the APVPHBs by the appropriate value for that proportion of the target population expected to receive the vaccine.

TABLE 9.5 Sensitivity Analysis: Effect of Discount Rate on Annualized Present Value of Potential Health Benefits for Various Vaccine Candidates

	Discount Rate					
	Central Analysis, 0.05		0.02		0.10	
Vaccine	Rank	Value (IME Units)	Rank	Value (IME Units)	Rank	Value (IME Units)
S. pneumoniae	1	1,363,943	1	1,770,510	1	897,358
Rotavirus (HPBRV)	2	521,852	5	603,244	2	413,552
Malaria (monovalent)	3	475,205	3	663,218	5	278,319
Rotavirus (LPBRV)	4	450,795	6	568,450	3	310,708
Rotavirus (RMRV)	4	450,795	6	568,450	4	310,708
S. typhi (Ty21a)	6	431,471	2	686,085	7	204,973
Malaria (multivalent)	7	426,640	4	640,191	6	222,440
Shigella	8	222,096	10	323,742	9	121,310
Hepatitis B	9	213,192	8	554,897	15	45,926
H. influenzae b	10	210,943	12	281,875	8	132,474
S. typhi (aa-strain)	11	194,745	9	363,189	12	71,630
Streptococcus group A	12	180,513	11	317,684	11	72,869
E. coli (attenuated live)	13	145,260	13	211,741	10	79,342
E. coli (purified antigens)	14	126,454	14	184,238	13	69,070
V. cholera (attenuated live)	15	94,986	16	126,925	14	59,652
M. leprae	16	88,481	17	162,639	19	33,310
V. cholera (inactivated)	17	65,548	17	82,656	16	45,179
RSV (attenuated live virus)	18	59,559	18	75,104	17	41,051
RSV (glycoprotein)	19	52,412	19	66,092	18	36,125
Parainfluenza viruses	20	43,692	20	60,101	22	26,192
Rabies (Vero cell derived)	21	41,910	21	52,088	20	29,566
Rabies (glycoprotein)	22	37,983	22	47,207	21	26,795
Hepatitis A (attenuated live virus)	23	15,112	23	20,787	23	9,059
Hepatitis A (polypeptide)	24	14,392	24	20,379	24	8,235
N. meningitidis	25	13,754	25	20,049	25	7,513
Yellow fever virus	26	11,127	26	19,301	26	4,598
Dengue virus	27	9,558	27	15,646	27	4,334
Rabies (live vector virus)	28	8,260	28	5,630	28	2,969
Japanese encephalitis virus	29	3,232	29	5,215	29	1,500

TABLE 9.6 Sensitivity Analysis: Effect of Discount Rate on Annualized Present Value of Expenditures to Achieve the Benefits of Various Vaccine Candidates

	Discount Rate					
	Central Analysis, 0.05		0.02		0.10	
Vaccine	Rank	Expenditure ($ million)	Rank	Expenditure ($ million)	Rank	Expenditure ($ million)
Rabies (live vector virus)	1	16	1	21	1	10
V. cholera (attenuated live)	2	24	2	29	2	18
V. cholera (inactivated)	3	44	3	51	3	34
E. coli (attenuated live)	4	69	4	96	4	42
Shigella	5	92	6	128	5	55
Yellow fever	6	93	5	107	6	75
Rabies (glycoprotein)	7	139	7	182	8	112
Rabies (Vero cell derived)	8	147	8	193	9	119
S. typhi (aa-strain)	9	152	9	195	7	103
Dengue	10	242	10	341	11	140
M. leprae	11	271	12	417	10	137
S. typhi (Ty21a)	12	358	11	390	12	312
H. influenzae b	13	527	13	663	14	364
Streptococcus group A	14	554	14	749	13	344
Japanese encephalitis	15	614	17	806	15	398
Rotavirus (LPBVR)	16	655	15	802	18	475
Rotavirus (RMRV)	17	656	16	802	19	476
N. meningitidis	18	708	18	945	17	447
E. coli (purified antigens)	19	722	20	1,021	16	415
Rotavirus (HPBRV)	20	853	19	957	23	709
Malaria (multivalent)	21	857	21	1,177	20	516
Malaria (monovalent)	22	967	23	1,236	21	653
RSV (attenuated live)	23	983	22	1,203	24	711
Hepatitis A (attenuated live)	24	1,058	24	1,373	22	697
Streptococcus pneumoniae	25	1,310	25	1,604	25	948
Parainfluenza	26	1,697	26	2,267	26	1,068
RSV (glycoprotein)	27	1,964	27	2,405	27	1,420
Hepatitis A (polypeptide)	28	4,029	28	5,383	28	2,542
Hepatitis B	29	8,859	29	9,664	29	7,700

TABLE 9.7 Sensitivity Analysis: Effect of an Alternative Development Scenario on Potential Health Benefits

Vaccine	Predicted Probability of Successful Development (Central Analysis)		100% Probability of Successful Development	
	Rank	Value (IME Units)	Rank	Value (IME Units)
S. pneumoniae	1	1,363,943	1	1,704,929
Rotavirus (HPBRV)	2	521,852	4	579,836
Malaria (monovalent)	3	475,205	2	950,410
Rotavirus (LPBRV)	4	450,795	5	563,494
Rotavirus (RMRV)	4	450,795	5	563,494
S. typhi (Ty21a)	6	431,471	7	479,412
Malaria (multivalent)	7	426,640	3	853,280
Shigella	8	222,096	9	317,280
Hepatitis B	9	213,192	13	215,346
H. influenzae b	10	210,943	11	234,381
S. typhi (aa-strain)	11	194,745	8	317,491
Streptococcus group A	12	180,513	12	225,641
E. coli (attenuated live)	13	145,260	14	207,514
E. coli (purified antigens)	14	126,454	10	252,908
V. cholera (attenuated live)	15	94,986	16	126,647
M. leprae	16	88,481	15	176,963
V. cholera (inactivated)	17	65,548	17	100,843
RSV (attenuated live virus)	18	59,559	18	74,449
RSV (glycoprotein)	19	52,412	19	65,515
Parainfluenza viruses	20	43,692	20	54,615
Rabies (Vero cell derived)	21	41,910	21	46,567
Rabies (glycoprotein)	22	37,983	22	44,686
Hepatitis A (attenuated live virus)	23	15,112	25	15,907
Hepatitis A (polypeptide)	24	14,392	26	15,149
N. meningitidis	25	13,754	23	27,509
Yellow fever virus	26	11,127	28	11,713
Dengue virus	27	9,558	27	12,744
Rabies (live vector virus)	28	8,260	24	16,520
Japanese encephalitis virus	29	3,232	29	6,465

CONCLUSIONS

Final decisions on the number of vaccines and the particular vaccines selected for accelerated development must incorporate various nonquantifiable factors, as well as information provided by the rankings that were derived with the proposed system for calculating benefits and expenditures. The additional factors include:

- goals of the responsible agency and its schedule for achieving them
- ethical questions on the distribution of benefits among socioeconomic or age groups, countries, or regions
- most appropriate points in the development process at which the agency can exert influence and the opportunity and need for such influence
- extent of private sector activities

- opportunities to accelerate vaccine development through collaboration with other countries or international organizations
- the desired balance of the development portfolio (e.g., pediatric versus adult vaccines, global versus regional diseases)
- arguments for treating certain vaccine development projects as unique because of their potential for facilitating immunization programs in general (e.g., by eliminating constraints on delivery, such as poor stability) or by improving public confidence (e.g., by reducing adverse reactions)
- the prospect that a particular project may serve as a useful model for a number of other desired vaccines
- disease related factors, such as epidemiologic and clinical characteristics likely to overwhelm medical services, and the availability of alternative control strategies or safe and effective therapy
- possible synergistic interaction with other diseases

TABLE 9.8 Sensitivity Analysis: Effect of an Alternative Development Scenario on Potential Expenditures

	Predicted Probability of Successful Development (Central Analysis)		100% Probability of Successful Development	
Vaccine	Rank	Expenditures ($ millions)	Rank	Expenditures ($ millions)
Rabies (live vector virus)	1	15.5	1	30.3
V. cholera (attenuated live)	2	23.8	2	31.3
V. cholera (inactivated)	3	43.6	3	66.8
E. coli (attenuated live)	4	69.2	5	98.0
Shigella	5	91.6	6	130.1
Yellow fever	6	93.0	4	97.9
Rabies (glycoprotein)	7	138.7	7	177.4
Rabies (Vero cell derived)	8	146.8	8	177.5
S. typhi (aa-strain)	9	152.2	9	304.2
Dengue	10	241.8	10	322.0
M. leprae	11	270.6	12	549.0
S. typhi (Ty21a)	12	358.0	11	397.8
H. influenzae b	13	526.6	13	585.0
Streptococcus group A	14	554.2	14	692.1
Japanese encephalitis	15	614.0	19	1,225.4
Rotavirus (LPBRV)	16	655.4	15	819.0
Rotavirus (RMRV)	17	655.9	16	819.5
N. meningitidis	18	708.1	21	1,414.7
E. coli (purified antigens)	19	722.3	22	1,443.3
Rotavirus (HPBRV)	20	852.7	17	947.4
Malaria (multivalent)	21	856.8	24	1,711.9
Malaria (monovalent)	22	967.3	25	1,933.3
RSV (attenuated live)	23	982.8	20	1,228.2
Hepatitis A (attenuated live)	24	1,058.0	18	1,113.7
Streptococcus pneumoniae	25	1,310.3	23	1,637.5
Parainfluenza	26	1,697.1	26	2,121.1
RSV (glycoprotein)	27	1,964.4	27	2,455.2
Hepatitis A (polypeptide)	28	4,029.0	28	4,240.9
Hepatitis B	29	8,859.3	29	8,948.7

- the immediate U.S. interest in diseases that may be imported into the United States, that threaten travelers or personnel stationed overseas, or that are existing problems in the United States
- the affordability of the potential health benefit, if not already used formally in the decision process

TABLE 9.9 Effect of Varying Probability of Success on the Health Benefits of S.pneumoniae Vaccine: Central Analysis

Probability of Success	Annualized Present Value of Potential Health Benefits (IME units)
1.0	1,704,929
0.9	1,534,236
0.8[a]	1,363,943
0.7	1,193,450
0.6	1,022,957
0.5	852,464
0.4	681,972
0.3	511,479
0.2	340,986
0.1	170,493
0.0	0

[a]Probability of success used in central analysis.

These factors are discussed in more detail in Chapter 8 and elsewhere in the report.

The analyses presented in this chapter indicate that of the 29 projects considered, vaccines for S. pneumoniae, Plasmodium spp. (malaria; both monovalent and multivalent circumsporozoite protein based versions), rotavirus (all three candidates), S. typhi (Ty21a), and shigella consistently rank in the top 10 positions in priority lists based on potential health benefits, under a wide range of assumptions and resource availability.

Vaccines for hepatitis B and H. influenzae type b rank in the top 10 in the central analysis but are dislodged under certain assumptions. Vaccines for E. coli (either candidate) or the alternative candidate for S. typhi (an aromatic amino acid requiring stain) move into the top

10 under certain assumptions: as willingness to pay drops to $1,000 or below per IME prevented, the ranking changes more significantly, as shown in Table 9.4, with vaccines for certain diarrheal diseases rising in the rankings.

A fairly consistent middle-tier of vaccines occurs in the ranking under a variety of assumptions. In addition to those candidates that will contend for higher ranking under certain assumptions, this middletier includes vaccines for Streptococcus group A, M. leprae, V. cholerae, respiratory syncytial virus, parainfluenza viruses, and rabies (Vero cell derived or glycoprotein).

Most of the vaccines that consistently rank low would prevent diseases that are often serious, but mostly restricted to relatively small regions of the developing world. In such areas they may have more benefit than the widespread diseases that rank higher when the developing world is considered as a whole.

Additional sensitivity analyses, discussed below, can be performed to identify elements that may alter decisions.

DISCUSSION

Scientific opinion differs on some of the judgments incorporated into the proposed method, and uncertainty surrounds some of the data. The system has been applied by using the best estimates and most reliable data the committee could obtain, given its resources. The attempt to be explicit about certain estimates should not be interpreted as indicating that precise, unanimous, or certain comparisons are possible with existing methods or data, when the lack of data makes expert judgment necessary. The implications of these information gaps and differences of opinion about estimates are discussed more fully in Chapter 1. In this light, the committee suggests additional analyses and research to provide further information on the key elements that may alter decisions.

Ideally, to fully assess the effect of alternative IME profiles on the rankings, calculations should be conducted using the whole range of individual sets of IME values. However, because of resource and time constraints, this was not possible in the present study. The perspective adopted to illustrate application of the system was the median set of values from responses of health professionals in developing countries. A median set of values derived from U.S. respondents differed somewhat from the perspective used (see Chapter 4, Tables 4.7 and 4.8).

It is also possible to develop hypothetical age-neutral perspectives as was done for the committee's first report (Institute of Medicine, 1985). The committee, however, does not endorse either set of median values or the age-neutral perspective for policy formulation. The effect of adopting various IME values is discussed in Chapter 4.

Selecting or constructing a small number of profiles that have distinct differences from the committee median or the age-neutral set would be a practicable way to further examine how various opinions on the undesirability of disease conditions might affect vaccine rankings. For example, IME profiles could be developed that show more or less

aversion to chronic or acute morbidity than the median set and a constructed age-neutral profile (i.e., for each morbidity category, calculate the geometric mean of median IME values across different age groups). The results of the ranking process with these profiles would then identify the extent to which differences of opinion regarding chronic or acute morbidity could alter rankings. (For a range of 14 important diseases in the United States, adopting a hypothetical age-neutral IME perspective, rather than the committee median that disfavored death and morbidity most in the 15–24 years age group, did not significantly alter the ultimate rankings [Institute of Medicine, 1985]).

Other sensitivity studies around the central analysis are also possible. These include the effect on the rankings of various predictions about the number of vaccine doses needed (which would affect expenditures on vaccines) or various predictions about individual vaccines (e.g., the probability of successful development of a vaccine).

The impact on rankings of using alternative assumptions for choosing the target population for some vaccines could also be tested, it would entail, however, more extensive recalculations, including reestimation of the disease proportion that is vaccine preventable.

RECOMMENDATIONS

The committee believes that a major strength of this analysis is that it encourages those using it to examine all judgments and assumptions about the selected vaccine preventable diseases. The committee recommends use of the proposed system by government decision makers. New candidates should be assessed as they become technically feasible and new data should be incorporated as they become available.

Data for disease comparisons are lacking in some areas and are of variable reliability in others. Further, data on the pathogen serotypes prevalent in particular regions may also be lacking.

Better data bases in these areas would facilitate making rational choices on vaccine development priorities and vaccine formulation. Therefore, NIAID and other national and international organizations should consider means to improve available epidemiological data on infectious diseases.

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Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume I. Diseases of Importance in the United States. Washington, D.C.: National Academy Press.

Appendix A

Selection of Vaccine Candidates for Accelerated Development

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. Diverse 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 kind 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 technically possible within 10 years. Candidates excluded from the analysis are described briefly in the supplement to this volume (see Appendix I), or in the committee's first report (Appendix B, Institute of Medicine, 1985).

The knowledge required to determine the feasibility 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 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 nonhuman 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 a reality in the future because of one unexpected development in the laboratory. Such developments are especially likely in the fields relevant to vaccine development because modern biotechnology has only begun to be explored.

ACCELERATED VACCINE DEVELOPMENT AND BASIC RESEARCH PRIORITIES

The criteria for selecting candidates for accelerated vaccine development do not address the general question of which vaccines are most needed in the developing world or its particular regions. For some diseases that impose major burdens, the knowledge base is insufficient to allow consideration of 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 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.

SELECTING CANDIDATES FOR ACCELERATED DEVELOPMENT

The committee believed that its major contribution to establishing priorities would be the clear explication of a logical method for this task and that it probably could never satisfy all potential critics with its choice of candidates for assessment. As noted in Chapter 3, if a candidate is omitted from the full assessment, no conclusions should be made regarding its position in the priority rankings relative to the assessed contenders. When the prospects for vaccine control of disease were reasonable, however, the committee tried to include in the full analysis those candidates generally recognized in the developing world and the United States as major disease problems.

The process involved a number of iterations of selection, review, and revision. At an international workshop in Washington, D.C., on August 1–3, 1984, a draft list of infectious diseases prevalent in the developing world was reviewed and revised. This list was the starting point for candidate selection and is shown in Table A.1.

About 40 diseases were chosen from Table A.1 by the workshop participants as major health problems in the developing world. These diseases are listed in Table A.2. Some diseases were included in this list as models because vaccine prospects had been carefully reviewed in the committee's prior assessment.

A working group at the workshop then assessed the state of knowledge on these diseases in three areas: disease mechanisms, protective mechanisms, and protective antigens. A simple scoring system was used (+/++/+++), and on the basis of scores, pathogen/disease entities were assigned to one of three categories: good prospects for the technical feasibility of vaccine development, promising prospects, or insufficient knowledge to evaluate prospects. Based on these judgments, candidates were either included in the full assessment, excluded from it, or subjected to further review by a committee subgroup which consulted with experts on relevant vaccine development efforts.

Appendixes D-1 through D-19 describe the prospects for immunizing against the candidate pathogens, and the supplement to this volume describes prospects and knowledge gaps for a range of diseases prevalent in the developing world and for which accelerated development efforts are not feasible or appropriate at this time.

For a number of the pathogens considered in the supplement, vaccine development prospects are such that their exclusion from consideration was a difficult decision. Because of rapid technologic advances in the vaccine development field, the state of knowledge and vaccine development prospects for these potential candidates should be regularly reviewed.

Table A.3 lists the pathogens for which the vaccine development prospects were reviewed in the committee's first report. For various reasons, these pathogens were not included as primary contenders in the assessment of vaccine priorities for important diseases in the United States, although some are now included in this analysis.

REFERENCE

Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume I. Diseases of Importance in the United States. Washington, D.C.: National Academy Press.

TABLE A.1 Important Diseases in Developing Countries

Amebiasis	Herpes simplex virus	Respiratory infections, acute bacterial
E. histolytica	Herpesvirus varicellae	B. pertussis
Ancylostomiasis (hookworm disease)	Japanese encephalitis	S. pneumoniae
N. americanus	Leishmaniasis, cutaneous	M. pneumoniae
A. duodenale	Old world, L. tropica	H. influenzae
A. ceylanicum	New world, L. brasiliensis and L. mexicana	L. pneumophilia
Ascariasis	Leishmaniasis, visceral	Rift Valley fever
A. lumbricoides	L. donovani	Rift Valley fever virus (group B togavirus)
Brucellosis	Leprosy	Rubella
B. abortus, biotypes 1–9	M. leprae	Rubella virus
B. canis	Malaria	Russian spring-summer encephalitis
B. melitensis, biotypes 1–3	P. vivax	Group B togavirus
B. suis, biotypes 1–4	P. malariae	Salmonellosis
Chlamydial infections (see also trachoma)	P. falciparum	S. typhimurium
Chlamydia	P. ovale	S. heidelberq
Cholera	Measles (rubeola)	S. newport
V. cholerae	Measles virus	S. infantis
Cryptosporidiosis	Meningitis, aseptic	S. enteritidis
Cryptosporida spp.	Enteroviruses (picornaviruses)	S. st. paul
Cytomegalovirus	Coxsackie virus group A, types 2, 3, 7, 9	Schistosomiasis
Dengue fever	Coxsackie virus group B, types 2–5	S. mansoni
Immunological types 1–4	Echovirus types 2, 5–7, 9–11, 14, 18, 30	S. haematobium
Group B togaviruses	Poliovirus	S. japonicum
Dengue hemorrhagic fever	Arboviruses	S. intercalatum
Diarrheas, viral	Mumps	Shigellosis
Norwalk agent	H. simplex and varicella viruses	S. dysenteriae, group A
Rotaviruses	Adenovirus	S. flexneri, group B
Diarrheas, bacterial	Meningitis, meningococcal	S. boydii, group C
Enteropathic E. coli	N. meningitidis	S. sonnei, group D
Enterotoxigenic E. coli	Mumps	Streptococcus group A
C. jejuni	Mumps virus, a myxovirus	Streptococcus group B
Salmonella (nontyphoid)	Onchocerciasis (skin disease and river blindness), O. volvulus	Syphilis
Shigella		T. pallidum

Diarrheas, parasitic	Paratyphoid fever	Tetanus
E. histolytica	S. paratyphi A (S. enteritidis serotype paratyphoid A)	C. tetani
G. lamblia	S. schottmuelleri (S. paratyphi B, S. enteritidis serotype paratyphoid B)	Trachoma
Diphtheria	S. paratyphi C (S. hirschfeldii, S. enteritidis serotype paratyphoid C)	C. trachomatis
C. diphtheriae	Plague	Trichuriasis
Dracunculiasis (Guinea worm disease)	Y. pestis (P. pestis)	T. trichiura (T. trichiurus)
Eastern equine encephalitis	Poliomyelitis	Trypanosomiasis, African
Epstein-Barr virus	Poliovirus types 1, 2, 3	T. gambiense
Filariasis	Q fever	T. rhodensiense
W. bancrofti	C. burneti (R. burneti)	Trypanosomiasis, South American
B. malayi	Rabies	T. cruzi
Giardiasis	Rabiesvirus, a rhabdovirus	Tuberculosis
G. lamblia	Relapsing fever	M. tuberculosis
Gonorrhea	B. recurrentis	Typhoid
N. gonorrhoeae	Respiratory infections, acute viral	S. typhi
Hantaan viruses and related agents	Parainfluenza types 1–4	Typhus
Hepatitis A	Respiratory syncytial virus	Rickettsia
Hepatitis B	Adenovirus, types 1–7, 14, 21	West Nile fever
Hepatitis non-A, non-B	Rhinoviruses	West Nile fever virus (group B togavirus)
	Coronaviruses	
	Types of coxsackie virus groups A and B	
	Echoviruses	

TABLE A.2 Potential Candidate Diseases for New or Improved Vaccine Development

Amebiasis	Leprosy
Ancylostomiasis (hookworm)	Malaria
Ascariasis	Measles
Brucellosis	Meningococcal meningitis
Chlamydial infections	Onchocerciasis
Cholera	Skin disease
Dengue fever	River blindness
Diarrheas	Pertussis
E. coli	Rabies
Norwalk agent	Respiratory infections
Salmonella (nontyphoid)	Parainfluenza
Shigella	Respiratory syncytial virus
Rotavirus	Adenovirus
Campylobacter	Streptococcus pneumoniae
Filariasis	Hemophilus influenzae
Giardiasis	Schistosomiasis
Gonorrhea	Streptococcus group A
Hantaan virus	Streptococcus group B
Hemophilus influenzae type B	Trichuriasis
invasive disease	Trypanosomiasis
Hepatitis A	African
Hepatitis B	South American
Influenza virus	Tuberculosis
Japanese encephalitis	Typhoid
Leishmaniasis	Yellow fever

TABLE A.3 Pathogens Not Included as Candidates but Discussed in the Committee's First Report (Appendix B)

Acquired immune deficiency syndrome agent	Human papilloma virus
Adenovirus (respiratory disease)	Kawasaki disease agent
Anaerobic bacteria	Legionella spp. (Legionnaire's disease)
Clostridium botulinum	Mycoplasma pneumoniae
Clostridium difficile	Rhinovirus
Clostridium perfringens	Rickettsia rickettsii (Rocky Mountain spotted fever)
Clostridium tetani	Salmonella spp. (nontyphoidal)
Chlamydia	Staphylococcus aureus
Epstein-Barr virus	Streptococcus mutans
Giardia lamblia	Treponema pallidum (syphilis)
Hospital acquired infections (gram-negative bacteria)	Treponema-like spirochete of Lyme disease
Nontypable Hemophilus influenzae	
Non-A, non-B hepatitis	
Histoplasma capsulatum	

Appendix B

The Burden of Disease Resulting from Acute Respiratory Illness

This appendix reports estimates of the burden of illness (particularly mortality) associated with three vaccine development candidates that cause acute respiratory illness (ARI) in children in developing countries. These pathogens are respiratory syncytial virus (RSV), the parainfluenza viruses, H. influenzae type b, and S. pneumoniae.

Table B.1 shows the population distribution in regions where developing countries predominate. Table B.2 shows the estimated mortality resulting from acute respiratory infections. Application of the rates in Table B.2 to the population data in Table B.1 yields the ARI mortality distribution shown in Table B.3.

The number of ARI deaths estimated by this method accounts for about 13.5 percent of the 10.4 million infant deaths (under 1 year of age) and 22 percent of the 4.4 million child deaths (1 to 4 years of age) estimated to occur in developing countries in 1984 (United Nations Children's Fund, 1983). Combined, they represent about 18 percent of all deaths in the under 5 years age group.

Bulla and Hitze (1978) reported that about 10 percent of all ARI deaths were attributable to influenza. Of the remainder, most were viral and bacterial pneumonias (80 percent), and the balance involved acute upper respiratory tract infections. Table B.4 shows the estimated total noninfluenza ARI mortality for children.

Little information from developing countries is available on the etiology of lower respiratory tract infections or their impact on mortality rates. Even less is available on serious or fatal upper respiratory tract infections. One of the difficulties in obtaining data on the etiology of lower respiratory tract infections is that ethical requirements dictate that lung aspiration (to identify pathogens) is performed only for medical indications (e.g., to aid in selection of appropriate treatment of patients with selected bacterial pneumonia). Accordingly, this procedure is not used routinely.

The committee gratefully acknowledges the advice and assistance of F.W.Denny, W.P.Glezen, and A.S.Monto. The committee assumes full responsibility for all judgments and assumptions.

TABLE B.1 Population Distribution in Regions Where Developing Countries Predominate (thousands)

	Age Group (years)					
Region	Under 1	1–4	Total Under 5	5–14	15–59	60 and Over
Africa	23,040	73,762	96,802	141,459	265,451	27,288
Asia	73,400	270,300	343,700	666,402	1,472,242	179,656
Latin America	12,736	44,499	57,235	100,220	214,415	25,130
Oceania	187	635	822	1,285	2,620	273
Total	109,363	389,196	498,559	909,366	1,954,728	232,347

TABLE B.2 Estimated Mortality in Developing Countries Due to Acute Respiratory Infections (deaths/100,000 population/yeara)

	Age Group (years)				
Region	Under 1	1–4	5–14	15–59[b]	60 and Over
Africa	1,500	500	20	—	150
Asia	1,200	200	20	—	150
Latin America	1,300	130	13	—	400
Oceania	200	10	1	—	100

[a]Modified from Bulla and Hitze (1978). Rates in some categories are based on a small number of reporting countries.
[b]Not calculated.

Pio et al. (1985) reviewed the results of bacteriological studies on lung aspirates from children (birth to 8 years of age) in developing countries who had pneumonia and no previous antimicrobial treatment. About 55 percent of these aspirates were culture positive for bacteria. Of these, 22.5 percent contained S. pneumoniae, and 11.5 percent contained H. influenzae. Staphylococcus aureus (4.4 percent), mixed infections, or other bacteria accounted for the balance of positive cultures. These proportions may be underestimates because the appropriate lung lesion may not have been reached with the aspiration needle or because laboratory methods may have been inadequate. Lung aspirate sampling may overestimate the significance of bacterial pathogens because of the kinds of patients selected for testing (see above). However, it is not possible to estimate how much these considerations affect the accuracy of available data.

TABLE B.3 Deaths due to Acute Respiratory Infections in Developing Countries (thousands)a

	Age Group (years)			
Region	Under 1	1–4	Total Under 5	5–14
Africa	345.6	368.810	714.41	28.3
Asia	880.8	540.6	1,421.4	133.3
Latin America	165.6	57.8	223.4	13.0
Oceania	0.374	0.064	0.44	0.0129
Total	1,392.4	967.3	2,359.7	174.6

[a]Derived by application of the rates shown in Table B.2 to the population estimates shown in Table B.1.

Few studies have been undertaken on viruses as a cause of lower respiratory tract infection or mortality in developing countries. Denny and Clyde (1983) reported on the isolation of viruses and mycoplasma from children with lower respiratory tract disease in the United States. No isolate was obtained in 74 percent of cases. Parainfluenza viruses were isolated in 9.4 percent of cases and RSV in 5.2 percent of cases. A variety of other viruses and Mycoplasma pneumoniae accounted for the balance of identified agents.

TABLE B.4 Annual Deaths from Acute Respiratory Infections Other than Influenza

		Age Group (years)	
Pathogen	Proportion of Deaths (percent)[a]	Under 5	5–14
H. influenzae	11.5	244,260	18,071
Parainfluenza viruses	5.5	116,820	8,643
Respiratory syncytial virus	7	148,680	11,000
S. pneumoniae	22.5	477,900	35,357
Total[b]		2,124,000	157,140

[a]These proportions are based on a very limited number of reports and assume that the distribution of deaths parallels the isolation of pathogens from individuals with lower respiratory tract infection.
[b]The total includes deaths caused by other pathogens for which vaccine prospects are considered poor, or for which an etiologic agent is not yet identified.

Berman et al. (1983) reported data on acute lower respiratory tract infections in children under 5 years of age attending ambulatory clinics in Colombia. A viral diagnosis was reported in 20 percent of cases: RSV was found in 9 percent and parainfluenza viruses in 2.1 percent. Serologic data reported by Monto and Johnson (1968) for three areas in Latin America suggest that the behavior and distribution of viral respiratory disease agents in the tropics are generally similar to those of the same agents in the temperate zones.

The data discussed above appear to be the best basis on which to estimate the disease burden proportion of noninfluenza ARI that can be attributed to the pathogens that are candidates for vaccine development. No direct information is available on the proportions of deaths due to the various pathogens incriminated in ARIs. To estimate deaths, it is therefore assumed that the proportion of deaths due to each agent parallels its isolation in lower respiratory tract illness/pneumonia cases. This assumed relationship is likely to be imprecise because certain agents, like respiratory syncytial virus, are more virulent than others, such as parainfluenza virus type 1.

The proportion of lower respiratory tract illness/pneumonia cases attributed to a particular pathogen sometimes differed between studies. In these instances, intermediate values have been used in the calculations if reported figures vary considerably. The resulting distribution of deaths due to noninfluenza ARI is assumed to be as follows: RSV, 7 percent; parainfluenza viruses, 5.5 percent; H. influenzae, 11.5 percent; and S. pneumoniae, 22.5 percent.

Table B.4 shows the results of combining the above assumptions with the estimates of annual noninfluenza ARI mortality.

To complete the disease burden estimates in the format required for the disease comparison method used in this report, it is necessary to estimate the number of disease episodes at various levels of severity. No specific information on the ratio of deaths to severe cases of ARI is available. However, the number of severe cases of parainfluenza and RSV disease can be calculated by presuming a case fatality rate of 10 percent for severe cases of these diseases. The relative distributions of less severe episodes are assumed to be the same as those estimated

TABLE B.5 Relative Case Frequenciesa

Category	H. influenzae	Parainfluenza Viruses	Respiratory Syncytial Virus	S. pneumoniae
Mild (A)		500	300	
Moderate (B)		100	100	
Severe (C)	7	10	10	7
Death (H)	1	1	1	1

[a]These ratios are assumed from limited data (see text).

TABLE B.6 Disease Burden Estimates by Morbidity Category, Disease, and Age Group (years)

	H. influenzae		Parainfluenza Viruses		Respiratory Syncytial Virus		S. pneumoniae	
Morbidity Category	Under 5	5–14	Under 5	5–14	Under 5	5–14	Under 5	5–14
A	—	—	58,410,000	4,321,500	44,604,000	3,300,000	—	—
B	—	—	11,682,000	864,300	14,868,000	1,100,000	—	—
C	1,709,820	126,497	1,168,200	86,430	1,486,800	110,000	3,345,300	247,500
H	244,260	18,071	116,820	8,643	148,680	11,000	477,900	35,357

TABLE B.7 Disease Burden: Hemophilus influenzae--Respiratory Component

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work								
C	Severe pain, severe short-term impairment, or hospitalization	1,709,820	7	126,497	7				
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	244,260	n.a.	18,071	n.a.		n.a.		n.a.

TABLE B.8 Disease Burden: Parainfluenza Viruses

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	58,410,000	3	4,321,500	3				
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	11,682,000	5	864,300	5				
C	Severe pain, severe short-term impairment, or hospitalization	1,168,200	7	86,430	7				
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	116,820	n.a.	8,643	n.a.		n.a.		n.a.

TABLE B.9 Disease Burden: Respiratory Syncytial Virus

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	44,604,000	3	3,300,000	3				
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	14,868,000	5	1,100,000	5				
C	Severe pain, severe short-term impairment, or hospitalization	1,486,800	7	110,000	7				
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	148,680	n.a.	11,000	n.a.		n.a.		n.a.

TABLE B.10 Disease Burden: S. Pneumoniae--Respiratory Component in Children

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work								
C	Severe pain, severe short-term impairment, or hospitalization	3,345,300		247,500					
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	477,900	n.a.	35,357	n.a.		n.a.		n.a.

for the diseases domestically (Institute of Medicine, 1985): for parainfluenza, 50 mild and 10 moderate episodes for each severe case, and for RSV, 30 mild and 10 moderate episodes for each severe case. In the absence of pathogen-specific data for developing countries, a case fatality rate (CFR) of 15 percent is assumed for H. influenzae and S. pneumoniae (based on CFRs for untreated and hospitalized ARIs; Pio et al., 1985). Hence, seven severe cases are presumed to occur for each death. All H. influenzae and S. pneumoniae episodes are assumed to be severe.

The relative case frequencies shown in Table B.5 are based on these assumptions. They were used to derive the disease burden distributions shown in Table B.6, and in Tables B.7, B.8, B.9, and B.10 for the individual pathogens.*

UNCERTAINTY IN THE DISEASE BURDEN ESTIMATES

Advisers to the committee expressed concerns about the limited knowledge from which the estimates described above are derived. Certain features of acute respiratory infections led the committee to conclude that the available data are probably not entirely reliable because of suspected bias.

For example, many children with pneumonia may not reach the hospital, and those who do may represent a skewed sample. How to adjust available data for suspected biases is not known; hence, the procedures described above represent the only practical approach to developing the disease burden estimates needed for the overall assessment.

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*The disease burdens for disease caused by H. influenzae type b and S. pneumonia have also been computed separately in Appendixes D-3 and D-17.

Appendix C

The Burden of Disease Resulting from Diarrhea

Various publications contain (or provide information for developing) estimates of the total burden of illness (deaths and episodes) that results from all diarrheal disease. Few publications, if any, however, provide the data necessary for estimating the global morbidity and mortality burdens that arise from specific pathogens. To arrive at such estimates in the form required for comparing diseases and vaccine benefits, the committee adopted the approach described below.

On the basis of published data and field experience, a group of persons familiar with diarrheal diseases in developing countries estimated the number of diarrheal episodes per individual in various age groups for the four major regions where developing countries predominate. These estimates are shown in Table C.1.

Applying these incidence rates to the relevant population estimates (Table C.2, from Chapter 4) yields, for the various regions, the estimated number of diarrheal episodes in the age groups shown in Table C.3.

The estimated distribution of diarrheal episodes by severity within age groups is shown in Table C.4.

Combining the estimates in Tables C.3 and C.4 yields the estimates of the burden of diarrheal disease distributed by age and severity shown in Table C.5.

An estimated 10.4 million infant deaths (under 1 year of age) and 4.4 million child deaths (1 to 4 years of age) occur annually in the developing world (United Nations Children's Fund, 1983). Of deaths in the 1 to 4 years age group, one-third probably occur in the second year of life. Hence, the total number of deaths in children under 2 years of age is probably about 11.9 million, and in the 2 to 4 years age group—2.9 million. Since about 25 percent of infant and child deaths in developing countries are due to diarrhea, this means there are 2.97 million diarrheal deaths in children under 2 years of age and 0.7 million in the 2 to 4 years age group (i.e., a total of about 3.7

The committee gratefully acknowledges the advice and assistance of R.E.Black, R.Glass, M.M.Levine, R.B.Sack, B.Stoll, and R.G. Wyatt. The committee assumes full responsibility for all judgments and assumptions.

million deaths). This total reasonably agrees with the estimated 3.5 million derived by the foregoing approach.

TABLE C.1 Annual Incidence of Diarrheal Diseasea (episodes per individual per year)

	Age Group (years)					
Region	Under 2[b]	2–4[b]	Under 5	5–14	15–59	60 and Over
Africa	7.0	3.0	5	1	0.3	0.3
Asia	5.25	1.5	3	0.5	0.2	0.2
Latin America	6.0	2.0	4	1	0.25	0.25
Oceania	3.5	1.0	2	0.5	0.2	0.2
More developed countries	1–2	0.5	0.5	0.1	0.1	0.1

[a]Modified from Programme for Control of Diarrhoeal Diseases (1984).
[b]Under 5 years episodes are estimated to be distributed 0.7:0.3 between under 2 years and 2 to 4 years age groups.

TABLE C.2 Estimated 1984 Population for Regions Where Developing Countries Predominatea (thousands)

	Age Group (years)				
Region	Under 5	5–14	15–59	60 and Over	Total
Africa	96,802	141,459	265,451	27,288	531,000
Asia	343,700	666,402	1,472,242	179,656	2,662,000
Latin America	57,235	100,220	214,415	25,130	397,000
Oceania	822	1,285	2,620	273	5,000
Total	498,559	909,366	1,954,728	232,347	3,595,000

[a]Derived by applying the proportions of the 1980 population in various age groups to the mid-1984 population projections. See Chapter 4, Table 4.4, for the countries included.

Tables C.6 and C.7 show the estimated distribution of the diarrheal disease burden by etiology. These estimates were derived from expert judgment after a review of available publications and from personal field experience. Only those etiologies for which vaccine prospects are reasonably promising were considered. Salmonella was subsequently dropped from consideration.

TABLE C.3 Estimated Annual Number of Diarrheal Episodes for Various Regions (thousands)

	Age Group (years)			
Region	Under 5	5–14	15–59	60 and Over
Africa	484,010	141,459	79,635	8,186
Asia	1,031,100	333,201	294,448	35,931
Latin America	228,940	100,220	53,604	6,283
Oceania	1,644	643	524	55
Total	1,745,694	575,523	428,211	50,455

TABLE C.4 Estimated Proportion of Diarrheal Episodes by Severity and Consequences, Assuming Current Levels of Interventiona

	Age Group (years)			
Category	Under 5	5–14	15–59	60 and Over
A (mild)	0.9	0.99	0.99	0.95
B (moderate)	0.08	0.008	0.008	0.04
C (severe)	0.02	0.002	0.002	0.01
H (death)	0.002	0.0004	0.0003	0.0005

[a]These values are estimated average proportions for all diarrheal etiologies. The number of episodes, which was ultimately derived by the methods presented here, reflects that for some pathogens severe cases are relatively more common than for all diarrheas aggregated (see Table C.9).

TABLE C.5 Morbidity Episodes and Mortality Arising from Diarrheal Disease

	Age Group (years)			
Category	Under 5	5–14	15–59	60 and Over
A (mild)	1,571,125	569,768	423,929	47,932
B (moderate)	139,656	4,604	3,426	2,018
C (severe)	34,914	1,151	856	505
H (death)	3,491	230	128	25

TABLE C.6 Distribution of Mild and Moderate Diarrheal Episodes by Etiology (percent)a

	Age Group (years)					
Pathogen	Under 2	2–4	Under 5	5–14	15–59	60 and Over
E. coli (enterotoxigenic)	25	20	22.5	25	20	20
Rotavirus	10	5	7	1	1	1
Salmonella	2	1	1	1	1	2
Shigella	5	10	8	10	10	15

[a]Percentages do not total 100 because some pathogens that cause diarrhea are not included due to poor vaccine prospects.

TABLE C.7 Distribution of Severe Diarrheal Episodes and Deaths by Etiology (percent)a

	Age Group (years)					
Pathogen	Under 2	2–4	Under 5	5–14	15–59	60 and Over
E. coli (enterotoxigenic)	20	20	20	20	20	20
Rotavirus	30	10	25	0	0	0
Salmonella	2	1	1	1	1	1
Shigella	10	20	15	20	20	25

[a]Percentages do not total 100 because some pathogens that cause diarrhea are not included due to poor vaccine prospects.

Combining estimates in Tables C.5, C.6, and C.7 yields (for enterotoxigenic E. coli, rotavirus, and shigella) distributions of illness burden shown in Tables C.8, C.9, and C.10, respectively. These estimates are used in the calculation of total disease burden values (see Chapter 4).

TABLE C.8 Disease Burden: Enterotoxigenic E. coli

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	353,503,000	4	142,442,000	4	84,786,000	4	9,586,000	4
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	31,423,000	5	1,151,000	5	685,000	5	404,000	5
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea	6,983,000	6	230,000	6	171,000	6	101,000	6
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		698,000	n.a.	46,000	n.a.	26,000	n.a.	5,000	n.a.

TABLE C.9 Disease Burden: Rotavirus

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	109,979,000	6	5,698,000	4	4,239,000	4	479,000	4
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	9,776,000	6	46,000	6	34,300	5	20,200	6
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea	8,729,000	7		7		7		7
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		873,000	n.a.		n.a.		n.a.		n.a.

TABLE C.10 Disease Burden: Shigella

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	125,690,000	5	56,977,000	5	42,393,000	5	7,190,000	5
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	11,172,000	7	460,000	7	342,000	7	303,000	7
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea	5,237,000	11	230,000	10	171,000	10	126,000	10
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		52,370	n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		576,000	n.a.	46,000	n.a.	26,000	n.a.	6,000	n.a.

MODIFICATION OF DISEASE BURDENS BY APPLICATION OF CURRENTLY AVAILABLE REMEDIES

The burdens of illness shown in Tables C.8, C.9, and C.10 are those thought to occur with the present level of intervention. The committee examined how these burdens might be altered by increased application of currently available therapeutic intervention. Among the interventions considered to be of potential major impact were general access to health care and, particularly, the use of oral rehydration therapy (ORT). The committee felt that by the time vaccines became available, the burden of diarrheal illness from enterotoxigenic E. coli and rotavirus might be reduced by increased use of ORT.

To assess the effect of therapeutic intervention on the vaccine candidate priority rankings, the committee calculated the potential health benefits of vaccines for enterotoxigenic E. coli. and rotavirus under two assumptions. The first assumption did not change the current level of intervention. The second one increased ORT (and general access to health care) and resulted in a reduction of deaths from these diseases by 50 percent of current levels. The disease burdens assuming increased ORT use are shown in Tables C.11 (enterotoxigenic E. coli) and C.12 (rotavirus).

For shigellosis, the committee believed that ORT would not have major influence on the disease consequences but that increased use of antibiotics could potentially reduce the mortality resulting from this disease. Realizing this benefit may be impeded by the increasing prevalence of antibiotic-resistant strains of shigella; the consequent need for accurate diagnosis/resistance testing, which may not be available; and in some cases, the need for more expensive antibiotics, which may not be affordable to developing countries. If desired, the effect of wider antibiotic use on the shigellosis disease burden and the ultimate rankings of vaccine benefits can be tested in a manner similar to that used for E. coli and rotavirus.

SECOND-ORDER EFFECTS OF DISEASES

The committee and subgroups had much discussion on the interaction of diseases causing mortality, and whether or how to quantitatively incorporate these interactions into the calculation of potential vaccine benefits. A notable example is the enhanced mortality among children with diarrhea and measles.

Few attempts have been made to evaluate quantitatively this type of interaction (e.g., Feachem and Koblinsky, 1983). The committee developed a questionnaire to evaluate possible second-order effects of reducing diseases, including the “replacement” of one cause of mortality by another.

For diarrheal diseases, the committee judged that the available data, in general, were not precise and could not suggest the possible effects of disease interactions on a vaccine's potential health benefit. The capacity of all diarrheal disease to debilitate patients and enhance

TABLE C.11 Disease Burden: Enterotoxigenic *E. coli*, Assuming Increased Use of Oral Rehydration Therapy

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	353,503,000	4	142,442,000	4	84,786,000	4	9,586,000	4
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	31,423,000	5	1,151,000	5	685,000	5	404,000	5
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea	6,983,000	6	230,000	6	171,000	6	101,000	6
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		349,000	n.a.	23,000	n.a.	13,000	n.a.	2,500	n.a.

TABLE C.12 Disease Burden: Rotavirus, Assuming Increased Use of Oral Rehydration Therapy

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	109,979,000	6	5,698,000	4	4,239,000	4	479,000	4
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	9,776,000	5.5	46,000	5.5	34,300	5	20,200	5.5
C	Severe pain, severe short term impairment, or hospitalization	Severe diarrhea	8,729,000	7		7		7		7
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		436,500	n.a.		n.a.		n.a.		n.a.

their susceptibility to other diseases should be weighed in the final choice of priorities.

UNCERTAINTY IN THE DISEASE BURDEN ESTIMATES

The estimated number of diarrheal episodes caused by specific pathogens (attempted above) is based largely on expert judgments, and committee advisers had different opinions on certain estimates. For example, some individuals disagreed with the majority opinion on the numbers of diarrheal episodes per individual in Asia and Latin America, under 5 years, believing that these numbers should be reversed. Such estimate modifications and their effect on the ultimate ranking can be evaluated. Preliminary calculations of the example cited above suggest an increase in disease burdens of less than 20 percent. The effects on vaccine benefits would be proportional, and the effects on the rankings easily calculated.

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Appendix D-1

The Prospects for Immunizing Against Dengue Virus

DISEASE DESCRIPTION

Dengue viruses cause two clinically important syndromes: classical dengue fever and dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS).

Dengue fever is an age-dependent syndrome, usually most severe in adolescents and adults. It is an acute, relatively short febrile disease (the mean duration is 5 days) characterized by headache, myalgias, lack of appetite, gastrointestinal disturbance, severe prostration, and a rash (Halstead, 1981a). The severe prostration extends into the convalescent phase and is not proportional to the shortness of the illness. Because of this debilitation and its potential effect on combat readiness, dengue is always high on lists of diseases of military importance.

Dengue hemorrhagic fever/dengue shock syndrome is also age-dependent; it primarily affects children. This acute vascular permeability produces one of the most dramatic syndromes seen in human medicine. Previously healthy children may turn pale and cyanotic, collapse, sometimes pass blood from the mouth or rectum, and expire after a short, stormy course of 6 to 24 hours. Shock is evident first and then hemorrhage, which may not be apparent or occur before death. Reported fatality rates have ranged from as low as 1 percent to a high of 20 to 50 percent (Halstead, 1981a). The disease begins with a febrile phase, often with innocuous upper respiratory symptoms. With the return of a normal temperature, the vascular permeability phase begins. There also appears to be other severe expressions of dengue virus infection such as a syndrome in which severe hemorrhage appears without increased vascular permeability (Halstead, personal communication, 1985).

The committee gratefully acknowledges the efforts of S.B.Halstead, who prepared major portions of this appendix, and the advice and assistance of T.Bektimirov. The committee assumes full responsibility for all judgments and assumptions.

Limitations of Existing Vaccines

Numerous dengue vaccines have been produced and tested in small numbers of human beings, but vaccines have not yet been made for all four dengue virus types. Early live attenuated vaccines against dengue were made in suckling mouse brain (Hotta, 1957; Sabin and Schlesinger, 1945; Schlesinger et al., 1956; Wisseman et al., 1963), a substrate no longer considered acceptable for human use. Recently, dengue 1, 2, and 4 attenuated viruses, grown in tissue cultures and produced under U.S. Army sponsorship, have been tested in humans. None have all of the attributes thought to be necessary for an acceptable vaccine, and large-scale production is not contemplated. Attenuated dengue 1, 2, 3, and 4 virus strains have been selected at the dengue laboratory, Ramathibodi Hospital, Bangkok. To date, dengue 2 has been tested in 10 human volunteers; the results apparently were successful. All volunteers responded and none developed dengue-like symptoms (Halstead, personal communication, 1985).

PATHOGEN DESCRIPTION

Dengue viruses are togaviruses of the genus flavivirus and are transmitted by the mosquito vector Aedes aegypti. They are enveloped, single-stranded RNA viruses. There are four distinct antigenic types, dengue types 1, 2, 3, and 4, and several antigenic and biologic subtypes. All dengue serotypes produce the dengue fever syndrome; dengue 2 and possibly dengue 3 and 4 have been implicated as the proximal causes of DHF/DSS (Halstead, 1981b).

HOST IMMUNE RESPONSE

Infection with a dengue serotype results in life-long immunity to that type. From a single infection, short-lived cross protection against disease produced by a different virus type may persist for 6 to 12 weeks. DHF/DSS may be regarded as a complication of the immune response; certain individuals who experience an initial dengue infection are at risk of developing severe disease following infection with a different virus serotype (Halstead, 1981b). This phenomenon has been documented prospectively; dengue types 1, 3, or 4 infections followed by dengue type 2 produces DSS.

The underlying mechanism in DHF/DSS is thought to be as follows. Dengue virus appears to replicate in mononuclear phagocytes. Antibody to one dengue serotype reacts with a second serotype producing immune complexes that attach to and infect mononuclear phagocytes, a phenomenon known as antibody-dependent infection enhancement (Halstead, 1980a). This infection causes the cells to release proteolytic enzymes, thromboplastin, and vascular permeability factors, which in turn lead to hemorrhage and vascular collapse (Halstead, 1983).

DISTRIBUTION OF DISEASE

Geographic Distribution

The geographic distribution of dengue infection and disease has increased steadily since World War II, and the virus may be more widely circulating now than at any time in history. Certainly more people are infected annually than at any previous time (Halstead, 1980b). The virus is endemic or enzootic in the warm areas of virtually all tropical countries. The vector, Aedes aegypti, does not thrive at altitudes above 1,000 meters; hence, dengue is a lowland or coastal disease. The virus has the potential to spread to temperate zones during summer months, as in the recent dengue epidemics in Queensland, Australia. Much of the southern United States is receptive to dengue transmission.

DHF/DSS is endemic in all tropical Southeast Asian countries. A single large outbreak (116,000 hospitalizations) occurred in Cuba in 1981.

Disease Burden Estimates

An estimated 1.5 billion persons live in countries with dengue activity (Halstead, 1980b). In dengue endemic areas of tropical Asia, virtually all adults have flavivirus hemagglutination inhibition (HI) antibody, presumably dengue in origin. Therefore, a conservative estimate is that in endemic areas, dengue viruses infect 10 percent of the susceptible population per year. Infections at this rate effectively mean that most adults are immune. If it is estimated that 40 percent of tropical populations are children 15 years and younger (600 million children), then there are about 60 million dengue infections per year. These figures ignore the circulation of multiple types, which will cause an upward revision of the estimate.

As shown in Table D-1.1, cases are assumed to occur only in the three younger age groups, with 90 percent in the two youngest groups. All cases fall into acute morbidity categories A, B, and C. Illness usually results in a visit to the physician, drug prescription for symptomatic relief, and treatment at home. Hence, cases of dengue fever are assigned to categories A and B. For all cases in category A, there is likely to be an equal number of asymptomatic infections (22.5 million). In tropical Southeast Asia, DHF/DSS has produced 1.3 million hospitalizations and 23,000 deaths in a 30-year period. DHF/DSS incidence is increasing, with a mean annual incidence for the past 5 years of about 60,000 hospitalizations and 1,500 deaths (Halstead, personal communication, 1985).

PROBABLE VACCINE TARGET POPULATION

The potential target population for a safe and effective dengue vaccine includes (1) infants and children in DHF/DSS endemic areas and (2) infants and children (and initially adults) in countries with

TABLE D-1.1 Disease Burden: Dengue Fever

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Dengue fever	7,500,000	4	14,500,000	4	500,000	4		
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Dengue fever	4,000,000	5	7,000,000	5	4,000,000	5		
C	Severe pain, severe short-term impairment, or hospitalization	Dengue hemorrhagic fever	20,000	6	40,000	6				
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		5,000	n.a.	9,900	n.a.	100	n.a.		n.a.

periodic epidemics of dengue fever. Tourists and military personnel visiting dengue endemic areas would also probably receive the vaccine, but their numbers are small compared to the major populations at risk.

Of the estimated 1.5 billion people living in areas endemic for dengue fever and areas that have recently had epidemics, about 38 percent, or 570 million, are under the age of 15 and would require vaccination in the initial years. Assuming a crude birth rate of 32 per 1,000 population, 48 million infants would need vaccination in all subsequent years.

There appears to be no insurmountable problem associated with incorporating dengue vaccine into the World Health Organization Expanded Program on Immunization (WHO-EPI) in appropriate areas.

Vaccine Preventable Illness*

Some cases of DHF occur in children under 1 year of age, most often between 6 and 12 months. For calculations it is assumed, though it is not yet certain, that it will be possible to vaccinate successfully children 6 months of age or younger.

The major risk of disease occurs after infancy even in endemic areas. Hence, in DHF/DSS endemic areas, 100 percent of the disease burden could be prevented by a vaccine that was 100 percent effective and that could be successfully administered to the entire target population at an early age. Herd immunity has not been studied in dengue infections, but it is possible that the disease burden could be eliminated even if vaccine coverage were not complete.

SUITABILITY FOR VACCINE CONTROL

Disease-induced serotype-specific immunity and the age distribution of disease suggest that vaccine prevention is feasible.

Alternative Control Measures and Treatments

Aedes aegypti control, even eradication, is technically feasible. However, given current financial and organizational constraints, successful mosquito control is not politically feasible.

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

PROSPECTS FOR VACCINE DEVELOPMENT

The challenge in developing a dengue vaccine is that it must protect against DHF/DSS while not making the population susceptible to DHF/DSS. Such a task poses a most difficult problem to workers in the vaccine development field.

Hotta (1957), Sabin and Schlesinger (1945), Schlesinger et al. (1956), and Wisseman et al. (1963) demonstrated the ease and reproducibility of selecting an attenuated live dengue virus vaccine by serial passage in the brains of suckling mice.

More recently, dengue attenuation strategies have used clonal selection of viruses grown in tissue culture to pick variants from wild virus populations. These variants (dengue 1, 2, and 4) demonstrated temperature sensitivity, reduced suckling mouse neurovirulence, reduced rhesus monkey viremia, and somewhat lower antibody responses in infected monkeys, attributes thought to indicate attenuation for humans (Bancroft et al., 1984; Eckels et al., 1984; Halstead et al., 1984a,b,c,d). When tested in humans, however, the variants either were overattenuated, yielding unacceptably low seroconversion rate in susceptibles (dengue 2 and 4), or were underattenuated, producing symptoms in human volunteers (dengue 1 and 4). A dengue 2 vaccine serially passaged 50 times in primary dog kidney cells has been shown to be acceptably immunogenic and nonreactogenic in 10 adult volunteers tested in Thailand (Halstead, personal communication, 1985). However, it shares with all other vaccine strains limited growth potential in suitable mammalian cells, and thus the maximum titer of the vaccine probably will be about 10^5.

Any dengue vaccine program must have as major components ongoing epidemiological studies of risk factors, surveillance for DHF/DSS cases among vaccinees, and fundamental immunological studies designed to elucidate the mechanisms of DHF/DSS. A coherent understanding of risk factors is essential for the successful development, testing, and use of dengue vaccines. Current knowledge indicates that use of nonpersisting antigens would be extremely dangerous in situations in which dengue viruses continue to circulate in human populations. The existence of a jungle dengue cycle clearly means that the disappearance of one or more dengue viruses from circulation would be transient. As long as an efficient urban vector is established, dengue transmission must be expected at any time.

Unless virological risk factors for dengue shock syndrome can be authoritatively determined for residents of all countries in DHF/DSS endemic areas, a tetravalent vaccine appears to be the best option available. Recent studies from Thailand, however, suggest that only secondary dengue 2 infections in children result in DSS, allowing for the possibility of a monovalent dengue 2 vaccine to protect against severe disease and death (Sangkawibha et al., 1984). Studies in monkeys show that neutralizing antibodies can be developed to all four components of a tetravalent vaccine (Halstead and Palumbo, 1973). The success of the combined measles, mumps, and rubella vaccines demonstrates that multiple live viruses can be inoculated in man without interference.

Strategies for genetic manipulation of RNA viruses comparable to the insertion of DNA segments in vaccinia viruses are only now being developed. Conceivably, cDNA segments could be inserted into DNA vectors, allowing for production of the antigenic proteins or peptides required to induce immunity to all four dengue serotypes. Genetic mapping of the dengue virus genome is under way (National Institute of Allergy and Infectious Diseases, 1985).

Other strategies for developing second generation vaccines include (1) engineering dengue vaccines by substituting immunoprotective epitopes into the 17D yellow fever virus and using this virus as a possible vector; (2) experimentation with other vectors, such as bacteria or other viruses; and (3) definition of epitopes that induce the formation of protective rather than enhancing antibodies in a manner similar to that demonstrated for yellow fever (Schlesinger et al., 1985).

Among the various vaccine approaches discussed above, the committe chose to evaluate an attenuated live vector virus containing the gene for a broadly cross reacting protective antigen. Such an antigen has yet to be identified; if one does not exist, or its use proves impracticable, then a vector containing a gene for a protective antigen from each of the four dengue virus types will be the preferred approach. Predictions for vaccine development are similar for either strategy.

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Appendix D-2

The Prospects for Immunizing Against Escherichia coli

DISEASE DESCRIPTION

Escherichia coli strains that produce enterotoxins are important causes of diarrhea in developing countries. The illness resulting from infection with these organisms ranges from mild diarrhea to a dehydrating diarrheal illness. It is usually characterized by watery, nonbloody diarrhea lasting up to 7 days. Dehydration may result if stool losses are not replaced, and in severe cases the clinical features are similar to those of cholera (Dupont, 1982).

PATHOGEN DESCRIPTION

Information on the pathogenesis of E. coli diarrhea pertinent to vaccine development has recently been exhaustively reviewed by Levine et al. (1983). The information presented below summarizes that review.

Escherichia coli are gram-negative bacilli that are found in the normal intestinal flora of humans and many animals; but certain strains can cause enteric illness. Researchers first recognized that some E. coli produce enterotoxins in the late 1960s. Enterotoxigenic E. coli are now known to produce two plasmid-mediated enterotoxins: one is heat-labile (LT) and the other is heat-stable (ST).

Heat-labile toxin is a high molecular weight protein that resembles cholera toxin in structure, function, and mechanism of action. It is composed of one enzymatically active A subunit joined to five binding B subunits. The receptors for the B subunits found on enterocytes include GM1 ganglioside and a recently described glycoprotein. After binding to the enterocyte, the A subunit gains entrance to the cell and activates adenylate cyclase, leading to an accumulation of cyclic AMP. This in turn causes secretion by the crypt cells and decreased absorp

The committee gratefully acknowledges the efforts of R.E.Black, who prepared major portions of this appendix, and the advice and assistance of C.C.J.Carpenter. The committee assumes full responsibility for all judgments and assumptions.

tion by villus tip cells, resulting in loss of electrolyte-rich fluid, which appears clinically as watery diarrhea.

E. coli heat-stable toxin is a small polypeptide that activates guanylate cyclase activity, leading to an accumulation of cyclic GMP. This alters the enterocyte membrane function, resulting in net secretion and diarrhea.

Enterotoxigenic E. coli have accessory virulence properties in addition to LT or ST that are important factors in their ability to cause disease. The best-characterized accessory virulence properties are colonization factors that allow the E. coli to adhere to specific receptors on enterocytes of the proximal small intestinal mucosa. These colonization factors have been identified as fimbriae found on the surface of bacteria. There are at least three distinct types of adhesion fimbriae detected in enterotoxigenic E. coli of human origin, including colonization factor antigen (CFA) I, CFA II, and E8775 fimbriae. Several other fimbriae that may serve as colonization factors of E. coli also have been described.

HOST IMMUNE RESPONSE

Persons with illness caused by enterotoxigenic E. coli develop both serum and intestinal secretory IgA (SIgA) antibody responses to the homologous O antigen. The serum antibody against the O antigen is predominantly in the IgM class and peaks approximately 10 days after the onset of illness. In addition, persons who have diarrhea due to LT-producing strains of E. coli manifest significant rises in serum antitoxin. Increases in the level of secretory IgA antitoxin in intestinal fluid also have been detected after infection with LT-producing E. coli. Persons infected and ill with E. coli that produce only ST do not appear to develop neutralizing or binding antitoxin to ST. After infection with strains producing colonization factor antigens, rises in serum IgG and intestinal secretory IgA antibodies have been demonstrated (Levine et al., 1983).

DISTRIBUTION OF DISEASE

Geographic Distribution of Disease

Enterotoxigenic E. coli have been shown to cause diarrhea worldwide, but seem to be far more common as a cause of diarrhea in developing countries (Dupont, 1982).

Disease Burden Estimates

The disease burden estimates for enterotoxigenic E. coli assuming the current level of intervention are shown in Table D-2.1. Table D-2.2 shows the disease burden estimates based on a scenario in which oral rehydration therapy prevents 50 percent of enterotoxigenic E. coli

TABLE D-2.1 Disease Burden: Enterotoxigenic E. coli

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	353,503,000	4	142,442,000	4	84,786,000	4	9,586,000	4
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	31,423,000	5	1,151,000	5	685,000	5	404,000	5
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea	6,983,000	6	230,000	6	171,000	6	101,000	6
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		698,000	n.a.	46,000	n.a.	26,000	n.a.	5,000	n.a.

TABLE D-2.2 Disease Burden: Enterotoxigenic *E. coli*, Assuming Increased Use of Oral Rehydration Therapy

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	353,503,000	4	142,442,000	4	84,786,000	4	9,586,000	4
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	31,423,000	5	1,151,000	5	685,000	5	404,000	5
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea	6,983,000	6	230,000	6	171,000	6	101,000	6
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		349,000	n.a.	23,000	n.a.	13,000	n.a.	2,500	n.a.

deaths. The derivation of both sets of estimates are discussed in Appendix C.

PROBABLE VACCINE TARGET POPULATION

In developing countries, the incidence of disease associated with enterotoxigenic E. coli appears to be highest in children during the first 2 years of life, when one or even two episodes per year per child have been noted. The incidence remains high for the first 5 years of life and moderately high for children 5 to 9 years old (Black, personal communication, 1984). Although older children and adults also suffer from E. coli diarrhea, partial immunity does appear to develop after childhood. Thus, the probable vaccine target population would be children within the first 6 months of life. The vaccine could be incorporated into the World Health Organization Expanded Program on Immunization (WHO-EPI) with delivery at the earliest current age of vaccine administration.

Travelers to developing countries, primarily adults, constitute a second potential vaccine target group.

Vaccine Preventable Illness*

Two considerations influence the estimation of vaccine preventable illness for vaccines against enterotoxigenic E. coli. First, knowledge is incomplete regarding which components should be included in a vaccine to cover all, or a high proportion of, possible natural challenges. Known adhesion determinants (which are relatively few in number) are encountered in about 65 to 75 percent of LT^+/ST^+ strains (which cause most of the severe disease). The percentage is lower (up to 25 percent) in strains that produce only LT or ST, but these strains probably cause most of the cases (Levine et al., 1983). Thus, it is difficult to estimate the coverage of strains that a vaccine could currently achieve. Work is currently under way to identify the adhesion determinants or other colonization factors present on strains lacking CFA I and CFA II or other known determinants. Thus, in a few years it may be possible to better identify the determinants that should be included in the vaccine. For the calculations, it is assumed that by the time of licensure a vaccine could probably be formulated with a reasonable number of purified components (CFA I and CFA II, adhesion factors, and possibly other components, e.g., toxoids) that would cover about 70 percent of strains. (It is recognized that this assumption is more optimistic than some researchers believe.)

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

Second, a small amount of disease occurs at an early age, before completed immunization schedules can confer full protection. Taking into account these two factors, the proportion of illness that is vaccine preventable with a subunit vaccine is estimated to be about 60 percent.

In the case of a genetically attenuated strain, engineering a strain to carry a sufficient number of antigens to cover all strains might be difficult, so a somewhat lower proportion of the total disease burden is assumed to be potentially vaccine preventable (i.e., about 50 percent).

Efficacy (as predicted in Chapter 5, Table 5.1) in both cases is estimated against challenge by strains in the vaccine. In both cases the vaccine is assured to confer long-lasting immunity.

SUITABILITY FOR VACCINE CONTROL

Diarrhea due to enterotoxigenic E. coli would be suitable for vaccine control if relatively long-lasting protection could be elicited at an early age to carry children throughout the early childhood period when they are at greatest risk of dehydration and death. The prevalence of this and other diarrheal diseases in areas of developing countries where medical care services are rarely available suggests that a prevention approach is desirable.

Alternative Control Measures and Treatments

Death from acute diarrhea most often results from dehydration caused by unreplaced losses of body water and electrolytes. The treatment of diarrhea due to enterotoxigenic E. coli depends primarily on replacement of these deficits. The increased use of oral rehydration therapy (ORT) could have a considerable impact on the disease burden, especially deaths. However, the application of ORT depends on the availability of oral rehydration salt preparations and community education programs explaining how to use them. A scenario assuming increased ORT application is included in the calculations described in Chapter 7, based on the estimates in Table D-2.2 and discussed in Appendix C.

Adjunctive therapy with antibiotics also may reduce the duration and volume of diarrhea. Co-trimoxazole is the only drug that has been evaluated, and it has been studied mainly in adults with experimentally induced diarrhea or with travelers' diarrhea.

Transmission of enterotoxigenic E. coli is thought to be primarily by water and food. Presumably, the disease could be prevented by avoidance of fecally contaminated water and attention to hygienic food handling techniques. The provision of clean water and improved sanitation in developing countries is desirable on many grounds but is unlikely to be a rapid solution to diarrhea prevention.

In addition, for travelers, prophylactic antibiotics have been utilized and appear to prevent enterotoxigenic E. coli diarrhea. However, because of the risks involved in taking antibiotics, chemo

prophylaxis is currently recommended only for persons who cannot obtain safe food and water and who would be endangered or greatly inconvenienced if they were to get diarrhea while traveling. This particularly includes persons with serious underlying medical conditions, in whom diarrhea could present a difficult management problem.

PROSPECTS FOR VACCINE DEVELOPMENT

Current work in vaccine development against enterotoxigenic E. coli. diarrhea involves vaccines that stimulate antitoxic (antitoxin) or anti-adhesion immunity or both by means of killed antigens or attenuated strains. Recent developments have been reviewed by Levine et al. (1983). The most effective vaccines may contain antigens that stimulate both antitoxic and antibacterial immunity, producing a synergistic protective effect. It is believed that the critical site of immunity is the mucosal surface of the upper intestinal tract and that this site is protected mainly by secretory IgA antibody.

Enterotoxigenic E. coli also cause serious diarrhea and death in animals. Extensive veterinary research has focused on the development of vaccines against the organisms that produce these problems. In the veterinary studies, purified fimbrial vaccines protected newborn piglets and calves, which were suckled on immunized mothers, against death from diarrhea caused by challenge with enterotoxigenic E. coli bearing the homologous fimbriae. In addition, CFA I and CFA II fimbrial vaccines administered orally or enterally stimulated intestinal SIgA antibody to CFA and resulted in protective immunity in animal models. Studies in humans with purified CFA vaccines are beginning. If a prototype CFA vaccine is found to protect against E. coli with the homologous fimbriae, intensive research will be pursued to identify other colonization factors. Only a small number of pathogenic enterotoxigenic E. coli possess currently recognized colonization factors; other factors must be identified to ensure broad-spectrum protection by a polyvalent fimbrial vaccine.

Another approach to the development of a vaccine against enterotoxigenic E. coli involves the use of toxoids. Animal studies have shown that immunization with either B subunit or LT holotoxin elicits an immune response and a protective effect, and that holotoxin is the superior immunogen. The technology for large-scale production of B subunit has not yet been described, but the successful cloning of LT genes from a human pathogen into a high-copy plasmid vector indicates that it is possible.

Heat treatment of cholera enterotoxin results in a high molecular weight toxoid called procholeragenoid, which is comparable in immunogenicity to the parent toxin. This has been used to immunize pregnant sows. Piglets born to and suckled on the immunized sows were protected against diarrhea and death due to infection with enterotoxigenic E. coli, suggesting that procholeragenoid might serve as an oral vaccine to enhance protection against enterotoxigenic E. coli, as well as Vibrio cholerae.

Because a large portion of the enterotoxigenic E. coli that cause disease produce only ST, attempts have been made to immunize against this toxin, despite its poor immunogenicity. Encouraging results were obtained by conjugating ST to porcine IgG. Subsequently, a bivalent toxoid was prepared by cross-linking ST to LT. Testing of a bivalent toxoid consisting of a laboratory-synthesized ST conjugated to the B subunit also has begun. Both of these bivalent toxoids have demonstrated immunogenicity and protective effects in animal models.

Another approach toward prevention of enterotoxigenic E. coli diarrhea involves the use of attenuated strains of E. coli bearing critical antigens. These strains should be capable of colonizing the small intestine and stimulating an immune response, without causing adverse reactions. One live strain, a CFA II-positive, LT- and ST-negative variant of a previously enterotoxigenic strain, has been evaluated in humans. When given to volunteers, all excreted the strain, most had positive cultures of jejunal fluid, and most had serological responses. About 10 percent of the volunteers developed mild diarrhea, however, presumably as a consequence of colonization of the proximal small intestine.

With the advent of recombinant DNA technology, it is possible to construct an E. coli vaccine strain engineered to produce large quantities of multiple colonization factor antigens, B subunit, and perhaps an ST toxoid. Further work will be necessary to understand, and if possible eliminate, the mild diarrhea resulting from CFA-positive strains of E. coli.

A potential problem with all of the proposed vaccines is that there is no assurance they will provide long-term (up to 5 years) protection. This is an important goal, especially for vaccine use in developing countries.

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Appendix D-3

The Prospects for Immunizing Against Hemophilus influenzae Type b

DISEASE DESCRIPTION

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 occurrence and characteristics of meningitis caused by H. influenzae type b in developing countries have been described by Cadoz and coworkers (1981, 1983). Other invasive forms of the disease include epiglottitis, pneumonia, bacteremia, and cellulitis. Very little literature exists on nonmeningitic illnesses caused by H. influenzae type b in the developing world. Much of the following discussion is based on information from the United States and presumes that the disease process is similar throughout the world.

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 noncapsulated strains have been associated with some infections, such as otitis media. 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.

The committee gratefully acknowledges the efforts of C.Frasch, who prepared major portions of this appendix, and the advice and assistance of C.V.Broome, S.L.Cochi, L.K.Gordon, D.M.Granoff, J.M.Griffiss, A.L.Reingold, J.B.Robbins, and J.I.Ward. The committee assumes full responsibility for all judgments and assumptions.

A polysaccharide-based vaccine for H. influenzae type b was licensed in the United States in April 1985. An improved vaccine is desirable for the reasons discussed in the last section of this appendix.

PATHOGEN DESCRIPTION

Noncapsulated 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.

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)-β-D-ribose-(1 → 1)-ribitol-5-phosphate.

HOST IMMUNE RESPONSE

Protection against invasive H. influenzae disease is due primarily to humoral immunity (Solotorovsky 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 2 and 3 months of age, bactericidal antibodies generally are not detectable for about 3 years. They then rise slowly, reaching adult levels by about age 8. 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 5 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 toward a vaccine that would be effective in younger children because of the distribution of the disease described below.

DISTRIBUTION OF DISEASE

Geographic Distribution

H. influenzae type b disease occurs worldwide. The pattern of disease in developing countries is similar to that in the United States with two exceptions. The first is that the disease occurs at a younger age: 40 to 50 percent of cases occur between 6 and 9 months of age. The second is that the mortality rate for H. influenzae type b meningitis can reach 40 percent even with treatment, in contrast to 5 percent for treated cases in the United States (Cadoz et al., 1983; Cochi, personal communication, 1983; Griffiss, personal communication, 1985; Hill, 1983; Norden, 1982). Also, about 30 to 40 percent of survivors exhibit neurological sequelae (Cadoz et al., 1983; Griffiss, personal communication, 1985).

Disease Burden Estimates

Very few studies are available on which to base estimates of the burden of disease from H. influenzae type b in developing countries. The most comprehensive reports appear to be those of Cadoz et al. (1981, 1983). These, however, are for a single location, Dakar, Senegal, and reflect a population with access to hospital care. The authors reported that H. influenzae meningitis was most frequent between 6 months and 2 years of age, rarely occurring before 2 months or after 5 years. Ninety-seven percent of cases were caused by type b. The incidence for infants and children under 5 years was 60 cases per 100,000 (Cadoz et al., 1983). This rate is slightly higher than that observed for typical U.S. populations, but lower than that reported for Navajo Indian and Alaskan Eskimo populations (Norden, 1982). For the disease burden calculation, the rate reported by Cadoz et al. (1983) is assumed to be reasonably representative of that in all developing countries. Fatality rates for H. influenzae type b meningitis are assumed to be 33 percent, and neurological sequelae are assumed to occur in 33 percent of survivors (Cadoz et al., 1983; Griffiss, personal communication, 1985).

Table D-3.1 shows the disease burden due to meningitis caused by H. influenzae type b. Sequelae are assumed to be distributed in severity in about the same proportion as those in the United States (Institute of Medicine, 1985).

The number of cases of nonmeningitic H. influenzae type b invasive disease can be estimated only by analogy with the situation in the United States. Various studies in the United States have reported that nonmeningitic conditions account for 30 to 80 percent of invasive illness caused by all types of H. influenzae (Institute of Medicine,

TABLE D-3.1 Morbidity and Mortality Associated with Hemophilus influenzae Type b Meningitisa

	Cases
Number of cases of meningitis (morbidity category C) (60/100,000 infants and children under 5 years of age, i.e., 498.6 million)	299,000
Fatalities (33 percent of cases)	99,000
Survivors (33 percent sustain sequelae)	200,000
Distribution of sequelae	
Morbidity category D (12 percent of cases)	24,000
Morbidity category E (15 percent of cases)	30,000
Morbidity category F (6 percent of cases)	12,000

[a]All cases assumed to occur in infants and children under 5 years of age.

TABLE D-3.2 Morbidity and Mortality Associated with Nonmeningitic Hemophilus influenzae Type b Invasive Disease

	Cases
Number of cases pneumonia, bacteremia, and epiglottitis (morbidity category C)	299,000
Age distribution of cases	
Under 5 years (70 percent)	209,000
5–14 years (10 percent)	30,000
15–59 years (15 percent)	45,000
60 years and over (5 percent)	15,000
Total fatalities (15 percent)	45,000
Age distribution of fatalities	
Under 5 years (70 percent)	32,000
5–14 years (10 percent)	5,000
15–59 years (15 percent)	7,000
60 years and over (5 percent)	2,000

1985). To estimate the total burden of illness from H. influenzae type b it is assumed that the ratio of meningitis to nonmeningitic invasive disease is 50:50. Thus, the number of cases in the developing world is 299,000. (An obvious potential source of error in this estimate is the greater relative frequency of invasive lower respiratory tract disease in the developing world as compared to the United States.) The case fatality rate of these conditions (pneumonia, bacteremia, epiglottitis) is assumed to be about 15 percent.

The age distribution of nonmeningitic invasive H. influenzae type b cases is assumed to be somewhat similar to the distribution assumed for the United States (i.e., under 5 years, 70 percent; 5–14 years, 10 percent; 15–59 years, 15 percent; 60 years and over, 5 percent [Institute of Medicine, 1985]). It is assumed that the occurrence of chronic sequelae arising from nonmeningitic invasive disease is negligible.

Table D-3.2 shows the disease burden associated with nonmeningitic H. influenzae type b.

Table D-3.3 shows the total disease burden resulting from H. influenzae type b meningitis (Table D-3.1) and other invasive disease (Table D-3.2). The estimated durations shown for category C illness under 5 years of age (12 days) is intermediate between that estimated for meningitis (14 days) and that estimated for other invasive disease (10 days). All episodes over 5 years of age are assumed due to nonmeningitic disease (duration about 10 days).

PROBABLE VACCINE TARGET POPULATION

The distribution of H. influenzae illness is described above. Up to 2 to 3 months of age, most infants exhibit declining maternal antibodies. In the developing world, most illness probably occurs between 4 and 12 months of age (Cadoz et al., 1983). Hence, the target population for active immunization probably will be all infants at about 2 to 3 months of age. Such a vaccine could readily be incorporated into the delivery schedules of the World Health Organization Expanded Program on Immunization (WHO-EPI). An earlier age of initial immunization may be practicable if a vaccine can be developed that induces immunity in younger infants.

Vaccine Preventable Illness*

The H. influenzae type b vaccine probably would be administered first at about 2 to 3 months of age when maternal antibody has

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

TABLE D-3.3 Disease Burden: *Hemophilus influenzae* type b--Meningitis and Nonmeningitis Invasive Disease

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work								
C	Severe pain, severe short-term impairment, or hospitalization	508,000	12	30,000	10	45,000	10	15,000	10
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	24,000	n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	30,000	n.a.		n.a.		n.a.		n.a.
F	Total impairment	12,000	n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	131,000	n.a.	5,000	n.a.	7,000	n.a.	2,000	n.a.

declined. Because the immune response at this age is limited, no vaccine would be likely to reach full protective efficacy until after further doses had been administered. Meningitis incidence begins to rise rapidly after 4 months of age, peaks at 6 to 8 months, and declines to become relatively rare after 2 years of age (Cadoz et al., 1983). Only partial protection would be provided until 2 to 3 doses of vaccine had been administered to infants.

About 20 percent of meningitic illness occurs before 6 months of age (Cadoz et al., 1983); hence, about 80 percent of meningitis is considered vaccine preventable and all other invasive disease—most of which occurs at an older age—should be preventable. Because the number of cases of meningitis is assumed to equal the number of cases of other invasive disease, about 90 percent of invasive illness caused by H. influenzae type b would be preventable with a vaccine that is 100 percent effective (after 2 to 3 doses) and that is delivered to the entire target population.

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 (2 to 3 months) and the peak of illness (see above).

Alternative Control Measures and Treatments

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; however, secondary disease probably represents a small proportion of the total disease burden, and these agents are not as practical as prevention in developing countries.

Success in vaccine prevention of invasive disease, particularly meningitis, will depend on the development of a vaccine capable of inducing immunity in infants. Progress toward this goal is described below.

PROSPECTS FOR VACCINE DEVELOPMENT

Two major approaches have been taken toward development of an effective vaccine against invasive H. influenzae type b disease: (1) 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, 3 months to 5 years of age (Mäkelä 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 currently licensed in the United States apparently produces such reactions less frequently (Broome, personal communication, 1985).

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 a purified polysaccharide vaccine (which was licensed in the United States in April 1985) 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 6 months of age respond, about 40 percent between 6 and 12 months respond, and 80 percent or more respond after 24 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 a conjugate vaccine, prepared using high-molecular-weight polysaccharide attached to diphtheria is clearly superior to the polysaccharide alone in children under 3 years of age. It induces antibody levels above those considered to be protective in 100 percent

of children over 9 months of age (Lepow et al., 1985) and 90 percent of infants (Eskola et al., 1985). These results have been confirmed in clinical studies conducted with the PRP-D vaccine in over 2,000 children between 2 and 24 months of age (Gordon, personal communication, 1985). The National Institutes of Health-National Institute of Allergy and Infectious Diseases initiated an efficacy study with this vaccine in Alaska in 1984. This vaccine may be available for use in pediatric immunization programs within the next 1 to 2 years. Successful immunization of infants with conjugates appears likely to require at least two doses.

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.

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Appendix D-4

The Prospects for Immunizing Against Hepatitis A Virus

DISEASE DESCRIPTION

Hepatitis A virus (HAV) infection is a more prevalent but less serious disease than that caused by hepatitis B virus. It has a worldwide distribution, but the age of infection varies depending on socioeconomic and hygienic conditions. In the least developed areas, it is a disease of early childhood, with essentially all children except those of the highest socioeconomic classes experiencing asymptomatic or mild infection during the first years of life. As socioeconomic conditions improve, the usual age of infection shifts upward and the clinical manifestations of the disease become more severe; infection in adulthood normally results in frank icteric hepatitis.

Hepatitis A is spread primarily by the fecal-oral route, directly from person to person. While in the poorest areas the disease remains uniformly endemic and rarely causes epidemics (due to low numbers of susceptible persons), in areas of moderate or better socioeconomic conditions the infection may cause cyclical communitywide or nationwide epidemics, with interepidemic intervals of 7 or more years. In the highest socioeconomic areas, epidemic cycles disappear and endemic foci of the disease may become uncommon; in these areas, the majority of cases occur among travelers to more highly endemic areas. The virus also may be spread by contaminated food or water, causing large common-source outbreaks in areas where a substantial proportion of the population remains susceptible. Some researchers suspect that HAV also may spread by the respiratory route, but there is no conclusive evidence to support this theory.

In children under age 5, HAV illness is usually anicteric and may be entirely subclinical. When symptoms do occur, they may include fever, malaise, fatigue, headache, anorexia, nausea, vomiting,

The committee gratefully acknowledges the efforts of S.C.Hadler, who prepared major portions of this appendix, and the advice and assistance of R.H.Purcell. The committee assumes full responsibility for all judgments and assumptions.

abdominal pain, and jaundice. 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 infection, there has been no identification of viremic carriers (Mosley, 1975). Socioeconomic status and general hygienic standards are the major risk factors for acquiring disease in most areas of the world. Specific risk factors for hepatitis A infection in developed areas include involvement in day care, homosexuality, personal contact with infected individuals, and foreign travel to endemic areas.

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 the 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 3 to 6 months. Cell-mediated immunity to HAV infection has not been reported.

DISTRIBUTION OF DISEASE

Geographic Distribution

Hepatitis A virus infection and illness occur worldwide. As noted above, the severity of symptoms is related to the age at infection, which is dependent on the socioeconomic development of the region or country. Hence, the proportion of cases with moderate or severe symptoms is likely to be greater in the developed and more advanced developing countries, but the number of cases may be greater in the poorer countries. The rates of disease in different countries are discussed further below.

Disease Burden Estimates

Estimates of the numbers of cases of clinical hepatitis A illness worldwide are based on limited information and are therefore uncertain. Seroprevalence data show that hepatitis A is an infection of early

childhood in the poorest areas, and therefore almost entirely limited to mild or asymptomatic infection. As socioeconomic conditions improve, infection is successively delayed to later childhood, to adulthood with a high proportion of the population infected, and finally, to adulthood with smaller proportions of the population infected. As infection is delayed, an increasing proportion of cases are symptomatic; paradoxically, the clinical disease burden may increase as socioeconomic standards rise.

Actual data on disease incidence are limited; the most comprehensive source is the World Health Organization Annual Statistical Reports. This presents data on rates of reported clinical infectious hepatitis for many countries, with breakdowns by age of infection for some countries. These data do not distinguish hepatitis cases by type (A, B, or non-A, non-B), because such data are available only in the most highly developed areas. Furthermore, they provide no information about case-reporting efficiency; presumably, reporting is best in most developed areas and poorest in the least developed areas.

Disease burdens were estimated from the most recent available data for both different regions and different socioeconomic development levels within certain regions, as follows (Hadler, personal communication, 1985). Reported age-specific incidences of "infectious" hepatitis were compiled for individual countries from World Health Organization (WHO) annual statistics (1975–1981) as available. Data from serologic studies of acute hepatitis cases from the United States, western Europe, South America, and other selected areas were used to estimate the proportion of reported hepatitis cases that are due to hepatitis A. Generally, such studies have shown that a high proportion (80 percent) of hepatitis in childhood is due to HAV in all areas of the world and that a variable proportion, with a median of about 30 percent, of hepatitis cases in adults is due to hepatitis A virus. Although the latter figure varies widely and may be higher in more developed than in less developed areas, for simplicity the 30 percent figure was used throughout. These proportions were applied to available age-specific hepatitis rates for different countries. Representative rates of hepatitis A were then selected for each subregion, to be applied throughout that region. Because reporting is highly variable and underreporting is the rule, higher estimates were used where data were available from several countries in a given area. Rates for each region estimated in this manner are shown in Table D-4.1, along with the estimate of the number of cases that would result (based on 1979 population data—the last reliable data available to the author). Table D-4.2 shows the estimated numbers of cases adjusted for the 1984 population numbers. Assuming only 20 percent of cases are likely to be reported, the probable true number of cases in the developing world is estimated to be 4.765 million.

In general, developed areas in the United States, western Europe, Asia, and Oceania have modest estimated rates of hepatitis A, from 0 to 15 cases per 100,000 per year. Areas with moderate development consistently show the highest disease rates, ranging from 20 to 100 cases per 100,000 per year, and occasionally higher in parts of South and Central America, eastern Europe, the Middle East, and China. Finally,

TABLE D-4.1 Estimated Rates of Hepatitis A Worldwide by Continental Regions

			Estimated Hepatitis A	
Region	Socioeconomic Status	1979 Population (millions)	Rate/100,000/Year	Cases/Year (thousands)
North America				
United States, Canada	High	247.6	10	25
Central and South America				
Argentina, Brazil, Chile, Uraguay, Colombia, Venezuela, Costa Rica, Mexico Cuba	Moderate	280.4	40	112
Others	Low	70.2	20	14
Europe				
North	High	82.0	5	4
West, central, south	High	284.3	10	28
East (including USSR)	Moderate	381.3	60	229
Africa				
North	Low-Moderate	88.6	40	35
Sub-Sahara	Low	353.8	30	106
Middle East	High	15.3	60	9
	Low-Moderate	116.7	20	23
Asia				
India, Nepal, Ceylon, etc.	Low	862.2	20	173
Southeast Asia, Korea	Low	406.9	20	82
China	Low-Moderate	946.6	30	284
Japan, Singapore, Hong Kong, Taiwan	High	123.4	10	12
Oceania				
New Zealand, Australia	High	17.5	15	3
Others	Low-Moderate	5.0	30	2
Total				1,141

SOURCE: Hadler, personal communication, 1985.

the lowest socioeconomic areas in all parts of the world show the most variation in rates, from less than 1 to 90 cases per 100,000 per year. In these areas it is least certain whether low rates are due to asymptomatic infection during early childhood, or simply to poor reporting. For these areas, modest rates of 20 to 30 cases per 100,000 per year have been used. It should be noted, however, that the incidences of clinical illness in such areas may be expected to increase as socioeconomic conditions improve. Finally, the estimates used here have minimal correction for reporting efficiency; incorporating a correction factor to adjust for this probably would increase frequency of disease by 2- to 10-fold. A 5-fold underreporting is assumed in the calculation for this report to reflect the probable number of cases.

TABLE D-4.2 Cases of Hepatitis A Likely to be Reported in the Developing World in 1984

Region	Number of Cases per Year
Africa	172,000
Asia	637,000
Latin America	142,000
Oceania	2,000
Total	953,000

NOTE: Numbers are based on estimates derived in Table D-4.1 and are adjusted for the increase in population between 1979 and 1984 (see Chapter 4) .

Because of the scarcity of worldwide data on frequency of hospitalization or death rates due to hepatitis A, further refinement of the “clinical” or icteric disease load is difficult. The estimated mortality rate from the United States (3 per 1,000 clinical cases) has been applied throughout the world for the committee's calculations. The proportion of severe cases, for which hospitalization would be desirable, has been estimated from U.S. data (i.e., one-third); however, actual rates of hospitalization in different areas may vary much more than mortality rates. The number and distribution of cases resulting from these assumptions is shown in Table D-4.3. There is little data from the developing world on which to base the distribution of cases among the age groups used in this disease comparison. For the purposes of this effort, the age distribution is assumed to be similar to that estimated for the United States and is shown in Table D-4.4 (Institute of Medicine, 1985). Application of these proportions to the estimated number of cases in Table D-4.3 yields the disease burden estimates shown in Table D-4.5.

TABLE D-4.3 Estimated Morbidity and Mortality from Hepatitis A in the Developing World

Category	Number of Cases
Typical cases of illness (morbidity category B)	3,178,255
Severe cases of illness (morbidity category C)	1,586,745
Fatalities (morbidity category H, 3/1,000 clinical cases)	14,295

TABLE D-4.4 Clinically Symptomatic Illness Caused by Hepatitis A Virus in Specific Age Groups

Age Group (years)	Typical Cases (morbidity category B) (percent)	Severe Cases (morbidity category C) (percent)	Deaths (percent)
Under 5	4.4	2.0	0
5–14	20.0	10.0	8.0
15–59	71.0	77.0	36.0
60 and over	4.7	13.0	56.0
All ages	100	100	100

NOTE: Age distributions are based on reporting in the United States and are assumed 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.

PROBABLE VACCINE TARGET POPULATION

The target population for an HAV vaccine would be young (preschool) children in all parts of the world and, ultimately, the cohort of babies born each year. The accessibility of this population has been demonstrated by the success of childhood immunization programs in all parts of the world. Childhood vaccination would directly benefit the most commonly affected group in the least developed areas. In more developed areas, it also would benefit adults because herd immunity plays a significant role in this disease, and because children are usually responsible for introducing infection into the household.

In areas of moderate to good hygienic/socioeconomic conditions, where the major proportion of cases occur in older children or adults, initial vaccine programs also might focus on the specific highest risk groups, such as children in day-care centers or adults (travelers to highly endemic areas, military, homosexual men). The accessibility of

TABLE D-4.5 Disease Burden: Hepatitis A Virus

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	139,843	7	635,651	7	2,256,561	7	149,378	7
C	Severe pain, severe short-term impairment, or hospitalization	31,735	14	158,675	14	1,221,794	14	206,277	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	0	n.a.	1,144	n.a.	5,146	n.a.	8,005	n.a.

these groups will vary widely with the group (the military will be most accessible) and with the health care system of the area.

Incorporation of the HAV vaccine into the WHO Expanded Program on Immunization (WHO-EPI) would be the key to implementing HAV control in the poorer areas of the world. The feasibility of this depends on the nature of the vaccine (live versus killed), the number and schedule of doses necessary, the vaccine potency under various handling conditions (necessity for cold chain), and other circumstances. A single-dose live vaccine would be more easily incorporated into the program than a multi-dose killed vaccine, but it also might require more rigorous handling conditions for preservation of potency. Vaccines that have good potency when given within the first year of life would be more easily incorporated into the schedule than a vaccine that must be given later to have maximal potency.

Vaccine Preventable Illness*

Because HAV infection in infants and young children is almost always subclinical, and because it probably will be practical to deliver an HAV vaccine (that has shown to be safe and effective) at an early age, it is reasonable to assume that, theoretically, all illness associated with HAV vaccine could be vaccine preventable.

SUITABILITY FOR VACCINE CONTROL

Both the human immune response to HAV infection and vaccine studies in experimental animals 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).

Alternative Control Measures and Treatments

Improved hygiene and sanitation are effective techniques for reducing the transmission and incidence of HAV infection, and immune

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (See Chapter 7).

globulin administration can diminish or eliminate symptoms in exposed individuals. Improvements in hygiene and sanitation in the developing world will reduce many diseases. For HAV, however, the picture will shift from one of predominantly subclinical infections in infancy to clinical disease that occurs with infections in older children and young adults, because the average age of infection will increase due to lowered transmission. Thus, only a vaccination program will provide true control of the disease.

PROSPECTS FOR VACCINE DEVELOPMENT

During early research, 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; Purcell et al., 1984).

Because until recently the yield of virus from cell cultures was relatively low and involved lengthy culture periods, most vaccine development efforts have focused on live attenuated vaccines or, more recently, on molecular cloning approaches. However, a formalin inactivated hepatitis A vaccine has been prepared by investigators at the Walter Reed Army Institute of Research. Preclinical testing in animals indicated that it was safe and immunogenic. Phase 1 clinical trials for humans are projected to begin in 1986 (National Institute of Allergy and Infectious Diseases, 1985).

Sequential passage of the virus in cell culture attenuated it for chimpanzees, yet it retained the ability to elicit antibodies (Provost et al., 1983; Purcell et al., 1984). Studies are now under way to find the optimal level of attenuation for a human vaccine (Purcell et al., 1984).

Recently, questions have been raised regarding whether a live attenuated vaccine will be feasible. Purcell et al. (1984) noted that some evidence exists to suggest that host cytopathic and immunologic components of HAV infection may be responsible for the observed damage to hepatocytes. If this is confirmed it may be difficult to develop a live virus sufficiently modified to avoid such reactions and provide the desired level of safety, information from a small clinical trial of attenuated live vaccine has not yet been published but is reported to suggest that the approach may be feasible (Emini, personal communication, 1985).

An alternative vaccine might employ one or a number of antigens of the virus prepared by recombinant DNA technology, probably in commercial yeast cells. Much progress on this approach has been made by a number of groups recently (National Institute of Allergy and Infectious Diseases, Chiron Corporation, Merck Sharp & Dohme [National Institute of Allergy and Infectious Diseases, 1985]) and has been reviewed by Purcell et al. (1984). One of these noninfective antigens 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).

Other approaches to hepatitis A vaccines include the use of synthetic peptides mimicking portions of the viral coat proteins. These would be used with adjuvants or carriers.

A single injection of live virus vaccine would be expected to induce lifetime immunity. The noninfective antigens might have to be administered intermittently. Predictions on the prospects of vaccine development are shown in Table 5.1.

Clinical testing of an attenuated live virus vaccine prepared by the National Institute of Allergy and Infectious Diseases has been projected for 1986 (National Institute of Allergy and Infectious Diseases, 1985).

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Appendix D-5

The Prospects for Immunizing Against Hepatitis B Virus

Effective, plasma-derived hepatitis B virus (HBV) vaccines have been marketed internationally by at least three companies. Licensees of these companies, plus new independent producers of similar vaccines, are working to broaden the distribution of these products. In addition, recombinant HBV vaccines are nearing licensure and their prospects appear favorable. Officials of most endemic countries are eager to incorporate an HBV vaccine into their immunization programs. Suitable candidates should be safe, immunogenic, low cost, and easy to deliver.

DISEASE DESCRIPTION

The diseases associated with HBV occur at two intervals after infection: acute hepatitis appears within several weeks; the manifestations of chronic hepatitis B infection may not appear until many years later.

Symptoms of acute hepatitis B virus 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, about 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 1 in 100 HBV infections in newborns is symptomatic (Schweitzer et al., 1973; Stevens et al., 1975).

The late manifestations of HBV occur almost exclusively among chronic carriers of the virus. The proportion of infected people who

The committee gratefully acknowledges the efforts of D.P.Francis, who prepared major portions of this appendix. The committee assumes full responsibility for all judgments and assumptions.

become chronic carriers is highly age-dependent. It ranges from about 80 to 90 percent for offspring of e-antigen positive mothers to 5 to 10 percent for adults (Francis and Maynard, 1979; 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 nm) 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 of the virus contains the core antigen (HBcAg) which, in solution, has a conformational variant, 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 nm) spherical and tubular forms that consist entirely of HBsAg. HBsAg has several major antigenic determinants. The a antigen is shared by all known 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 RESPONSE

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 HBV infection and is the antibody that is considered protective (Francis and Maynard, 1979). Anti-HBc and anti-HBe may be present during acute or chronic HBV infection, as well as following resolution. Their contribution to protection against HBV, if any, has not been fully elucidated. 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.

Investigations are under way to elucidate the role of the so-called preS region of the surface antigen protein (s). The preS region is removed in the processing of plasma derived vaccines and appears to enhance the protection provided by the s protein (National Institute of Allergy and Infectious Diseases, 1985).

DISTRIBUTION OF DISEASE

Geographic Distribution

The disease burden of hepatitis B varies significantly in different parts of the world. The combined total of chronic carriers and healthy immune individuals provides a good measure of the rate of infection. Using this measure, the world can be divided into areas of high infection rate (sub-Saharan Africa, east Asia, and the Pacific Islands), moderate infection rate (Middle East, central Asia, South America, eastern Europe, and Arctic), and low infection rate (North America, western Europe, and Australia) (Francis, 1983).

Lack of surveillance and lack of serologic testing hamper quantitation of disease incidence in many of the high-rate areas. Nevertheless, available estimates demonstrate the enormity of the problem.

Acute HBV manifestations are relatively less common in endemic countries than in other areas because much of the disease burden occurs during childhood, when symptoms are less frequent. However, the total burden of acute disease is large in these countries because the disease is so widespread.

The total disease burden resulting from HBV in endemic areas is large because of the high infection rates at early ages, with the late sequelae that result from persistent infection. For example, the incidence of primary hepatocellular carcinoma in many areas of the world exceeds the incidence of acute hepatitis B in the United States (Maupas and Melnick, 1981).

The largest number of HBV infections occurs in China (60 million HBV carriers). Actual mortality rates in China have been reported for primary hepatocellular carcinoma (PHC) (Armstrong, 1980). The rate is extremely high in southeast China (50 to 60 per 100,000 per year). Throughout China, the rate is reported to be about 20 per 100,000 per year (Francis, personal communication, 1984). Less information is available on cirrhosis deaths, but a Taiwanese study found that there were 0.43 deaths from HBsAg-positive cirrhosis for every PHC death (Beasley et al., 1981). Complete data are not available for acute hepatitis B in China, but the annual incidence is estimated to be about 700,000 cases, and half of the infectious disease beds are occupied by hepatitis patients (over half of which are HBV-related).

Disease Burden Estimates

The disease burden estimates include three major disease states: acute hepatitis B, primary hepatocellular carcinoma, and cirrhosis.

Acute Hepatitis B

Cases and deaths due to acute hepatitis B were calculated as shown in Table D-5.1.

TABLE D-5.1 Morbidity and Mortality due to Acute Hepatitis B

Region	Population at Risk (millions)	Annual Incidence Rate (per 100,000)	Number of Cases	Deaths[a]
High Risk Regions				
South and east Asia	1,516	68[b]	1,030,880	1,546
Sub-Saharan Africa	407	68[b]	276,760	415
Oceania	5	68[b]	3,400	5
Moderate Risk Regions				
Central Asia	1,146	60[c]	687,600	1,031
North Africa	124	60[c]	74,400	112
South America	397	40[d]	158,800	238
Total			2,231,840	3,347,

[a]Assuming a case fatality rate of 1.5 per 1,000 cases.
[b]Incidence rate in China assumed applicable to all high-risk regions.
[c]Assumed to be close to Israel's rate of 50 to 80 per 100,000.
[d]Assumed to be between rates in Israel and the United States.
SOURCE: Francis, personal communication, 1985.

Cases and deaths were divided proportionally by population size into the 5 to 14 and 15 to 59 years age groups. It was assumed that all cases in the under 5 years age group are asymptomatic, and that the number of cases in people 60 years of age and over is insignificant.

Cases were distributed into the acute categories as follows: 5 to 14 years age group, 25 percent in category A, 50 percent in category B, and 25 percent in category C; 15 to 59 years age group, 25 percent in category A, 25 percent in category B, and 50 percent in category C. An additional 3 percent of cases in each age group were assigned to category E, representing cases of chronic acute hepatitis (Berlin, 1980). Table D-5.2 shows the disease burden resulting from acute hepatitis B.

Primary Hepatocellular Carcinoma

PHC may occur in chronic hepatitis B carriers 20 years or more after an acute infection. The average survival rate of PHC is 6 months, so the numbers of cases and deaths are equal. The incidence rates in different populations are shown in Table D-5.3. Because of the time lag between acute hepatitis infection and PHC onset, it was assumed that the disease affects only two age groups. Cases and deaths were distributed proportionally according to the size of the population in each age group, and all cases were assigned to category E. Table D-5.4 shows the disease burden estimates for PHC.

TABLE D-5.2 Disease Burden: Hepatitis B--Acute Illness

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity			178,547	7	379,413	7		
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work			357,095	14	379,413	14		
C	Severe pain, severe short-term impairment, or hospitalization			178,547	28	758,826	28		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.s.		n.s.		n.s.		n.s.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.s.	21,426	n.s.	45,530	n.s.		n.s.
F	Total impairment		n.s.		n.s.		n.s.		n.s.
G	Reproductive impairment resulting in infertility		n.s.		n.s.		n.s.		n.s.
H	Death		n.s.	1,071	n.s.	2,276	n.s.		n.s.

TABLE D-5.3 Morbidity and Mortality due to Primary Hepatocellular Carcinoma

	Population at Risk (millions)	Incidence Rate (per 100,000)	Number of Cases=Number of Deaths
High HBV Risk			
South and east Asia	1,516	20	303,200
Sub-Saharan Africa	407	30	122,100
Oceania	5	10	500
Moderate HBV Risk			
Central Asia	1,146	10	114,600
North Africa	124	10	12,400
South America	397	5	19,850
Total			572,650

SOURCE: Francis, personal communication, 1985.

Cirrhosis

Incidence rates of cirrhosis as a complication of hepatitis B have not been well documented. Beasley et al. (1981) found in Taiwan that for every death due to PHC there were 0.43 deaths from HBsAg-positive cirrhosis. This rate was applied to all PHC deaths. Cirrhosis deaths were assumed to equal 25 percent of cirrhosis cases. Cirrhosis cases were assigned to category E. Table D-5.5 shows the disease burden estimates for cirrhosis resulting from hepatitis B. Table D-5.6 shows the total disease burden estimates for hepatitis B.

PROBABLE VACCINE TARGET POPULATION

In highly endemic areas, the goal of HBV vaccination is to prevent both infection and the chronic carrier state. Because most population members of these areas are at risk of infection, universal vaccination is required. Furthermore, infection in these areas often occurs early in life, so the age of immunization must be adjusted accordingly. For areas of the world where perinatal infection is common, the first dose of vaccine should be given at birth (with the addition of hepatitis B immunoglobulin [HBIG] if vaccine alone is not effective in preventing perinatal infection) and subsequent doses delivered later. This approach is practical in many Asian countries because a substantial proportion of mothers deliver their infants in medical facilities. For areas of the world where perinatal infection is not a major problem, vaccination could be given simultaneously with other infant vaccinations. Thus, HBV vaccination could be incorporated into the World Health Organization Expanded Program on Immunization (WHO-EPI), with administration at the earliest current time of vaccine delivery.

TABLE D-5.4 Disease Burden: Hepatitis B--Primary Hepatocellular Carcinoma

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work								
C	Severe pain, severe short-term impairment, or hospitalization								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.	509,659	n.a.	62,991	n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death		n.a.		n.a.	509,659	n.a.	62,991	n.a.

TABLE D-5.5 Disease Burden: Hepatitis B--Cirrhosis

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work								
C	Severe pain, severe short-term impairment, or hospitalization								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.	876,612	n.a.	108,344	n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death		n.a.		n.a.	219,153	n.a.	27,086	n.a.

TABLE D-5.6 Disease Burden: Hepatitis B--All

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity			178,547	7	379,413	7		
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work			357,095	14	379,413	14		
C	Severe pain, severe short-term impairment, or hospitalization			178,547	28	758,826	28		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.	21,426	n.a.	1,431,801	n.a.	171,335	n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death		n.a.	1,071	n.a.	731,088	n.a.	90,077	n.a.

Assumptions about the proportion of the disease burden this would prevent are discussed below. The need for booster doses requires further evaluation.

Vaccine Preventable Illness*

Assuming that the entire target population could be vaccinated at birth, nearly all illness theoretically could be prevented (some infections occur in utero). Because early infection in infancy is common in highly endemic areas, and because incorporation into the current WHO-EPI probably would result in delivery of the first dose at a few weeks to a few months of age, the proportion of the total disease burden that would be vaccine preventable under these circumstances is judged to be about 60 percent. If vaccination at birth is adopted, as might be the case in some regions (e.g., some Asian countries) this estimate may underestimate the potential benefits of the vaccine in the calculations in Chapter 7.

SUITABILITY FOR VACCINE CONTROL

Plasma-derived HBV vaccines have been shown to be safe and effective for adults (Coutinho et al., 1983; Francis et al., 1982; Szmuness et al., 1980) and children (Maupas and Melnick, 1981). Recent studies of perinatal infection have reported efficacies of more than 90 percent for vaccine and HBIG together (Beasley et al., 1983), and ongoing studies of vaccine alone indicate efficacies of between 75 and 95 percent (Xu et al., 1985).

Alternative Control Measures and Treatment

No effective treatment for acute or chronic hepatitis B exists. Although some researchers have shown that the combination of alphafetoprotein screening and surgery can effectively treat primary hepatocellular carcinoma, the logistics and expense of this combination make widespread application impractical for the developing world.

PROSPECTS FOR VACCINE DEVELOPMENT

Plasma-derived HBV vaccines are now being produced in some of the more technically advanced developing countries. The technical problems

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

involved in establishing production facilities and procedures and developing quality and safety controls are substantial; these ventures generally have involved collaboration with the United States, Europe, or Japan.

Efforts to produce HBV vaccines using recombinant DNA technology (Burrell et al., 1979; McAleer et al., 1984; Miyanohara et al., 1983; Valenzuela et al., 1979) and synthetic polypeptides (Dreesman et al., 1982a; Gerin et al., 1983a,b; Hopp, 1981; Lerner et al., 1981) are under way in numerous laboratories. Several groups have introduced the HBsAg genome of HBV into bacteria, yeast, and mammalian cells. These laboratories include Merck Sharp & Dohme, Am Gen, Wellcome Biotechnology, and Smith-Klein-RIT in yeast cells; Genentech, Inc., Connaught Laboratories Ltd., and Institut Pasteur in mammalian cells (National Institute of Allergy and Infectious Diseases, 1985). Thus far, the most successful have been those that express HBsAg in yeast (McAleer et al., 1984) and mammalian cells (Patzer et al., 1984). At least two of these recombinant vaccines are permitted for investigational use in humans by the U.S. Food and Drug Administration.

Safety and immunogenicity studies for yeast-derived vaccines began in late 1983 and for mammalian cell-derived vaccines shortly thereafter. For the yeast vaccine, Scolnick et al. (1984) report that in two groups of healthy, low-risk volunteer adults the vaccine was highly immunogenic. The 37 subjects each received a 10 μg dose of HBsAg at 0, 1, and 6 months. By 3 months, 80 to 100 percent of vaccinees were antibody positive. Large boosts in titer followed the third dose. Phase 1 clinical trials with the Genentech mammalian cell derived vaccine suggest that it is at least as immunogenic as the presently licensed vaccine (National Institute of Allergy and Infectious Diseases, 1985). There have been no serious reactions attributable to either candidate vaccine.

Based on these results and other findings, it is estimated that a recombinant vaccine made in yeast or mammalian cells or both will be available in 1 to 2 years. Studies are under way with rDNA vaccines that contain the preS region (National Institute of Allergy and Infectious Diseases, 1985).

The gene coding for HBsAg 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 (Paoletti, 1984; Smith, 1984). 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; (3) uncertainty about successful “takes” following administration and the effectiveness of booster doses;

and (4) possible alteration of the tissue tropism of vaccinia virus by modification.

Several laboratories have identified the major antigenic site of HBsAg, a hydrophilic sequence of 8 to 12 amino acids (Dreesman et al., 1982b; Gerin et al., 1983a,b; 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 remain uncertain.

A further approach to vaccination against hepatitis B has been investigated, namely the use of anti-idiotype vaccines. This approach has been reported to provide protection in chimpanzees against challenge with HBV (Kennedy et al., 1985). Further investigations of this approach are required to evaluate its safety and suitability for use in humans and for HBV. Yet other possibilities include the development of hepatitis B polypeptide micelle vaccines (Howard et al., 1984).

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Appendix D-6

The Prospects for Immunizing Against Japanese Encephalitis Virus

DISEASE DESCRIPTION

Japanese encephalitis (JE) is an acute inflammatory disease of the brain, spinal cord, and meninges. Afflicted patients complain of fever and headache for 1 to 3 days, then typically present to medical facilities with signs of generalized impaired function of the nervous system, such as grand mal seizures or a depressed sensorium. Some patients exhibit focal neurologic signs, usually signifying upper motor neuron involvement. Lumbar puncture reveals a normal or slightly elevated pressure, a modest increase in the number of leukocytes, and little or no increase in the total protein concentration. Case fatality rates among all hospitalized patients in endemic countries typically range from 20 to 50 percent (Okuno, 1978); among patients in coma at the time of admission the fatality rate may be greater than 50 percent. A substantially lower case fatality ratio has been observed among U.S. servicemen in Asia (Dickerson et al., 1952; Ketel and Ognibene, 1971). Death probably results from compromise of brain stem respiratory control. Complete recovery takes weeks to months and occurs in 30 to 50 percent of patients. Persistent motor or psychological sequelae can be detected in 20 to 40 percent of surviving patients (Schneider et al., 1974).

An accurate and rapid diagnosis can be made by ELISA (enzyme-linked immunosorbent assay) detection of Japanese encephalitis virus (JEV) IgM antibodies in cerebrospinal fluid (CSF) at admission in 80 percent of cases; the remaining 20 percent develop antibodies within a few days (Burke et al., 1985a, 1985b). Virus can be isolated from the CSF in 10 to 15 percent of patients with acute disease and from postmortem brain tissue in almost all fatal cases (Burke et al., 1985c). A retrospective diagnosis can be made with any of a variety of conventional tests by demonstrating a rise in specific antibody titer in paired serum samples.

The committee gratefully acknowledges the efforts of D.S.Burke, who prepared major portions of this appendix, and the advice and assistance of R.E.Shope. The committee assumes full responsibility for all judgments and assumptions.

Only a small fraction of persons infected with the virus develop acute encephalitis; the majority of infections are asymptomatic. Estimates of the ratio of apparent to inapparent infections range from 1:63 among American military personnel (Benenson et al., 1975; Halstead and Grosz, 1962) to 1:1,000 among Asian children (Grossman et al., 1974; Southam, 1956). Undifferentiated fever or aseptic meningitis also may result from infection with JEV.

Existing Vaccines and Limitations

An estimated 0.5 billion doses of various Japanese encephalitis vaccine preparations have been manufactured and administered to humans in Asia over the past 20 years, principally in the People's Republic of China, Japan, and Korea. This enormous, sustained effort reflects the importance placed on JE control in countries stricken by the epidemic disease. However, none of the vaccines in use is ideal by current standards (see below), and none is licensed for use outside Asia.

PATHOGEN DESCRIPTION

Japanese encephalitis virus is a 45-nm enveloped, single (+) stranded RNA virus composed of three structural proteins (envelope, membrane, and core). The genome is 12,000 nucleotides in length and codes for seven to nine poorly characterized nonstructural proteins, as well as the three structural proteins (Shapiro et al., 1971; Westaway, 1973). The virus is antigenically related to a large number of other arthropod-borne viruses recently placed in their own family, the Flaviviridae. The family includes yellow fever and dengue, as well as several viruses closely related to JEV that produce epidemic encephalitis in other parts of the globe (St. Louis encephalitis virus in the Americas, West Nile encephalitis virus in Southwest Asia and Africa, and Murray Valley encephalitis virus in Australia). Preliminary analysis of the nucleotide sequence of JEV (Fournier, personal communication, 1986) shows a genome organization similar to that of the more completely characterized yellow fever virus (Rice et al., 1985).

JEV exists in nature as a mosquito-borne zoonosis, with birds and domestic mammals (principally pigs) serving as the vertebrate hosts (Buescher and Scherer, 1959). Infections in these vertebrate hosts are essentially asymptomatic, and the viremia is relatively short-lived but of high titer. Man is a nontransmitting host; the viremia in humans is probably too low to provide an efficient inoculum to biting mosquitoes. Principal vectors of JE are rice-field-breeding mosquitoes of the Culex vishnui group. Female mosquitoes usually become infected by feeding on a viremic animal and, after a temperature-dependent extrinsic incubation period of 3 days to 3 weeks, can transmit the virus during subsequent blood meals. Infected adult female mosquitoes can transmit JEV to their progeny through transovarial transmission (Rosen et al., 1978), but the epidemiologic significance of this mechanism is unknown.

HOST IMMUNE RESPONSE

The only known route of human infection with JEV is through the bite of an infected mosquito. Virus growing in the mosquito salivary glands (Takahashi and Suzuki, 1979) is inoculated into the skin and directly into capillaries; thousands of infectious particles are probably delivered. The initial site or sites of replication are unknown. The patient is asymptomatic while the virus multiplies and then viremia ensues. Circulating virus penetrates into the central nervous system, probably through defects in the endothelium, although infection through the cribriform plate or olfactory tract has been hypothesized (Albrecht, 1969). Symptoms begin 7 to 14 days after initial infection. JE is a diffuse encephalitis (Miyake, 1964); virus usually can be recovered from most if not all regions of the brain. Neurons containing JE antigens can be demonstrated throughout the brain, and the thalamus typically shows heavy involvement (Johnson et al., 1985). Glial elements are largely spared, and necrotic foci, when present, are of microscopic proportions.

When brain tissues from fatal cases are examined by immunohisto-chemical techniques, the earliest detectable host response is extra-vascular migration of mononuclear phagocytes (Johnson et al., 1985). These cells, accompanied by T-lymphocytes, cluster around infected (antigen-bearing) neurons. Simultaneously, meningeal exudates and perivascular cuffs composed of monocytes, T-cells, and B-cells accumulate. The infected neurons undergo pyknosis and fragmentation, and traces of antigen appear within the mononuclear cells in the nodules. Antibody synthesis by cells within the central nervous system can be detected directly by culture of CSF leukocytes early in the course of infection (Burke et al., 1985a, 1985b). A low or slow antibody response is associated with cultivable virus in the CSF and portends a grave prognosis (Burke et al., 1985c).

When JE occurs in a patient previously immune to another flavivirus (e.g., dengue), the IgG antibody response to JEV is brisk and strong, and an adverse outcome is less likely than in an individual experiencing JE as a first flavivirus infection (Edelman et al., 1975; Hammon, 1969; Sather and Hammon, 1970). The relative contributions of cellular and humoral immunity in these cross-flavivirus anamnestic responses in humans are unknown. Passively administered antibody has a protective effect in JE-challenged mice, even when administered 48 hours after virus challenge (Hammon and Sather, 1973; Ohyama et al., 1959). Inoculation with subimmunizing low doses of inactivated JE vaccine can prime nonhuman primates for an anamnestic antibody response to subsequent challenge, even in the absence of a detectable antibody response to the original immunization (Hoke and Burke, personal communication, 1985).

There is no evidence that the immune response contributes to the pathology in JE. Cyclophosphamide immunosuppression shortens the survival time in JE animal models (Nathanson and Cole, 1970). Little data exist on the role of interferon or that of cell-mediated immunity in JE.

DISTRIBUTION OF DISEASE

Geographic Distribution

Japanese encephalitis was first recognized in Japan in 1871, and epidemics recurred every few years until the late 1960s (Ishii, 1983; Okuno, 1978). All parts of the country were affected except Hokkaido, the northern most island. The worst epidemics occurred in the years immediately following World War II, with 3,000 to 5,000 cases per year and 1,000 to 2,000 deaths (representing an attack rate of 4 to 6 per 100,000). Children were predominantly affected. In the immediate postwar period, major annual epidemics also were recorded in Korea (2,000 to 6,000 cases per year) (Okuno, 1978; Paik, 1983). The maritime provinces of mainland China were also affected. In these latter two countries, the disease was confined largely to children under the age of 15.

Between 1967 and 1970 the geographic distribution of JE shifted dramatically. Annual morbidity rates in Japan dropped from 2–4 to 0.1–0.2 per 100,000, and the peak age-specific attack rate shifted to adults over age 50 (Ishii, 1983). Simultaneously, rates in Korea dropped from 5–30 to 1–2 per 100,000 (Okuno, 1978). This regional decline has been attributed to a combination of increased distribution of vaccine, altered agricultural practices and insecticide use, and improved housing standards. Rates have remained low in Japan, but in 1982 the southwestern provinces of Korea were struck by the first major epidemic there in 12 years, involving almost 3,000 children (attack rates 5 to 10 per 100,000 in affected provinces) (Paik, 1983).

During the same 4-year period between 1967 and 1970, epidemic JE was recognized for the first time in northern Vietnam, where annual morbidity rates for acute encephalitis jumped from 2–4 to 9–22 per 100,000 (Okuno, 1978). Simultaneously, rates in Thailand increased from less than 0.1 to 3–4 per 100,000 total population (Jatanesen, personal communication, 1985; Okuno, 1978). In Thailand, epidemic JE was confined to the northern parts of the country, where rates reached 10 to 30 per 100,000; among children in northern Thailand, annual rates in excess of 100 per 100,000 have been recorded. Epidemics continue to recur in these countries. Three-fourths of all cases are among children less than 15 years old. In China, reported cases of JE, relatively stable at 2,000–9,000 cases per year, dramatically increased during the late 1960s, to 20,000–40,000 cases per year. Since 1975 the incidence of cases has declined to a relatively stable 10,000–15,000 cases per year (Quan, 1983). All provinces except the two most western, Xinjiang and Xizong, have the disease (Huang, 1982).

JEV has been known (by virus isolation) to exist in southern India and Sri Lanka for decades (Carey, 1969), but the proportion of the total number of acute encephalitis cases attributable to JE is uncertain; it may be less than 30 percent (Vitarana, 1982). In 1978, a major epidemic of JE was recorded in the northern India states of Bihar and Uttar Pradesh, with 7,600 recorded cases (Mathur et al., 1982; Rodrigues, 1982). Since then, smaller epidemics have recurred annually. Concurrently with the north Indian epidemics, JE appeared in the nearby

lowland regions of Nepal: between 1978 and 1982, more than 2,000 cases were recognized (Joshi, 1983). In north India and Nepal, adults and children are affected equally.

Sporadic, well-documented cases of human JE have occurred in southern Thailand, Malaysia, Indonesia, and the Philippines, but attack rates in these regions are low (less than 0.1 per 100,000) and epidemic disease has never been observed (Okuno, 1978). One puzzling feature of the epidemiology of JE is that the virus can be isolated with relative ease from mosquitoes or sentinel animals in these regions, but human disease is rare (Burke et al., 1985d; Simpson et al., 1970; Trosper et al., 1980; Van Peenan et al., 1974).

Foreign visitors to epidemic regions in Asia also are at risk. Sporadic cases have occurred among tourists and within expatriate diplomatic and business communities. Epidemics of JE, involving hundreds of U.S. troops, have occurred during every recent military conflict in Asia (World War II and the Korean and Vietnam wars).

Disease Burden Estimates

Special difficulties impede efforts to determine the total disease burden of Japanese encephalitis. Incidence rates and age distribution patterns may vary dramatically within a single country. Table D-6.1 shows the incidence rates used to determine total numbers of cases and deaths due to Japanese encephalitis in endemic regions. The proportion of cases in each age group is shown in Table D-6.2. For countries for which incidence rates and age distributions were not available, estimates were based on the epidemiology of disease in surrounding countries.

The proportion of cases in each morbidity category is assumed to be the same for each age group. All cases require hospitalization. Twenty-five percent of patients die about 1 week after hospitalization, and another 25 percent develop chronic sequelae (10 percent fall into each of categories D and E, and the remaining 5 percent in category F).

Total disease burden estimates are shown in Table D-6.3.

PROBABLE VACCINE TARGET POPULATION

In most areas JE occurs in children, although as discussed above, epidemics in some regions have shown a peak incidence among adults. The target population for an improved vaccine probably would be all infants in areas of potential JE occurrence; but immediately after introduction it is likely that the vaccine also would be administered to susceptible older children and adults.

Potential target areas include Japan, China, Thailand, Korea, Vietnam, Kampuchea, Laos, Malaysia, Indonesia, the Philippines, Nepal, northern India, and Sri Lanka. To simplify the calculations, the potential target population is considered to be the entire birth cohort of all countries in affected regions (see Table D-6.4).

TABLE D-6.1 Disease Estimates: Cases and Deaths

Country	Population (millions)	Annual Incidence per 100,000[a]	Cases per Year	Deaths[b]
Southeast Asia				
Burma	38.9	1.0	389	97
Indonesia	161.6	0.1	162	40
Kampuchea	6.1	1.0	61	15
Laos	3.7	5.0	185	46
Malaysia	15.3	0.1	15	4
Philippines	54.5	1.0	545	136
Thailand	51.7	5.0	2,585	646
Vietnam	58.3	5.0	2,915	729
East Asia				
China	1,034.5	1.5	15,518	3,880
Japan	119.9	0.2	240	60
North Korea	19.6	2.4	490	122
South Korea	42.0	2.4	1,000	250
Taiwan	19.2	1.0	192	48
Mid-South Asia				
India	746.4	0.4	2,986	746
Nepal	16.6	3.4	564	141
Sri Lanka	16.1	3.2	515	129
Total			28,852	7,213

[a]Burma—Fukunaga, 1983; Khin, 1982; Okuno, 1978.
Indonesia—Okuno, 1978; Thaib, 1982.
Kampuchea—Assumes rates similar to northeast Thailand.
Laos—Assumes rates similar to northern Thailand.
Malaysia—Lam, personal communication, 1985; Okuno, 1978.
Philippines—Chan, 1982; Okuno, 1978.
Thailand—Jatanesen, personal communication, 1985; Okuno, 1978; Sangkawibha, 1982.
Vietnam—Assumes rates similar to Thailand.
China—Chu, 1982; Quan, 1983.
Japan—Ishii, 1983; Okuno, 1978.
North Korea—Assumes rates similar to South Korea.
South Korea—Okuno, 1978; Paik, 1983.
Taiwan—Assumes rates intermediate between Japan and China.
India—Mathur et al., 1982; Pavri and Rodrigues, 1982; Rodrigues, 1982.
Nepal—Joshi, 1983.
Sri Lanka—Vitarana, 1982..
[b]Assuming a 25 percent case-fatality rate.

TABLE D-6.2 Distribution of Cases by Age Group

		Age Group (years)							
		Under 5		5–14		15–59		60 and Over	
Distribution Pattern	Total Number of Cases	Cases	Percent	Cases	Percent	Cases	Percent	Cases	Percent
Distribution 1[a]	6,135	1,841	30	3,681	60	614	10	—	—
Distribution 2[b]	722	101	14	181	25	390	54	50	7
Distribution 3[c]	17,498	1,750	10	12,249	70	3,500	20	—	—
Distribution 4[d]	432	43	10	43	10	130	30	216	50
Distribution 5[e]	3,501	525	15	1,400	40	1,225	35	350	10
Distribution 6[f]	564	113	20	226	40	226	40	—	—
Total	28,852	4,373		17,780		6,085		616	

[a]Includes Burma (Fukunaga, 1983; Khin, 1982; Okuno, 1978), Kampuchea (assumes rates similar to northeast Thailand), Thailand (Jatanesen, personal communication, 1985; Okuno, 1978; Sangkawibha, 1982), Laos (assumes rates similar to northern Thailand) , Vietnam (assumes rates similar to Thailand) .
[b]Includes Indonesia (Okuno, 1978; Thaib, 1982), the Philippines (Chan, 1982; Okuno, 1978), Malaysia (Lam, personal communication, 1985; Okuno, 1978).
[c]Includes North Korea (assumes rates similar to South Korea), South Korea (Okuno, 1978; Paik, 1983), China (Chu, 1982; Quan, 1983).
[d]Includes Japan (Ishii, 1983; Okuno, 1978) and Taiwan (assumes rates intermediate between Japan and China).
[e]Includes India (Mathur et al., 1982; Pavri and Rodrigues, 1982; Rodrigues, 1982) and Sri Lanka (Vitarana, 1982); distributions speculative because India has two very different patterns.
[f]Includes Nepal (Joshi, 1983).

TABLE D-6.3 Disease Burden: Japanese Encephalitis

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Years	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work								
C	Severe pain, severe short-term impairment, or hospitalization	4,373	11	17,780	11	6,085	11	616	11
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	437	n.a.	1,778	n.a.	609	n.a.	62	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	437	n.a.	1,778	n.a.	609	n.a.	62	n.a.
F	Total impairment	219	n.a.	889	n.a.	304	n.a.	31	n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	1,093	n.a.	4,445	n.a.	1,521	n.a.	154	n.a.

TABLE D-6.4 Estimates of Vaccine Target Population

Country	Population (millions)	Birth Rate[a]	Birth Cohort
Southeast Asia			
Burma	38.9	38	1,478,200
Indonesia	161.6	34	5,494,400
Kampuchea	6.1	38	231,800
Laos	3.7	42	155,400
Malaysia	15.3	31	474,300
Philippines	54.5	32	1,744,000
Thailand	51.7	26	1,344,200
Vietnam	58.3	34	1,982,200
East Asia			
China	1,034.5	21	21,724,500
Japan	119.9	13	1,558,700
North Korea	19.6	32	627,200
South Korea	42.0	23	966,000
Taiwan	19.2	23	441,600
Mid-South Asia			
India	746.4	34	25,377,600
Nepal	16.6	43	713,800
Sri Lanka	16.1	28	450,800
Total			64,764,700

[a]Number of births per 1,000 population.

Foreign visitors also might avail themselves of a new vaccine, but their numbers are considered negligible compared with the main target population.

Because the virus is transmitted in a zoonotic cycle, with man as an incidental host, a vaccination program would not provide herd immunity. Thus, disease reduction would be directly proportional to vaccine coverage of the population. With this approach, vaccination would have to be continued indefinitely. A safe and effective vaccine that could confer immunity in a single or limited number of doses probably could be incorporated into the World Health Organization Expanded Program on Immunization (WHO-EPI) for delivery to infants or young children.

Vaccine Preventable Illness*

Although some cases of JE may occur in young infants, the disease occurs primarily in children and, in some areas, adults (see above).

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

For the calculations conducted here, it is assumed that all JE is potentially preventable by administration of a hypothetical, totally efficacious vaccine administered to the entire target population.

SUITABILITY FOR VACCINE CONTROL

Alternative Control Measures and Treatments

JEV exists in nature as an arthropod-borne zoonosis; man becomes infected only incidentally. In theory, preventive measures could be directed toward control of the mosquito vector, or toward immunization of the nonhuman vertebrate hosts. In fact, neither of these approaches is feasible.

The principal vector species of JE are common rice-field-breeding mosquitoes present in huge numbers throughout Asia; no practical vector control measures are available or are likely to be available in the near future. Because these species feed largely at night, window screens and mosquito nets probably are useful devices for limiting, but not eliminating, exposure.

Immunization of pigs, the major amplifying host, has been seriously considered. However, the domestic pig population in many of the affected countries is roughly equal to that of the human population. Further, the average life span of a pig raised for slaughter is only 1 to 2 years. A pig immunization program that would require distribution of a quantity of vaccine equal to the human population every year is unacceptably expensive. Elimination or immunization of the wild bird hosts is equally impractical.

There are no known specific therapeutic agents for the treatment of acute JE in humans; treatment is entirely supportive (World Health Organization, 1979, 1983).

PROSPECTS FOR VACCINE DEVELOPMENT

Status of Existing Vaccines

JEV was first isolated more than 50 years ago, in 1934. Ten years later, toward the end of World War II, the first large-scale JEV immunization program was conducted: 77,000 U.S. troops, stationed on Okinawa in preparation for the invasion of mainland Japan, received an inactivated mouse brain JEV vaccine. No attempt was made to study protective efficacy. Since then, an estimated 0.5 billion doses of various JE vaccine preparations have been manufactured and administered to humans in Asia. Regrettably, there are still no published studies presenting the details of a field trial of vaccine efficacy.

Three main types of JE vaccine have been used extensively in humans.

Formalin-Inactivated Mouse Brain Vaccine

This is the major vaccine currently used in Japan, Korea, and Taiwan. Over the past 20 years, about 8.2 million doses of vaccine have been distributed by the major Japanese commercial producer, The Research Foundation of Osaka University (logo="Biken"). The vaccine is administered to children starting at school age; an initial two doses are administered 1 week apart, followed by a booster at 1 year and then every 3 years thereafter. Coverage is nearly universal in southern Japan.

Preparation of the vaccine involves purification of virions from a mouse brain suspension by ultracentrifugation (Fukai, 1983; Takaku et al., 1971). Biken research workers are unable to detect myelin basic protein in the final product, and Biken officials state that, to the best of their knowledge, no case of neurologic complications of vaccination has been reported. Minor side effects of fever or local tenderness are encountered in a few percent of vaccinees. The vaccine has never been evaluated completely in a controlled field efficacy trial (two trials were begun, but neither was completed). Boosters are required to maintain serum neutralizing titers at detectable levels.

The vaccine is prepared from a strain of the prototype Nakayama virus that was isolated in 1935 (Mitamura et al., 1936). In tests in mice, vaccine prepared from this strain induced antibody that neutralized the homologous virus well but that neutralized less well several other strains isolated from more western parts of Asia. A bivalent vaccine, consisting of equal parts of the Nakayama strain and the Beijing strain, was shown to induce satisfactory levels of neutralizing antibodies to all known JEV strains (Fukai, 1983). This bivalent Biken inactivated mouse brain vaccine is currently undergoing controlled field testing in northern Thailand.

Formalin-Inactivated Cell Culture Vaccine

Since 1967, JE vaccines have been produced in China on a large scale by infecting roller bottle cultures of primary hamster kidney cells with the P3 (Beijing, 1949) strain. Six Institutes of Biological Products around the country produce a total of about 100 million doses of vaccine per year. Vaccine is administered to children under the age of 10 years: two doses separated by a 1-week interval, followed by boosters at 1 year and every 3 years thereafter. Low-grade fever and local reactions are encountered occasionally, but neurological complications have not been reported. Controlled field trials involving 360,000 children are said to have been conducted between 1967 and 1969 (He Shi-min, 1983). Efficacy rates of 85 percent, 76 percent, and 87 percent were reported for three trials, but details are not available.

Live Attenuated Vaccine

Three different live attenuated JE vaccines have been tested in humans in China. All three vaccine strains derive from a single parent virus, the SA14 mosquito field isolate, which was passed 100 times in hamster kidney cells to yield the avirulent 12–1–7 strain.

The 2–8 vaccine strain was developed from the 12–1–7 strain by ultraviolet irradiation and passage in adult mice. The resultant live vaccine was shown to have a protective efficacy of 87 percent in a trial involving 500,000 horses, but only 50 percent of 8,000 children inoculated with this vaccine developed neutralizing antibody. No further trials were conducted.

The 5–3 vaccine strain was derived from the 12–1–7 strain by 12 sequential plaque clonal selection passages. Detailed characteristics of this vaccine virus, such as the actual dose used for human immunization, are not available. After one dose of the vaccine, 80 percent of children developed neutralizing antibodies (Li Ho-mia, 1983). In a brief report of a controlled trial involving more than 200,000 children, a protective efficacy of 85 percent was reported (Li Ho-min, 1983). More than 5 million children have been immunized with the 5–3 vaccine.

The 14–2 strain was derived from the 5–3 strain by serial passage in murine subcutaneous tissues and subsequent cloning. This was done to increase the infectivity and immunogenicity. Compared to the 5–3 strain, about 100-fold less of the infectious virus is required to infect humans. Only a few dozen children have been inoculated with this strain; seroconversion rates and mean titers are higher following 14–2 vaccination than following 5–3 vaccination (Li Ho-min, 1983).

Potential for New Vaccines

Fatal encephalitis can be induced in essentially any rodent and primate species when the challenge virus is inoculated directly into the brain. However, animal models based on direct intra-cranial inoculation are at best a poor reflection of the pathogenesis of JE in man, where the virus multiplies for several days in peripheral tissues before the brain is invaded. Aerosol challenge (Larson et al., 1980) or intra-nasal inoculation (Harrington et al., 1977) of primates or rodents can lead to fatal encephalitis, probably by passage of virus through the cribiform plate, but the relevance of this route of challenge to natural human infections is also questionable.

Peripheral challenge of sub-human primates regularly results in a sub-clinical infection with viremia but without evidence of viral replication in the brain (Morris et al., 1955; Nathanson and Harrington, 1966). In rodents, the response to peripheral JEV challenge is strikingly age dependent; suckling mice are regularly susceptible, while adult mice are usually resistant (Taylor et al., 1980). Genetically determined resistance of mice to lethal flavivirus encephalitis has been determined to be inherited as a simple, autosomal dominant trait (Bang, 1978). However, peripheral inoculation of older weanling or

adult mice of susceptible strains with virulent JEV does not always reliably produce encephalitis; titration end-points are not sharp. Other less well defined host factors are also important in susceptibility (Huang, 1957; Huang and Wong, 1963).

As noted in previous sections, several different types of reportedly efficacious JE vaccines have been developed and administered to large numbers of humans; feasibility of vaccine construction is not an issue. However, none of the existing vaccines is ideal; significant problems still exist regarding vaccine safety, cost, and the requirement for booster immunizations.

1. Life-threatening adverse effects may be associated with currently available vaccines: although no cases of vaccine-related allergic encephalomyelitis have been attributed to the inactivated mouse brain vaccines, it is possible that some cases have occurred and were missed. The same is possible for cases of acute viral encephalitis, which could result from growth of the live attenuated vaccine virus within the central nervous system. The frequencies of these complications presumably are very low, but finite. The third major type of existing JE vaccine, the inactivated hamster kidney cell culture product, would appear theoretically to be relatively free from encephalitic complications. However, the possibility of a disaster resulting from inadvertent incomplete virus inactivation always exists.
2. The inactivated mouse brain vaccine is expensive: production costs are about $2.30 per dose or $4.60 per primary immunization (U.S. dollars). Information is not available on the costs of the two vaccines prepared in China. Both are probably less expensive than the mouse brain vaccine. The yield of JE virus in cell cultures is considerably lower than that of other viruses for which inactivated cell culture vaccines are practical (e.g., poliovirus), so it is likely that the cost per dose is proportionally much greater for the inactivated hamster kidney JE vaccine than for polio. Cost per dose of the live attenuated 5–3 strain vaccine is unknown.
3. Periodic booster immunizations are required for all three of the existing vaccines; none induces solid lifelong immunity with a single inoculation.

Induction of humoral immunity (neutralizing antibody) appears to be a good predictor of vaccine efficacy (Hammon and Sather, 1973; Morris et al., 1955). Because neutralizing antibodies are directed against the virion surface, a subunit vaccine prepared from the JE virus envelope glycoprotein (E protein) appears to be the safest alternative. However, available methods for separation of the E protein from virions or infected cells are too laborious for commercial application. Research on the molecular biology of the flaviviruses using recombinant DNA techniques is proceeding rapidly, and the gene coding for the E protein of JEV probably will be cloned and sequenced in the near future. The ideal JE vaccine would induce sustained (lifelong) antibody production to the E protein. To achieve this goal, novel E protein delivery systems must be developed, such as sustained release "depot" vaccine carriers, or self-replicating avirulent vectors into which the E protein

gene has been inserted, for example, vaccinia. The practicality of producing a safe E protein subunit vaccine through recombinant DNA technology remains to be determined.

Adequate field testing of a new JE vaccine will be difficult. The relatively low clinical attack rate of JE (maximum 100 to 200 per 100,000 in an epidemic in a highly selected population) will necessitate an extremely large study to document vaccine efficacy. To test a new vaccine with a predicted efficacy of 80 percent in a placebo-controlled trial, a study population in excess of 100,000 subjects would be required in most affected regions.

The need exists for an inexpensive JE vaccine of proven safety and efficacy. Although there are several apparently promising approaches to achieve such a vaccine, there are also a number of problems to be overcome, including ethical questions concerning the testing of a new vaccine against a product of presumed (but not proven) efficacy.

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Appendix D-7

The Prospects for Immunizing Against Mycobacterium leprae

DISEASE DESCRIPTION

Leprosy is a chronic infectious disease caused by Mycobacterium leprae, which grow predominantly in the skin and nerves. It is a spectral disease, in that patients present a wide variety of forms and symptoms. At one pole of the spectrum is tuberculoid leprosy: a strong cell-mediated immune response is mounted and the infection is localized and restricted, although often with concomitant damage to nerves. At the opposite pole is lepromatous leprosy: cell-mediated immune responses to antigens of M. leprae fail, and the organisms spread throughout the skin and nerves, often reaching 10 billion acid-fast bacilli per cm^2 skin.

Responses in the majority of patients are between these extremes. Because the organism grows in Schwann cells around the nerves, the classical symptoms of anesthesia, nerve damage, mutilation, and deformity are still found in about one-third of all cases. A comprehensive review of leprosy and strategies for its control has been presented by Bloom and Godal (1983).

The historical stigma associated with leprosy, which remains very strong in most countries of the world, often results in socioeconomic disruption of the lives of patients and their families, irrespective of treatment. Fear of this prejudice may inhibit patients who have early lesions from seeking treatment.

PATHOGEN DESCRIPTION

Mycobacterium leprae remains the only major human bacterial pathogen that cannot be cultivated in the laboratory. Until recently, scientific research depended on the ability to grow large quantities of

The committee gratefully acknowledges the efforts of B.R.Bloom, who prepared major portions of this appendix, and the advice and assistance of S.K.Noordeen. The committee assumes full responsibility for all judgments and assumptions.

the organism in the nine-banded armadillo and on studies of localized infection in mice. A new report on laboratory-induced leprosy in monkeys suggests that mangabey monkeys may provide an important nonhuman primate model in which to study the transmission and pathogenesis of the disease (Wolf et al., 1985).

The waxy coat and cell wall structure of M. leprae are similar to those of other acid-fast bacilli, including M. tuberculosis, but DNA hybridization studies indicate that M. leprae has a rather distant taxonomic relationship to other known mycobacteria. M. leprae is thought to grow very slowly in vivo, with a doubling time of between 7 and 14 days (Shepard and McRae, 1965).

HOST IMMUNE RESPONSE

Antibodies against M. leprae are found in patients with all stages of the disease and may be most prevalent in those with lepromatous leprosy. There is a remarkable inverse correlation between the histopathological classification of disease severity in leprosy and the level of cell-mediated immune responses. Patients at the tuberculoid end of the spectrum have cell-mediated immunity and few bacilli; patients at the lepromatous end exhibit no cell-mediated immunity to M. leprae and high bacillary loads (Bloom and Godal, 1983).

DISTRIBUTION OF DISEASE

Geographic Distribution

Leprosy is found in virtually all tropical and subtropical countries. A third of all cases occur in Southeast Asia, and the remainder occurs primarily in Africa and South America. At one time, the disease existed in epidemic form in Norway and in other parts of Europe and the Mediterranean, but for reasons not entirely clear it has been largely eliminated from Europe (Irgens, 1980; Sansarricq, 1981, 1982).

Disease Burden Estimates

Considerable disagreement and uncertainty exist regarding the epidemiology of leprosy infection, transmission, and pathogenesis (Fine, 1982). The estimates given below relate to clinically symptomatic cases of disease, that is, where permanently impaired neurological function or tissue damage is apparent.

The Special Programme for Research and Training in Tropical Diseases (SPRTTD, 1985) conservatively estimates the global prevalence of leprosy to be 10.6 million cases, the vast majority of which are in developing countries. Information on incidence is scant, but several studies suggest that the annual incidence roughly approximates one-tenth of existing prevalence (Noordeen, personal communication, 1984). On

this basis, the annual global incidence would be about 1.06 million cases. For the purposes of this assessment, all new cases are assumed to have some clinical symptoms that result in some permanent (but possibly mild) disability (category D) —such as minor neurological deficit. The proportion of cases in children (14 years of age and younger) is approximately 20 percent of detected cases (17.4 to 29 percent; Noordeen, personal communication, 1984) and is probably higher for new cases. Hence, it is assumed that 25 percent of new cases occur in the 5 to 14 years age group and 75 percent in the 15 to 59 years age group.

One-third of leprosy patients face the threat of progressive disease, which can result in severe physical disability and social stigmatization (SPRTTD, 1985). Patients who contract the disease early in life or who progress rapidly will spend part of their remaining lifetime with mild, moderate, and then severe chronic disability (categories D, E, and F). Patients who contract the disease later in life or who progress slowly may not experience the most severe consequences (some patients will not progress but will have already incurred mild chronic disability, category D). Most of the progression is thought to occur before the age of 60 (Bloom, personal communication, 1985). Hence, for ease of calculation, all transitions to moderate or severe categories are assumed to occur in the 15 to 59 years age group.

Leprosy is unique in exhibiting such progression and variability; it does not easily lend itself to description by the use of the morbidity category/age group matrix used in this exercise to display the incidence of disease consequences. To permit comparison of leprosy with other diseases by this method, some simplification of the epidemiological presentation of the disease is necessary.

One-third of all cases in any cohort are assumed to progress. This represents, on the average, 353,333 patients moving each year to the moderate or severe status. Half of these transitions are assumed to be to the moderate category and half to the severe category (176,667 to each). The annual number of new cases in category D in the 15 to 59 years age group (795,000) is reduced accordingly (by 353,333).

The life expectancy of leprosy patients is probably shortened by a few years, more so in the lepromatous forms (Sansarricq, 1981). Deaths are probably a consequence of other infections or intoxications (e.g., tetanus) resulting from physical injury or mutilation and/or depressed immune function. However, few data exist on which to base death estimates. It has therefore been assumed (arbitrarily) that leprosy patients have a 1 percent higher death rate than the general population. For a normal crude death rate of 10 per 1,000 for developing countries, this would result in about 1,060 premature deaths within a population of 10.6 million leprosy patients.

These deaths are assumed to occur predominantly before the age of 60 years (i.e., 90 percent in the 15 to 59 years age group and 10 percent in the 60 years and over age group).

The annual disease burden estimated to result from leprosy is shown in Table D-7.1.

TABLE D-7.1 Disease Burden: *Mycobacterium leprae*

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work								
C	Severe pain, severe short-term impairment, or hospitalization								
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.s.	265,000	n.s.	441,667[a]	n.s.		n.s.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.s.		n.s.	176,667	n.s.		n.s.
F	Total impairment		n.s.		n.s.	176,667	n.s.		n.s.
G	Reproductive impairment resulting in infertility		n.s.		n.s.		n.s.		n.s.
H	Death		n.s.		n.s.	954	n.s.	106	n.s.

[a]Number represents new cases (795,000) minus progressing cases (353,333).

PROBABLE VACCINE TARGET POPULATION

Epidemiologists disagree about the probable vaccine target population for a leprosy vaccine. Some have argued that it would be most cost-effective to restrict vaccination to high-risk individuals identified by traditional case detection methods. Another alternative would be to target the vaccine for newly infected individuals. Recent serologic studies indicate that there is at least one unique antigen on M. leprae, a phenolic glycolipid (SPRTTD, 1985). It may be possible to develop serologic techniques using the glycolipid and monoclonal antibodies to screen high-risk populations. The practicality and cost of screening, if it becomes feasible, would have to be weighed against the simplicity of general communication to populations at risk.

The committee chose to focus on a vaccine candidate for leprosy that could be delivered to the general population. If the candidate were sufficiently immunogenic in young children, it could be delivered as part of the World Health Organization Expanded Program on Immunization (WHO-EPI).

Vaccine Preventable Illness*

An exceptionally small proportion of all leprosy cases (probably less than 0.1 percent) occurs in children under 5 years of age. Thus, a vaccine that is 100 percent effective, that could be delivered in infancy, and that could provide long-lasting immunity theoretically could prevent 100 percent of leprosy cases.

SUITABILITY FOR VACCINE CONTROL

The belief that leprosy is suitable for vaccine control is based, in part, on reports of successful immunotherapy in patients with lepromatous leprosy (Convit et al., 1979, 1983; Samuel et al., 1984; SPRTTD, 1985). These patients received a mixture of killed armadillo-derived M. leprae and live BCG (Bacillus Calmette-Guérin) vaccine. Skin test conversions and histopathological upgrading of lesions occurred in about 65 to 85 percent of the lepromatous patients, and some appeared to be cured. It should be noted that all patients in this study received concurrent antimicrobial chemotherapy (ethical considerations require that such therapy be provided).

Results from four major controlled trials provide other evidence for the suitability of leprosy for vaccine control. In those trials, BCG had some protective efficacy against leprosy, ranging from 80 percent in Uganda to 20 percent in Burma (Fine, 1985).

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

It is expected that immunization of uninfected or unexposed individuals also could produce a cell-mediated immune response. Ideally, this could thwart development of overt clinical disease. However, if the vaccine were somewhat less effective, it might only reduce the severity of the disease (i.e, convert multibacilliferous lepromatous forms of the disease to borderline or tuberculoid forms).

Alternative Control Measures and Treatments

Problems in leprosy control have been extensively reviewed (Bloom and Godal, 1983; Sansarricq, 1981; SPRTTD, 1985).

Despite the efforts of governmental and private agencies and the availability of an inexpensive and nontoxic therapeutic drug, control of leprosy transmission has not been achieved. A significant amount of transmission probably occurs prior to the diagnosis of leprosy. Also, it appears that some organisms that are not genetically drug resistant, persist in sequestered places and are protected from the effects of chemotherapy; these may reappear and disseminate when chemotherapy is stopped. Finally, drug resistance has become a problem.

The recent emergence of both secondary and primary resistance to dapsone, the principal drug used to treat leprosy patients for the past 20 years, is a compelling reason for vaccine development. The prevalence of drug resistance has risen in some areas from 1 to 2 cases per 1,000 in 1966 to as high as 100 per 1,000 in 1981 (SPRTTD, 1983). Resistance to dapsone, compounded by the considerable expense of rifampin and the generally unacceptable side effects (skin coloration) of clofazimine, necessitates the pursuit of preventive, immunization strategies.

PROSPECTS FOR VACCINE DEVELOPMENT

Approaches to immunotherapy and immunoprophylaxis for leprosy have recently been reviewed in the report of the SPRTTD (1985), which provides an extensive bibliography of research on leprosy treatment and prevention.

Efforts to develop potential leprosy vaccines are based on the following premises and observations:

- Cell-mediated immunity rather than antibody production against M. leprae antigens is required for protection.
- Human M. leprae can be grown in sufficient amounts in armadillos to provide a first-level vaccine for human use.
- Purified, killed, armadillo-derived M. leprae have been shown to produce cell-mediated immunity in mice and guinea pigs (Mehra and Bloom, 1979; Shepard et al., 1978).
- Killed, purified M. leprae have been shown to induce protection in mice against challenge with viable M. leprae (Shepard, 1983).

- Armadillo-derived M. leprae vaccine has been purified to exclude virtually all contaminating armadillo proteins and is currently being produced by the Wellcome Research Laboratories in the United Kingdom. It is being used in Phase 1 sensitization studies in 31 normal human volunteers in Norway, where it has been found to engender delayed hypersensitivity without untoward side effects (SPRTTD, 1985). It also is being tested in 64,000 contacts in Venezuela as part of a controlled prophylactic trial.
- BCG trials provided some degree of protection against leprosy in Burma (22 percent), New Guinea (44 percent), S. India (33 percent), and Uganda (80 percent) (Fine, 1985). These results suggest that more specific vaccines are needed and that different levels of protection may be obtained in different populations. Consequently, multiple field trials will be needed to evaluate any candidate vaccine(s).

Researchers are now examining the characteristics of three potential leprosy vaccines: a killed M. leprae vaccine; a combined M. leprae and BCG vaccine; and a vaccine containing cultivable, cross-reactive mycobacteria.

Initial studies with volunteers have focused on the capacity of the purified, killed M. leprae vaccine to induce cell-mediated immunity in naive individuals in a nonendemic area (Gill et al., In press). All recipients became sensitized to skin test reactivity, and there were no untoward side effects. If it were to be tested in the field, an M. leprae vaccine could lead to resistance or could limit any future disease to a subclinical infection. At a minimum, it might decrease transmission by shifting potential cases of the disease from the multibacilliferous lepromatous form to the tuberculoid form. The disadvantage of this strategy is that patients already harboring lepromatous leprosy in a subclinical or unrecognized form would not be protected and would continue to spread infection.

The combined vaccine, consisting of killed M. leprae and live BCG, has been shown by Convit to induce cell-mediated immunity in previously unresponsive lepromatous patients and to markedly improve their disease status (see above). A large percentage of patients showed a dramatic reduction in the number of bacilli in the tissues. Field trials of this combined vaccine in prophylactic studies involving 64,000 patient contacts in Venezuela and a total population in Malawi (108,000 people) are based on the premise that the combined vaccine will both immunize naive individuals and have some immunotherapeutic effects in patients harboring subclinical infections (SPRTTD, 1985).

Recently, two strains of cultivable mycobacteria isolated in India, ICRC bacillus and Mycobacterium W, have been reported to be immunologically cross-reactive with M. leprae and capable of inducing sensitization to M. leprae antigens in lepromatous patients. The results appear to be similar to those produced by the combined vaccine described above (Deo et al., 1983; Talwar and Fotedar, 1983). However, in a mouse model neither vaccine was effective in preventing M. leprae infections (SPRTTD, 1985). While both sets of findings are only preliminary, the possibility exists that a cultivable organism that can be mass-produced at much lower cost than armadillo-derived bacilli

might possess both specific components cross-reactive with antigenic determinants required for protection against M. leprae and foreign determinants comparable to those in BCG (capable of exerting an adjuvant effect or altering unresponsiveness).

Following Phase 1 trials with vaccines produced from these organisms and some small-scale sensitization studies, several large vaccination trials should be carried out to compare them with the combined vaccine and the killed M. leprae vaccine. The relative effectiveness of these vaccines should be examined in several different populations. Plans for the testing of these various vaccine candidates are described in the report of the SPRTTD (1985).

Efforts are under way to produce a second stage vaccine using recombinant DNA technology. Little is known about the molecular biology of mycobacteria, but researchers recently have been able to clone and express M. leprae genes in E. coli (Young et al., 1985). Clones producing M. leprae-specific antigenic determinants can be identified using monoclonal antibodies. Recent evidence suggests that some recombinant clones express antigens recognized by immune T-lymphocytes, and it will be important to develop means of introducing these potentially protective genes into a cultivable mycobacterium. The result would be specific protective antigens in an inexpensive and easily cultivable vaccine. If this introduction can be achieved, the possibility of introducing genes for antigens of a variety of infectious agents into BCG that have unique adjuvant activity could lead to the development of a unique multivaccine vehicle (Bloom and Mehra, 1984).

Neither the killed preparation of M. leprae nor the cross-reactive cultivable organism is expected to produce significant untoward side effects, although they will have to be monitored in early Phase 1 trials. BCG has been used in hundreds of millions of people over the past 50 years with remarkably few side effects, can be given at birth, and costs only 5 cents per vaccination. It is anticipated that if there are any side effects, they will occur primarily in members of the general population who harbor subclinical infections. Theoretically, the induction of cell-mediated immunity through vaccination could result in some nerve damage in these individuals. The Venezuelan trials of the combined M. leprae and BCG vaccine have found no evidence of such an effect (Convit et al., 1983).

Because leprosy develops slowly and has a relatively low prevalence, comprehensive vaccine field trials generally will require 5 to 15 years of follow-up. To optimize the chances of early demonstration of protection, the early studies of vaccines were undertaken in contacts of lepromatous patients, who are thought to have an increased risk (four-to sixfold) of contracting leprosy.

The discovery of a potential animal model for lepromatous leprosy (Wolf et al., 1985) may mean that vaccine efficacy trials in humans will require less time and resources than previously expected. However, determination of the duration of protection in humans will still be a lengthy process.

Problems to be Overcome

Major economic, political, and social problems may hamper efforts to evaluate potential vaccine candidates for leprosy. Research and field studies to determine which vaccines are most appropriate for specific populations will be expensive. Some areas of the developing world that possess the field and clinical expertise to participate in vaccine trials and evaluations lack the national political commitment to initiate and carry out essential background work. The most significant social question will be whether the identification of an effective vaccine for leprosy and the development of suitable delivery systems can overcome the universal stigma associated with the disease.

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Appendix D-8

The Prospects for Immunizing Against Neisseria meningitidis

This appendix addresses both the prospects for improving vaccines against groups A, C, Y, and W135 Neisseria meningitidis, which are relatively promising, and vaccines against group B, for which significant problems remain to be resolved. Meningococcal disease, the associated immunological phenomena, and vaccination strategies have been recently reviewed (Frasch, 1983, 1985; Griffiss, 1982; Peltola, 1983).

DISEASE DESCRIPTION

Neisseria meningitidis causes about one-third of all cases of bacterial meningitis worldwide. The disease is severe; the untreated case fatality rate approaches 100 percent. The case-fatality rate for properly treated meningitis ranges from 5 percent toward the end of an epidemic when disease is expected, to 15 percent earlier in an epidemic or for sporadic cases. About 10 percent of survivors have neurological sequelae, primarily hearing and vision loss, but motor disorders, seizure disorders, and mental retardation also may occur. This pathogen also causes fulminant meningococcemia, a syndrome of rapidly developing intravascular coagulation and profound shock, pneumonia, arthritis, and carditis. The case-fatality rate for fulminant meningococcemia is from 50 to 70 percent, despite treatment. During epidemics, fulminant

meningococcemia accounts for about 5 percent of cases. Meningococcal disease occurs in two epidemiologic forms: endemic and epidemic. Endemic disease is caused by strains of differing serogroups and serotypes (i.e., A, B, C, Y, and W135), occurs with greatest frequency in infants and very young children, and is uniformly distributed throughout the world. In developed countries, strains of

The committee gratefully acknowledges the efforts of J. McL.Griffiss, who prepared major portions of this appendix, and the advice and assistance of R.Austrian, C.Broome, C.Frasch, E.C.Gotschlich, and A.Reingold. The committee assumes full responsibility for all judgments and assumptions.

serogroups B, C, Y, and W135 account for almost all cases. It is unknown whether a similar distribution of serogroups accounts for endemic disease in developing countries.

Epidemic meningococcal disease occurs both as focal outbreaks and diffuse epidemics. Outbreaks are usually caused by strains of a single serogroup or serotype (the epidemic strain) or both. Epidemic disease often occurs in older children and young adults (as well as in infants and young children) and is geographically restricted. In the developed world prior to World War II, most outbreaks were caused by strains of serogroup A; this remains the case in most developing countries today. Epidemics of group A disease occur at roughly 10-year intervals in the African meningitis belt and may be associated with periods of warfare or economic decline. Group B and group C strains are also capable of causing epidemics, although the epidemics are usually less severe than those caused by group A strains. Group W135 has only a limited epidemic potential, and group Y is not known to have caused outbreaks.

Previous Efforts at Vaccination

Six purified capsular polysaccharides have been tested as vaccines in man. In individuals over 2 years of age, vaccines from strains of groups A, C, Y, and W135 reliably induce bactericidal antibodies that provide protection. The group C polysaccharide is not effectively immunogenic in children under 2 years of age. The group A polysaccharide induces low but protective levels of antibody in this age group. Protection as predicted by antibody levels afforded by the group C vaccine is long-lived in those who respond. The duration of protection against group A meningococcal disease appears to be related to world geography and age at time of immunization. Children under 4 years of age have a rapid fall off in antibody. In comparing the African and Finnish experience, the duration of protective efficacy appeared shorter in Africa. One contributing factor may be the presence of endemic malaria; Williamson and Greenwood (1978) observed a rapid decline in group A polysaccharide antibodies in individuals with malaria. Studies have not been conducted of the kinetics of antibodies to the polysaccharides of groups Y and W135.

The group B capsule is a homopolymer of alpha 2–8 linked sialic acid and, as such, closely resembles the terminal sialic acid residues on a number of gangliosides, and on polysialyl glycopeptides found in fetal brains. The polysaccharide is also found on the common gut organism E. coli K1; and, as a result, most individuals have primarily IgM antibodies to the B polysaccharide. These antibodies apparently do not facilitate bactericidal killing of the group B organisms.

In assessing the effectiveness of the current A, C, Y, and W135 tetravalent vaccine, it is imperative to distinguish between efficacy in the individual vaccinee and efficacy as a public health policy. in vaccinees older than 2 years of age, these four polysaccharides are highly immunogenic (about 85 to 95 percent) with no significant adverse reactions. Administration of the tetravalent vaccine may be less than optimally effective as a public health policy, however, for at least two reasons:

- Epidemics frequently occur in highly mobile populations in which new "recruits" enter the epidemic focus as older residents leave. In such settings, vaccination programs must occur frequently or be continuous. The model for this setting is the military recruit camp, but similar situations have existed during outbreaks of group A disease in the U.S. Pacific Northwest and in Africa.
- Endemic disease is concentrated in infants and very young children who do not respond to antigens in the existing vaccine(s) or in whom the duration of immunity is short.

In general, public health policy has resulted in the utilization of a staggered, case-triggered, pulse-vaccination model that has been shown to be only partially effective. When vaccination has been maintained for long periods of time, as in Finland and in the U.S. military, meningococcal disease has been reliably controlled. Such an approach is quite expensive and involves a level of medical infrastructure that is not present in most countries, even the most highly developed. Thus, even though safe and effective for certain age groups, the currently available vaccines have been used infrequently in the developed world. Their potential benefits in developing countries are difficult to predict from studies conducted in developed countries or from their even more limited use in developing countries. Certain improvements (described below) would undoubtedly render existing meningococcal vaccines more valuable in combating meningococcal diseases in developing countries.

PATHOGEN DESCRIPTION

The meningococcus is a common commensal of human nasopharyngeal mucous membranes. It spreads from person to person by aerosol droplets. Its colonization of the nasopharynx is often unnoticed in terms of causing disease, and it may persist there for up to 18 months. Factors that influence acquisition are poorly understood.

Only encapsulated N. meningitidis strains can cause disseminated disease. The capsule is composed of linear polymers of various sugars that have been chemically characterized. Of the 12 defined capsular groups, only groups A, B, C, Y, and W135 are clinically important. Because the capsular polysaccharides are both chemically and immunologically distinct, a polyvalent approach to vaccine development using these polysaccharides has been necessary. Only the group B polysaccharide is not effectively immunogenic in humans.

The outer membrane of the meningococcus also contains protein and lipooligosaccharide (LOS) antigens that, collectively, comprise the serotypes. The same serotype antigens may be found in different serogroups, although those of group A strains are largely distinct from those of the other serogroups. To date, at least five protein serotypes and five LOS serotypes have been associated with epidemic disease. Endemic disease, in contrast, is caused by strains of much greater serotype diversity. However, vaccines containing noncapsular surface antigens are the only practical option for a group B vaccine.

Progress has been made in developing vaccines containing the outer membrane protein antigens. Recent studies using such vaccines adsorbed to adjuvants indicate that the immunogenicity of some proteins can be markedly improved. Vaccines utilizing LOS antigens have not been clinically evaluated.

HOST IMMUNE RESPONSE

Organisms residing in the nasopharynx are able to invade the blood stream through as yet unknown mechanisms. Once in the bloodstream, they are rapidly lysed by complement-mediated mechanisms if antibodies are present. Their clearance from the blood stream is markedly improved by the presence of bactericidal antibodies that initiate immune lysis and by the presence of polymorphonuclear leukocytes (Reller et al., 1973). Such antibodies may be directed at the capsular polysaccharides (Käyhty et al., 1981) or at LOS and proteins. The former are responsible for serogroup designations, the latter two for serotype designations (Griffiss et al., 1984).

In the absence of antibody, the capsular polysaccharides interfere with the deposition of complement components on the surface of the organism. Among the various capsular groups, the group B capsule is the most "anticomplementary." This property allows bloodstream survival of the organism, which is necessary for invasion of the meninges. Organisms are able to survive in the sera of infants who lack maternally passed bactericidal antibodies and whose complement systems are poorly developed. They are also able to survive in individuals with isolated deficiencies of immunoglobulins, particularly IgM, and complement components, and in those in whom circulating IgA blocks bactericidal activity (Griffiss, personal communication, 1985). Griffiss (1982) has theorized that the first two mechanisms could account for endemic disease, the third for epidemic disease.

Protection against invasive N. meningitidis disease results primarily from circulating antibodies that induce immune lysis (Goldschneider et al., 1969). Protective antibodies are induced to the capsular polysaccharides and to protein and LOS antigens. The antigenic determinants found on the meningococcal capsular polysaccharides are also present on a number of other gram positive and gram negative bacteria. Naturally acquired immunity as measured by the presence of bactericidal antibodies is directed primarily against the capsular polysaccharides and is largely derived from exposure to cross-reacting organisms. Following the decline of maternally acquired antibodies (primarily directed at serotype antigens) between 2 and 6 months of age, serum bactericidal activity gradually rises (to an extent that varies with location and individual) and is clearly detectable in most children by 18 to 36 months of age. It then rises slowly, reaching adult levels by 12 years of age.

The mechanism by which bactericidal antibodies are induced is unclear. Colonization with N. lactamica has been documented in populations throughout the world. It occurs at an earlier age than does colonization with N. meningitidis and is often, but not invariably,

associated with the induction of bactericidal activity. Nasopharyngeal colonization with meningococcal strains also results in the induction of bactericidal antibody, although induction of antibody to the capsular polysaccharides is variable. Enteric colonization with organisms of other genera that elaborate the same or similar surface antigens as those of the meningococcus occurs commonly and also probably induces bactericidal antibody. Induction of capsular antibodies early in life is the goal of the current polysaccharide vaccines.

DISTRIBUTION OF DISEASE

Geographic Distribution

The Sahel region of Africa represents a geographic and epidemiologic special case. The climatically defined area between the 300 mm and 1,100 mm isohyets (lines joining points receiving equal amounts of precipitation over a specified period of time) has been termed the "meningitis belt." It extends across the Sahel from Ethiopia to eastern Senegal and The Gambia. An extension extends southward through Uganda, Kenya, and Tanzania. All or parts of the following countries are included in the belt: Ethiopia, Sudan, Central African Republic, Chad, Niger, Nigeria, Cameroon, Benin, Ghana, Ivory Coast, Burkina Faso (formerly Upper Volta), Mali, Guinea, Senegal, The Gambia, and Mauritania. In this belt, massive epidemics of group A meningococcal disease occur about every 10 years. Because of the devastating nature of these predictable epidemics, global strategies for preventing meningococcal disease must be targeted to this area to be successful.

Meningococcal disease is seasonal. Survival of the meningococcus in aerosolized droplets is highly dependent on humidity, but not temperature. Humidity conditions favorable to transmission of the meningococcus can occur in temperate climes in late winter and early spring, and with the transition from dry to wet seasons in South America and sub-Saharan Africa. During these times the incidence of endemic disease increases and epidemics occur.

Epidemics have also occurred in recent years in southwest Asia, Nepal, India, China, Brazil, and Finland. Epidemic meningococcal disease does not occur in deserts or in invariably humid climates, such as in rain forests or deserts. Endemic meningococcal disease is presumed to be distributed worldwide, although data are not available from most areas.

Disease Burden Estimates

Little reliable data are available on the worldwide incidence of meningococcal meningitis from which to estimate the disease burden arising from endemic and epidemic disease caused by N. meningitidis. The following calculations have been extrapolated from those studies that have been published and rely, of necessity, on informed judgment.

TABLE D-8.1 Population of Countries in the African Meningitis Belt

Country	Population (millions)
Benin	3.9
Burkina Faso	6.7
Cameroon	9.4
Central African Republic	2.6
Chad	5
Ethiopia	32
Ghana	14.3
Guinea	5.6
Ivory Coast	9.2
Kenya	19.4
Mali	7.6
Mauritania	1.8
Niger	6.3
Nigeria	88.1
Senegal	6.5
Sudan	21.1
Tanzania	21.2
The Gambia	0.7
Uganda	14.3
Total	275.7

SOURCE: Population Reference Bureau (1984).

Epidemic Meningococcal Meningitis

Incidence rates in epidemic years were estimated from data for the 1979 epidemic in Burkina Faso (Broome et al., 1983). The rates derived by this approach are consistent with those reported from Zaria, Nigeria (Greenwood, 1984), with the exception of the youngest age groups, for which they are higher. To derive an estimate of the population at risk of epidemic disease, the total population of countries in the African meningitis belt was assumed to be at risk (Table D-8.1). No attempt was made to include estimates of epidemic disease occurring in other parts of the world. This omission is counterbalanced to an unknown extent by including in the calculation of populations at risk, portions of some countries (e.g., Ivory Coast, Cameroon, and Guinea) or major population centers (e.g., The Gambia, Nigeria, Kenya, and Benin) that lie outside the belt.

Epidemics are assumed to occur about every 10 years, and an average fatality rate of 10 percent is assumed on the basis of reported fatality rates in recent epidemics (Broome et al., 1983; Greenwood, 1984; Greenwood et al., 1979).

Table D-8.2 shows the annual number of epidemic N. meningitidis cases and deaths estimated to occur on adopting these assumptions.

TABLE D-8.2 Estimated Annual Number of Epidemic N. meningitidis Cases and Deaths

Age Group (years)	Incidence per 100,000 Population	Population	Number of Cases	Average Number of Cases	Case Fatality Rate (percent)	Average Number of Deaths
Under 5	736	50,337,040	370,481	37,048	10	3,705
5–14	600	73,588,680	441,532	44,153	10	4,415
15–59	200	138,034,520	276,069	27,607	10	2,761
60 and over	50	14,189,760	7,095	709	10	71

TABLE D-8.3 Estimated Annual Number of Endemic N. meningitidis Cases and Deaths

Age Group (years)	Incidence per 100,000 Population	Population	Number of Cases	Case Fatality Rate (percent)	Number of Deaths
Under 5	5.4	498,559,000	26,922	20	5,384
5–14	6.1	909,366,000	55,471	10	5,547
15–59	2.4	1,954,728,000	46,913	25	11,728
60 and over	0.8	232,347,000	1,859	80	1,487

Endemic Meningococcal Meningitis

Incidence rates for endemic meningococcal meningitis can be derived from the data reported by Cadoz et al. (1981) for Dakar, Senegal (a city that lies outside the major meningitis belt). In the absence of alternative methods for estimating the disease burden, these rates are assumed to apply to the populations of all developing countries. Age-specific mortality rates were estimated from data presented by Cadoz et al. (1981). The number of endemic meningococcal cases and deaths derived from the application of these assumptions is shown in Table D-8.3.

It is assumed that all acute cases of N. meningitidis fall into morbidity category C. The total average number of endemic and epidemic N. meningitidis cases and deaths is shown in Table D-8.4.

Information is scant on the sequelae of meningococcal meningitis in developing countries. On the basis of observations of a recent epidemic in The Gambia by Griffiss (personal communication, 1985), it was assumed that 15 percent of survivors suffer mild (category D) neurological sequelae (e.g., hearing loss), and that 1 percent suffer moderate (category E) chronic neurological problems. Adopting these assumptions yields the total disease burden for N. meningitidis shown in Table D-8.5.

TABLE D-8.4 Disease Burden: Neisseria meningitidis--Acute Epidemic and Endemic Cases

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity									
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work									
C	Severe pain, severe short-term impairment, or hospitalization	Meningitis	63,970	14	99,624	14	74,520	14	2,568	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		9,089	n.a.	9,962	n.a.	14,489	n.a.	1,558	n.a.
	Survivors		54,881		89,662		60,031		1,010	

TABLE D-8.5 Disease Burden: Neisseria meningitidis--Total Disease Burden

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity									
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work									
C	Severe pain, severe short-term impairment, or hospitalization	Meningitis	63,970	14	99,624	14	74,520	14	2,568	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	Neurological sequelae, e.g., mild hearing loss, motor disorders	8,232	n.s.	13,449	n.s.	9,005	n.s.	152	n.s.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Neurological sequelae, e.g., vision loss	549	n.s.	897	n.s.	600	n.s.	10	n.s.
F	Total impairment			n.s.		n.s.		n.s.		n.s.
G	Reproductive impairment resulting in infertility			n.s.		n.s.		n.s.		n.s.
H	Death		9,089	n.s.	9,962	n.s.	14,489	n.s.	1,558	n.s.

Uncertainty in the Disease Burden Estimates

The omission of epidemic disease occurring outside the sub-Saharan meningitis belt from the estimates is probably only partly counterbalanced by including certain nonepidemic risk areas or major population centers from some countries within the belt in estimated calculations. Major epidemics occur in regions of the world other than the recognized belt (e.g., South America), and minor ones occur in many parts of the world, including such developed countries as Finland (Feldman, 1982). These facts suggest that the estimate, at least for epidemic disease, is probably a minimal one.

Calculations for endemic disease—based on the extrapolation of data from one region to the entire developing world—are highly uncertain because of the limited data base. Rates of incidence of endemic disease suggested by Gotschlich (1984) would yield lower estimates of the total burden of disease.

PROBABLE VACCINE TARGET POPULATION

Two separate vaccine strategies are required to combat disease caused by N. meningitidis—one for endemic disease and another for epidemic disease. Endemic disease is frequently caused by serogroup B. Most of this endemic disease would not be preventable by the candidate vaccine for serogroups A, C, Y, and W135 considered in this report. Some endemic disease caused by serogroups C, Y, and W135 might be prevented, however, by a conjugated polysaccharide vaccine administered universally to infants and young children through the World Health Organization Expanded Program on Immunization (WHO-EPI). Such a vaccine would have to be efficacious with doses given to children under 1 year of age. For the calculations that follow (and that are shown in Chapter 7), the vaccine target population for endemic disease is considered to be the birth cohort in developing countries.

Epidemic disease most often occurs in young children, but it also may occur in older children and young adults. It is most frequently caused by serogroup A strains. Because persons over age 2 generally respond well to immunization with polysaccharides from serogroups A, C, Y, and W135, successful prevention of most epidemic disease should be feasible with the candidate vaccine. The universal immunization program described above eventually would (in the steady state for which calculations have been made) protect against most epidemic disease. However, an interim vaccine strategy would be necessary to prevent disease in persons too old to have been included in the initial WHO-EPI effort. Two alternative strategies could be used: one would involve targeted vaccination of susceptible individuals in areas where epidemics are anticipated, the other would consist of universal preschool immunization.

Vaccine Preventable Illness*

Estimates of the proportion of the disease burden that is potentially vaccine preventable are based on the assumptions that an improved vaccine for groups A, C, Y, and W135 (but not B) that confers long-lasting immunity when administered to infants is developed and used universally in the developing world.

Estimates provided by Griffiss (personal communication, 1985) suggest that, for the meningitis belt, about 95 percent of epidemic disease is caused by group A, 4 percent by group C, and 1 percent by group W135. Group Y does not appear to cause epidemics, and epidemic group B disease has rarely been reported from developing countries. (However, an epidemic of group B disease is currently occurring in Chile.) Of endemic disease in the Sahel (i.e., in the absence of epidemics), about 60 percent is caused by group C, 35 percent by group A, 3 percent by group W135, and the remainder by groups B and Y (Griffiss, personal communication, 1985). (Endemic cases may continue to occur during an epidemic.) These estimates are in agreement with the suggestion by Feldman (1982) that group B is responsible only for localized outbreaks or sporadic cases.

These patterns cannot be extrapolated, perhaps, to the entire developing world. However, in parts of the world other than the meningitis belt, the general pattern that group B is a relatively minor cause of disease seems to be consistent. For example, the Brazilian epidemics of the 1970s were caused by group A or group C (Feldman, 1982). Although there are some indications that group B is now a problem in Niger (Griffiss, personal communication, 1985), there is little basis on which to predict shifts from the pattern described above.

The small proportion of the total meningococcal disease burden in developing countries that is caused by group B (for which the vaccine will not provide protection) suggests that a very high proportion of the disease burden will be vaccine preventable. In the youngest vaccine recipients, only partial protection will be provided until the full course of immunization (probably at least two doses) has been completed. However, relatively little disease occurs in children under 6 months of age.

Based on the above considerations, it is estimated that 95 percent of meningococcal meningitis is theoretically preventable with a hypothetical fully effective improved vaccine for groups A, C, Y, and W135.

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

SUITABILITY FOR VACCINE CONTROL

Meningococcal disease theoretically is well suited to control by active immunization for several reasons: the organism is pathogenic only in man, antibody appears to provide protection, protective antibody is reliably induced in infancy in most individuals, and an opportunity to induce humoral immunity exists between the decline of maternal antibodies (2 to 6 months) and the onset of disease (after 6 months). Current treatment regimens are quite effective if initiated promptly, but they are expensive and difficult to administer in developing countries. They are followed also by unacceptably high rates of neurologic sequelae. The social and economic burden of this disease, particularly in Africa, is enormous. There is a critical need to develop an appropriate preventive strategy.

Alternative Control Measures and Treatments

Chemoprophylaxis provides an alternative approach to the prevention of meningococcal disease. Prior to the development of polysaccharide vaccines, Chemoprophylaxis with sulfonamides was used routinely. Since 1960, many strains of meningococci have become resistant to sulfonamides, and sulfonamide prophylaxis can no longer be recommended.

Chemoprophylaxis with rifampin is an alternative that has been used in developed countries. Because of its expense, however, it is unsuited for use in developing areas (Blakebrough and Gilles, 1980). Minocycline is also effective, but it causes a rather high rate of side effects (18 to 35 percent).

In most of Africa, meningococcal meningitis is treated with a single dose (3 g) of chloramphenicol in oil (Wali et al., 1979). The case fatality rate following such treatment is about 10 percent. Other treatment regimens have been developed, but none is superior to chloramphenicol.

PROSPECTS FOR VACCINE DEVELOPMENT

Gotschlich (1984) has comprehensively reviewed the development of existing meningococcal vaccines and their characteristics.

The principal drawback of the existing polysaccharide vaccines against N. meningitidis (groups A, C, Y, and W135) is their inability to induce protective, long-lasting immunity in young children and in some older individuals. The reasons for this failure are poorly understood. Additional research is required into the basic mechanisms of the immune response to polysaccharides. The poor immunogenicity of some capsular polysaccharides may be a result of immunologic tolerance, suggesting the presence of cross-reactive human epitopes. Genetic differences and environmental factors (such as co-existing infection) also may affect the response to polysaccharide antigens. Finally, researchers need to learn more about the optimum size and physiochemical form of polysaccharides selected for use in vaccines.

Additional research is required on the basic mechanisms of the immune response to polysaccharides, including the role of serum IgA in meningococcal immunity.

Potential New Vaccines

To gain worldwide acceptance, a new vaccine for N. meningitidis should (1) be safe; (2) be immunogenic in infancy, or at least by 6 months of age; (3) be inexpensive to make and administer; (4) be easy to administer; and (5) provide long-term protection. The capacity to provide herd immunity, possibly via reduction in carriage of meningococci, would be an added advantage. The most promising candidates to date are the protein conjugate vaccines.

Polysaccharide-protein conjugates have been studied extensively in the preparation of H. influenzae type b vaccines. Early clinical studies demonstrated that these vaccines, prepared with high molecular weight polysaccharide attached either to diphtheria or to tetanus toxoid, provide greater immunogenicity than the polysaccharide alone in children under age 3 (Lepow and Gordon, 1984; Zahradnik and Gordon, 1984). Research on the potential use of such conjugates in N. meningitidis vaccines will focus on determination of the best polysaccharide-protein combinations, the optimal chain length of the polysaccharide, and the degree and method of coupling the protein.

The committee believes the prospects for improved (conjugate) vaccines for groups A, C, Y, and W135 are promising, but that for reasons discussed below the short-term prospects for a broadly effective vaccine against group B are not good.

Other potential candidates for N. meningitidis vaccines include the lipopolysaccharide-derived (LPS) vaccines (Zollinger and Mandrell, 1980; Zollinger et al., 1979), live vaccines, immune complex vaccines, vaccines from surface peptides and fimbriae, and anti-idiotype vaccines.

The development of successful immunization programs would also be greatly aided by better descriptive epidemiological and immunologic information for meningococcal disease from various populations over time. Conclusions drawn from studies in developed countries are of limited use for developing areas of the world. Also, a standardized methodology for measuring antipolysaccharide antibodies of different isotypes does not yet exist. The development of new laboratory methods to profile the immune response to N. meningitidis and to identify bacterial strains will increase the usefulness of future clinical trials.

Obstacles to Development of Vaccines Against Group B Strains

The major obstacle to preparation of a vaccine against this important cause of meningococcal meningitis is that the group B capsular polysaccharide is not an effective immunogen in mice or in 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 and Mandrell, 1983; Zollinger et al., 1979, 1982). 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 by using adjuvants or 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 cross-reactivity 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 8 months, appear to be of reasonably high avidity, and are bactericidal with human complement (Zollinger and Mandrell, 1983; Zollinger et al., 1979, 1982). 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.

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Appendix D-9

The Prospects for Immunizing Against Parainfluenza Viruses

Much of the information available on morbidity and mortality arising from parainfluenza virus infections is contained or referenced in the proceedings of two recent symposia on acute respiratory infections (Clyde and Denny, 1983; Douglas and Kerby-Eaton, 1985).

DISEASE DESCRIPTION

The disease problems caused by the four parainfluenza viruses (PIV) in developing countries have not been well characterized. Most of the specific information comes from developed countries. In the latter, PIV-1 and PIV-2 usually have been associated with croup (laryngotracheal bronchitis), while PIV-3 has been found more frequently with bronchiolitis and pneumonia. These are broad generalizations, however, and symptoms vary widely even on first infection. PIV-4 appears to cause only mild upper respiratory infections and has never been associated with severe disease in young children. The parainfluenza viruses reinfect frequently during childhood, but the diseases associated with reinfections are generally milder than those caused by initial infections.

PATHOGEN DESCRIPTION

The parainfluenza viruses are species in the Paramyxoviridae family. Much 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

The committee gratefully acknowledges the efforts of A.S.Monto, who prepared major portions of this appendix, and the advice and assistance of F.W.Denny, W.P.Glezen, and K.McIntosh. The committee assumes full responsibility for all judgments and assumptions.

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 glycoprotein 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 denatured 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 (Chanock et al., 1963). In addition, evidence from volunteer studies in adults suggests 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 the assumption 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.

DISTRIBUTION OF DISEASE

Geographic Distribution

Seroepidemiological studies indicate that the parainfluenza viruses are ubiquitous; even isolated populations have been found to possess antibodies against them. The severity of diseases caused by the viruses and the age of initial infection may vary in different parts of the world, but little information is available on these topics.

Croup appears to be less common in the developing world than in developed countries, but the reasons for this situation are not known: it is possible that the PIV infection simply takes a different clinical form. Also, it is unclear to what extent PIV infections play a role in the life-threatening respiratory diseases often seen in children in developing countries.

Disease Burden Estimates

Examining mortality statistics provides some perspective on the burden of parainfluenza virus infection in children in developing countries, especially those under age 5. The causes of childhood mortality often change as a country develops. Initially, diarrheal diseases may be the leading cause of death. General development and the implementation of oral rehydration programs may reduce the impact of these diseases and increase the proportion of deaths due to respiratory infections. With further development, mortality from acute

respiratory infections also begins to decline. The reasons for these shifts are complex, in part because of the effects of malnutrition, environmental pollution, and other risk factors.

Even with complete mortality statistics it is difficult to establish the role of the parainfluenza viruses, because numerous other pathogens also cause respiratory infections in children. Respiratory syncytial virus (RSV) and adenoviruses (particularly in the Far East) produce similar symptoms. In addition, bacterial superinfections may occur and can contribute to mortality.

The disease burden estimates for parainfluenza virus infection are shown in Table D-9.1, and their derivations are described in Appendix B. It should be emphasized that these estimates are uncertain because of the lack of data on parainfluenza in developing countries. Acute lower respiratory tract illness from parainfluenza virus infection may eventually contribute to chronic obstructive pulmonary disease (Glezen, 1984). However, no attempt has been made to include such a contribution in chronic morbidity estimates. This aspect of the disease burden of the parainfluenza viruses requires periodic reevaluation.

PROBABLE VACCINE TARGET POPULATION

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 the first 6 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 (at least in the United States). It is likely that a subunit vaccine could be incorporated into the World Health Organization Expanded Program on Immunization (WHO-EPI) delivery schedules, possibly in combination with other vaccines that are delivered at an early age, e.g., DTP.

Because 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., 1984), a vaccine administered to pregnant women also might be effective. 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.

Vaccine Preventable Illness*

The vaccine envisaged by the committee would require two early doses and probably additional doses to boost or maintain immunity. In

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

TABLE D-9.1 Disease Burden: Parainfluenza Viruses

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	58,410,000	3	4,321,500	3				
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	11,682,000	5	864,300	5				
C	Severe pain, severe short-term impairment, or hospitalization	1,168,200	7	86,430	7				
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	116,820	n.a.	8,643	n.a.		n.a.		n.a.

the United States, the major portion of illness caused by PIV-1 and PIV-2 occurs after 6 months, but the pattern of PIV-3 illness is similar to that of RSV, involving a considerable amount of severe illness under 6 months of age. The first dose of vaccine probably could be administered at about 6 weeks, with a second dose 2 to 3 months later. Vaccinees would be only partially protected during this period. All cases occurring in older age groups (6 months to 4 years) would be vaccine preventable. Deaths probably would occur predominantly in infants, with a disproportionate number in very young infants who would not be fully protected.

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. Given these considerations, an estimated 80 percent of the total disease burden arising from parainfluenza virus illnesses in the developing world theoretically would be vaccine preventable.

SUITABILITY FOR VACCINE CONTROL

Diseases caused by parainfluenza viruses types 1 and 2 occur predominantly after 6 months of age in the United States, so an opportunity exists to deliver the vaccine prior to the peak of illness, assuming the distribution is the same in developing countries. A lower proportion of parainfluenza virus type 3 disease 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.

Alternative Control Measures and Treatments

No specific treatment exists for parainfluenza virus infection that is suitable for widespread use in developing countries. Antibiotic therapy may reduce the problems associated with secondary bacterial infections if they occur. In severe cases, supportive care (i.e., hospitalization) may reduce the fatality rate. Aerosolized ribavirin has been found to be useful in some situations (Gelfand et al., 1983; McIntosh et al., 1984).

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.

Very little ongoing work is directed toward a PIV vaccine. All early attempts were with high-titer inactivated vaccines; mutant attenuated vaccines have not been examined.

Predictions about the chances of successful development of PIV vaccines are difficult to make. Because reinfections with PIV-1 and PIV-2 appear to be less frequent than 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 epidemicity at 2-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, which are a possible source of large quantities of inexpensive antigen, which in turn 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, that is, 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.

Some recent progress toward PIV vaccines has been reported by the National Institute of Allergy and Infectious Diseases (1985). Purified HN and F glycoproteins from PIV 3 have been developed by the University of Alabama as a candidate vaccine. Cold adapted PIV 3 mutants have been developed by investigators at Marshall College of Medicine, and tests in humans are planned. In addition, approaches using purified viral fusion proteins are being investigated (National Institute of Allergy and Infectious Diseases, 1985).

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Appendix D-10

The Prospects for Immunizing Against Plasmodium spp.

DISEASE DESCRIPTION

Malaria is a leading cause of death in the developing world. The pathogenic agents are four protozoan species of the genus Plasmodium. The disease is characterized by the destruction of erythrocytes and by a systemic inflammatory response resulting in chills, fevers, headache, and other manifestations. Malaria caused by Plasmodium falciparum, or "malignant malaria," is fatal in a high proportion of cases if untreated, but responds well to appropriate chemotherapy. Although a variety of drugs are highly effective against malaria parasites, the organisms, especially P. falciparum, develop resistance to drugs in general use. For this reason, the control of malaria through chemotherapy requires continuous development of new drugs. A comprehensive review of recent research on malaria and its control has been prepared by the Special Programme for Research and Training in Tropical Diseases (SPRTTD, 1985).

PATHOGEN DESCRIPTION

The four protozoa that cause malaria in humans, P. falciparum, P. vivax, P. ovale, and P. malariae, have complex life cycles (Reisberg, 1980). Sporozoites are inoculated into humans by female anopheline mosquitoes during a blood meal. The sporozoites rapidly disappear from the circulation into liver parenchymal cells. There, each proliferates into thousands of individual merozoites. When mature, the merozoites rupture the hepatocytes and enter the circulation. Many are cleared from the circulation and destroyed, but the remainder attach to specific receptor sites on the red blood cell where they penetrate the red cell membrane and begin further development.

The committee gratefully acknowledges the efforts of C.L.Diggs, who prepared major portions of this appendix. The committee assumes full responsibility for all judgments and assumptions.

During the intraerythrocytic phase, the merozoite develops into a trophozoite (ring form), which then enlarges and begins to divide. Nuclear division initiates the schizont stage. Each schizont contains 6 to 24 merozoites, depending on the species. Proliferation of the merozoites leads to rupture of the erythrocyte, and the cycle begins again. A small number of the merozoites that enter red blood cells develop into male and female gametocytes. These do not rupture the red blood cells and require ingestion by the anopheline mosquito for further development.

Fertilization of the gametocytes occurs within the stomach of the mosquito. The parasite then undergoes several additional changes that lead to the production of sporozoites. Their inoculation into a new human host starts the cycle again.

In P. vivax and P. ovale, some sporozoites may remain dormant in hepatic cells for months or years; these are referred to as hypnozoites. When they do begin to proliferate, they may cause a relapse, often long after the primary infection. Such relapses do not occur with p. falciparum or P. malariae. The four species also differ in disease manifestations.

HOST IMMUNE RESPONSE

The immune response to malaria also is quite complex. Shortly after infection, antibodies that react with a wide variety of parasite antigens can be detected in the blood; however, this serologic response does not indicate a significant degree of immunity to subsequent infection. Reinfections usually are clinically less severe, as judged by the fever curve, although this effect is minor. individuals reexposed to infected mosquitoes have repeated episodes of malaria (Miller et al., 1984).

Repeated infections eventually lead to a relative increase in immunity, however, which is made apparent by the profound difference between the clinical manifestations of malaria in young children and in adults. Young children have the most severe attacks, often resulting in death if untreated. By adulthood, most individuals who live in endemic areas have developed a degree of immunity such that reinfection results in a relatively mild disease. After repeated episodes of infection, some individuals may become almost entirely refractory to challenge with P. falciparum (Miller et al., 1984). Nevertheless, absolute immunity is difficult to establish; instead, a continuum appears to exist from high susceptibility to high resistance.

Immunity to malaria is largely antibody-mediated. The classic studies by Cohen et al. (1961) in The Gambia indicated that antiparasitic activity could be transferred with IgG from donors in endemic areas, but not with control IgG from Europeans. The antiparasitic activity of immune serum also can be demonstrated in in vitro experiments (Chulay et al., 1981).

The immune response to sporozoites, the stage of the parasite responsible for transmission of disease from mosquito to man, is of great interest. Antibodies to sporozoites can be found in individuals

living in areas endemic for malaria (Nardin et al., 1979). It is possible that these antibodies may convey immunity to challenge, but this has not been well studied. The recent review by Miller et al. (1984) provides further detailed information on the immune response to malaria, as well as on prospects for vaccination.

DISTRIBUTION OF DISEASE

Geographic Distribution

Malaria can exist in any climate suitable for the anopheles mosquito. Although the highest incidence of malaria is in the tropics, temperate zones are not immune. In the past, such areas as the southern United States had very high incidences of the disease. At present, the bulk of the malaria disease burden is in sub-Saharan Africa, South Asia, Oceania, and South America (Stürchler, 1984).

Disease Burden Estimates

It is difficult to obtain reliable information on the worldwide incidence of malaria. The World Health Organization is the major source of such information. Estimates over the past decade have been in the range of 100 to 300 million cases of malaria and 1 to 2 million malaria-related deaths annually (Lancet, 1975; Wyler, 1983). Sub-Saharan Africa is the largest endemic focus. Asia and Central and South America also have large areas where malaria is highly prevalent. It is estimated that 365 million people live in areas where malaria is highly endemic and where no specific antimalaria measures are used. Those living in areas where malaria is endemic but where some measures are used number an additional 2.217 billion. Thus, nearly half of the world's population is at some risk (SPRTTD, 1985).

Estimates of disease rates provided by Walsh (personal communication, 1985) have been used as a starting point for disease burden calculations. In the most highly endemic areas (without control), it is presumed that all infants (birth cohort about 11 million, presuming a crude birth rate of 32 per 1,000; see Chapter 4, Table 4.1) become infected in the first year of life. In other endemic areas with some control it is assumed that 20 percent of the birth cohort (about 90 million) becomes infected in the first year of life, that is, about 14 million, for a total of 25 million infant infections each year.* An

additional 25 million cases are assumed to occur during the annual seasonal malaria epidemics that are common in India, Pakistan, the Middle East, southern China, and Central America. In addition, about 100 million reinfections are estimated to occur annually in heavily endemic regions, as immunity to the parasite wanes, for a total annual incidence of about 150 million cases.

Seasonal epidemic and reinfection cases are divided into the four age groups used in the disease burden analysis according to the relative populations of these age groups (see Chapter 4 and Population Reference Bureau, 1984). Annual deaths in the under 5 years age group are assumed to be about 1 million, in line with an estimate by Gilles (1981). This yields a case fatality rate of 3.5 percent for this group. Although no data exist on which to base case fatality rates in older age groups, they have been estimated in such a manner as to reflect a decline in disease severity through middle age (5 to 14 years, 0.75 percent; 15 to 59 years, 0.25 percent), followed by an increase in older populations (60 years and over, 0.47 percent). These computations yield a total of 1.5 million deaths, or an overall case fatality rate of 1 percent.

The assignment of cases to morbidity categories used in this analysis reflects the general pattern of increased severity in younger age groups (under 5 years, 10 percent in morbidity category A, 40 percent in category B, 50 percent in category C; 5 to 14 years, 25 percent in category A, 50 percent in category B, 25 percent in category C; 15 to 59 years, 50 percent in category A, 40 percent in category B, 10 percent in category C; 60 years and older, 50 percent in category A, 40 percent in category B, 10 percent in category C).

Table D-10.1 shows the distribution of morbidity and mortality estimated to arise from malaria infections using the assumptions outlined above.

PROBABLE VACCINE TARGET POPULATION

The total population at risk of malaria is estimated to be 2.6 billion (SPRTTD, 1985). This includes 365 million persons in highly endemic regions and an additional 2.217 billion in areas where control measures have reduced the endemic level. Table D-10.2 shows the size of the birth cohort at risk of malaria based on the most recent available data for specific regions.

For calculation of the potential benefits of each vaccine candidate, it is necessary to decide the likely target population. For the envisaged second generation vaccine, anticipated to be based on the circumsporozoite proteins of P. falciparum, P. vivax, P. ovale, and P. malariae, it is assumed that it eventually would routinely be delivered to the whole birth cohort at risk, that is, 78 million infants.

*It is possible that less than one-fifth of children in moderately endemic areas contract the disease in the first year of life because the risk in some of these areas may be relatively low. It is also likely that the estimated birth cohort for heavily endemic areas may be low since the crude birth rate of 32 per 1,000 reflects the developing world average. Many of the heavily endemic areas are in

sub-Saharan Africa, where the birth rate is much higher—45 per 1,000 in some areas. These two considerations would counterbalance each Other.

TABLE D-10.1 Disease Burden: Malaria--All

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Chills, mild fever	2,850,000	3	8,812,500	2	38,250,000	2	4,750,000	3
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Fever	11,400,000	4	17,625,000	2	30,600,000	2	3,800,000	4
C	Severe pain, severe short-term impairment, or hospitalization	Severe fever, complications of malaria	14,250,000	6	8,812,500	4	7,650,000	3	950,000	5
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		1,000,000	n.a.	264,375	n.a.	191,250	n.a.	44,375	n.a.

TABLE D-10.2 Derivation of Birth Cohort at Risk of Malaria, 1982

Region	Population in Malarious Areas (millions)	Birth Rate (per 100,000)	Births/Year (millions)
Africa (sub-Saharan)	350	45	16
Central America	53	31	2
South America	72	31	2
Asia (west of India)	154	30	5
Asia (mid-south)	794	30	24
East Asia and Oceania	973	30	29
Total	2,396		78

NOTE: Figures are the most recently available data for specific regions.
SOURCE: World Health Organization (1984).

For the envisaged first generation vaccine, anticipated to provide protection only against P. falciparum, there are reasons to believe that the target population would be smaller. Although it is estimated that 80 percent of malaria worldwide is caused by P. falciparum, there are regions where other strains are equally or more prevalent (World Health Organization, 1984). In these areas it is possible that a vaccine likely to protect against only one strain would not be used, especially if expensive. However, if a vaccine gave long-lasting protection (as assumed in the predictions on vaccine development), then it might be used despite these considerations since it would provide protection against the most serious form of the disease caused by P. falciparum It is therefore assumed that a P. falciparum vaccine would eventually be used routinely in the entire birth cohort of the at-risk population. This assumption may overestimate its potential health benefits since malaria may occur in areas where it may not be used, but it also overestimates the costs of vaccine where it may not be purchased. Immediately after licensure, both first and second generation vaccines are likely to be used in most of the other at-risk age groups.

Both vaccines probably will be used by travelers and the military. However, these groups are small in number relative to the local population at risk.

Assuming that a vaccine can be developed that induces immunity at an early age, it appears that a malaria vaccine could be introduced into the World Health Organization Expanded Program on Immunization. Such a vaccine would probably be readily adopted in endemic areas.

Vaccine Preventable Illness*

Because of its high burden of morbidity and mortality, P. falciparum malaria is now the focus of vaccine development. The first generation vaccine is likely to be limited to this strain; hence, it may only prevent that portion of the disease burden caused by P. falciparum.

The SPRTTD (1985) estimates that 80 percent of all malaria cases worldwide, including most of the serious disease, are caused by P. falciparum. Estimates for the proportion of deaths due to P. falciparum are not available, but it is assumed in estimating the disease burden for P. falciparum (Table D-10.3) that it is responsible for nearly all mortality (99 percent) in all age groups. The relatively greater severity of P. falciparum compared to the other Plasmodium species also is reflected in the distribution of cases into each severity category; for each age group, 70 percent of cases in group A are assumed to be due to P. falciparum, 80 percent of cases in group B, and 95 percent of cases in group C. All of the disease burden represented in Table D-10.3 is potentially preventable with the first generation P. falciparum vaccine. These estimates yield a disease burden value of 2,082,083, which represents 0.9859 of the total burden of malaria as potentially preventable with the first generation P. falciparum vaccine. A second generation vaccine against P. falciparum, P. vivax, P. malariae, and P. ovale could potentially prevent all malaria in humans.

SUITABILITY FOR VACCINE CONTROL

Control of malaria is badly needed, and vaccination offers the most hopeful approach. Vaccination could be achieved before the peak of disease because it appears that immunity can be induced. Immunization has the potential for preventing disease without manipulation of the environment and, therefore, is simpler than mosquito control. In addition, it is hoped that vaccine-induced immunity will last for months or years; protection by drugs and/or vector control is measured in days after cessation of administration. These theoretical advantages make vaccination highly suitable for malaria control.

Alternative Control Measures and Treatments

Various measures have been shown to be effective against malaria, and all should be exploited fully for the foreseeable future, whether or not a vaccine becomes available (Bruce-Chwatt, In press). The

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

TABLE D-10.3 Disease Burden: P. falciparum

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	1,995,000	3	6,168,750	2	26,775,000	2	3,325,000	3
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	9,120,000	4	14,100,000	2	24,480,000	2	3,040,000	4
C	Severe pain, severe short-term impairment, or hospitalization	13,537,500	6	8,371,875	4	7,267,500	3	902,500	5
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	990,000	n.a.	261,731	n.a.	189,338	n.a.	43,931	n.a.

first general category is vector control, which involves control of breeding sites and the use of insecticides to suppress vector populations. Efforts of this type have been successful in freeing limited areas from malaria, but the magnitude of the continuing effort required on a global scale would be prohibitive. The development of vector resistance to insecticides has forced vector control programs to use new and more expensive insecticides, which further complicates the effort.

The second major alternative, which has been highly successful in some instances, is chemoprophylaxis and chemotherapy. The development of parasite resistance to drugs, however, renders this approach less than optimal (SPRTTD, 1985). Currently, for example, there is no adequate prophylactic drug for prevention of P. falciparum malaria in Southeast Asia. Resistance to chloroquine and Fansidar are widespread. Mefloquine is highly effective as a prophylactic agent, but because resistance to this drug already has occurred in Southeast Asia (SPRTTD, 1985), its use as a prophylactic agent would certainly accelerate widespread resistance to it.

PROSPECTS FOR VACCINE DEVELOPMENT

Interest in vaccination against malaria is strong, and knowledge is accumulating rapidly on various aspects of the associated problems (Miller, 1985; Norrby, 1985; SPRTTD, 1985). A comprehensive review of strategies for the development of antimalarial vaccines has recently been published (Ravetch et al., 1985). Therefore, this section will be restricted to an outline of approaches and problems.

The prospects for vaccination against malaria were greatly aided by the development in the mid-1970s of methods for malaria culture in vitro (Traeger and Jensen, 1976). Modern immunologic and genetic engineering techniques have subsequently made possible various approaches to the problem of vaccination.

Several vaccination strategies are being investigated. Vaccines are being targeted against the sporozoite stage, with the objective of blocking infection and eliminating subsequent disease (and hence transmission). Vaccines targeted at merozoites (blood stage) or their interaction with erythrocytes could result in reduced morbidity and transmission. Additionally, blocking the development of the sexual stages of the parasite could interrupt transmission but would not affect any individual's illness.

Work is in progress on all these possibilities (Ravetch et al., 1985). Work on immunization against sporozoites is the most advanced. Possibly, a combination of these approaches will be necessary to provide the most effective protection.

Immunization with irradiated sporozoites provides protection against malaria in rodents (Nussenszweig et al., 1969). The surface of a sporozoite is largely composed of a single protein termed the circumsporozoite protein (Ravetch et al., 1985). The gene coding for the circumsporozoite protein of P. falciparum has been cloned, and the antigen has been expressed in E. coli (Dame et al., 1984). Knowing the

exact structure of the protein has made possible the design of a wide variety of antigens that can be tested for their ability to induce protective immunity (Ravetch et al., 1985). These antigens are being used in three different ways:

1. Synthetic peptides representing the relevant portions of the antigen molecule can be used in combination with a carrier of suitable molecular size in a semisynthetic vaccine (Miller, 1985; Nussenszweig et al., 1985).
2. Recombinant DNA products (fusion proteins), including the relevant antigenic sequences, can be used in a vaccine (Young et al., 1985).
3. Genes can be inserted into a microorganism, which then serves as the vehicle for immunization.

An example of the third approach is the experimental use of vaccinia virus as a carrier for Plasmodium knowlesi circumsporozoite protein genes in the immunization of experimental animals (Smith et al., 1984). Phase one clinical trials of candidate vaccines using the first two approaches with P. falciparum are expected to begin in the near future.

Unfortunately, the circumsporozoite protein may not be an optimal approach to vaccination against malaria. Sporozoites disappear rapidly from the circulation into hepatic cells, leaving little or no time for an anamnestic response after challenge. The escape of even a few sporozoites from the immune surveillance system could result in disease. For this reason, work continues on the development of vaccines based on the complex array of blood-stage and gametocyte antigens.

Progress and problems associated with the development of vaccines against the asexual erythrocyte stages of the parasite have been described by Ravetch et al. (1985). Such efforts currently have two major thrusts: identification of merozoite antigens for testing as potential immunogens, and investigation of the possibility of interfering with the interaction of merozoites with erythrocytes. Although these approaches appear to have considerable promise, more basic research is needed to identify a particular approach that is most likely to yield success.

Antigametocyte antibodies would prevent fertilization and development of the zygote in the stomach of the mosquito after a blood meal. A vaccine based on this approach would block transmission of the parasite but would not affect the clinical course of the disease in immunized persons; hence, it has been termed “altruistic.” Such vaccines might be used in combination and might slow the evolution of mutant parasites that escape destruction by developing new sporozoite/ merozoite antigens. Ravetch et al. (1985) also reviewed progress in this approach.

In summary, three potentially viable approaches for the production of a malaria vaccine are currently being studied. The sporozoite approach, which theoretically applies to all four Plasmodium species, is most advanced. Probably, a vaccine based on these antigens will be ready to be fielded within the next 5 years.

Problems

Although various observations suggest that vaccination against malaria may be possible, a number of factors suggest that development of a vaccine conferring effective long-lasting immunity against all or most strains and species will be difficult. Recrudesent infections may last as long as 2 years for P. falciparum to 30 years for P. malariae. Natural immunity builds slowly, and sterile immunity is rarely achieved (Miller, 1985; Perrin et al., 1984).

It may be possible, however, to raise the level of immunity (e.g., to sporozoite antigens) to a greater extent by vaccination since natural exposure to sporozoite before sequestration of the parasite in the liver is brief. In the case of antigenic fragments (e.g., from sporozoites), it may be possible to develop vaccines conferring long-lasting immunity by coupling fragments to carriers (e.g., toxoids), or by incorporating fragments into immunogenic bacterial fusion proteins. That protracted exposure to the natural disease is required for the development of immunity suggests that the parasite has evolved mechanisms for evading the human immune response. This may be particularly problematic in selecting merozoite antigens as candidate immunogens. Knowledge of parasite immune variation is incomplete, as is knowledge of the roles of humoral and cell-mediated responses in combatting the disease. These and other potential problems are discussed more fully by Ravetch et al. (1985).

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Appendix D-11

The Prospects for Immunizing Against Rabies Virus

DISEASE DESCRIPTION

Rabies is a rapidly progressive and uniformly fatal viral meningoencephalitis in humans caused by the bullet-shaped viral particles of the rabies group of Rhabdoviridae, genus Lyssavirus (Shope, 1984). All mammals are susceptible to rabies, although canine rabies presents the greatest threat to humans. Exposure to rabid dogs is responsible for about 99 percent of the approximately 35,000 reported cases of human rabies in the world each year (World Health Organization, 1984). The disease is a major viral disease in humans living in the tropics, but it is enzootic worldwide.

Rabies virus usually enters the body through breaks in the skin caused by the bite of an infected animal, but it also may be transmitted across mucous membranes, via the conjunctiva, and perhaps in aerosolized form across respiratory membranes. The virus is neurotropic, entering local nerve endings directly or after primary replication in muscle cells near the site of entry into the body. It then moves through the axonal cytoplasm toward the central nervous system, where the infection becomes symptomatic. The period from inoculation of virus to overt clinical disease may be as short as 10 days or as long as a year or more depending on several factors. These include the severity of the bite, the size of the inoculating dose, unknown factors leading to sequestration at the site of inoculation (Shope, 1984), and distance between the site of inoculation and the central nervous system.

Clinical illness begins with prodromal symptoms including moderate fever, malaise, headaches, and nausea. Paresthesias at the original inoculation site may occur as well. The illness progresses in 2 to 4 days to a full-blown meningoencephalitis, with typical symptoms of hyperexcitability, photophobia, paralysis, stiff neck, and convulsions. There is often increased muscle tension, which can be quite painful.

The committee gratefully acknowledges the advice and assistance of W.H.Wunner. The committee assumes full responsibility for all judgments and assumptions.

Hyperactivity of the sympathetic nervous system causes increased sweating, salivation, and lacrimation. Periods of extreme anxiety and maniacal behavior alternate with periods of calm awareness of surroundings, tempered with an ever-present sense of foreboding. Painful spasm of the muscles of deglutition leads to active refusal to take liquids (hydrophobia). This spasm may be elicited even by fanning the patient's face (aerophobia), a useful diagnostic sign. Periods of obtusion occur and progress into coma. Death ensues secondary to cardiac or respiratory failure, usually within a week of the onset of symptoms.

Presumptive diagnosis may be made by consideration of the history, presenting signs and symptoms, and clinical course. The diagnosis is confirmed by one of four methods: (1) observation of the typical inclusion bodies (Negri bodies) in nerve cells after appropriate staining of pathological specimens; (2) immunofluorescence staining of pathological specimens; (3) virus isolation through culturing in mice or other animals; and (4) direct and indirect immunoperoxidase staining of tissue (Shope, 1982, 1984).

Existing Vaccines and Limitations

A 1982 survey identified 74 manufacturers of rabies vaccine worldwide. Most produced vaccine on a small scale and used outdated and suspect technologies, such as adult animal brain cultures (World Health Organization, 1984). Vaccines produced in this way contain myelin, which can provoke a demyelinating immunological disease in the vaccinee.

Vaccines consisting of inactivated viruses grown in the brains of suckling animals are used in South America (Shope, 1984). Seven to fourteen injections are required. The virus is purified by centrifugation to reduce the vaccine's myelin content. Neurological reactions still occur with a frequency of about 5:100,000 vaccinees (Acha, 1981). These vaccines are effective and relatively inexpensive.

Prior to 1980, the rabies vaccine most used in developed countries for pre- and post-exposure prophylaxis was the duck embryo vaccine (DEV). It is inexpensive and potent, but requires from 17 to 23 separate injections to provide adequate levels of protective antibody. It does not induce the anti-N antigen response (described below) as well as do newer nerve tissue or cell culture derived vaccines (Shope, 1982). Immunological and neurological complications occur at low frequencies; neurological complications, including postvaccinal encephalitis and transient neuroparalytic illness, occur in 1:25,000 vaccinees and lead to death in 1:225,000 (Rubin et al., 1969). The DEV remains the major rabies vaccine in many parts of the world.

The newest available vaccine treatment for rabies is the human diploid cell vaccine (HDCV), which is an adapted, inactivated Pasteur strain of rabies virus. It is grown in human cell culture, inactivated, and purified by centrifugation. HDCV is very effective and produces protective post-exposure immunity with as few as six doses when used in conjunction with rabies hyperimmune globulin (RIG). It is less aller

genic than the DEV, although nonfatal allergic reactions do occur with a frequency of 1:625 vaccinees (Shope, 1984). In addition, a type of serum sickness may occur after administration of a booster dose following a completed primary immunization series (American Public Health Association, 1985).

Limitations on the use of the HDCV include the expensive production technology, difficulties with large-scale production, and the comparatively low yield of the method (Barth et al., 1984; World Health Organization, 1984). HDCV production may be too expensive for transfer to developing countries at this time.

Modified live virus (MLV) vaccines for immunization of animals are in use worldwide. These vaccines give about 3 years of immunity per series of injections. Adverse reactions include both immunological and neurological disease. Rabies itself can be produced by these live virus vaccines in animals immunosuppressed by steroids or by hematologic malignancies, such as feline leukemia. MLV vaccines recently have been field tested successfully in Europe as oral (enteric) vaccines for wild animals (World Health Organization, 1984). Previous attempts to use inactivated vaccines in this way were not successful.

There is a continuing need for a safe, easily produced, inexpensive vaccine for rabies in the developing world.

PATHOGEN DESCRIPTION

Rabies virus is a bullet-shaped particle 175 to 180 nm in length and 60 to 75 nm in width. Its capsid consists of five proteins designated G, N, M_1, M_2, and L. These include a glycoprotein (G), two matrix proteins, and a nucleoprotein (N). They are arranged helically and are enclosed in a lipid envelope through which the glycoprotein molecules extend 6 to 8 nm. In the center of the particle is a negative-sense RNA virion constituting the genetic material of the virus. A virion-associated RNA transcriptase is required to produce an active mRNA molecule from which protein translation can occur.

Attenuation of rabies virus has been shown to be related to replacement of arginine in position 333 by either isoleucine or glutamine in the viral glycoprotein (World Health Organization, 1984). Virus adapted to laboratory conditions is characterized by a fixed and shortened incubation period and by a tendency for viral particles to bud from the plasma membranes rather than from intracytoplasmic membranes as is typical of wild virus (Shope, 1984).

The nucleocapsid protein, N, is the antigen detected in immunofluorescence and complement fixation tests. The glycoprotein, G, induces neutralizing antibody (Shope, 1984). Four serotypes of the rabies group of Rhabdoviridae are recognized, and typing can be done using monoclonal antibodies. Differences among serotypes are apparently small enough that a vaccine made with a single type can protect against all types.

Rabies virus is able to maintain itself in an enzootic condition in many mammalian species, including dogs, foxes, raccoons, and bats. In part, this broad susceptibility results from an adaptation of the virus

leading to the production of large numbers of viral particles in the salivary glands. This replication may occur before clinical symptoms appear, facilitating transmission through the saliva. In addition, some animals may become viral secretors, spreading disease over long periods of time without developing the disease.

Humans are nontransmitting hosts for rabies virus. There are no documented cases of human-to-human spread of rabies, other than several cases resulting from corneal transplantation from unrecognized rabies victims.

HOST IMMUNE RESPONSE

Infection with rabies virus induces a humoral immune response, which in humans is not sufficient to prevent disease and death. Antirabies antibodies can prevent disease, however, if given passively before or shortly after infection. Possible explanations for this situation are that the humoral immune response is not rapid enough after infection, that a disrupted cell-mediated immune response (CMI) interferes with eradication of the virus, or that the intraneural infection is protected from the antibody response.

Rabies virus does cause immunosuppression of the CMI response through enhancement of suppressor T-cell action. A state of anergy develops in which cytotoxic T-cells fail to act against rabies and other antigens.

It also appears that low levels of protective antibody, resulting either from a suboptimal or decayed vaccination response, or from inadequate passive immunization, can lead to paradoxical immunosuppression and accelerated disease (Shope, 1984). The possibility of such an occurrence dictates that any new vaccine must be strongly immunogenic and that the duration of protective immunity be predictable.

Rabies infection also induces interferon production, which may provide some protection by slowing the progress of disease. It is not yet known if the interferon response could be utilized therapeutically in early post-exposure prophylaxis or treatment.

Finally, incomplete viral particles, called T particles (Shope, 1984), may be present in the infective inoculum or produced during the early course of disease. These particles cannot cause disease, but may interfere with the early course of infection by competing for cell membrane receptor sites, for example. The effect of T particles on the development of the immune response is not clear, although they may prolong the incubation period and allow more time for post-exposure prophylaxis.

DISTRIBUTION OF DISEASE

Geographic Distribution

Canine rabies is enzootic in at least 87 countries and on every continent except Australia. Such islands as Hawaii, New Zealand, and

Cyprus may never have experienced rabies. Such countries as Japan, Norway, Sweden, the United Kingdom, Taiwan, and Iceland have eliminated it and maintain this situation by strict quarantine (American Public Health Association, 1985). Ninety-nine percent of human rabies is related to exposure to canine rabies.

Although the distribution of rabies is worldwide, human and animal cases occur more frequently in the tropical zones (Schneider and Bögel, 1983). Rabies has become a particular problem in the growing urban areas of developing countries. All age groups are susceptible, but a disproportionate number of cases occur in those under 15 years of age, perhaps because of increased contact with animals.

The World Health Organization (WHO Expert Committee on Rabies, 1984; World Health Organization, 1984) collects information on the number of reported rabies cases worldwide. There are about 100 human cases in Europe each year; the primary reservoir of disease is sylvatic (in foxes) with spread to humans via dogs. South America has about 300 human deaths per year. Again, canines are the primary source, with an estimated 18,000 canine cases per year in the 1970s (World Health Organization, 1984). Rabies also is transmitted to cattle by vampire bats and is a major economic problem in South America. Africa and Asia are estimated to have 5,000 and 30,000 human cases per year, respectively. Wild dogs, through contact with domesticated dogs, are the primary source. These figures may be underestimates because of inadequacies in disease surveillance and death registration in many countries.

Disease Burden Estimates

The estimated human deaths from rabies in the developing world, by continent, are shown in Table D-11.1. The estimate for Oceania is based on an assumed incidence of 1 per 100,000 population. Other figures are based on information from the World Health Organization (1984). Population figures for calculating rates are from the 1984 World Population Data Sheet (Population Reference Bureau, 1984). The breakdown of cases by age group is based on the assumption that the incidence rates in the two younger age groups are twice those in the two older age groups. Disease burden estimates for rabies in the developing world are shown in Table D-11.2. These estimates are based on reported cases and may therefore underestimate the total disease burden.

PROBABLE VACCINE TARGET POPULATION

A few identifiable groups are at high risk for rabies and warrant pre-exposure immunization. They include veterinarians, wildlife conservation personnel in endemic areas, animal quarantine facility personnel, and laboratory and field personnel working with rabies (American Public Health Association, 1985). Unfortunately, it is difficult to identify other well-defined risk groups in the general

TABLE D-11.1 Estimated Number of Deaths from Rabies in Various Regions of the Developing World

			Age Group (years)							
			Under 5		5–14		15–59		60 and Over	
Continent	Total Number of Reported Deaths	Death Rate (per 100,000)	Number of Deaths	Death Rate (per 100,000)	Number of Deaths	Death Rate (per 100,000)	Number of Deaths	Death Rate (per 100,000)	Number of Deaths	Death Rate (per 100,000)
South America	300	0.076	62	0.11	108	0.11	116	0.05	14	0.05
Africa	5,000	0.942	1,258	1.3	1,839	1.3	1,725	0.65	177	0.65
Asia	30,000	1.130	5,616	1.63	10,889	1.63	12,028	0.817	1,468	0.817
Oceania	50	1	12	1.4	18	1.4	18	0.7	2	0.7
Total	35,350		6,948		12,854		13,887		1,661	

TABLE D-11.2 Disease Burden: Rabies Virus

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity									
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work									
C	Severe pain, severe short-term impairment, or hospitalization	Meningoencephalitis, paralysis, convulsions	6,948	7	12,854	7	13,887	7	1,661	7
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		6,948	n.a.	12,854	n.a.	13,887	n.a.	1,661	n.a.

population. Rabies transmission to humans depends primarily on the rabies situation in the local canine population, which fluctuates from place to place and from time to time. A rabies vaccination program would have to target most of the developing world's population to eliminate the incidence of human rabies. However, universal human pre-exposure immunization for the entire developing world is probably not a cost-effective strategy for rabies control.

The main role of a rabies vaccine for humans is to provide post-exposure prophylaxis for dog and other animal bites. Post-exposure prophylactic regimens have been published widely (American Public Health Association, 1985) and are effective, especially when used in conjunction with local wound care and rabies immunoglobulin (RIG). An estimated 5.6 million people worldwide need post-exposure treatment for rabies annually, but only 3.5 million actually receive it (WHO Expert Committee on Rabies, 1984). Efforts should continue to make rabies vaccine available to this high-risk group of exposed individuals through improved production and distribution networks. Educational efforts to increase awareness of this treatment also would be helpful. Such efforts are under way (World Health Organization, 1984).

The target population for two of the envisaged vaccines—the vero cell derived vaccine and the glycoprotein vaccine produced by rDNA technology—would be the group requiring post-exposure prophylaxis, estimated by the World Health Organization (1984) to be 5.6 million people each year.

The third envisaged vaccine—a live vector virus carrying the gene for the immunogenic glycoprotein—would, it is hoped, be economical for delivery as pre-exposure prophylaxis to high risk populations. These populations include all of India, Thailand, Pakistan, Bangladesh, Sri Lanka, Nepal, Indonesia, the Philippines, and Turkey, and the urban populations of Africa and Latin America (excluding Chile, Guyana, Jamaica, and Uruguay, where rabies is reportedly not a severe problem). In the steady state of vaccine usage, a vaccination program would be directed at the birth cohort in these regions, which is estimated from Population Reference Bureau (1984) data to be 53 million. Such a vaccine could probably be delivered through the World Health Organization Expanded Program on Immunization (WHO-EPI) to infants or young children.

Vaccine Preventable Illness*

Nearly two-thirds of individuals who require post-exposure prophylaxis currently receive it (World Health Organization, 1984). Extending this protection will need educational efforts to ensure that

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective.

exposed individuals seek and receive immunization, as well as a supply of potent vaccine that is more readily available in developing countries at an affordable price. Assuming that coverage can be extended to those who need it, the burden of illness represented in Table D-11.2 is fully preventable by post-exposure prophylaxis; that is, the proportion of the disease burden that is theoretically vaccine preventable is 1.0. Such an estimate is recognized to be optimistic for the near future, but as primary health care services are extended in the coming decades, it will become more realistic. The number of cases that occur because of modes of transmission that are difficult to recognize (i.e., other than animal bites) is considered to be negligible.

The vaccine that would be delivered to the birth cohort in high-risk areas (see above) would need to provide long-lasting, probably lifetime, protection. Based on this assumption, the entire disease burden in the populations of those regions is potentially vaccine preventable.

After review of information presented by Schneider and Bögel (1983), a value of 0.75 was chosen to represent that portion of the total disease burden that falls in the high-risk populations and that is theoretically preventable by the envisaged "vector" rabies vaccine.

SUITABILITY FOR VACCINE CONTROL

As stated above, rabies is potentially controllable through the use of rabies vaccine. However, suitable target populations are difficult to define at this time. Universal immunization may be too difficult technically and too costly to be a viable control strategy. Efforts in the near future should be directed toward providing post-exposure treatment for those in need.

Alternative Control Measures and Treatments

Post-exposure prophylaxis can be an effective prevention strategy. It requires production and distribution of a suitable vaccine, including an adequate cold chain. Optimal treatment also includes vigorous local wound cleansing and debridement and the use of RIG both systemically (parenterally) and infiltrated locally around the area of the wound. Education of the population to seek medical care after a possible exposure also is important.

Animal control, and specifically dog control, is the foundation of any rabies control program. According to the World Health Organization (1984), a national program for control of rabies in dogs should include (1) epidemiological surveillance to monitor canine rabies at the local level; (2) community education and participation to teach the importance of rabies, to elicit cooperation in dog control efforts, and to reduce exposure, especially among children; (3) immunization of family dogs and cats; (4) dog control through immunization and registration of family pets, and destruction of stray populations (control efforts could include animal contraception and mass immunization of dogs in endemic areas); and (5) centralized organization and implementation.

Finally, control measures can be taken with respect to wild animal reservoirs of rabies. Enteric immunization, using vaccine in bait food, may be a viable strategy. It is unlikely, however, that the disease can be eradicated from wild animal populations; thus rabies is likely to be a public health problem for the foreseeable future.

PROSPECTS FOR VACCINE DEVELOPMENT

New vaccine development is aimed at producing safe, effective, and inexpensive vaccines that can be given with a short immunization schedule. Several prospective vaccines are in various stages of development. A purified chick embryo cell vaccine (Barth et al., 1984) has been shown to induce antibodies in monkeys and to protect guinea pigs from disease after parenteral rabies virus challenge. The vaccine is inactivated using betapropiolactone, and is purified and concentrated by continuous zonal centrifugation. This is becoming a standard technique for removing allergenic materials from vaccine preparations.

Highly purified and concentrated forms of the standard duck embryo vaccine (DEV) also are being developed (Keller et al., 1984). These appear to be more immunogenic and less allergenic than their predecessors, allowing a reduced vaccination schedule. DEV has the advantage of being relatively inexpensive.

An alternative cell culture medium is a continuous, aneuploid cell line derived from the vervet monkey kidney, called Vero (WHO Expert Committee on Rabies, 1984). This process allows higher yields of vaccine antigens than the HDCV approach and may be cheaper and more appropriate for use in the developing world.

Wunner et al. (1983) have isolated rabies virus G protein fragments using an isoelectric focusing column. The G proteins form the glycoprotein knobs projecting through the viral lipid envelope and are responsible for eliciting virus neutralizing antibodies. The amino acid sequence of the G protein has been determined, and it has been produced using recombinant DNA technology (Malek et al., 1984). However, the product was not immunologically active, possibly due to a discrepancy in amino acid sequences. Correction of this discrepancy by site-directed mutagenesis appears to be possible (Koprowski et al., 1985; Lathe et al., 1985), which suggests that it may be possible to develop a totally synthetic rabies vaccine. Such a vaccine would contain neither whole virus particles nor the reactogenic components of cell culture vaccines. Thus, inactivation procedures would be unnecessary, and less complex purification techniques might be possible.

A recombinant vaccinia virus expressing the rabies G protein has also been developed (Koprowski et al., 1985; Wiktor et al., 1984). Inoculation of mice with the altered vaccinia vector virus induced immunity that was protective even against severe intracerebral challenge with live rabies virus (Lathe et al., 1985).

Finally, synthetic peptide and anti-idiotypic approaches to vaccines against rabies are under investigation (Koprowski et al., 1985).

From among these various vaccine strategies the committee chose to evaluate three candidates that it felt were technically feasible within a decade and were representative of fundamentally different strategies. The three candidates selected were a vero cell derived vaccine, a glycoprotein based vaccine, and a vector vaccine approach.

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Appendix D-12

The Prospects for Immunizing Against Respiratory Syncytial Virus

DISEASE DESCRIPTION

Information on morbidity caused by respiratory syncytial virus (RSV) infection in developing countries is very limited. Much of the available information is contained or referenced in the proceedings of two recent symposia on acute respiratory infections (Clyde and Denny, 1983; Douglas and Kerby-Eaton, 1985). Studies in South America and other regions have identified the virus in association with outbreaks of bronchiolitis and pneumonia. In developed countries, the agent reinfects frequently during childhood, but illness produced by reinfection is generally milder than that associated with the initial infection and rarely causes major problems. A similar pattern probably occurs in developing countries; therefore, a suitable vaccine should be able to reduce the severity of the initial infection.

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 was long considered by most to be a single serotype, but recent evidence suggests that two serotypes exist (National Institute of Allergy and Infectious Diseases, 1985). Early studies described aberrant strains that were poorly neutralized by postinfectious 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 about the surface structure of the virus and the antigens that may be

The committee gratefully acknowledges the efforts of A.S.Monto, who prepared major portions of this appendix, and the advice and assistance of F.W.Denny, W.P.Glezen, and K.McIntosh. The committee assumes full responsibility for all judgments and assumptions.

important for vaccine development. There are two major 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).

Monoclonal antibody that immunoprecipitates 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 yet been purified.

DNA complementary to the RSV genome has been cloned (Collins and Wertz, 1983; Venkatesan et al., 1983), and which of the cloned fragments correspond to the messages for the two surface glycoproteins has been investigated (Collins and Wertz, 1985). The genes coding for the major glycoprotein and fusion protein have apparently now been cloned (National Institute of Allergy and Infectious Diseases, 1985).

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 immunity, although this point cannot be made with certainty.

DISTRIBUTION OF DISEASE

Geographic Distribution

The presence of respiratory syncytial viruses as respiratory pathogens is quite uniform worldwide, but the severity and characteristics of disease caused by RSV probably vary. The age of initial acquisition also may vary, although antibody prevalence studies do not show any clear-cut differences between developed and developing countries.

Disease Burden Estimates

Examining mortality statistics provides some perspective on the burden of RSV infection in children in developing countries, especially those under age 5. The causes of childhood mortality often change as a country develops. Initially, diarrheal diseases may be the leading cause of death. General development and the implementation of oral rehydration programs may reduce the impact of these diseases and increase the proportion of deaths due to respiratory infections. With further development, mortality from acute respiratory infections also begins to decline. The reasons for these shifts are complex, in part because of the effects of malnutrition and other risk factors.

Even with complete mortality statistics it is difficult to establish the role of RSV, because numerous other pathogens also cause respiratory infections in children. Parainfluenza viruses and adenoviruses produce similar symptoms. In addition, bacterial superinfections may occur and can contribute to mortality.

The disease burden estimates for RSV are shown in Table D-12.1 and are described in Appendix B. It should be emphasized that these are uncertain estimates because of the lack of data on RSV in developing countries. The association between acute lower respiratory tract illness from respiratory syncytial virus infection and the development of chronic obstructive pulmonary disease remains speculative (Glezen, 1984). No attempt has been made to estimate possible chronic morbidity associated with RSV infection.

PROBABLE VACCINE TARGET POPULATION

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. This population could be reached through the World Health Organization Expanded Program on Immunization (WHO-EPI).

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).

TABLE D-12.1 Disease Burden: Respiratory Syncytial Virus

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	44,604,000	3	3,300,000	3				
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	14,868,000	5	1,100,000	5				
C	Severe pain, severe short-term impairment, or hospitalization	1,486,800	7	110,000	7				
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	148,680	n.a.	11,000	n.a.		n.a.		n.a.

Vaccine Preventable Illness*

If the distribution of RSV illness in developing countries is similar to that in developed countries, then a large proportion of RSV illness in the first year of life occurs below the age of 6 months. Thus, a vaccine would have to be delivered starting at a very early age. With the glycoprotein vaccine, partial protection would be achieved after the first dose, but full protection probably could not be achieved before age 6 months. An attenuated live vaccine might be expected to provide full protection at an earlier age if it only required a single dose. Because of these considerations, it is judged that only about two-thirds of the burden of RSV would be preventable with a glycoprotein vaccine, and about three-quarters would be preventable with an attenuated vaccine.

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. Calculations in Chapter 7 are based on the assumption that this will be possible (see Chapter 5). 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.

Alternative Control Measures and Treatments

There is no specific treatment for RSV infection that is suitable for widespread use in developing countries. Antibiotic therapy may reduce the problems associated with secondary bacterial infections. In severe cases, supportive care (i.e., hospitalization) may reduce the fatality rate. Aerosolized ribavirin has been found to be useful in some U.S. situations (Hall et al., 1983; Taber et al., 1983).

PROSPECTS FOR VACCINE DEVELOPMENT

History

Early investigators attempted to prevent RSV infection by inoculating susceptible children with a formalin-inactivated,

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

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 hyperreactivity 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. 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.

Other expected difficulties involve growing this virus in large quantities and also purifying it or its proteins.

Current Vaccine Development

Recent vaccine development has focused primarily on three approaches: live vaccines administered parenterally, live attenuated vaccines administered in the respiratory tract, and investigations of the RSV genome with a view to producing virus antigens by recombinant DNA techniques. 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. The genome of RSV has been sequenced and major products identified and cloned, as noted above (Collins and Wertz, 1985). This could lead the way to production of viral antigens by recombinant DNA techniques.

Clinical Trials

The major problem anticipated in clinical trials of RSV vaccines is 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 minimally 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.

Needs for Further 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.

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Appendix D-13

The Prospects for Immunizing Against Rotavirus

DISEASE DESCRIPTION

Rotavirus infection causes an acute diarrheal disease, although both in developed and developing countries there is a greater incidence of asymptomatic infection than there is of disease (Black et al., 1982a; Champsaur et al., 1984). In developing countries, rotavirus diarrhea persists for 10 or more days in 20 percent of patients and often results in moderate to severe dehydration (Black et al., 1982a).

In young infants, the illness generally begins with vomiting, followed by an explosive watery diarrhea and fever. Diarrhea is severe enough to result in isotonic dehydration in 15 to 20 percent of patients (Black et al., 1982a). The stools contain a relatively low concentration of sodium and may be mucoid in about 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 may occur in up to one-third of infants; however, recent epidemiological studies suggest that these signs are not specifically associated with rotavirus infection as previously believed (Champsaur et al., 1984).

Mortality may occur in patients with severe dehydration if adequate fluid replacement is delayed. This situation is more frequent in developing countries. Because the risk of significant dehydration is 10 times greater with rotavirus than with other etiologic agents in young infants (Black et al., 1982a), it is probably a major contributor to diarrheal deaths in this age group (Soenarto et al., 1981). 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). Surprisingly, however, Black et al. (1984) were unable to demonstrate a relationship between rotavirus infection and growth in Bangladeshi

The committee gratefully acknowledges the advice and assistance of R.E.Black, C.C.J.Carpenter, and H.F.Clark. The committee assumes full responsibility for all judgments and assumptions.

infants. This may be related to the lower incidence of rotavirus infection in this environment relative to E. coli infection. The incidence of rotavirus diarrhea in Bangladesh is estimated to be about 0.5 episodes per child per year (Black et al., 1982a). Neonatal infection is most commonly asymptomatic; the vast majority of neonates with evidence of rotavirus in the stool can be classified as carriers based on both lack of symptoms and the absence of an antibody response (Champsaur et al., 1984).

PATHOGEN DESCRIPTION

Rotavirus is a double-stranded RNA virus in the Reoviridae family, with a distinctive genome of 11 segments. Serological classification has been somewhat confusing; however, recent work permits separation of distinct serotypes based on outer capsid antigens detected by neutralization with hyperimmune sera (Wyatt et al., 1982). Serotype specificity may, in fact, be determined by two distinct genes, as is the case with influenza virus (i.e., the genes for neuraminidase and hemagglutinin). Four human serogroups have been defined, two of which contain cross-reactive animal rotaviruses, and at least three other serogroups exist containing animal rotaviruses (Hoshino et al., 1984). 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. Serotype 3 appears to be less prevalent, and serotype 4 has been found only in Europe (Kapikian, personal communication, 1984). Some heterologous cross-reactivity has been reported between animal and human serotypes 3 and 4 (Hoshino et al., 1984). The number and cross-reactivity of serotypes is obviously important for vaccine development.

Rotavirus serotypes may be divided into subgroups based on inner capsid antigens detected by complement fixation, ELISA (enzyme-linked immunosorbent assay), or immune adherence assays (Kapikian et al., 1981). The two well-defined subgroups, 1 and 2, also can be identified by differences in RNA patterns detected by electrophoresis in polyacrylamide-agarose gels (Kalica et al., 1981). Subgroup and serotype antigens are controlled by different segments of the virus genome.

In vitro cultivation of human rotaviruses has been difficult in the past. Strain Wa, the prototype serotype 1 rotavirus, was originally propagated in African green monkey kidney cells following 11 passages in newborn, germ-free piglets (Wyatt et al., 1980). Other strains, including DS-1, the serotype 2 prototype strain, were grown following rescue by genetic reassortment with readily cultivated bovine rotaviruses (Greenberg et al., 1981). Recently, many human rotaviruses (up to 75 percent of stool isolates) have been grown successfully 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 to 24 months age group, and by the third year of life essentially all members of populations in developing countries have serologic evidence of prior infection (Black et al., 1982b). 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 titer of 1:320 or greater in children less than 2 years of age is indicative of protective immunity and results in a relative risk of 0.3 for rotavirus diarrhea compared to individuals with low titers. The antibody measured may not be directed to the actual protective antigen, however, because titers of 1:320 in the child under 2 are still associated with a relative risk of 6.1 for rotavirus diarrhea compared to older children with similarly high titers (Black et al., 1982b). Although less well documented, an inverse relationship also appears to exist between intestinal antibody level and susceptibility to rotavirus diarrhea.

Asymptomatic, naturally acquired, neonatal rotavirus infection has been shown to reduce the severity of subsequent infections, but not to confer immunity against reinfection (Bishop et al., 1983). Recent studies employing a live oral bovine rotavirus vaccine (RIT 4237) indicate that a heterologous antibody response occurs in humans as well (Vesikari et al., 1983). Significant protection in immunized compared to nonimmunized infants was observed during a natural outbreak of rotavirus infection following the immunogenicity and safety trials of this vaccine in Finland (Vesikari et al., 1984).

At present no longitudinal data are available to address the question of the duration of protection. However, the period of vulnerability to symptomatic rotavirus infection is largely restricted to the first 2 to 3 years of life, indicating that immunity is acquired and may last for decades, if not for a lifetime.

DISTRIBUTION OF DISEASE

Geographic Distribution

Rotavirus infection has worldwide distribution. The 6 to 24 months age group is the principal target of infection in all regions. In temperate climates, the disease has a distinct seasonality, occurring

predominantly in the cold months of the year (Kapikian et al., 1982; Rodriguez et al., 1980). In contrast, in the tropical developing countries, rotavirus infection occurs year-round (Soenarto et al., 1981).

Disease Burden Estimates

The disease burden estimates for rotavirus, assuming current levels of intervention, are shown in Table D-13.1, and their derivations are discussed in Appendix C. The estimates based on a scenario in which oral rehydration therapy prevents 50 percent of rotavirus deaths are shown in Table D-13.2.

PROBABLE 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 should reduce the morbidity and mortality associated with clinical rotavirus infection in the early years. A secondary target might be women of childbearing age. This approach could increase the titer of rotavirus antibody in breast milk to protect nursing infants. The advantage of such passive protection is reduced by the already generally mild or asymptomatic nature of neonatal rotavirus infection and by the small protection afforded by maternal antibody against future symptomatic disease.

Rotavirus vaccine appears to be an ideal candidate for inclusion in the World Health Organization Expanded Program on Immunization (WHO-EPI). The target for rotavirus vaccine is precisely the age group currently covered by the EPI program. The immunogenicity of a rotavirus vaccine in this age group remains to be demonstrated, but no special problems are anticipated (in contrast to bacterial polysaccharide vaccines, which may elicit a poor antibody response). In addition, the compatibility of the live virus vaccine with other vaccines given by the oral route must be determined. These are vaccine development problems, and there are no theoretical reasons why they cannot be solved.

Vaccine Preventable Illness*

Assuming administration of a hypothetically perfect vaccine (conferring long-lasting immunity with one dose) in the first few months of life, the overwhelming majority of the disease burden

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

TABLE D-13.1 Disease Burden: Rotavirus

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	109,979,000	6	5,698,000	4	4,239,000	4	479,000	4
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	9,776,000	6	46,000	6	34,300	5	20,200	6
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea	8,729,000	7		7		7		7
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		873,000	n.a.		n.a.		n.a.		n.a.

TABLE D-13.2 Disease Burden: Rotavirus, Assuming Increased Use of Oral Rehydration Therapy

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	109,979,000	6	5,698,000	4	4,239,000	4	479,000	4
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	9,776,000	5.5	46,000	5.5	34,300	5	20,200	5.5
C	Severe pain, severe short term impairment, or hospitalization	Severe diarrhea	8,729,000	7		7		7		7
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		436,500	n.a.		n.a.		n.a.		n.a.

(mostly in children 6 to 24 months of age) could be averted. Hence, 100 percent of the total disease burden is assumed to be vaccine preventable.

SUITABILITY AND NEED FOR VACCINE CONTROL

Rotavirus is a major cause of diarrheal disease in infants in the developing world and accounts for a disproportionate percentage of dehydration episodes in this population. Because dehydration is a major cause of mortality in developing nations, the need to reduce the incidence of rotavirus disease is evident. The high incidence of this infection in the children of developed nations with excellent standards of hygiene (sanitary feces disposal, clean water supply, and adequate housing) suggests that improvements in the environment of developing nations will not reduce the incidence of the infection. Although breast-feeding has an impact on reducing neonatal infection, the prevalence of rotavirus infection in young infants in the developing world who continue to breast-feed indicates that breast-feeding alone will not be very helpful. Thus, vaccine control should become the major weapon against rotavirus.

Alternative Control Measures and Treatments

As noted above, alternative measures to control rotavirus are unlikely to succeed. There is no doubt that early use of oral rehydration therapy (ORT) will reduce the incidence of complicating dehydration in rotavirus infection and thus contribute to a reduction in mortality; however, this will not affect the incidence of infection and disease (Sack et al., 1978). Significant and unacceptable morbidity and mortality will continue to occur until a vaccine is available, especially in the areas with inadequate access to medical care. No practicable chemotherapeutic or chemoprophylactic agents are available other than ORT.

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 preexisting 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; National Institute of Allergy and Infectious Diseases, 1985). One approach uses a bovine rotavirus that grows well in tissue culture for induction of protection to cross-related human viruses. The most studied of such candidates is the Nebraska calf diarrhea virus, strain RIT 4237, which already has been tested in adults and young children (Vesikari et al., 1983). (This is designated attenuated high passage bovine rotavirus in Table 5.1.) 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 in at least 80 to 90 percent of infants 6 to 12 months of age (Vesikari et al., 1985). The bovine virus is from subgroup 1 and appears to provide protection against serotypes 2 and 3 as well (Vesikari et al., 1985). It is not yet clear whether this vaccine will provide adequate protection when administered in the first few months of life, whether it can be administered with oral polio vaccine, and what effect breast-feeding has on protection (Vesikari et al., 1985).

Another group of candidate rotavirus vaccines derived from bovine strains are also in development. These differ from RIT 4237 in strain origin, mode of passage, manner of propagation, as well as total cell passage level (Clark, personal communication, 1985). Collectively, these candidates are designated attenuated low passage bovine rotavirus in Table 5.1.

The third rotavirus vaccine candidate for which predictions are made in Table 5.1 is based on a rhesus monkey rotavirus isolate (RRV). This was passaged nine times in primary monkey kidney cell culture and seven times in FRhL-2 cell culture, a rhesus monkey lung diploid cell strain developed by the Food and Drug Administration as a potential substrate for vaccine production. Eighty-four percent of adult volunteers developed a neutralizing antibody response to RRV after oral administration of it. Studies in children are in progress (Kapikian et al., 1985; National Institute of Allergy and Infectious Diseases, 1985).

Human rotavirus grown in cell culture is another possible vaccine candidate (Kapikian et al., 1985). 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.

Another 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 used 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.

An additional 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 or coupling to carriers. Although some work is now being done in this area, the synthetic peptide 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 controlled challenge studies cannot be performed, 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, production and testing of human cultivated rotavirus vaccine strains in experimental animals and human volunteers, and 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.

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Appendix D-14

The Prospects for Immunizing Against Salmonella typhi

DISEASE DESCRIPTION

Typhoid fever is an enteric fever caused by the bacterium Salmonella typhi. The disease is characterized by systemic symptoms of fever, malaise, and abdominal discomfort. A transient rash, splenomegaly, and leukopenia often occur. The major complications of the disease are intestinal hemorrhage, occurring in 2 to 8 percent of cases, and intestinal perforation, occurring in 3 to 4 percent of cases. The rate of mortality with the uncomplicated disease is generally low (less than 1 percent), especially if appropriate antibiotic treatment is provided; however, cases with severe illness and complications have a higher mortality rate (3 to 30 percent; Hornick, 1982).

Protection from disease by vaccination was first attempted at the end of the nineteenth century, and for the next 70 years efforts focused primarily on killed-parenteral vaccines. The history of these efforts has been comprehensively reviewed by Germanier (1984). Several varieties of killed, whole-cell parenteral S. typhi vaccines have been studied in field trials to determine safety and efficacy. These parenteral, whole-cell vaccines caused significant adverse reactions, including fever, malaise, and severe local pain and swelling. Because of the frequency of such reactions to parenteral typhoid vaccines, these vaccines have not been considered useful public health tools. Thus, the major thrust in the development of new immunizing agents against typhoid fever has been to identify agents that are at least equal in efficacy to the whole-cell parenteral vaccine, but that cause no adverse reactions (Germanier, 1984).

A candidate live attenuated vaccine based on S. typhi Ty21a is in an advanced stage of development.

The committee gratefully acknowledges the efforts of R.E.Black, who prepared major portions of this appendix, and the advice and assistance of P.A.Blake. The committee assumes full responsibility for all judgments and assumptions.

PATHOGEN DESCRIPTION

Salmonella typhi, an obligate intracellular pathogen, is the cause of typhoid fever. The organism is a gram-negative, nonsporing bacillus, actively motile with numerous long peritrichous flagellae. Other salmonellae, S.paratyphi A and B, cause paratyphoid fever, which is similar to typhoid fever but usually a milder disease clinically. These organisms can be differentiated based on their cultural characteristics. S. typhi and S. paratyphi have a strong host specificity for man and do not naturally infect animals. In most countries in which these diseases have been studied, the ratio of disease caused by S. typhi to that caused by S. paratyphi is about 10 to 1. (For further information on S.typhi, see Hornick, 1982, 1985.)

HOST IMMUNE RESPONSE

Infection with S. typhi confers some immunity, but second illnesses can occur following reexposure. It appears that immunity can be overwhelmed by the ingestion of a large number of S. typhi, as was suggested by studies in which volunteers with previously documented typhoid fever ingested 10^5 S. typhi and had a clinical attack rate similar to that of a control group.

Several specific antibody responses have been demonstrated after typhoid fever. However, there is no evidence that these responses to O, H, and Vi antigens are protective against infection or illness. It is likely that secretory IgA is also produced in the small intestine, but this has not been well documented.

Animal models indicate that the cellular immune response probably is of primary importance in the protection against typhoid fever. Host defense relies on macrophage microbicidal mechanisms to kill phagocytosed bacteria. Enhancement of macrophage function is directed by specifically committed activated T-lymphocytes and controlled by a family of effector and regulatory T-cells. Current knowledge about immunity to S. typhi in humans does not permit more than general speculation about the way in which cell-mediated immunity is stimulated by either prior disease or a vaccine to prevent acute typhoid fever and its complications, or the development of the chronic carrier state (Germanier, 1984; Hornick, 1982, 1985; Levine et al., 1983).

DISTRIBUTION OF DISEASE

Geographic Distribution

Typhoid fever has worldwide distribution, but is especially prevalent in less-developed countries. Areas with environmental conditions conducive to the spread of the disease or with populations with a high prevalence of biliary tract disease and chronic carriage of S. typhi have higher rates of the disease (Germanier, 1984).

Disease Burden Estimates

Table D-14.1 shows the estimated incidence by age of typhoid fever cases in Africa, Asia, Latin America, and Oceania. Febrile, unrecognized cases of typhoid are assigned to morbidity category A; recognized moderate cases are assigned to category B; and recognized severe cases are assigned to category C. It is estimated that the number of mild cases of typhoid fever (probably undiagnosed) equals the number of recognized cases. It should be noted that the fatality rates in different regions vary: Table D-14.2 presents reported typhoid case-fatality rates in selected countries from 1951 to the present.

Figures from Table D-14.1 were used as a basis for the disease burden estimates in Table D-14.3.

PROBABLE VACCINE TARGET POPULATION

The incidence of clinically recognized typhoid fever appears to be highest in school-age children and young adults in endemic areas (Punjabi, 1984). Relatively few cases of typhoid fever are reported in children younger than 2 years of age in the same populations. There is some evidence that when these young children are exposed to S. typhi, they develop a bacteremic but clinically milder illness. Prospective studies of the age-specific incidence of the disease are needed to determine the best strategy for controlling endemic typhoid fever by vaccination. Additional information also is needed on the duration of protection afforded by such vaccines as Ty21a S. typhi and their efficacy when administered to young children.

It will be impossible to incorporate a typhoid fever vaccine into the existing World Health Organization Expanded Program on Immunization (WHO-EPI) if the primary target population is restricted to school-age children and young adults. However, if a candidate vaccine proves to be effective when given to small children and to have a long duration of protection (20 to 30 years), this situation could change. Development of a vaccine formulation other than enteric-coated capsules (which cannot be swallowed by infants and young children) will be necessary for this to happen. The calculation of vaccine benefits is based on the assumption that efforts in this direction will be successful.

Vaccine Preventable Illness*

Crude estimates indicate that at least 75 percent of the disease burden falls upon school-age children and young adults up to 34 years

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

TABLE D-14.1 Estimated Typhoid Fever Cases in the Developing World by Region and Age Group

Region	Total Population (millions)	Incidence of Recognized Typhoid Fever per 100,000 (all ages)	Total Number of Moderate and Severe Cases	Number of Moderate Cases (0.67)	Number of Severe Cases (0.33)	Fatality Rate[c] (percent of severe cases)	Number of Deaths	Number of Mild Cases (febrile-unrecognized)
Africa	531	500[a]	2,655,000	1,778,850	876,150	15	131,422	2,655,000
Asia	2,662	500[a]	13,310,000	8,917,700	4,392,300	10	439,230	13,310,000
Latin America	397	150[b]	595,500	398,985	196,515	5	9,826	595,500
Oceania	5	150[b]	7,500	5,025	2,475	5	124	7,500
Total			16,568,000	11,100,560	5,467,440		580,602	16,568,000

NOTE: Percentage of cases by age group: under 5 is 6 percent; 5–14 is 37 percent; 15–59 is 55 percent; 60 and over is 2 percent.

[a]Based on India (540, 543, and 634) and Indonesia (450).

[b]Based on Chile (110).

[c]Punjabi (1984)

TABLE D-14.2 Typhoid Incidence and Case-Fatality Rates (CFR)

Location	Year	Patient Population	Number of Cases of Typhoid Fever	Deaths	CFR (percent)
South Korea	1951	U.S. and United Nations soldiers	81,575	14,051	17
Indonesia	1950	Hospitalized Indonesians	17	1	6
Egypt	1950	Hospitalized Egyptians	200	13	7
South Africa	1951	Hospitalized South Africans	139	17	12
India	1953	Hospitalized Indians	1,064	180	17
Iran	1954–1967	Hospitalized Iranian children	35	3	8
India	1959–1965	Hospitalized Indians	340	19	6
South Africa	1959–1967	Hospitalized South African children	298	21	7
Nigeria	1959–1970	Hospitalized Nigerians	959	172	18
Iran	1961	Hospitalized Iranians	530	19	4
Indonesia	1961	Hospitalized Indonesian children	68	4	6
India	1967	Hospitalized Indians	98	13	13
India	1969–1970	Hospitalized Indians	100	7	7
Ethiopia	1975–1980	Hospitalized Ethiopians	50	6	12
Nigeria	1972–1978	Hospitalized Nigerian children	101	32	32
Indonesia	1971–1972	Hospitalized Indonesians	188	28	15
South Vietnam	1971–1974	Hospitalized Vietnamese	101	8	8
Indonesia	1977–1978	Hospitalized Indonesians	60	7	12
Indonesia	1976–1979	Hospitalized Indonesians	542	46	9
India	1977–1982	Hospitalized Indians	410	73	18
Indonesia	1980	Hospitalized Indonesians	33	6	18

SOURCE: Punjabi (1984).

TABLE D-14.3 Disease Burden: *Salmonella typhi*

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Malaise, mild fever	994,080	3	6,130,160	3	9,112,400	3	331,360	3
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderate fever, abdominal pain	666,034	6	4,107,207	6	6,105,308	6	222,011	6
C	Severe pain, severe short term impairment, or hospitalization	Fever, intestinal hemorrhage	328,046	12	2,022,953	12	3,007,092	12	109,349	12
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		34,836	n.a.	214,823	n.a.	319,331	n.a.	11,612	n.a.

of age. However, if all preschool children could be vaccinated with a vaccine that provided 100 percent protection over a long period, it would be possible to eliminate 100 percent of the disease. This assumption, adopted for calculations, assumes that a formulation acceptable and effective in infants and young children can be developed.

SUITABILITY FOR VACCINE CONTROL

Typhoid fever appears to be quite suitable for vaccine control, especially given the possibility of vaccines developed from oral, nonreactogenic strains of S. typhi, such as Ty21a. Such a vaccine probably could be delivered before the youngest age at which disease occurs.

If the new vaccine prevents people from becoming carriers, benefits would be extended to unvaccinated individuals because of reduced exposure.

Alternative Control Measures and Treatments

There is no animal host or environmental reservoir of S. typhi. Patients with typhoid fever, asymptomatic transient carriers, and chronic carriers are the only sources of infection. S. typhi can be spread by either food or water. Alternative strategies to prevent disease would be to reduce the number of infected persons, including carriers, and to ensure that food and water are not contaminated by them or are not consumed by susceptible persons. In many areas of the world, these strategies are not feasible at this time.

Effective antibiotic treatment with chloramphenicol, co-trimoxazole, or other drugs can shorten the duration of disease and reduce the mortality rate. However, in some areas the mortality rate remains high despite effective antibiotic treatment. It recently has been demonstrated that the death of some severely ill patients can be prevented by the use of high-dose corticosteroids in combination with antibiotics. In addition, management of hospitalized patients requires attention to nutrition, fluid and electrolyte balance, and prompt treatment of complications, such as intestinal perforation or bleeding.

PROSPECTS FOR VACCINE DEVELOPMENT

Two comprehensive reviews have recently dealt with vaccines directed against S. typhi. Germanier (1984) has described the history of efforts to date to develop effective vaccines against S. typhi and provides a detailed account of trials on the live attenuated strain Ty21a. Levine et al. (1983) dealt with this and other vaccine candidates under development. Therefore, this section is a brief overview of these vaccines; further details on specific candidates can be found in these two publications.

Of the killed whole-cell parenteral S. typhi vaccines, the acetone-killed typhoid vaccine is perhaps the best. In field trials in Guyana, two subcutaneous doses of the vaccine provided about 88 percent efficacy for at least 7 years (Germanier, 1984). Because of the frequency of adverse reactions, such as fever, malaise, and abdominal pain, this vaccine has not been widely used.

One relatively new approach for a typhoid vaccine has involved the use of purified Vi antigen as a parenteral vaccine. In initial safety testing, it appeared that this vaccine did not elicit severe adverse reactions and that it stimulated high titers of circulating IgG Vi antibody (Levin et al., 1975; Wong et al., 1974). It was postulated that such antibody would prevent the primary bacteremia, during which the reticuloendothelial system becomes seeded with S. typhi after penetration of the intestine. However, in further studies with the purified Vi vaccine, nearly half of the vaccinees had a moderate or severe systemic reaction, and 8 percent had fever. The reaction rate was similar to that of the whole-cell parenteral typhoid fever vaccine. Furthermore, sera from volunteers given the purified Vi vaccine showed rises in antibody to S. typhi lipopolysaccharide, indicating that the vaccine was contaminated with small amounts of this antigen.

Another approach has been the development of live attenuated strains of S. typhi. One such vaccine candidate that showed initial promise was the streptomycin-dependent mutant of S. typhi. In volunteer studies, this oral attenuated vaccine was well tolerated and highly protective against experimental challenge. However, when lyophilized vaccine was given, no protection was conferred. Because a lyophilized vaccine formulation is required for field studies and eventual use, further studies with this strain were abandoned (Germanier, 1984).

An important advance was the development of the attenuated ga1E mutant S. typhi strain Ty21a, developed by Dr. Rene Germanier (Germanier and Furer, 1975). This mutant is devoid of the enzyme UDP-galactose-4-epimerase and shows reduced activity of two other enzymes. Grown in the presence of galactose, smooth lipopolysaccharide O antigen is produced. However, because of its lack of epimerase, strain Ty21a accumulates intermediate products of metabolism, which results in bacterial lysis. Studies in North American volunteers and field trials in Egypt and Chile have demonstrated that this vaccine is safe and easily administered orally (Germanier, 1984). Recent results from field trials in Santiago, Chile, showed that three doses of the vaccine contained within enteric-coated capsules provided about 75 percent protection for at least 1 year (National Institute of Allergy and Infectious Diseases, 1985).

Another method of attenuation that has been used for Salmonella typhimurium and that could perhaps be applied to S. typhi is to derive aromatic amino acid-dependent strains of bacteria (Hoiseth and Stocker, 1981; Stocker et al., 1983). Some auxotrophic mutants that require a metabolite not available in vertebrate tissue would be unable to grow in such tissues and thus would be nonvirulent. Such strains of S. typhimurium have been examined in calves. The vaccine was given

orally or parenterally, and 3 weeks later the vaccinated and control calves were challenged orally with pathogenic S. typhimurium (Robertsson et al., 1983). The oral attenuated vaccine protected significantly better than the parenteral killed vaccine. These results are sufficiently promising to evoke interest in analogous aromatic-dependent S. typhi oral vaccine strains for human use.

New vaccines to protect against typhoid fever, particularly the live oral vaccines, provide an opportunity for the disease control in endemic areas. However, further vaccine studies are impeded by the lack of understanding of the immunological basis of protection and the lack of suitable animal models for typhoid fever. At this point, the only way to assess the efficacy of a vaccine is through large-scale field trials in endemic areas.

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Appendix D-15

The Prospects for Immunizing Against Shigella spp.

DISEASE DESCRIPTION

Shigella species cause an acute, usually febrile, gastrointestinal disease manifested by watery diarrhea, which may progress to a bloody diarrhea or dysentery (Keusch, 1982). The latter is a clinical syndrome composed of a classic triad of signs and symptoms including abdominal cramps, tenesmus (painful and ineffectual straining at stool), and the passage of frequent (up to 40) small volume bloody-mucoid stools per day. Constant straining at stool can result in rectal prolapse, especially in young children. In many patients, the initial presentation is watery diarrhea, which becomes bloody or dysenteric in a matter of hours to a day or two. The severity of the disease is determined in part by the infecting species; Shigella sonnei generally causes a self-limited watery diarrhea, whereas Shigella dysenteriae 1 usually progresses rapidly to bloody diarrhea or dysentery. Clinical manifestations thus depend, in part, on the prevalence of the different shigella species.

In the United States, where S. sonnei predominates, watery diarrhea is most common. In Bangladesh, where S. dysenteriae and S. flexneri are common, bloody diarrhea and dysentery are most frequent (Stoll et al., 1982). Watery shigella diarrhea may be voluminous and result in clinical dehydration, especially in young infants, but this is usually not as profound as that caused by cholera, enterotoxigenic E. coli, or rotavirus infection. S. flexneri and S. dysenteriae 1 often result in a chronic infection characterized by significant protein-losing enteropathy, especially in malnourished infants and children. This can lead to the development of kwashiorkor with its attendant high mortality rate from secondary infections.

Shigellosis has a number of extraintestinal manifestations (Keusch, 1982). The rapid rise in temperature is often associated with seizures, which may be the initial manifestation of illness. These behave very

The advice and assistance of R.E.Black, C.C.J.Carpenter, and R.B.Sack are gratefully acknowledged. The committee assumes full responsibility for all judgments and assumptions.

much like febrile seizures, except that they may occur in children with no or only low-grade fever and are prominent in children beyond the usual age of susceptibility to febrile seizures (2 to 3 years of age). Shigella bacteremia is more common than previously believed (especially with infection due to S. dysenteriae 1), has been detected in about 4 percent of patients with shigellosis admitted to the International Centre for Diarrhoeal Disease Research hospital in Bangladesh (ICDDR,B); and is associated with increased mortality (Struelens et al., 1985). Denudation of the intestinal epithelium increases the likelihood of gram-negative sepsis with other Enterobacteriaceae, especially in malnourished children, and has been documented in another 4 percent of hospitalized patients in Dhaka, Bangladesh. Denudation also dramatically increases the mortality rate.

Infection due to S. dysenteriae 1, and to a lesser extent S. flexneri, is associated with the development of a leukemoid reaction in 4 percent of hospitalized patients with shigellosis. Of these, one-third have evidence of hemolysis, one-third develop a hemolytic-uremic syndrome, and a few have transient uremia alone (Butler et al., 1984). The mortality rate for those with uncomplicated or complicated leukemoid reactions is about 20 percent. Bacteremia, leukemoid reactions, and hemolytic-uremic syndrome occur most often in poorly nourished children infected with S. dysenteriae 1, and are therefore more common in developing countries. Reactive arthritis with or without other classical manifestations of Reiter's syndrome occurs more frequently with some types of shigella (e.g., S. flexneri) and is often seen in individuals positive for HLA-B27 histocompatibility antigen (Keusch, 1982).

PATHOGEN DESCRIPTION

Shigellas are classified in the family Enterobacteriaceae, tribe Escherichieae, and are closely related to E. coli. They are nonmotile, rod shaped, gram-negative bacteria that ferment glucose but do not produce gas. They are usually recognized first by their inability to ferment lactose, although S. sonnei is capable of late lactose fermentation. Selective media are employed for this purpose; these media contain bile salts to inhibit the growth of other fecal organisms and a dye indicator to demonstrate lactose fermentation. Although many media have been devised, some are highly inhibitory to shigellas, especially to S. dysenteriae 1. The genus is subdivided into four species, dysenteriae, flexneri, boydii, and sonnei. These have antigenically distinct lipopolysaccharides and may be recognized through the use of grouping antisera, as well as by biochemical reactions. There are multiple subtypes of S. dysenteriae, flexneri, and boydii and multiple colicin types of S. sonnei. Generally, however, a limited number of subtypes prevail in any given geographic area. Two major virulence attributes are involved in pathogenesis: the ability to invade epithelial cells, which is under polygenic control, and toxin production, the genetics of which are still uncertain.

HOST IMMUNE RESPONSE

Epidemiological evidence suggests that there is acquired immunity to shigellosis; however, it is species- and subtype-specific. Endemic shigellosis is primarily a childhood disease, although introduction of a new strain into a population results in disease in all age groups (Keusch, 1982). The best evidence for type-specific immunity comes from trials using live streptomycin-dependent shigella vaccine strains in a large community field study in Yugoslavia (Mel et al., 1968). In this study, two groups of subjects received different vaccine strains. The overall rate of shigellosis did not differ between the groups, but each group was protected only against the strains included in the vaccine it received. This finding is supported by experimental vaccine studies in volunteers, which demonstrate serotype-specific protection when challenged with the same strain (Dupont et al., 1972). These findings indicate that antibacterial immunity is involved. Although patients develop antibodies to the homologous somatic O antigens of the infecting strain, primarily of the IgM isotype, there is no evidence that this serum antibody is protective.

Patients with shigellosis also develop IgM-neutralizing serum antibody to the shigella toxin. Current evidence indicates, however, that serum-neutralizing antibody is not protective against oral challenge with the organism (Keusch, 1982). Indeed, parenteral immunization of Rhesus monkeys with toxoid resulting in high serum antitoxin titers does not protect against clinical shigellosis following oral bacterial challenge (McIver et al., 1977).

DISTRIBUTION OF DISEASE

Geographic Distribution

Shigellas are worldwide in distribution, but the prevalence of different species varies from country to country. For unexplained epidemiological reasons, S. dysenteriae 1, which was the predominant worldwide isolate for the first 30 years after its discovery in 1898, was replaced by S. flexneri in the years before World War II. For the past 2 decades, S. sonnei has become the dominant organism in the industrialized nations, while S. flexneri has persisted in the developing countries, punctuated by outbreaks of epidemic dysentery due to S. dysenteriae 1 (Keusch, 1982). Because the more virulent species are more prevalent in developing countries, where malnutrition, poor hygiene, and lack of medical care are also widespread, morbidity and mortality are considerably more severe.

Disease Burden Estimates

The disease burden estimates for shigella are shown in Table D-15.1. The derivation of the number of acute cases is described in Appendix C.

TABLE D-15.1 Disease Burden: Shigella

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	125,690,000	5	56,977,000	5	42,393,000	5	7,190,000	5
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderately severe diarrhea	11,172,000	7	460,000	7	342,000	7	303,000	7
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea	5,237,000	11	230,000	10	171,000	10	126,000	10
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		52,370	n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		576,000	n.a.	46,000	n.a.	26,000	n.a.	6,000	n.a.

The number of acute cases suggested by the calculations in Appendix C has been modified in light of knowledge about chronic diarrhea and wasting associated with Shigella (Keusch, 1982; Rahaman and Wahed, 1983). Such conditions can last from weeks to months, often leading to protein-energy malnutrition. Two percent of severe cases in children under 5 years of age (morbidity category C, hospitalization indicated) are assumed to incur such illness, with about half progressing through morbidity category E to death. These deaths are added to those from acute illness (see Appendix C). The extended illness (assumed to be of about 3 months duration) experienced by the survivors in this subgroup of morbidity category C cases raises the average duration for all cases from 10 days for uncomplicated cases to about 11 days.

PROBABLE VACCINE TARGET POPULATION

Shigellosis is primarily a pediatric disease. In the developing countries it becomes a problem by the second half of the first year of life, although the highest incidence is in the 2 to 4 years age group. Immunization of infants during the first 6 months of life would allow administration of a shigella vaccine through the World Health Organization Expanded Program on Immunization (WHO-EPI); however, immunization at 12 or even 24 months of age would substantially reduce the rate of shigellosis. With epidemic spread of newly introduced strains, such as observed with S. dysenteriae 1 in Central America, India, and Bangladesh, and in central Africa during the past 15 years, all age groups should be immunized because all are susceptible (Keusch, 1982).

Vaccine Preventable Illness*

A vaccine incorporating protective antigens from the most common infecting strains in a given geographic area should prevent 80 to 90 percent of the shigella infections, depending on the prevalence of these strains and assuming total coverage of the target population with a “perfect” vaccine delivered at the earliest feasible age. Observed or apparent vaccine efficacy will depend, therefore, on knowledge of appropriate antigens from the different strains infecting the population in the regions where vaccine is used.

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

SUITABILITY FOR VACCINE CONTROL

Shigellosis accounts for 12 percent of the etiologically diagnosed diarrhea among patients presenting to the Dhaka Diarrhoeal Disease Centre Hospital, and, because dehydration is not the major manifestation, oral rehydration is less successful in averting death than it is for cholera and other watery diarrheas (Stoll et al., 1982). In prospective field studies, Mata (1978) has shown that children in the highlands of Guatemala suffer two infections per child per year with shigella species, from age 6 months to 3 years. Because these infections are often chronic (Mata, 1978), and are associated with a significant protein-losing enteropathy (Rahaman and Wahed, 1983), they are important causes of secondary malnutrition and thus increase both the short-term and long-term mortality of shigellosis.

Alternative measures for control of shigellosis are not likely to have an important impact in the developing world for the foreseeable future (see below), which means that vaccines must be the major strategy for intervention. Because shigellas are highly host-adapted to humans, there is no animal reservoir to cause concern.

Alternative Control Measures and Treatments

One of the hallmarks of shigellosis is the small infectious inoculum needed to cause disease. In otherwise healthy adult volunteers, the ID10 is in the range of 10 to 100 organisms, while the ID50 is only 1,000 organisms (Dupont et al., 1969; Levine et al., 1973). In young infants and children, especially those compromised by marginal or poor nutritional state, the infectious dose is probably even smaller. For these reasons, direct person-to-person contact is the common transmission route, and contaminated food and water sources are much less important than for other enteric pathogens. There is little doubt that sanitary fecal waste disposal, environmental hygiene, and the availability of sufficient water for personal hygiene can reduce the incidence of shigellosis (Keusch, 1982). Handwashing with soap and water has been shown to reduce the secondary infection rate in the childhood target group in Bangladesh households from approximately 40 percent to around 10 percent (Khan, 1982). However, there is little likelihood that such measures will become generally available in the rural areas of developing countries over the next few decades.

Transferable antibiotic resistance, first documented in the genus Shigella 30 years ago, has increased in prevalence, and the proportion of isolates with multiple resistance is becoming alarming. Epidemic S. dysenteriae 1 infection caused by multiply resistant organisms is now occurring in India, Bangladesh, and Central Africa. In some instances, the only usable drugs are expensive third generation penicillins or cephalosporins (Kabir et al., 1984), which are economically unfeasible for developing countries. The rate of acquisition of antimicrobial resistance suggests that new antibiotics are at best a temporizing measure. Vaccines, therefore, are imperative if shigellosis is to be controlled.

PROSPECTS FOR VACCINE DEVELOPMENT

In both humans and experimental animals, parenteral administration of killed whole cell vaccines is ineffective in stimulating protection against orally administered shigellas (Levine et al., 1983). Similarly, parenteral administration of toxoid prepared with formalin from the shigella toxin is without effect in the Rhesus monkey model of shigellosis.

In contrast, oral immunization using live attenuated shigella strains or mutants to induce local immunity has been effective. While none of the attenuated candidate vaccine strains developed thus far (including colonial mutants, streptomycin-dependent mutants, and hybrids prepared by insertion of E. coli genes into Shigella strains, or vice versa) have been sufficiently safe from the danger of reversion to be used clinically, studies of these vaccine strains have established the importance of local immunity in protecting against this infection and have contributed to our understanding of the protective antigens (Levine et al., 1983).

Recent work of particular importance has established the role of certain outer membrane proteins (OMPs) in S. sonnei and S. flexneri in the initial invasive step in shigella pathogenesis (Kopecko et al., 1980; Sansonetti et al., 1982). The genes controlling these OMPs are contained on large plasmids in these species, and they can be transferred to other organisms, rendering them invasive. If the plasmid is cured from the shigella strain, it is rendered noninvasive and avirulent. These OMPs are therefore primary candidates for the development of a new generation of shigella vaccine.

A very promising approach involves the use of the well-defined and safe oral typhoid vaccine strain, Salmonella typhi Ty21a, as a vehicle to carry the plasmid containing the OMP genes (Formal et al., 1981). The transconjugant expresses both typhoid and shigella somatic antigens and is protective against intraperitoneal challenge in mice.

The initial studies of orally administered transconjugant vaccine in humans have been very promising (Levine et al., 1983). The vaccine strain multiplies, invades the tissues, and expresses antigens, inducing an immune response. Because of its metabolic defect (the absence of the enzyme galactose epimerase), the organism dies off without causing systemic illness. It is uncertain at this time how many plasmids can be stably inserted into the carrier organism and still be expressed in an immunologically useful fashion; this question appears to be the major limiting factor.

The lack of a representative animal model for shigellosis other than the Rhesus monkey, and the lack of any suitable animal model for S. typhi infection (because the host range for this organism is entirely restricted to humans), means that vaccine testing must be conducted in humans. Initial studies can be performed in medical centers in the United States or overseas. However, human field trials must be an important early step in vaccine evaluation because of the absence of animal models. Such studies could be conducted in a number of places in the world, notably the ICDDR,B.

At the time of publication of this report, a vaccine candidate based on Salmonella typhi Ty21a was scheduled for a safety and antigenicity trial in children and a field trial for efficacy in children and adults. Another recombinant approach, an E. coli strain carrying the protective S. flexneri type 2A gene, also awaited human trials. In addition, attempts were under way to obtain, for testing in the United States, an apparently protective attenuated strain of S. flexneri developed as an oral vaccine in Rumania (National Institute of Allergy and Infectious Diseases, 1985).

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Appendix D-16

The Prospects for Immunizing Against Streptococcus Group A

DISEASE DESCRIPTION

The group A streptococcus (GrAS) is a ubiquitous microorganism that causes a wide range of human infections, including acute tonsillopharyngitis, sinusitis, otitis, scarlet fever, erysipelas, impetigo, cellulitis, lymphangitis, pneumonia, and endometritis. The impetus for vaccine development, however, stems from the propensity of the organism to elicit the delayed nonsuppurative sequelae of acute rheumatic fever (ARF) and acute post-streptococcal glomerulonephritis (AGN). Because the two sequelae appear to be caused by different GrAS serotypes, and because ARF appears to present a much greater worldwide health threat than does AGN, this brief review will focus exclusively on the prospects for prevention of ARF. However, the technology of vaccine production, once perfected, would be directly applicable to prevention of AGN.

Essential for the development of ARF is an antecedent GrAS infection of the upper respiratory tract. This scenario differs from AGN, which may follow either pharyngeal or cutaneous streptococcal infection. ARF usually manifests itself 1 to 4 weeks (median, 19 days) after the GrAS infection, at a time when all symptoms of the acute bacterial process have abated. Only a small proportion of individuals experiencing such an infection will, however, develop ARF. Depending on the epidemiologic setting, this proportion varies from about 3 percent to less than 1 percent of patients experiencing an untreated GrAS infection.

The five major clinical manifestations of ARF are well known because of their inclusion in the modified Jones criteria for diagnosis of this disease. These manifestations are: carditis, polyarthritis, Sydenham's chorea, subcutaneous nodules, and erythema marginatum. The clinical presentation of the disease is quite variable, because the individual manifestations may occur singly or in combination. The degree of attendant systemic toxicity may likewise vary greatly. An acute attack

The committee gratefully acknowledges the efforts of A.L.Bisno and E.H.Beachey, who prepared major portions of this appendix, and the advice and assistance of S.Dodu and H.B.Houser. The committee assumes full responsibility for all judgments and assumptions.

of rheumatic fever, although often disabling, runs its course in a matter of weeks, and death during such an attack is rare nowadays in the developed world. When fatalities do occur, they are due to intractable rheumatic carditis. Detailed clinical descriptions of ARF are available in numerous reviews (Bisno, 1982, 1985; Stollerman, 1975; Whitnack and Bisno, 1980).

From a public health standpoint, the intense concern with ARF stems from its propensity to inflict permanent heart damage. Such damage usually takes the form of chronic, deforming rheumatic valvulitis leading to insufficiency and stenosis of the mitral or aortic valves or both and occasionally of the valves of the right heart as well. Moreover, patients who have suffered a single attack of ARF are highly susceptible to recurrent attacks following immunologically significant GrAS upper respiratory infections. As the rheumatic attacks tend to be mimetic, individuals who experienced carditis with the first attack are likely to experience progressive heart damage with succeeding episodes.

The long-term prognosis of ARF is closely correlated with the cardiac status during the acute attack. This was shown most conclusively in the joint United Kingdom/United States collaborative study (United Kingdom and United States Joint Report, 1965), wherein some 494 children under the age of 16 were studied; about 70 percent of these were followed up over many years. Among patients free of carditis during their acute attack, only 6 percent had residual heart disease. Patients with no preexisting heart disease who experienced mild carditis during their acute attack (i.e., apical systolic murmur without pericarditis or heart failure) had a relatively good prognosis in that only about 30 percent had heart murmurs 19 years later. About 40 percent of subjects with apical or basal diastolic murmurs and 70 percent of subjects with congestive heart failure or pericarditis or both during their acute attacks had residual rheumatic heart disease. The prognosis was worse in patients with preexisting heart disease and in those who experienced recurrent attacks of ARF.

Thus, as a general rule, patients who do not experience carditis during an initial attack of ARF and who are protected from recurrent rheumatic attacks will not go on to develop rheumatic heart disease. Individuals with "pure" chorea represent an exception to this rule, because 25 percent of them may go on to develop rheumatic heart disease.

Although the figures vary widely, in most modern studies about 50 percent of patients diagnosed as having ARF experience some carditis during the acute attack. One might estimate that some 33 to 50 percent of such patients will be left with residual rheumatic heart disease of varying severity. Thus, perhaps one-quarter of all ARF patients develop chronic cardiac involvement. In many of these patients, the involvement is characterized by severe valvulitis with chronic congestive heart failure. A sizeable number of patients eventually require valve replacement or die from the effects of rheumatic heart disease.

PATHOGEN DESCRIPTION

Streptococci are spherical or ovoid bacteria that grow in pairs or chains of varying lengths. They are gram-positive, non-spore-forming, catalase-negative, and ordinarily nonmotile. They have complex and variable nutritional requirements.

Taxonomically, these organisms belong to the family Sreptococcaceae, genus Streptococcus, of which there are 21 identified species. When streptococci are cultivated on blood agar plates, they may produce complete (beta) hemolysis, partial (alpha) hemolysis, or no (gamma) hemolysis. More precise differentiation of streptococci can be made by immunologic means. The organisms may be separated into serogroups by means of antigenic differences in the cell wall carbohydrates or teichoic acids. The group A streptococcus, also known as Streptococcus pyogenes, is facultatively anaerobic, beta-hemolytic (with very rare exceptions), and contains in its cell wall a group-specific carbohydrate composed of rhamnose and N-acetyl-glucosamine. There are a number of other important substances expressed on the streptococcal surface. These include lipoteichoic acid, the principal ligand responsible for adherence of GrAS to epithelial surfaces, and a variety of proteins designated as M, T, and R. Of these, by far the most important is M protein.

M protein is the major virulence antigen of GrAS. Strains rich in this protein are resistant to phagocytosis by polymorphonuclear leukocytes, multiply rapidly in fresh human blood, and are capable of initiating disease. Strains lacking M protein are avirulent. Group A streptococci may be divided into serotypes on the basis of antigenic differences in M protein molecules. Over 70 such serotypes are currently recognized. Human immunity to streptococcal infection is based on the development of type-specific opsonic antibodies directed against the anti-phagocytic moiety of M protein. In rare instances, cross-protection by antibody to one type against organisms of a heterologous type has been demonstrated.

The M protein molecule penetrates the cell wall; this configuration localizes the type-specific antigen on the tips of hair-like fimbrillae protruding from the cell surface. The manner in which M protein exerts its anti-phagocytic effect is under investigation. The protein prevents interaction of the streptococcal cell wall with complement components, an effect that is enhanced by the ability of M protein to precipitate fibrinogen directly onto the bacterial surface. This protective effect is nullified by the presence of adequate concentrations of type-specific antibody.

T protein serves as the basis for a subsidiary typing system for GrAS. Another important somatic component of the streptococcus is the hyaluronic acid capsule. This capsule is also anti-phagocytic and serves as an auxiliary virulence factor.

For many years, it has been recognized that the ability to initiate AGN is limited to strains of certain GrAS serotypes (e.g., types 1, 4, 12, 49, 55, and a few others). Although this distinction between nephritogenic and nonnephritogenic GrAS is well established, there has been considerably more controversy over the issue of whether GrAS vary

in their rheumatogenic potential as well. A growing body of evidence now strongly supports the concept that a limited number of M protein serotypes account for the great majority of ARF cases in any particular epidemiologic setting (Bisno, 1980; Bisno et al., 1970). M type 5 appears to be the most highly rheumatogenic type, while others of the classic pharyngitis serotypes, such as 3, 6, 14, 18, 19, and 24, are also strongly implicated. This recognition of the variable rheumatogenicity of GrAS strains has given new impetus to laboratory analysis of the antigenic composition of GrAS and in addition provides important new insights into the most effective strategies for vaccine development and implementation.

HOST IMMUNE RESPONSE

During the course of human infection, the host mounts both humoral and delayed immune responses to a wide variety of streptococcal somatic and extracellular products. Patients with ARF are apparently hypersensitive to streptococcal antigens, because their mean antibody titers are significantly higher than similar titers among individuals with uncomplicated GrAS infection. For the purposes of this review, only humoral immune responses to GrAS extracellular products and M protein will be considered.

During the course of growth in vivo or in vitro, GrAS elaborates a multitude of extracellular products, many of which are antigenic. Measurement of antibodies to certain of these extracellular products has proved of great value, both to the clinician and the epidemiologist. The two most commonly used antibody tests clinically are the anti-streptolysin O (ASO) and anti-deoxyribonuclease B (anti-DNAse B) tests. Other tests used from time to time are the anti-hyaluronidase (AH), anti-NADase, and anti-streptokinase assays. One or more of these antibodies are elevated above the usual upper limits of normal in virtually all patients with ARF. The modified Jones criteria for the diagnosis of ARF require, in addition to a compatible clinical picture, evidence of recent streptococcal infection. Such evidence may be provided by a positive throat culture for GrAS, a classic scarlatinal rash, or, most frequently, an elevated or rising titer of antibodies to streptococcal extracellular products. Indeed, ARF rarely if ever occurs without evidence of an immunologically significant GrAS infection, as judged by elevation of one or more of these antibody titers. The appearance of these antibody titers may be delayed or their magnitude suppressed by prior antibiotic therapy.

Type-specific anti-M antibody responses are more difficult to measure than ASO or anti-DNAse B titers. While the latter are assayed by simple neutralization tests of the action of streptolysin O or DNAse B, the former require precise and cumbersome assays, such as mouse protection or opsonophagocytic tests. Type-specific anti-M responses occur following untreated GrAS pharyngeal infections but are markedly suppressed by effective antibiotic therapy. The immune response is type-specific, protective, and quite durable. Anti-M antibodies protect experimental animals from lethal streptococcal challenge and,

although the data are limited, appear to confer protection against reinfection in humans as well. Because M protein is the sole streptococcal antigen known to elicit protective antibodies, modern studies of streptococcal immunization have focused on development of a safe and immunogenic M protein preparation. Details of such studies are outlined below in the section on prospects for vaccine development. Although the pathogenesis of ARF remains unknown, most authorities believe that the disease results from host immune responses to certain streptococcal antigens that share antigenic determinants with human host tissues. For this reason, any putative M protein vaccine should consist of that portion of the M protein macromolecule that is responsible for eliciting type-specific immunity, while at the same time being free from antigens associated with M protein (so-called M associated proteins or non-type-specific M antigens) that might cross-react with host tissues.

DISTRIBUTION OF DISEASE

Geographic Distribution

Exact data on the geographic distribution of ARF and rheumatic heart disease are not available. However, the worldwide patterns of occurrence are clear. During this century, there has been a sustained and profound decline in rheumatic fever incidence in the developed countries of North America and Western Europe. Other highly developed countries, such as Japan, are also experiencing a marked drop in disease incidence. In contrast, ARF incidence is not declining, and may even be increasing, in many of the developing areas of the world. Such areas include the Indian subcontinent, the Arab countries of the Middle East, selected areas in sub-Saharan Africa and South America, and certain highly susceptible populations, such as the Maoris of New Zealand. The incidence of ARF tends to be highest in the thickly congested, low-income areas of the world's major cities.

Disease Burden Estimates

Although figures on the incidence of rheumatic fever are difficult to obtain and often unreliable, there is no doubt that rheumatic fever remains one of the major causes of cardiovascular morbidity and mortality in the developing nations of the world. As noted above, the disease is rampant in the Indian subcontinent, the Middle East, and many countries of Africa and South America. In Sri Lanka in 1978, for example, the morbidity rate of ARF was 47 per 100,000 population and over 140* for the 5 to 19 years age group (World Health Organization,

*All rates in this section are expressed as cases per 100,000 population at risk, unless otherwise indicated.

1980). At Rangpur Medical College Hospital in Bangladesh and Rangoon General Hospital in Burma, acute and chronic rheumatic heart disease account for about one-third of cardiac admissions and 2 percent of all hospital admissions. In India, the prevalence of rheumatic heart disease among children 5 to 15 years of age has been estimated at 600 per 100,000. A relatively recent aspect of the epidemiology of rheumatic fever is the recognition of its frequent occurrence in subtropical and tropical regions of the world. Prior to 1950, there was little or no awareness of the disease as a major public health problem in such areas (Markowitz, 1981). Although adequate longitudinal data are unavailable, ARF incidence actually may have increased substantially in the tropics during the middle of this century, a trend perhaps due in part to major population growth and increasing urbanization.

In contrast, morbidity and mortality of ARF and rheumatic heart disease have declined markedly in western Europe and North America, a decline that appears to have begun prior to the antibiotic era and is best documented in the Scandinavian data (Stollerman, 1975). While similar sequential data are lacking for most cities in the United States, one has only to query older physicians or to observe the closing of the famous rheumatic fever sanatoriums of the past to perceive how much the rate has fallen in certain areas.

Detailed epidemiological surveys of ARF incidence were conducted during the 1960s in several U.S. cities. In the borough of Manhattan (Brownell and Bailen-Rose, 1973), the overall annual rate among school-aged children was 61 per 100,000; the highest rates, 78 to 79, occurred in the most congested Puerto Rican neighborhoods, and the lowest rate, 23, in the district with the largest proportion of white middle-class families. Annual ARF incidence rates among school-aged children in Baltimore (Gordis et al., 1969) and Nashville (Quinn and Federspiel, 1974) were in the range of 24 to 34. In all these studies, rates for nonwhites were considerably higher than those for whites.

Studies conducted in the late 1970s have shown remarkably low rates of ARF incidence in the United States. For example, a careful survey of disease incidence in Memphis, Tennessee (Land and Bisno, 1983), for the years 1977 to 1981 indicated an incidence among 5 to 17 year olds of only 1.88 per 100,000 population per annum. Moreover, the ARF incidence among white school children dwelling in suburban and rural portions of Memphis was only 0.5. Since publication of the Memphis data, similar rates have been reported from Fairfax County, Virginia; Baltimore, Maryland; Los Angeles, California; and the state of Rhode Island.

A recent publication suggests that the developing world may also experience a decline in the ARF and RHD as the standard of living and medical care improve (Lancet, 1985).

Derivation of Estimates

The estimate of the disease burden from GrAS developed below focuses on acute rheumatic fever and its consequences; acute glomerulonephritis

is not included since it is not the target of the present vaccine development efforts (the strains that cause it differ from those that cause ARF, and it appears to be a much smaller worldwide health threat). The contribution of minor GrAS infections to the total disease burden has not been considered in this analysis.

Markowitz (1981), in reviewing the epidemiology of rheumatic fever, suggested that the incidence of ARF and RHD in developing countries approximated that found in western Europe and the United States 70 to 80 years ago, that is, 150 cases per 100,000 population. However, on the basis of recent studies in developing countries, the annual incidence of ARF is thought to range from 20 to 100 cases per 100,000 population, with 60 as an estimated average for the developing world (Dodu, personal communication, 1985). For any country or region, the rate would probably be higher in urban areas and lower in rural. This rate would yield a total of 2.157 million cases of ARF among the population of the developing world (about 3.595 billion). Markowitz (1981) estimated that 15 percent of all cases of rheumatic fever in developing countries are in the under 5 years age group. On the basis of the age distribution for ARF in developed countries (Quinn, 1982) and information supplied by Dodu (personal communication, 1985) that in developing countries the peak of illness is at a lower age (about 7 to 9 years), it is estimated that 80 percent of total ARF occurs in the 5 to 14 years age group and that only 5 percent occurs in the 15 to 59 years age group. Markowitz (1981) reported that for a number of developing countries, carditis occurs in 60 to 84 percent of ARF patients. Recent estimates suggest that the figure is in the range of 40 to 50 percent (Dodu, personal communication, 1985).

For the distribution of ARF cases between the acute morbidity severity categories used in this analysis, it is assumed that 60 percent fall into category C, 30 percent into category B, and 10 percent in category A. In developing countries, annual mortality from ARF currently ranges from about 0.1 death per 100,000 population to about 1.2 per 100,000 with an average of 0.5 deaths per 100,000 population (Dodu, personal communication, 1985). Thus, the total number of ARF-associated deaths in the developing world would be about 17,975. These are assumed to be distributed among age groups in a similar fashion to ARF cases (see above).

RHD represents a common sequela of ARF. For the purposes of these calculations, it is assumed that in developing countries an average of 50 percent of ARF cases develop RHD. Usually, RHD develops within about 5 years of ARF. Hence, most cases of RHD would become manifest in early adolescence (if the peak of disease in developing countries is assumed to be prior to 10 years of age). Cases of RHD are therefore assumed to be distributed between the 5 to 14 and 15 to 59 years age groups in the proportions 0.90:0.10. RHD cases are assumed to be distributed among the chronic morbidity severity categories D, E, and F in the proportions 0.2:0.6:0.2, respectively. Cases progressing to severity category F probably die. Current mortality from RHD in developing countries is probably on the order of 1 death per 100,000 population (Dodu, personal communication, 1985). Hence, total annual mortality from RHD in the developing world is estimated to be about

35,950. Deaths from RHD are assumed to be distributed equally between the 5 to 14 and 15 to 59 years age groups.

Table D-16.1 shows the distribution of ARF and RHD attributable to GrAS derived from adopting these assumptions.

VACCINE TARGET POPULATION

The peak incidence of ARF is in the 5 to 15 years age group in the developed world (Quinn, 1982), but it is lower in developing countries (Dodu, personal communication, 1985). However, in the developing countries, where a GrAS vaccine would be applied, immunization should be achieved as early as feasible. This is because of the intensity of the streptococcal exposure and because in certain developing countries, severe mitral valvular disease, presumably rheumatic in origin, develops much more precociously than it does among western populations.

The exact timing, number of doses, and number of required boosters for a streptococcus-ARF vaccine have yet to be ascertained. Nevertheless, it seems quite likely that such a vaccine, when developed, could be readily incorporated into the WHO Expanded Program on Immunization (WHO-EPI). Already, the WHO has major programs in most developing countries of the world related to prevention of rheumatic heart disease by secondary prophylaxis. Therefore, it would be natural for the organization to shift its emphasis in part or in whole to vaccine implementation, once this mode of prophylaxis becomes available. The vaccine probably should be administered to all children in countries where the ARF risk is high, although it initially could be selectively targeted to pockets of particularly intense ARF occurrence.

A second and extraordinarily important target population would be the individual who has had a single attack of ARF. Such individuals are exquisitely susceptible to recurrent attacks, and, as indicated above, such recurrent attacks can lead to severe and life-threatening forms of chronic rheumatic valvulitis. Thus, in the group of patients who have already experienced a single rheumatic attack, we have at once both the highest risk population for ARF and the population in greatest danger of serious sequelae, should the disease recur.

Vaccine Preventable Illness*

Given a perfect streptococcal-ARF vaccine, a very substantial proportion of the burden of rheumatic fever in the world could be prevented by an effective universal immunization program in early childhood. A large majority of initial attacks that occur in children

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

TABLE D-16.1 Disease Burden: Streptococcus A

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	32,355	7	172,560	7	10,785	7		
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	97,065	14	517,680	14	32,355	14		
C	Severe pain, severe short-term impairment, or hospitalization	194,130	21	1,035,360	21	64,710	21		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.	194,130	n.a.	21,570	n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.	582,390	n.a.	64,710	n.a.		n.a.
F	Total impairment		n.a.	194,130	n.a.	21,570	n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death, total	2,696	n.a.	31,355	n.a.	17,874	n.a.		n.a.
	Acute Rheumatic Fever	2,696	n.a.	14,380	n.a.	899	n.a.		n.a.
	Rheumatic Heart Disease		n.a.	16,975	n.a.	16,975	n.a.		n.a.

and early adolescents would be prevented, and recurrent attacks, which now account for 20 percent or more of all instances of ARF, also would be effectively prevented. There is considerable knowledge of the rheumatogenic potential of various serotypes (see above). However, no vaccine is likely to embrace all rheumatogenic types (there may well be types not yet identified), and because the vaccine could possibly induce some local shifts in the distribution of prevalent streptococcal serotypes, one might anticipate a small number of breakthroughs of rheumatic fever despite adequate immunization. Current vaccine research is focused, however, on the development of pools of small peptides that would protect broadly against a wide variety of streptococcal serotypes. Based on these considerations, it is estimated that 90 percent of the ARF and RHD burden is potentially vaccine preventable.

Even a more limited vaccine application, that is, to patients who have already had a single episode of ARF, would decrease rheumatic fever incidence by 20 percent and the incidence of severe carditis by a much greater amount.

SUITABILITY FOR VACCINE CONTROL

Because of the limitations inherent in currently available preventive measures and because of the devastating consequences of rheumatic fever throughout the developing world, new and innovative approaches to control are required. Clearly, the most appealing of such approaches, both theoretically and practically, would be the development of a safe and effective GrAS vaccine. Such a vaccine would be highly cost-effective because it would obviate the current expenditures in primary and secondary antimicrobial prevention, hospitalization of ARF patients, and other direct and indirect costs associated with the care of large numbers of relatively young individuals with crippling rheumatic cardiac disease.

Alternative Control Measures and Treatments

There are two existing strategies for the prevention of ARF. The first of these, labeled “primary prevention,” consists of identification of patients with streptococcal pharyngitis followed by effective antimicrobial therapy. Such therapy should be with penicillin, if the patient is not allergic. In high-risk areas of the world, the therapy of choice is a single intramuscular injection of benzathine penicillin G. This serves as treatment for the streptococcal infection and as prophylaxis for ARF. Unfortunately, primary prevention programs often have been difficult to implement in developing countries. in indigent families, little attention is paid to self-limited acute upper respiratory illnesses, and access to medical care is limited. Throat cultures for specific diagnosis of streptococcal sore throat generally are unavailable, and empirical therapy is the rule—often self-treatment with a variety of suboptimal regimens.

The second preventive strategy, called "secondary prophylaxis," consists of the continuous administration of antimicrobial agents to patients who have experienced an attack of ARF. This intervention is the most effective yet devised to prevent rheumatic fever and rheumatic heart disease. The approach is highly effective because it is directed at a group of patients at very high risk of developing repetitive episodes of ARF and of sustaining chronic valve damage. Even this therapy, however, has problems. As with primary prevention, secondary prevention is most difficult to accomplish in those areas where it is needed most. Identifying persons at risk, keeping them under continuous supervision, and arranging for monthly injections of benzathine penicillin G (the only practical means of prophylaxis in most developing countries) require a highly developed public health infrastructure, which is all too often lacking.

Once ARF has developed, there is no known therapeutic intervention that can alter the risk of developing carditis.

PROSPECTS FOR VACCINE DEVELOPMENT

For many years, attempts have been made to develop safe and effective vaccines against strains of group A streptococci that give rise to ARF and rheumatic heart disease. Vaccination efforts have been hampered by toxic reactions to almost any streptococcal product injected into human subjects (Stollerman, 1975). Moreover, a number of vaccine preparations have been associated with antigens that evoke antibodies that cross-react with host tissues, especially heart sarcolemmal membranes (Kaplan, 1963).

Protective immunity against group A streptococci is directed exclusively against the type-specific M protein on the surface of virulent organisms (Lancefield, 1962). Since this protein is often tenaciously associated with antigens that evoke toxic reactions, or worse, immunological cross-reactions with host tissues, efforts have been directed toward the isolation and purification of the protective M protein antigens. Recent studies of the immunogenicity of polypeptide fragments of M protein liberated from whole type 24 group A streptococci by limited peptic digestion have been promising. The purified extracts lacked detectable heart cross-reactive antigens, but retained protective determinants as demonstrated by vaccination of laboratory animals (Beachey et al., 1974, 1977) and by preliminary vaccine trials in human volunteers (Beachey et al., 1979).

Animal trials with another serotype of M protein (pep M5) extracted with pepsin from "rheumatogenic" type 5 GrAS, however, resulted in the development of heart cross-reactive antibodies in one of the first three rabbits immunized with the purified protein (Dale and Beachey, 1982). Detailed analyses revealed that the cross-reactive determinant resided in the M protein molecule itself rather than in a contaminant. Furthermore, antibody directed toward the heart cross-reactive determinant was shown to be opsonic and protective against types 5 and 19 streptococci, both of which had been shown by Kaplan (1963) to be associated with type-specific heart cross-reactive antigens. Cross-

absorption studies showed that the cross-protective, heart cross-reactive antigen represented only a minor determinant of the type 5 M protein molecule, since other protective determinants (probably the majority) on the pep M5 molecule were clearly not heart cross-reactive (Dale and Beachey, 1982). This raised the hope that one might be able to cleave M protein and eliminate potentially harmful regions of the molecule while retaining protective regions.

Immunogenicity of Native Peptide Fragments of M Protein

Several lines of evidence support the notion evoking protective immune responses by immunization with peptide fragments of M protein. First, the intact M protein molecule appears to be considerably larger than the polypeptide extracted by most methods from whole streptococci or cell walls (Phillips et al., 1982); thus far, most M protein vaccines extracted by a number of different methods (Beachey et al., 1977; Fischetti et al., 1976; Fox and Wittner, 1969; Lancefield, 1962; Russell and Facklam, 1975; Vosti and Williams, 1978) and studied for immunogenicity have consisted only of large polypeptide fragments of the M protein molecule.

Second, several laboratories have presented evidence that individual M protein molecules contain many antigenic determinants, most of which are type-specific (Beachey and Cunningham, 1973; Beachey et al., 1978; Cunningham and Beachey, 1975; Fischetti et al., 1976; Fox and Wittner, 1969; Hasty et al., 1982) but some of which are cross-reactive with other M serotypes (Beachey and Seyer, 1982; Dale et al., 1980; Fischetti 1977; Fox and Wittner, 1968; Wittner and Fox 1977).

Third, purified subpeptides derived by cyanogen bromide cleavage of type 24 M protein each evoked protective antibodies against the homologous serotype of streptococci (Beachey et al., 1980).

Finally, two chemically synthesized, 35-residue peptide fragments of pep M24 were shown to evoke similar type-specific protective antibodies without eliciting heart-reactive antibodies (Beachey et al., 1981a, 1983).

Structure of M Protein

Recent studies of the primary structure of three different serotypes of M protein have revealed several remarkable features. First, although the amino acid sequences of each of three different M serotypes (types 5, 6, and 24) are unique, certain amino acids are conserved among all three (Dale et al., 1980; Fischetti and Manjula, 1982; Manjula and Fischetti, 1980a, 1980b). Second, the M protein molecules are composed to varying degrees of internally repeating covalent structures (Beachey et al., 1978; Manjula and Fischetti, 1980b; Manjula et al., 1984). Third, the M proteins contain a seven-residue periodicity in their amino acid sequences that is reminiscent of an α-tropomyosin of muscle tissue (Hosein et al., 1979; Manjula and Fischetti, 1980b).

This periodicity accounts for the α-helical coiled-coil structure of the M protein molecule (Phillips et al., 1982); it is the first such conformation to be demonstrated for any surface appendage of bacteria (Phillips et al., 1982). Electron microscopy of the rotary shadowed coiled-coils of pepsin-, detergent-, and phage lysin-extracted M protein of type 6 streptococci suggests that the pepsin- and detergent-extracted M proteins represent the distal ends of these surface fibrillar structures, whereas the lysin-extracted M protein represents most, if not all, of these structures. Thus far, most of the primary structural studies have used pepsin or detergent extracts of M protein.

Chemically Synthesized M Protein Fragments

The synthesis of M protein polypeptides has been based on the covalent structures determined for the cyanogen bromide peptides of type 24 M protein (pep M24) and of the NH_2-terminal sequence analysis of type 5 M protein. The synthetic peptides studied thus far include synthetic copies of CB3 and CB7, designated S-CB3 and S-CB7, and subpeptides of the 35-residue S-CB7, including S-CB7(13–35), S-CB7(18–35), S-CB7(23–35) Cys, and S-CB7(18–29). S-CB7(18–29) overlaps two subpeptides derived by digesting lysyl-blocked CB7 (see below). A 20-residue peptide of pep M5, S-M5(1–20) also has been synthesized. Each of the peptides was synthesized by the solid phase method of Merrifield (1963), as previously described (Beachey et al., 1981a, 1981b, 1983; Jolivet et al., 1984). The identity of the synthetic peptides has been confirmed by amino acid analyses and automated Edman degradation (Beachey et al., 1980).

When emulsified in complete Freund's adjuvant and injected as a single 25 nmol dose, S-CB7 evoked antibody titers at 6 weeks of 1:400, 1:1,280, and 1:25,600, respectively, in each of three rabbits, as determined by enzyme-linked immunosorbent assays (ELISA). Only the serum of the rabbit showing the highest ELISA titer was able to opsonize type 24 streptococci. In contrast, the same dose of S-CB7 covalently linked to polylysine and emulsified in complete Freund's adjuvant evoked strong ELISA as well as opsonic antibody titers in each of three rabbits (Beachey et al., 1981a). The results obtained using S-CB3 instead of S-CB7 were virtually identical (Beachey et al., 1983). In opsono-bactericidal assays using types 5, 6, and 24 streptococci, the immune sera were capable of promoting phagocytosis of and killing only the type 24 streptococci, indicating that the humoral immune responses to S-CB7 were type-specific (Beachey et al., 1980).

Immunodiffusion tests of the immune sera revealed precipitin arcs of identity between wells containing polylysine conjugates of native and synthetic CB7, as well as with the intact pep M24. There was no cross-reactivity of the anti-S-CB7 antiserum with pep M5 or pep M6. None of the S-CB7 immune sera reacted with the sarcolemmal membranes of frozen sections of human heart, as determined by immunofluorescence (Beachey et al., 1979).

The protective activity of the S-CB7 immune sera was tested by positive mouse protection tests. Mice were injected with 0.2 m1 of a

pool of the immune sera and 24 hours later challenged with type 24 or type 6 streptococci. The immune sera clearly protected against the homologous type 24, but not against the heterologous type 6 streptococci (Beachey et al., 1981a).

Having demonstrated that a protective determinant of M protein resides in a synthetic peptide as small as 35 residues long, it was of interest to determine whether protective determinants were retained in even smaller peptide fragments. CB7 was cleaved with trypsin after blocking lysine residues with maleic anhydride. Because CB7 contains only one arginine residue at position 23, the molecule was cleaved into a COOH-terminal dodecapeptide and an NH_2-terminal 23-residue peptide. After deblocking the lysine residues with pyridine/acetate, the subpeptides were separated and purified by HPLC reverse-phase chromatography (Beachey et al., 1981a). The purified peptides were then tested for their abilities to inhibit opsonization by anti-S-CB7. The synthetic overlapping peptide, S-CB7(18–29), also was tested for inhibitory activity. The results clearly showed that the NH_2-terminal 23-residue peptide and the COOH-terminal 12-residue peptide were inhibitory, although higher concentrations than that of the intact CB7 were required to achieve equal levels of inhibition. The overlapping 12-residue peptide, S-CB7(18–29), in contrast, was without effect even at concentrations as high as 100 nmol (Beachey et al., 1981a).

These results indicate that a protective determinant of type 24 M protein resides in a peptide fragment containing only 12 residues. The inability of the overlapping synthetic peptide to block opsonization suggests that CB7 contains at least two distinct protective antigenic determinants, neither one of which resides in the overlapping peptide.

That protective epitopes reside in the subpeptides of CB7 was confirmed by studies of the immunogenicity of the synthetic subpeptides S-CB7-(13–35), -(18–35), and -(23–35)C covalently linked to tetanus toxoid (Beachey et al., 1981b). Each of these peptides evoked opsonic antibodies in rabbits. The substitution, however, of a single amino acid in the 13-residue M protein peptide, S-CB7(23–35)Cys, at position 33 (lysine substituted for glycine) rendered this protective peptide nonprotective (Dale et al., 1980).

In contrast to the high degree of type-specificity of the humoral immune responses to each of the synthetic peptides, the cellular immune responses were highly cross-reactive. The lymphocytes of rabbits immunized with S-CB7 were equally responsive in mitogenic assays to heterologous pep M5 as they were to the homologous pep M24 (Beachey et al., 1981a). Furthermore, immunization with S-CB7(18–29) covalently conjugated with polylysine, although failing to evoke effective humoral immunity, nevertheless induced non-type-specific cellular immunity similar to that of S-CB7. Neither of the synthetic peptides were of sufficient size to induce mitogenesis of lymphocytes from immunized rabbits (Beachey et al., 1980).

These studies provided evidence in support of the hypothesis that limited peptide regions of the M protein molecule would suffice as protective immunogens, especially when covalently linked to carrier molecules, such as polylysine or tetanus toxoid. Furthermore, they suggested that one might select for synthesis small peptide regions of

M protein that contain protective, but not tissue cross-reactive, antigenic determinants. This led to an examination of the protective effects and heart cross-reactivity of a 20-residue synthetic peptide of type 5 M protein, a molecule demonstrated to contain within its covalent structure an epitope(s) that raises antibodies cross-reactive with a protein in the sarcolemma of human heart tissue. When covalently linked to tetanus toxoid with glutaraldehyde, the synthetic peptide S-M5(1–20) evoked antibodies that were protective against the related type 5 streptococci (Dale et al., 1983). Even though each of the animals received five times the dose, on a molar basis, required to produce heart cross-reactive antibody with the intact pep M5 molecule, none of the immunized animals developed heart cross-reactive antibodies.

These studies should encourage the development of streptococcal vaccines composed of small synthetic peptide regions of M protein that contain protective, but not tissue cross-reactive, antigenic determinants. Knowledge of the complete covalent structures of several serotypes of M protein also should allow application of the principles recently reported by Hopp and Woods (1981) that predict which antigenic regions to isolate or synthesize based on the relative hydrophilicity of various peptide regions as determined by their amino acid sequences.

At the time of publication, phase 1 studies in humans on tetanus toxoid conjugated M protein peptides were expected to begin shortly and plans for more extensive efficacy trials, possibly to be conducted in India and Chile, were being prepared (National Institute of Allergy and Infectious Diseases, 1985).

Conclusion

The whole M protein molecule is not needed to effectively immunize against group A streptococcal infections. Chemically synthesized peptide fragments of carefully chosen regions of various M protein molecules should provide a vaccine that can be administered safely to humans without fear of evoking host tissue cross-reactive antibodies. There is some evidence to suggest that certain protective determinants of M protein may be shared among different serotypes. The identification and synthesis of such common protective determinants should provide the basis for the formulation of a broadly protective vaccine against many serotypes of rheumatogenic group A streptococci. Extensive work is currently under way directed at improving the immunogenicity of peptides through coupling to carriers or by the use of adjuvants. This should enhance the prospects for the success of the approach discussed above.

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Appendix D-17

The Prospects for Immunizing Against Streptococcus pneumoniae

DISEASE DESCRIPTION

Streptococcus pneumoniae is a major cause of three infections: pneumonia, otitis media, and meningitis (Austrian, 1984). The organism is a component of the normal bacterial flora of the human upper respiratory tract; it invades the lower respiratory tract or middle ear by direct extension from the nasopharynx when anatomic or physiologic defenses are compromised, most frequently by antecedent viral infection. Meningitis may occur either as a sequel to bacteremia secondary to pneumonia, or as a direct extension from an infected paranasal sinus or mastoid; or it may follow fracture of the skull. The pneumococcus also can infect other serous cavities, including the pleura, joints, peritoneum, and pericardium, and it is a cause of acute bacterial endocarditis.

Colonization of the nasopharynx with pneumococci may begin within 24 hours of birth. Defense against infection, once established, depends on phagocytosis of the bacteria by polymorphonuclear leukocytes in the presence of type-specific anticapsular antibody and complement.

Recovery from pneumococcal pneumonia usually results in restoration of the lung to its normal state. One or more attacks of pneumococcal otitis media may be followed by transient or permanent hearing impairment, either of which may retard learning. Pneumococcal meningitis has a high mortality rate, both in infancy and in the elderly, exceeding 40 percent in treated adults over age 40. Permanent neurologic damage follows pneumococcal meningitis in about 40 percent of children who survive the disease.

The committee gratefully acknowledges the efforts of R.Austrian, who prepared major portions of this appendix, and the advice and assistance of F.W.Denny and J.B.Robbins. The committee assumes full responsibility for all judgments and assumptions.

Limitations of Existing Vaccines

Polyvalent vaccines of killed whole pneumococcal cells were developed in the second decade of the twentieth century to prevent epidemic pneumococcal pneumonia in industrial populations, and they were shown to be safe. Demonstration of their efficacy remained uncertain, however, because of the design of trials employed for that purpose. Vaccines of purified capsular polysaccharides, introduced in the 1930s, were shown unequivocally to protect against infection with the types represented in them in the 1940s. In addition, the vaccine was shown to reduce by about half the likelihood of colonization of the upper respiratory tract with pneumococcal types represented in the vaccine. Vaccination had no demonstrable effect on previously established carriage of a type represented in the vaccine.

Vaccines composed of the purified polysaccharides of pneumococcal types responsible for the majority of pediatric infections have proved to be poorly immunogenic and to provide little or no protection against infection. Similar vaccines for the prevention of infection with H. influenzae and N. meningitidis group C also have been ineffective.

More details of the limitations of existing vaccines can be found in the recent review by Austrian (1984).

PATHOGEN DESCRIPTION

Streptococcus pneumoniae is a gram-positive capsulated coccus found commonly in pairs and is a normal inhabitant of the human upper respiratory tract. More than 80 capsular serotypes are known, each distinguished by the unique polysaccharide structure of its capsule. All serotypes are not equally invasive; about 90 percent of bacteremic infections are caused by 23 serotypes. The frequency with which different pneumococcal serotypes cause infection in infants and young children and in adults differs. In the pediatric population, pneumococcal types 6A, 6B, 14, 19F, 19A, and 23F account for more than half of all pneumococcal infections. In adults, types 1, 3, 4, 7F, 8, and 12F are seen more commonly. The currently licensed vaccine, which contains 23 capsular polysaccharides, includes antigens from types found at all ages. The chemical compositions of many of the polysaccharides in the U.S.-licensed vaccine are known.

HOST IMMUNE RESPONSE

In the normal human host, defense against invasion of internal bodily sites by pneumococci depends primarily on type-specific serum antibodies to pneumococcal capsular polysaccharides. This conclusion is based on epidemiologic studies of pneumococcal infections in man, on experiments in a variety of susceptible animal species, and on the therapeutic effect of type-specific anticapsular antiserum in the treatment of pneumococcal pneumonia prior to the advent of sulfonamides and antibiotics. In addition, previous trials in adults of vaccines of

purified pneumococcal capsular polysaccharides have shown that they are effective in stimulating type-specific immunity. Recovery from natural infection with a given pneumococcal type usually is followed by lifelong immunity to reinfection with that type.

Type-specific capsular antibodies of the IgG class may be transferred transplacentally from mother to fetus during pregnancy and provide some protection against infection with homologous types during the first 6 months of life. Maximum attack rates of pneumococcal infection, including otitis media and bacteremia, occur between the ages of 6 months and 2 years. Initial immunologic responses to vaccination with pneumococcal capsular polysaccharides in infancy are predominantly of the IgM class, and the protection afforded by such antibodies is of limited duration, usually not exceeding 6 months. The ability to respond to different pneumococcal capsular polysaccharides develops at different ages; immunity to type 3 capsular polysaccharide is observed as early as age 6 months. Responsiveness to the serotypes responsible for the majority of infections in early life (types 6A, 6B, 14, 19F, 19A, and 23F) may be delayed until the age of 4 or later. Preliminary studies of type 6A pneumoccocal capsular polysaccharide coupled to tetanus toxoid suggest that responsiveness to the conjugated antigen occurs at a significantly earlier age and induces IgG as well as IgM antibodies.

Limited data on the responsiveness of the elderly to parenteral administration of pneumococcal capsular polysaccharides suggest that, although they respond somewhat less vigorously than young adults, their responses are significant and result in protection against infection. Patients who have acquired immunologic deficiencies, such as those resulting from lymphocytic malignancies (e.g., multiple myeloma) respond feebly or not at all to the current polyvalent pneumococcal vaccine.

DISTRIBUTION OF DISEASE

Geographic Distribution

Pneumococcal pneumonia, otitis media, and meningitis occur throughout the world and have been found to be endemic wherever they have been sought. Higher than average attack rates have been observed in populations living in depressed socioeconomic conditions and in association with movement from rural to urban environments. Epidemics also may occur under conditions in which immunologically naive adults are congregated in industrial or military barracks, the so-called “recruit disease” phenomenon.

Disease Burden Estimates

The burden of pneumococcal infection is large, but it is difficult to obtain accurate data on the incidence of pneumococcal pneumonia and pneumococcal otitis media for a variety of reasons. The incidence of

pneumococcal meningitis is easier to document, in part because the clinical picture is more clearly defined. The estimates below are largely developed from the review by Austrian (1984).

The diagnosis of pneumococcal pneumonia on the basis of recovery of the organism from expectorated pulmonary secretions is uncertain because of contamination with organisms from the upper respiratory tract. The diagnosis can be established by direct recovery of pneumococci from the lower respiratory tract by transtracheal aspirate or lung puncture, but the routine employment of these invasive procedures cannot be justified on ethical grounds. The diagnosis can be confirmed also by isolation of the organism from the blood of approximately 25 percent of cases, by its recovery from a metastatic focus of infection, by demonstration of capsular polysaccharide in the blood or urine, or by the demonstration of antibodies developing in response to infection. Most of these procedures require isolation and identification of the capsular type of the organism. This may not be possible because the necessary micro-biological techniques have been abandoned by most routine diagnostic laboratories since the advent of antibiotics. The problem is confounded further by frequent failures to obtain material for culture prior to the initiation of antibacterial therapy, a practice that may preclude subsequent recovery of the organism causing illness. Diagnosis of the cause of otitis media is made infrequently today because tympanocentesis to recover the infecting organism from the middle ear is practiced only in a few clinical settings. Despite these limitations, sufficient data are available to estimate the disease burdens resulting from these two pneumococcal infections in some areas.

Studies of different populations in the United States have found attack rates of pneumococcal pneumonia that range from 1.5 to 10 cases per 1,000 persons per year. In general, the attack rate in developed countries is probably between 1 and 5 per 1,000 persons per year. Attack rates are highest in infancy and in persons over 50 years of age.

In some settings, the attack rate of pneumococcal pneumonia may reach 100 per 1,000 persons per year, as in gold mining novices in South Africa. Reports in central African medical journals indicate that in several countries the disease also occurs with high frequency in persons migrating from rural settings to urban centers.

One method of estimating disease burden for pneumococcal pneumonia in the developing world is to assume that rates are similar to those reported for lobar pneumonia in the United States during the 1920s, that is, prior to any antibiotic use.

Age-specific rates used in Table D-17.1 are adapted from Heffron (1939). Hypothetical age-specific case fatality rates for untreated cases of pneumococcal pneumonia are also shown in Table D-17.1 and reflect both the estimated overall rate of 20 to 40 percent (American Public Health Association, 1985; Austrian, 1984) for untreated cases in the United States, and the recognition that mortality is greatest in the extremes of age. Morbidity categories were assigned (Table D-17.2) to reflect the overall severity of pneumococcal pneumonia. Population estimates for calculating numbers of cases in the developing world are from the Population Reference Bureau (1984) (also see Chapter 4). Disease burden estimates for pneumococcal pneumonia are shown in Table D-17.3.

TABLE D-17.1 Incidence Rates and Case Fatality Rates for Pneumococcal Pneumonia by Age

Age Group	Incidence Rate[a] (per 1,000)	Case Fatality Rate[b] (percent)
Under 5 years	17.15	40
5–14 years	9.99	20
15–59 years	9.59	10
60 years and over	26.28	50
Overall	11.82	24

[a]Adapted from Heffron (1939).
[b]Adapted from American Public Health Association (1985).

TABLE D-17.2 Pneumococcal Pneumonia: Distribution of Morbidity Categories by Age

	Morbidity Category (percent distribution)		
Age Group	A	B	C
Under 5 years	10	20	70
5–14 years	10	40	50
15–59 years	10	40	50
60 years and over	10	10	80

Estimates (particularly for deaths) derived from this method are considerably higher than estimates derived in Appendix B for pneumococcal pneumonia in the under 5 and 5 to 14 years age groups. The estimates in Appendix B are derived from recent case reporting in developing countries, whereas those in Table D-17.3 are derived from reporting in the United States in the 1920s. One possible reason for this discrepancy is that a proportion of lobar pneumonia cases included in these rates may be due to organisms other than S. pneumoniae, such as Hemophilus influenzae, and Staphylococcus pyogenes. Radiological diagnoses also are not always consistent. Rates vary widely in different times and with differing socioeconomic circumstances. Thus, a wide range of estimates will arise when they are based on different studies. Another possible reason for the discrepancy is the likelihood that estimates in Appendix B reflect antibiotic use in certain regions

TABLE D-17.3 Disease Burden: Pneumococcal Pneumonia

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	855,030	5	908,457	4	1,874,585	4	610,605	6
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	1,710,061	7	3,633,826	6	7,498,340	6	610,605	8
C	Severe pain, severe short-term impairment, or hospitalization	5,985,213	10	4,542,283	9	9,372,926	9	4,884,842	12
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	3,420,122	n.a.	1,816,913	n.a.	1,874,585	n.a.	3,053,026	n.a.

for severe cases of pneumonia, whereas those in Table D-17.3 are based on rates for untreated cases. The approach adopted to determine the effect of this uncertainty on the ultimate ranking of an improved vaccine against S. pneumoniae is discussed below.

TABLE D-17.4 Incidence Rates and Case Fatality Rates for Isolated Pneumococcal Bacteremia by Age

Age Group	Incidence Rate (per 1,000)	Case Fatality Rate (percent)
Under 5 years	1.5	10
5–14 years	0.5	5
15–59 years	0.19	2.5
60 years and over	1.0	12.5
Overall	0.5	7.5

Retrospective studies of pneumococcal bacteremia, which significantly underestimate its incidence because of the failure to routinely obtain blood cultures or to obtain them only after initiation of therapy, suggest an incidence of 9 cases per 100,000 persons per year for the U.S. population at large. For children under age 2, the annual rate is 30 to 40 per 100,000 persons, and for those 60 years of age and older, it is about 20 per 100,000 persons (Austrian, 1984). The true incidence is probably two to five times that recorded. The mortality of bacteremic pneumococcal pneumonia is four times that of putative pneumococcal pneumonia in the absence of bacteremia, whether the cases compared are treated or nontreated.

For the purposes of this report, it is assumed that the overall incidence rate for pneumococcal bacteremia in the developing world is 1 per 1,000 per year, or about twice the estimated maximum U.S. rate of 50 per 100,000 per year (Austrian, personal communication, 1984). One-half of cases, however, are assumed to occur concomitantly with pneumonia (Health and Public Policy Committee, 1986) and meningitis, so that the rate for bacteremia without other chemical manifestations is 0.5 per 1,000 per year. The variation of incidence rates by age is assumed to be similar to that of U.S. rates, and is shown in Table D-17.4. Actual rates are about half those in the United States since cases with pneumonia and meningitis are counted in other tables. Case fatality rates, also shown in Table D-17.4, are distributed by age like those for pneumonia. However, they are lower because more severe cases with pneumonia and meningitis are counted elsewhere. It should be stressed that these figures are crude estimates; true incidence and case fatality rates for isolated pneumococcal bacteremia are not known.

Morbidity categories (Table D-17.5) are assigned to reflect generally more severe disease at the extremes of age. Disease burden estimates for pneumococcal bacteremia are shown in Table D-17.6.

Pneumococcal otitis media is one of the most common illnesses seen in pediatric practices—an estimated 20 percent of all children born in

the United States will experience an attack of pneumococcal otitis media in the first 2 years of life. Pneumococcus is the cause of one-half to two-thirds of all bacterial otitis media. The disease appears to be even more common among American Indians and Eskimos than it is in Caucasians. It may be complicated by mastoiditis or meningitis and may be followed by chronic otitis with permanent hearing impairment. For the purposes of this report, it is assumed that three-fourths of children in the developing world have an episode of otitis by age 5 years, and that two-thirds of these are pneumococcal (Austrian, 1984).

TABLE D-17.5 Pneumococcal Bacteremia: Distribution of Morbidity Categories by Age

	Morbidity Category (percent distribution)		
Age Group	A	B	C
Under 5 years	30	30	40
5–14 years	40	30	30
15–59 years	40	30	30
60 years and over	30	30	40

This assumption yields a crude incidence rate of 500 per 1,000 per 5 years or 100 per 1,000 per year (10 percent). This is in good agreement with empirical studies, such as the findings of a 15 percent yearly incidence rate for pneumococcal otitis media in children under age 5 reported by Mäkalä et al. (1983).

Assignment to morbidity categories for otitis media is estimated as follows: 50 percent of cases to category A, 30 percent category to B, and 20 percent to category C. In addition, chronic hearing loss is estimated to occur in mild form (category D) in 10 percent of untreated survivors, and in severe form (category E) in 1 percent. Disease burden estimates for pneumococcal otitis media are shown in Table D-17.7. Death is assumed to result in 1 percent of severe cases.

The pneumococcus is the second most common cause of bacterial meningitis in interepidemic periods of meningococcal infection. The annual U.S. attack rate is about 1.5 per 100,000 persons. Incidence rates are highest at the extremes of life, and both neurologic sequelae and mortality are common despite specific antipneumococcal therapy. Deaths in treated neonates and persons over age 60 exceed 50 percent. Similar data from other areas confirm the lethality of the infection. It has been estimated that the annual attack rate of pneumococcal meningitis in West Africa is about 14 per 100,000 persons (Diop Mar et al., 1979), almost ten times that in developed countries.

For the purposes of this report, incidence rates and case fatality rates for the developing world are taken from Cadoz et al. (1981; Figure 2 and Table 3 respectively). These rates are for hospitalized

TABLE D-17.6 Disease Burden: Pneumococcal Bacteremia

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	224,352	3	181,873	2	148,559	2	69,704	3
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	224,352	4	136,405	3	111,420	3	69,704	5
C	Severe pain, severe short-term impairment, or hospitalization	299,136	6	136,405	5	111,420	5	92,938	7
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	74,784	n.a.	22,734	n.a.	9,285	n.a.	29,043	n.a.

TABLE D-17.7 Disease Burden: Pneumococcal Otitis Media

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	24,928,000	4						
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	14,956,800	6						
C	Severe pain, severe short-term impairment, or hospitalization	9,971,200	8						
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	4,975,629	n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	497,563	n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	99,712	n.a.		n.a.		n.a.		n.a.

Senegalese over a 10-year period and are shown in Table D-17.8. They are in agreement with incidence rates in Zaire reported by Greenwood (1984). Estimates of morbidity categories for acute disease are shown in Table D-17.9, and reflect the overwhelmingly severe nature of the disease. It is also assumed that 10 percent of survivors suffer severe permanent neurological impairment (category E) and that 30 percent suffer mild impairment. Disease burden estimates for pneumococcal meningitis are shown in Table D-17.10.

TABLE D-17.8 Incidence Rates and Case Fatality Rates for Pneumococcal Meningitis by Age

Age Group	Incidence Rate (per 100,000)	Case Fatality Rate (percent)
Under 5 years	33.8	55
5–14 years	4.1	50
15–59 years	5.1	65
60 years and over	14.7	95
Overall	9.5	61

TABLE D-17.9 Pneumococcal Meningitis: Distribution of Morbidity Categories by Age

	Acute Morbidity Category (percent distribution)		
Age Group	A	B	C
Under 5 years	0	5	95
5–14 years	0	5	95
15–59 years	0	5	95
60 years and over	0	5	95

The total disease burden for S. pneumoniae derived using the assumptions described above is shown in Table D-17.11. Durations of illness are weighted averages of estimates for each condition. The predominant component in the estimates is the burden of pneumococcal pneumonia, which contributes about 95 percent of the S. pneumoniae— related deaths and disease in children under 15 years of age. The number of such deaths in Tables D-17.3 and D-17.11 is derived based on the assumption that current rates in the developing world approximate those before antibiotics in the United States. The other, much smaller components of the aggregate estimates in Table D-17.11 reflect estimates made from rates observed after the availability of

TABLE D-17.10 Disease Burden: Pneumococcal Meningitis

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity								
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	8,426	10	1,864	10	4,985	10	1,708	10
C	Severe pain, severe short-term impairment, or hospitalization	160,087	14	35,420	14	94,706	14	32,447	14
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	22,749	n.a.	5,593	n.a.	10,468	n.a.	512	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	7,583	n.a.	1,864	n.a.	3,489	n.a.	171	n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	92,682	n.a.	18,642	n.a.	64,799	n.a.	32,447	n.a.

TABLE D-17.11 Disease Burden: Streptococcus pneumoniae

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	26,007,382	4	1,090,330	4	2,023,144	4	680,309	6
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	16,899,639	6	3,772,095	6	7,614,745	6	682,017	8
C	Severe pain, severe short-term impairment, or hospitalization	16,415,636	9	4,714,108	9	9,579,052	9	5,010,227	12
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)	4,998,378	n.a.	5,593	n.a.	10,468	n.a.	512	n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	505,146	n.a.	1,864	n.a.	3,489	n.a.	171	n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	3,687,300	n.a.	1,858,289	n.a.	1,948,669	n.a.	3,114,516	n.a.

antibiotics. For the purposes of the discussion below and in Chapter 9, this estimated burden is termed the "preantibiotic" S. pneumoniae disease burden estimate; it does not necessarily represent an upper limit because pneumococcal pneumonia rates in developing countries may be higher than the rates assumed for calculations.

The precise extent of antibiotic availability and use in developing countries is not known, but it is significant and likely to increase by the time an improved vaccine might become available because of ARI treatment policies promulgated by the World Health Organization (1985). The committee believed that the disease burden estimates used in the central analysis comparisons should reflect this situation.

To account for the likely influence of present and future antibiotic use on the pneumococcal disease burden (particularly pneumonia deaths), the committee assumed that the total disease burden value (TDBV) that results from adopting the estimates in Table D-17.11 (13,224,522) would be reduced to half by antibiotic use (projected TDBV=6,612,261). This TDBV is used in the central analysis (Chapters 7 and 9).

Comparison of the estimates in Table D-17.11 with estimates for deaths and cases of pneumococcal pneumonia in children under 15 years of age derived by a different approach (Appendix B, Table B.6) reveals a considerable discrepancy, even when the disease burden shown in Table D-17.11 is assumed to be reduced by half from antibiotic use. While estimates shown in Table B.6 do not include pneumococcal meningitis and otitis media, calculations above suggest that these conditions would not proportionally add greatly to the pneumococcal pneumonia burden (i.e., probably less than 5 percent). The TDBV based on estimates in Table B.6 is 1,921,300. This is termed the "low" estimate for discussion purposes.

These discrepancies reflect the uncertainty of assumptions on which estimates of the true disease burden are based. To illustrate the effects of differences in assumptions about disease burden on the rankings of health benefits from vaccine candidates, analyses were conducted using the preantibiotic and low (Appendix B) estimates, as well as the projected estimate used in the central analysis. The results of this sensitivity analysis are discussed in Chapter 9.

PROBABLE VACCINE TARGET POPULATION

Persons of all ages, whether in good or impaired health, are at risk of pneumococcal infection. Attack rates of pneumococcal illness are highest at the extremes of age. Available evidence suggests that, although attack rates of pneumococcal infection in persons of the same age may not vary greatly with the state of health, mortality from such infection may be significantly higher in those whose health is compromised.

Infants and young children constitute a major target population because of the extremely high attack rate of pneumococcal otitis media in all societies. Because young children fail to respond immunologically to a number of bacterial polysaccharide antigens, vaccines with increased immunogenicity, such as polysaccharides conjugated to

proteins, probably will be needed to protect children from under 4 to 8 years of age.

An ideal strategy would be to immunize children with a polyvalent vaccine of conjugated pneumococcal capsular polysaccharides at about 4 to 6 months of age and, if proven desirable, a booster injection at 9 or 12 months. This program could be incorporated into the World Health Organization Expanded Program on Immunization (WHO-EPI). The protein moiety of the vaccine probably would be tetanus or diphtheria toxoid. The decision to give additional unconjugated capsular polysaccharides of types to which immunologic responsiveness is demonstrable during the first 2 years of life must await further study.

Calculations of potential vaccine benefits are based on the assumption of universal immunization of infants in developing countries.

Until universal immunization becomes routine, vaccines may be initially or additionally targeted at risk groups of other ages. Numerous studies have shown that persons of any age with one or more chronic illnesses who develop bacteremic pneumococcal infection are at significantly greater than average risk (17 percent) of a fatal outcome. This category includes persons with chronic cardiac, pulmonary, hepatic, renal, endocrine, or malignant disease; case fatality rates of treated bacteremic pneumococcal infections in these patients range from 25 to 50 percent in the United States and Europe (Austrian, 1985). For example, persons at especially high risk of death from pneumococcal bacteremia are those with anatomic or functional asplenia secondary to sickle cell anemia or thalessemia. Persons over 60 years of age also are at significantly greater risk of death. Because of these associations, the presently available 23-valent vaccine of pneumococcal capsular polysaccharides has been recommended in the United States for persons over 2 years of age with chronic illnesses or with anatomic or functional asplenia, and for individuals 65 years of age or older regardless of their state of health.

Vaccine Preventable Illness*

It is hoped that an improved vaccine for S. pneumoniae will be safe and efficacious when administered to infants, unlike the current vaccine, which is ineffective in children under 2 years of age. It is assumed that the vaccine will be administered at about 4 to 6 months of age with possibly a booster at 9 to 12 months of age.

Many studies indicate that the incidence of pneumococcal infections is highest in young children and the elderly. Although 83 pneumococcal capsular types have been identified, they differ in their propensity to cause human disease. Studies over decades in widely separated areas in

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

the United States indicate that the same 23 types account for the preponderance (more than 90 percent) of disease, although their relative frequencies vary with time and geographic area.

The WHO has established two Centres for Reference and Research on Pneumococci, one at the Statens Seruminstitut in Copenhagen, Denmark, the other at the University of Pennsylvania School of Medicine in Philadelphia. The Centres participate in world-wide surveillance of the distribution of pneumococcal capsular types isolated from blood or cerebrospinal fluid. Formulation of the currently available pneumococcal vaccine is based in part on data developed at the two Centres.

Knowledge of the distribution of agents that cause infection in any particular region is necessary before a vaccine can be formulated. This requires extensive study of isolates over a period of time, and little work of this sort has been conducted in developing countries. In a few areas, including Africa and Asia, capsular types 45 and 46 appear to cause a disproportionate amount of disease. Much additional work on the types prevalent in the developing world will be needed to achieve the possible benefits of vaccination.

It can be speculated that if predisposing factors, such as viral infections, are important in disease onset, then the viruses causing infection in children and the elderly may differ. This may affect the pneumococcal types causing disease in these age groups. Another source of uncertainty in estimating the vaccine preventable proportion of the disease burden is the duration of immunity achieved with conjugated capsular polysaccharides. Because researchers have not yet demonstrated this immunity to be as long lasting as that achieved with polysaccharides alone, infant vaccination possibly would not protect against disease in the elderly.

These uncertainties necessitate some simplifying assumptions to permit calculation of the likely benefits of a pneumococcal vaccine. For the spectrum of disease shown in Table D-17.11, the committee assumed that disease in adults and the elderly would not be prevented by infant immunization. Based on age group contributions to the TDBV, 58 percent of the disease burden falls in the under 15 years age group. Some of this burden will occur before vaccination. Hence, the committee assumed that about half of the total burden of pneumococcal illness was potentially vaccine preventable by infant immunization.

Other assumptions about the vaccine preventability of disease are plausible. Infant vaccination possibly could confer protection that would last until late in life, and thus it would not be feasible to include all capsular types causing disease in a vaccine, as assumed above. The procedures in Chapter 7 facilitate easy incorporation of alternative estimates for the vaccine preventable disease burden calculations.

SUITABILITY FOR VACCINE CONTROL

Polyvalent vaccines of pneumococcal capsular polysaccharides have been demonstrated to be safe and antigenic, and it is known that serum anticapsular antibodies, whether acquired actively or passively, provide

type-specific protection against infection. Despite the large number of pneumococcal capsular serotypes, most human infection is caused by a limited number of the more invasive types, which makes the production of polyvalent vaccines feasible.

Frequent administration of antibiotics to control infection has resulted in the selection of drug resistant strains in pediatric populations in several parts of the world, and multiply drug resistant strains may be difficult to control. The preponderance of deaths from pneumococcal infection in developed countries today results from irreversible physiologic injury early in the course of infection, injury unaffected by antimicrobial drugs. Prophylaxis is the only means now available for the protection of those identifiably at risk of such injury.

Alternative Control Measures and Treatments

No practical method for the long-term control of pneumococcal infection other than immunization is known. Antimicrobial prophylaxis, although feasible in special situations, has the potential risk of adverse drug reactions or drug resistance.

Although treatment with antibiotics, such as penicillin, has greatly reduced both the morbidity and mortality of established pneumococcal infections, a group of individuals remains at high risk of death. Currently, immunoprophylaxis is the sole available means for protecting such persons.

PROSPECTS FOR VACCINE DEVELOPMENT

Austrian (1984) recently published a major review of vaccination against pneumococcal infections, which includes the history of pneumococcal vaccine development and a review of the status of currently available vaccines. Therefore, the following section simply suggests the directions likely to lead toward improved vaccines.

Chemical conjugation of pneumococcal capsular antigens to proteins, such as diphtheria or tetanus toxoid, has been shown to alter their immunogenicity by converting the polysaccharide from a B-cell to a T-cell antigen. A vaccine of type 6A pneumococcal conjugated with tetanus toxoid has been tested in rhesus monkeys and in small numbers of human children and adults and is both immunogenic and safe. From these preliminary results, it is probable that similar conjugates of the polysaccharides of pneumococcal types 6B, 14, 19F, 19A, 23F and others could be developed in the next 5 to 7 years.

Several million persons have received vaccines of either whole pneumococci or of their capsular polysaccharides without permanent morbidity or a fatality. Transient local discomfort or pain, redness, induration, and swelling occur in 40 percent of adult recipients of the presently available vaccine, and up to 3 percent experience transient low-grade temperature elevations. Additional data are required to

establish the incidence of reactions to and the safety of conjugated capsular polysaccharides.

Accurate assessment of the efficacy of pneumococcal vaccines depends on establishing the causal role of the pneumococcus in an infection. Unfortunately, this role is usually uncertain. Assessing the efficacy of pneumococcal vaccines in preventing pneumococcal pneumonia must rest on the study of bacteremic pneumonia, for which the diagnosis is certain. Such studies will require large-scale, expensive clinical trials. Alternative modes of evaluation, such as case control studies and cohort studies (based on the design of Bolan et al., 1986), neither of which requires knowledge of the size of the vaccinated and unvaccinated populations at risk, are being used to refine efficacy assessments.

Evaluation of the efficacy of conjugated pneumococcal polysaccharide vaccines in preventing otitis media will require the routine use of tympanocentesis to establish causal diagnosis. This procedure is also therapeutic in that it drains pus from the middle ear and poses negligible risk when applied by trained hands.

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Appendix D-18

The Prospects for Immunizing Against Vibrio cholerae

DISEASE DESCRIPTION

Cholera is a diarrheal disease of the small bowel of humans. The causative bacteria is Vibrio cholerae, serogroup O1; only two biotypes, El Tor and classical composed of immunologically related serotypes, Inaba and Ogawa, cause epidemic cholera. The bacteria colonize the surface of the intestinal epithelium, but do not invade tissue. They elaborate a two-part protein enterotoxin that causes the diarrhea. This diarrhea is the cardinal, if not the sole, manifestation of the disease.

Recognized cases of cholera are, in general, more severe than other diarrheal diseases, but cholera has become the prototype of an increasingly recognized group of "enterotoxic enteropathies" (Finkelstein, 1984; Levine et al., 1983). These are far more significant causes of morbidity and mortality on a global scale than is cholera alone. Some of these agents also cause significant diarrheal disease in food supply animals. Many work through enterotoxins that are immunologically related to the cholera enterotoxin. At present, treatment depends on the vigorous replacement of fluid and electrolytic losses by oral or intravenous solutions of appropriate composition. Antibiotics serve an adjunctive role.

Vaccines against cholera, consisting of killed whole cells administered parenterally, have been used since the turn of the century. Extensive scientifically controlled field studies conducted in the 1960s and 1970s revealed that the protective effect of these vaccines is limited (Khan and Greenough, 1985). Many of the affected countries now have eliminated the requirement for cholera vaccine. The immunologically dominant component of the killed bacteria, the lipopolysaccharide somatic antigen, has been shown to have similar limitations as a vaccine (Finkelstein, 1984; Levine et al., 1983).

The committee gratefully acknowledges the efforts of R.A.Finkelstein, who prepared major portions of this appendix, and the advice and assistance of R.E.Black and J.B.Kaper. The committee assumes full responsibility for all judgments and assumptions.

Formalin and glutaraldehyde-treated toxoids, administered parenterally, also have been evaluated and found to be relatively ineffective (Finkelstein, 1984; Levine et al., 1983).

Studies in American volunteers and in endemic areas have established conclusively that the disease itself is an immunizing process (Finkelstein, 1984; Levine et al., 1983). The human host, presented with all the products of the cholera vibrio at the local level, undergoes maximal stimulation of secretory antibody. This finding has contributed to the notion that the best way to produce immunity against cholera would be to use a living, attenuated strain of V. cholerae that would colonize the gut and stimulate immunity, but not cause cholera.

PATHOGEN DESCRIPTION

The causative agent of epidemic cholera is Vibrio cholerae, serogroup 01. This group includes the El Tor biotype (the cause of the present pandemic) and the classical biotype, both of which occur as two serotypes, Inaba and Ogawa. The bacterium is gram-negative, comma-shaped, oxidase positive, and motile by means of a single polar flagellum. It is identified by its agglutinability in 0 group 1 and type-specific, Inaba or Ogawa, antisera. Other ancillary characteristics, such as growth and reaction on selective media (e.g., TCBS agar), and particular biochemical reactions (e.g., fermentations) can be useful in suggesting its identity, but confirmation depends on serologic reactions. The definition of the Vibrio cholerae species recently has been expanded to include a diverse variety of other vibrios that are known collectively as non-0 group 1 V. cholerae (because they do not agglutinate in O group 1 antisera). Occasional rare strains of non-O group 1 vibrios, formerly called NAG (nonagglutinable) or NCV (noncholera vibrios) produce a cholera-related enterotoxin and have been associated with diarrheal disease.

HOST IMMUNE RESPONSE

Despite the noninvasive nature of cholera, a vigorous immune response is induced in the host. This response is manifested both by circulating IgM and IgG antibodies and by secretory IgA antibodies against the lipopolysaccharide (LPS) somatic antigen, the enterotoxin, and other less well studied antigens. The antibacterial antibodies are vibriocidal (in the presence of complement) and agglutinating, and the anti-enterotoxin is neutralizing. Either or both are protective in animal models, and there is some evidence that they may interact synergistically. The disease is an immunizing process, and it has been demonstrated that volunteer convalescents are resistant to rechallenge for at least 3 years. In endemic areas, cholera is less frequent in adults who have circulating antibody.

DISTRIBUTION OF DISEASE

Geographic Distribution

Cholera has swept the world in seven great pandemic waves. From the early 1900s to 1961, cholera was virtually restricted to its endemic focus in the Indo-Pakistani subcontinent. The present pandemic, caused by V. cholerae of the El Tor biotype, began in 1958 in the Celebes Islands, Indonesia. It subsequently swept through and became endemic in the Philippines, Southeast Asia, and Africa. Outbreaks that have been more or less self-limited have occurred in the Soviet Union, Japan, Italy, Spain, northern Europe, and North America (including the United States). Cholera vibrios of the classical biotype appear to be reemerging in India and Bangladesh.

Disease Burden Estimates

The burden of disease caused by V. cholerae has been calculated only for areas in Africa and Asia where cholera is endemic. Table D-18.1 shows the estimated number of cases of the disease in Asia; Table D-18.2 presents the same information for Africa. The combined endemic disease burden for the two continents is shown in Table D-18.3.

No attempt has been made to estimate the disease burden produced by cholera epidemics or pandemics because it is very difficult to predict where and to what extent they will occur. This inability to identify a vaccine target population prevents calculation of potential health benefits that could be obtained from a vaccine. However, any vaccine developed to prevent endemic cholera could play a major role in curtailing epidemic cholera.

Traditionally, it has been assumed that cholera does not have any long-term sequelae. A recent epidemiological study in India suggests, however, that a strong association may exist between cataract development and episodes of cholera and other severe diarrheal diseases (Minassian et al., 1984). Because of the preliminary nature of this evidence, the committee chose not to include visual disability in the current disease burden estimates for cholera. Further research on this topic is warranted. Also omitted from disease burden calculations are possible adverse effects of cholera during pregnancy.

PROBABLE VACCINE TARGET POPULATION

In endemic areas, cholera occurs with greatest frequency in children between 2 and 15 years of age and in adult females. Children less than 2 years old have a relatively low incidence of the disease, particularly when breast-fed. Thus, vaccination in infancy would be appropriate, and a suitable vaccine could be incorporated into the World Health Organization Expanded Program on immunization (WHO-EPI).

In areas in which the introduction of cholera is recent (neoepidemic areas), the rates of disease are more uniform across the

TABLE D-18.1 Estimated Cholera Cases in Asia by Age Group

Age Group (years)	Total Population (millions)	Cholera Endemic Population[a] (millions)	Annual Incidence of Hospital Cases/1,000	Number of Hospital (Severe) Cases (8%)	Number of Moderate Cases (20%)	Number of Mild Cases (72%)	Number of Deaths (20% of severe)
Under 5	373	93	2.0[b]	186,000	465,000	1,674,000	37,200
5–14	639	160	0.75[c]	120,000	300,000	1,080,000	24,000
15–59	1,517	379	0.50[d]	189,500	473,750	1,705,500	37,900
60 and over	133	33	0.50[d]	16,500	41,250	148,500	3,300

[a]Twenty-five percent of total population, based on World Health Organization (1984).
[b]Based on Matlab, Bangladesh (3.9); Calcutta, India (1.0); and Surabaya, Indonesia (1.5).
[c]Based on Matlab, Bangladesh (4.0); Calcutta, India (0.65); and Surabaya, Indonesia (0.42).
[d]Based on Matlab, Bangladesh (2.0); Calcutta, India (0.65); and Surabaya, Indonesia (0.42).

TABLE D-18.2 Estimated Cholera Cases in Africa by Age Group

Age Group (years)	Total Population (millions)	Cholera Endemic or Neo-Endemic Population[a] (millions)	Number of Hospital Cases (8%)	Number of Moderate Cases (20%)	Number of Mild Cases (72%)	Number of Deaths (20% of severe)
Under 5	90	9.0	5,000[b]	12,500	45,000	1,000
5–14	149	14.9	15,000[b]	37,500	135,000	3,000
15–59	226	22.6	75,000[b]	187,500	675,000	15,000
60 and over	26	2.6	5,000[b]	12,500	45,000	1,000

[a]Ten percent of total population, based on Stock (1976) and World Health Organization (1984).
[b]Total cases and proportion by age group estimated from references in a proportion of cases: under 5 years, 5 percent; 5–14 years, 15 percent; 15–59 years, 75 percent; 60 years and over, 5 percent.

TABLE D-18.3 Disease Burden: *Vibrio cholerae*

Morbidity Category	Description	Condition	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
			Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Mild diarrhea	1,719,000	3	1,215,000	3	2,380,500	3	193,500	3
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	Moderate diarrhea	477,500	5	337,500	5	661,250	5	53,750	5
C	Severe pain, severe short-term impairment, or hospitalization	Severe diarrhea, dehydration	191,000	7	135,000	7	264,500	7	21,500	7
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)			n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)			n.a.		n.a.		n.a.		n.a.
F	Total impairment			n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility			n.a.		n.a.		n.a.		n.a.
H	Death		38,200	n.a.	27,000	n.a.	52,900	n.a.	4,300	n.a.

age groups. To avert a widespread epidemic in these areas, it may be necessary to vaccinate both adults and children. In developed countries, the potential vaccine target population consists of travelers and military personnel; however, the incidence of cholera among the former is very low and may not justify vaccination.

Vaccine Preventable Illness*

The target population for a cholera vaccine in endemic areas would be all children under 2 years of age (vaccinated through the WHO-EPI). Because the vast majority of cholera cases in these areas occur after age 2, the committee assumed that the entire disease burden could be prevented by the hypothetical vaccine.

The apparent nonhuman reservoirs of cholera found recently in the United States and Australia and suggested for other regions (Miller et al., 1985) make it unlikely that cholera could be eradicated completely, but this issue remains controversial.

SUITABILITY FOR VACCINE CONTROL

Because cholera itself is a highly effective immunizing process, it should be possible to duplicate this immunity artificially and without unacceptable side effects. Cholera is also a highly suitable candidate for control by vaccines because all of the epidemic cholera in the world is caused by only two serotypes (representing both biotypes) of V. cholerae and a single enterotoxin (or series of closely related enterotoxins).

Alternative Control Measures and Treatments

The incidence of cholera could be markedly reduced, if not totally eliminated, by sanitary measures: appropriate disposal of human feces and chlorination of water. However, achieving these goals is unlikely in the next few decades in areas where cholera occurs most commonly.

Oral rehydration or intravenous electrolyte replacement therapy prevents mortality from cholera, if it is used. However, current high mortality figures attest to inadequate treatment delivery systems. Treatment also represents a major expense to the developing nations. Epidemic cholera may overwhelm available medical services in some areas.

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

PROSPECTS FOR VACCINE DEVELOPMENT

Previous Work

Several studies have established that parenterally administered, killed whole cell vaccines are inadequate and are not cost-effective (Finkelstein, 1984; Levine et al., 1983). The evidence also suggests that the parenterally administered toxoids do not provide adequate protection, although relevant trials have been criticized on technical grounds (Finkelstein, 1984; Levine et al., 1983).

Current Activities

Current activities focus primarily on the development of orally administered cholera vaccines, containing either live attenuated strains or nonviable antigens. Other approaches also are discussed below.

Live Attenuated Vaccines

The most promising approach to cholera vaccines in terms of cost and efficacy are live attenuated vaccines. Attenuated bacterial strains for oral administration have been derived by chemical mutagenesis and by recombinant DNA techniques.

Two attenuated strains derived by chemical mutagenesis have been studied in man and have been demonstrated to produce significant protective immunity in American volunteers although not equivalent to that resulting from the disease. A hypotoxinogenic mutant, M-13, was unstable and some isolates from volunteers regained toxigenicity (Finkelstein, 1984; Levine et al., 1983; Woodward et al., 1976). Another mutant known as Texas Star-SR produces only the nontoxic immunodominant B region of the cholera enterotoxin (choleragenoid) and not the A or active portion of the molecule, and thus is incapable of causing cholera (Honda and Finkelstein, 1979). While the precise genetic lesion in the cholera toxin gene is unknown, the mutation appears to be stable. The vaccine efficacy was 61 percent, but approximately 25 percent of the recipients manifested one to a few loose stools following administration of the vaccine (Levine et al., 1984). There are no current plans to further evaluate this strain as a vaccine.

More recent attenuated strains have been derived using recombinant DNA techniques. Genes encoding the cholera enterotoxin have been cloned and sequenced, and substantial, non-reverting deletion mutations have been constructed in vitro. The mutated genes were then recombined into the chromosome of virulent V. cholerae strains to derive well-characterized, attenuated vaccine candidates (Kaper et al., 1984a,b; Mekalanos et al., 1983). The first two candidates to be evaluated in volunteers, JBK70 and CVD101, contain deletions of both the A and B toxin subunits (JBK70) or of the A subunit only (CVD101). Both strains

induced excellent immunity and JBK70, in the absence of any portion of the cholera toxin, conferred protective immunity equivalent to that resulting from the disease (Kaper et al., 1985). However, both of these strains were even more reactogenic than Texas Star-SR, inducing mild to moderate diarrhea in approximately 50 percent of volunteers upon immunization.

Additional vaccine strains have been constructed in an attempt to decrease the side effects seen with JBK70 and CVD101. One very promising vaccine candidate is CVD103 which is a derivative of the highly toxinogenic classical strain 569B Inaba which lacks the A subunit (Kaper et al., 1986). Minimal reactogenicity is seen with this vaccine strain with very mild diarrhea seen in only 2 of 37 (5.4 percent) volunteers so far tested. The strain confers excellent immunity and protection against homologous challenge with 569B. Additional clinical trials are underway with this strain and, if successful, should lead directly to a field trial in the very near future.

Nonviable Antigens for Oral Administration

Killed bacteria administered orally have been advocated as vaccines since the late 1800s. More recent studies (Cash et al., 1974) have shown that while repeated oral administration of massive doses of killed V. cholerae offers some protection against challenge, it is less effective than the vaccine administered parenterally (which has been discarded because of its lack of efficacy). More research is needed on the use of oral adjuvants to improve the immunogenicity of these preparations before their potential can be accurately evaluated.

Inactivated cholera enterotoxin also has been considered for oral administration. Inactivation can be accomplished by treatment with formalin or glutaraldehyde, by the removal of the A subunit from the pentameric B subunits (choleragenoid), or by controlled heating, which results in the formation of a relatively nontoxic, large molecular weight polymer called procholeragenoid (Finkelstein et al., 1971). Of these, only the glutaraldehyde-toxoid has been tested by itself for efficacy in volunteers, and it failed to induce demonstrable protection (Levine et al., 1983).

Many studies in animal models and man, however, have shown that various forms of the toxin administered orally can induce an immune response, either alone or in conjunction with parenterally administered antigen (Finkelstein, 1984; Levine et al., 1983). The toxin itself and procholeragenoid have been shown to be the most effective (Pierce et al., 1983).

Although it has been shown in many laboratories that choleragenoid (pentameric B subunit), when separated from the holotoxin, is a less effective antigen, “B-subunit” oral vaccine elicited a measurable antitoxic response in Bangladeshi recipients (perhaps already primed) who were given single or multiple oral doses of milligram quantities (Svennerholm et al., 1983).

Researchers also have assessed the efficacy of different combinations of killed bacteria and inactivated enterotoxin. Glutaraldehydetoxgid (2 mg weekly for 4 weeks) combined with killed V. cholerae (10^{10} vibrios twice weekly for 4 weeks) was found to provide 67 percent protection against subsequent challenge in small groups of volunteers (Levine et al., 1983). "B-subunit" (choleragenoid) in three oral doses of 5 mg each, together with three doses totaling 6×10^{11} of killed V. cholerae, also provided significant, but not absolute, protection to volunteers (Levine et al., 1983).

In contrast, procholeragenoid, administered in three doses totaling 300 μg, combined with a different preparation of 10^{11} heat- and formalin-killed bacteria, only marginally reduced the incidence of the disease in challenge volunteers, although the disease was significantly attenuated (Levine et al., 1983).

A large-scale field trial of "B-subunit" combined with killed vibrios given orally is being conducted in Bangladesh (Svennerholm, in press). Preliminary results are encouraging (Kaper, 1986, personal communication), but the duration of protection must be established in order to justify the expense and effort (three doses) of this vaccine.

One other oral, nonviable preparation that has recently been field-tested is a V. cholerae cell-wall fraction prepared by the Institut Pasteur. This vaccine was tested in Zaire and appeared to provide significant protection (Dodin et. al., 1983). Additional evaluation of this vaccine, including volunteer studies, is required to adequately compare it to other vaccine candidates.

The major drawback to nonviable vaccines is the much higher manufacturing cost relative to live attenuated strains. In addition, the live replicating antigen is significantly more immunogenic than non-replicating antigen vaccines. Whereas the nonviable preparations would require more than one dose (probably three doses), an attenuated strain should require only a single dose. In volunteer trials, the only cholera vaccines that have conferred protection equivalent to that conferred by the disease are the attenuated strains JBK70 and CVD103. It is certainly possible that vaccination of a population in a country endemic for cholera and perhaps already primed would provide better protection than that seen in U.S. volunteers. Currently, the leading candidates for cholera vaccines are the B subunit-whole cell vaccine and the attenuated strains. The issues of cost, immunogenicity, and reactogenicity will be significant considerations in deciding which type of vaccine would be more practical for developing countries where cholera is endemic.

Other Approaches

Four additional approaches appear to merit further study. These are the use of carrier bacteria containing cloned V. cholerae genes, the development of new nonviable preparations administered parenterally, the use of synthetic antigens, and the possible use of passively administered antibody, per os, to susceptible populations.

Carrier Bacteria

This approach utilizes the live, oral typhoid vaccine strain Ty21a into which genes encoding V. cholerae antigens have been cloned. Thus, the S. typhi strain serves as a "carrier" bacterial strain which can present foreign antigens to the local immune system. Details of this vaccine have not been published as of this writing, but clinical trials will soon be underway in Australia (New Scientist, 1986). Ty21a has proven to be extremely safe and non-reactogenic in field trials and it is thought that by adding genes for the LPS and outer membrane proteins of V. cholerae to Ty21a, it will be possible to protect against both typhoid and cholera with a single vaccine. This approach may prove useful for other vaccines in addition to cholera and clearly merits further study.

Nonviable Preparations

The limited efficacy of the previously evaluated parenterally administered products led many researchers to believe that no parenteral vaccine would merit further consideration. However, procholeragenoid has been shown to be superior to other forms of the toxin antigen in stimulating gut immunity following parenteral administration of moderate doses (Fujita and Finkelstein, 1972). This observation has been confirmed in many laboratories (Finkelstein, 1984).

Procholeragenoid has been shown to protect piglets against diarrheal disease due to E. coli strains that produce an immunologically related, but not identical, enterotoxin. It appears to be enriched in the A-subunit of the cholera enterotoxin in a relatively innocuous form. The cholera holotoxin is a potent immunologic modulator; it is conceivable that this property resides in the A-subunit, which is not highly immunogenic by itself. Thus, further consideration should be given to the evaluation of procholeragenoid, administered parenterally either by itself or, for possible synergistic effects, in combination with bacterial antigens. A recent study has shown that procholeragenoid-like products can be produced from the related E. coli heat labile enterotoxins, LTs (Finkelstein et al., 1984).

Synthetic Vaccines

Recent studies have shown that the cholera-related family of enterotoxins (which includes the E. coli LTs, Salmonella LT, some non-0–1 V. cholerae enterotoxins, and perhaps others) share common or conserved amino acid sequences that appear to be important to their function and immunogenicity. Furthermore, preliminary evidence indicates that certain synthetic small peptides that duplicate some of these sequences, when coupled to carrier proteins, elicit neutralizing antibody and some protection in animal models (Jacob et al., 1983).

It is conceivable that appropriate synthetic antigens administered either parenterally or orally (perhaps in protective microspheres as

suggested recently by Klipstein et al., 1983) could provide broad spectrum protection against a large proportion of diarrhea-producing agents. However, neither volunteer studies nor epidemiological data provide support for this concept. The possibility cannot be completely dismissed but considerably more basic research is required to clarify the prospects of success with this approach.

Passive Protection

Bovine colostrum and milk contain significant amounts of an immunoglobulin G class 1 antibody that retains immunologic reactivity after exposure to intestinal enzymes (McClead and Gregory, 1984). Conceivably, specific bovine colostral antibodies could be a source of passive immune protection for human infants and adults at risk for cholera and other diarrheal diseases. Promotion of breast-feeding may also reduce cholera but the mechanisms involved are not fully understood.

PROBLEMS TO BE OVERCOME

Several problems markedly inhibit further progress. The first, as noted above, is the slow development of vaccine candidates in the laboratory. This results partly from the lack of suitable animal models of cholera. Although a large number of different systems have been proposed and applied, it is doubtful whether any of them realistically reproduce the disease as it occurs in humans. Younger animals, such as mice and rabbits, are susceptible to moderate doses of V. cholerae, but are difficult to use in protection studies.

Other major limitations are the cost and organizational problems associated with conducting large-scale cholera vaccine efficacy trials, once suitable candidates have been developed and evaluated in volunteers. There are only a few places in the world where these trials can be conducted (e.g., the National Institute of Allergy and Infectious Diseases' vaccine development centers), and such facilities must devote time and resources to many different pathogens.

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Appendix D-19

The Prospects for Immunizing Against Yellow Fever

DISEASE DESCRIPTION

In its severe form, yellow fever (YF) is characterized by three clinical periods: the period of infection (about 3 days), the period of remission, and the period of intoxication. The incubation period ranges from 3 to 6 days. Onset is sudden, with fever accompanied by headache, weakness, lumbosacral pain, anorexia, nausea, and vomiting. Physical findings include torpor, relative bradycardia, conjunctival congestion, dry skin, fetid breath, and abdominal or lumbar tenderness. Fever may remit briefly on the second or third day, then return with increasing intensity. The period of intoxication is characterized by jaundice, oliguria, albuminuria, and hemorrhages (e.g., hemoptysis, epistaxis, metrorrhagia).

Death occurs usually between the seventh and tenth day of illness. Early death between the second and sixth day may be observed (Serie et al., 1968). Convalescence is slow and may last up to 3 months.

A live attenuated vaccine (17D strain) produced in embryonated chicken eggs has been used widely to prevent YF, especially in endemic areas of Africa and Latin America. The experience acquired over the last 4 decades, during which millions of doses of 17D vaccine have been administered, has demonstrated the immunogenicity of the vaccine (with a seroconversion rate of more than 99 percent), its relative safety, and its efficacy in preventing in clinical illness (Pan American Health Organization, 1981).

The need for a new vaccine stems in part from evidence that infants under 6 months of age may develop neurological complications when immunized with the 17D vaccine (Pan American Health Organization, 1984). Also, the reappearance of the insect vector of YF virus in some urban centers in South America and the potential for YF transmission to susceptible areas elsewhere has led to concern that the demand for the

The committee gratefully acknowledges the efforts of F.P.Pinheiro, who prepared major portions of this appendix, and the advice and assistance of A.Shelokov and T.Monath. The committee assumes full responsibility for all judgments and assumptions.

vaccine could increase suddenly. Modern cell culture techniques could greatly improve the speed and economy of vaccine production.

PATHOGEN DESCRIPTION

Yellow fever virus is an arthropod-borne virus in the Flavivirus genus of the family Togaviridae. It shares group-specific antigens with other members of the genus (former group B viruses, e.g., in Africa: Zika, West Nile, Wesselsbron, dengue, Uganda S, Spondweni, Banzi, and other viruses) (Wildy, 1971).

Yellow fever and other flaviviruses contain a single-stranded, positive-polarity RNA genome. Viral particles are 43 nm in size; they contain a ribonucleoprotein core and a lipoprotein envelope. The virus is inactivated by deoxycholate, ether, proteases, and lipases. The envelope contains a single glycoprotein with type- and group-specific antigens.

The morphogenesis of YF virus is similar to that observed for other flaviviruses; that is, viral synthesis and maturation appear to be predominant in the rough endoplasmic reticulum. The formation of the surrounding envelope of the virion remains unclear. Mature virus particles accumulate within the cisternae of membranous organelles and are released extracellularly by exocytosis or by plasma membrane rupture.

The virus is pathogenic for adult mice by intracerebral inoculation, and for suckling mice by intracerebral, subcutaneous, and intraperitoneal inoculation. The rhesus monkey is highly susceptible to YF virus, and this animal may be used as a model to define the pathogenesis of the disease (Monath et al., 1981).

Yellow fever virus replicates in cell cultures of different origin, but the cell cultures are variously sensitive. Cell lines of mosquito, monkey kidney, and hamster kidney are useful for propagation and assay. The 17D attenuated strain can be grown in several cell substrates, such as primary or subcultured chick embryo fibroblast and monkey kidney cells; virus titers observed in these systems are comparable to those obtained in embryonated eggs (Pan American Health Organization, 1981).

Wild strains of YF virus vary in their pathogenicity for hosts, but the molecular basis for virulence is poorly understood. Host factors, including genetic and immunological parameters, probably affect susceptibility.

HOST IMMUNE RESPONSE

Neutralizing antibodies usually are detectable on the sixth or seventh day after onset of primary infection and are responsible for immune elimination of the virus. It is not unusual to find both infectious virus and antibody in serum, but the role of immune complexes in the pathogenesis of the disease remains uncertain. Antibody responses may be accelerated and broadened in individuals with prior flaviviral immunity. Yellow fever virus infection also may alter the

immune response itself. Depression of delayed hypersensitivity (tuberculin skin test reactivity) has been observed after administration of 17D vaccine (Monath, 1984). Whether the B-cell necrosis described in YF of rhesus monkeys is associated with suppression of antibody formation is not known.

DISTRIBUTION OF DISEASE

Geographic Distribution

Yellow fever is endemic in extensive parts of tropical South America and sub-Saharan Africa. The annual incidence of officially reported YF cases varies from 50 to 300 cases in South America and from 5 to 700 cases in Africa (Table D-19.1). Investigations during several outbreaks indicate that morbidity and mortality rates are significantly under-estimated (Monath, 1984).

Bolivia, Brazil, Colombia, Ecuador, and Peru account for the majority of cases in South America. Virus reservoirs are maintained in tropical forests, such as those of the Amazon region and the Orinoco and Magdalena valleys. In some years, the virus can extend to other areas, including Central America, northern Argentina and Paraguay, and Trinidad and Tobago, causing significant outbreaks. Currently YF in the Americas occurs exclusively in its jungle form.

In Africa, YF is endemic or epidemic in 29 countries of the tropical zone between the fifteenth parallel north and the tenth parallel south. It occurs as sporadic cases of jungle YF, or as outbreaks mainly in savannah areas. Several sizable epidemics have occurred during the past 5 years, such as in Ghana (1977 to 1979 and 1983), Gambia (1978 to 1979), Senegal (1981), Ivory Coast (1982), and Burkina Faso (formerly Upper Volta) in 1983.

Disease Burden Estimates

The disease burden estimates for YF appear in Tables D-19.2. through D-19.4.

Disease burden estimates were based on reported cases of YF to the World Health Organization, multiplied by a correction factor. The correction factor was determined by dividing the number of reported cases in certain areas into more realistic assessments based on epidemiological investigation in these areas. A median value was taken from the range of values derived from one South American and five African studies (Table D-19.5).

From Table D-19.1 an average reported annual incidence was derived from the most recent 10 years for Africa and South America. These values, 181.3 and 136.3, were multiplied by the correction factor of 257.6 to get an annual incidence rate of 46,707 and 35,114 for Africa and South America, respectively.

Because of YF's different epidemiological patterns, the distribution of cases into categories of severity and age groups was calculated

TABLE D-19.1 Yellow Fever in Africa and the Americas During the Period 1965 to 1983

Country	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983
Africa																			
Angola							65												
Equitorial Guinea						4													
Ethiopia		350																	
Gambia														30					
Ghana					5	12	3	5	5	1	2	2	110	219	494	8	4	6	372
Ivory Coast																		25	
Liberia			5																
Mali					21														
Nigeria					208	4			2	25					11	1			
Senegal	243														3		3		
Sierra Leone											130								
Congo					1	2													
United Republic of Cameroon						1		2	1	1	2	1				7			
Upper Volta					87														356
Zaire							2												
Total	243	350	5		322	23	70	7	8	27	134	3	110	249	508	16	7	31	728
Americas																			
Argentina	2	51	1																
Bolivia	19	69		27	8	2	8	9	86	12	151	19	2	11	10	46	102	95	11
Brazil	14	167	2	2	4	2	11	12	70	13	1	1	9	27	12	26	22	24	6
Colombia	2	3	5	11	7	7	9	3	16	36	12	22	9	105	51	7	7	1	1
Ecuador			1								3	1		1	14	2	2		5
Guyana				1															
Panama										4									
Paraguay										9									
Peru	45	9	3	5	28	75		7	33	2	1	1	82	93	97	25	98	17	27
Suriname				1	1			2											
Trinidad and Tobago															18				
Venezuela	5	5						22	7					3	3	4			
Total	87	304	12	47	48	86	28	55	212	76	168	44	102	240	205	110	231	137	50

SOURCE: Pan American Health Organization (1984).

TABLE D-19.2 Disease Burden: Yellow Fever (Africa)

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	3,503	7	8,408	10	5,605	10		
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	2,102	14	6,305	20	5,605	20		
C	Severe pain, severe short-term impairment, or hospitalization	1,401	21	6,305	30	7,473	30		
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	701	n.a.	3,153	n.a.	3,737	n.a.		n.a.

TABLE D-19.3 Disease Burden: Yellow Fever (Americas)

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	211	7	702	10	5,969	10	140	10
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	737	14	2,458	20	20,893	20	491	20
C	Severe pain, severe short-term impairment, or hospitalization	105	21	351	30	2,985	30	70	30
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	53	n.a.	176	n.a.	1,492	n.a.	35	n.a.

TABLE D-19.4 Disease Burden: Yellow Fever--All

Morbidity Category	Description	Under 5 Years		5-14 Years		15-59 Years		60 Years and Over	
		Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration	Number of Cases	Duration
A	Moderate localized pain and/or mild systemic reaction, or impairment requiring minor change in normal activities, and associated with some restriction of work activity	3,714	7	9,110	10	11,574	10	140	10
B	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., housebound or in bed, and associated with temporary loss of ability to work	2,839	14	8,763	20	26,498	20	491	20
C	Severe pain, severe short-term impairment, or hospitalization	1,506	21	6,656	30	10,458	30	70	30
D	Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work)		n.a.		n.a.		n.a.		n.a.
E	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)		n.a.		n.a.		n.a.		n.a.
F	Total impairment		n.a.		n.a.		n.a.		n.a.
G	Reproductive impairment resulting in infertility		n.a.		n.a.		n.a.		n.a.
H	Death	754	n.a.	3,329	n.a.	5,229	n.a.	35	n.a.

differently for the two continents. For Africa, the estimated age distribution of cases is 15 percent in the under 5 years age group, 45 percent in the 5 to 14 years age group, 40 percent in the 15 to 59 years age group, and virtually 0 in the 60 years and over age group. The estimated breakdown of cases in each age group is as follows: under 5 years of age, 50 percent in morbidity category A, 30 percent in category B, 20 percent in category C; 5–14 years of age, 40 percent in category A, 30 percent in category B, 30 percent in category C; 15 to 59 years of age, 30 percent in category A, 30 percent in category B, 40 percent in category C. Deaths (category H) are estimated to be half of the severe cases (category C) in each age group.

TABLE D-19.5 Comparison of Epidemiologically Determined Cases to Reported Cases of Yellow Fever

Country	Year	Number of Cases	Number of Epidemiologically Determined Cases	Ratio of Epidemiologically Determined Cases to Number of Reported Cases
Senegal	1965	243	11,000	45.3
Upper Volta	1969	87	3,000	34.5
Nigeria	1969	208	100,000	480.8
	1970	4	786	196.5
Gambia	1978– 1979	30	6,500	216.7
Brazil	1972– 1973	71	21,000	295.8
Median value				257.6

SOURCE: Monath et al. (1984); Pinheiro et al. (1978).

For South America, the age distribution is estimated differently: under 5 years, 3 percent; 5 to 14 years, 10 percent; 15 to 59 years, 85 percent; and 60 years and over, 2 percent. For each age group, 20 percent of cases are assumed to fall in category A, 70 percent in B, and 10 percent in C. Half of category C cases die, and they comprise category H.

PROBABLE VACCINE TARGET POPULATION

Yellow fever vaccination is recommended for all persons who live in rural communities in endemic areas and whose occupations bring them into forests where the virus circulates. It is also recommended for persons who plan to visit an endemic zone.

The majority of cases recorded in South America involve males 15 to 45 years old, but children in the 1 to 4 years age group also can be affected (Pan American Health Organization, 1983).

In Africa, children and young adults up to 15 years of age are mainly affected by the severe form of the disease. In recent outbreaks recorded in Ivory Coast (1982) and Burkina Faso (1983), most cases occurred among children (World Health Organization, 1984).

There is evidence that a significant proportion of infants under 6 months of age may develop neurological complications when immunized with the 17D vaccine (Louis et al., 1981). Hence, the existing vaccine should be given only after 6 months of age, and some authorities withhold it until 1 year of age (Pan American Health Organization, 1984).

General adoption of the World Health Organization Expanded Program on Immunization (WHO-EPI) offers an opportunity to add an improved YF vaccine to the six vaccines already included in the program, providing a vaccine that is adequately safe in young children can be developed. In risk areas (which have to be defined in each country), the YF vaccination could be coupled with the measles vaccine; a single injection should provide lifelong immunity. The cold chain requirements would be similar to those for the measles vaccine. Herd immunity could be built up progressively in endemic areas, but national authorities would have to be aware that a risk group would remain among individuals older than the EPI-vaccinated group. New techniques for the preparation of YF vaccine should lower the cost of the vaccine to about the same as that of the measles vaccine.

Vaccine Preventable Illness*

The 17D embryonated egg vaccine demonstrates a seroconversion rate of more than 99 percent with a single dose (Pan American Health Organization, 1981). Moreover, neutralizing antibodies have been shown to persist for at least 35 years in the great majority of those vaccinated (Pinheiro, 1982; Poland et al., 1981). It seems logical to assume that a 17D cell culture vaccine would yield similar results.

Theoretically, complete prevention of the disease would be possible if a vaccine (that is safe for young infants) could be administered to 100 percent of the population at risk, since very little disease occurs among infants. Widespread use of the current 17D embryonated egg vaccine over the past 4 decades has resulted in a considerable reduction in the incidence of the disease among population groups at risk. In areas where vaccination coverage is insufficient or immunization procedures are not followed correctly, the disease continues to inflict a significant toll.

Inaccessibility of the target population poses an important problem for vaccine delivery. High-risk groups live in rural or forested areas, which often are quite remote. Nomadic groups and immigrants

*Vaccine preventable illness is defined as that portion of the disease burden that could be prevented by immunization of the entire target population (at the anticipated age of administration) with a hypothetical vaccine that is 100 percent effective (see Chapter 7).

who come to jungle YF areas also may not be readily available for vaccination.

Past experience has shown that mobile teams are useful for reaching persons who live in remote rural areas (World Health Organization Expert Committee on Yellow Fever, 1971). This approach is still being used in several countries, particularly when outbreaks occur. It requires major logistical support and planning, but may be the most effective way for obtaining good vaccination coverage. Inclusion of YF vaccine in the WHO-EPI seems to be a desirable goal. However, even if extensive vaccination coverage could be attained through the WHO-EPI, vaccination of older susceptible groups would continue to be required for some time. This is of particular importance in South America, where most persons affected by YF are adult males.

SUITABILITY FOR VACCINE CONTROL

The epidemiological features of YF dictate that its prevention by active immunization is highly desirable and practicable.

Large-scale immunization against YF has been performed for more than 4 decades with considerable success. Certain problems (failure to immunize, post-vaccinal encephalitis, and hepatitis) observed in early years of the vaccination program were readily overcome by adopting appropriate measures. For the reasons noted above, an improved vaccine is needed.

If urban YF were to reappear in South America, the consequences could be catastrophic. However, an urban population can be immunized rapidly if adequate stocks of vaccine exist and vaccination teams are available.

Alternative Control Measures and Treatments

Urban YF, which was common in the past in many cities of the Americas was controlled through the elimination of Aedes aegypti, the urban vector in the region.

Jungle YF is now the only form of the disease that occurs in the Americas, and the most common form in Africa. Control of forest vectors of YF is extremely difficult and virtually impossible under most circumstances.

There is no specific treatment for YF. High case-fatality rates (40 to 60 percent) continue to be observed among hospitalized patients (Pinheiro, 1981) for several reasons: lack of recognition of the disease in its early stage, misdiagnosis, and the absence of adequate medical facilities in most endemic areas.

Considering the above problems, prevention of YF by immunization is a matter of highest priority. Vector control in urban centers infested with Aedes aegypti, especially those located in endemic zones, also should be maintained to reduce the risk of YF urbanization.

PROSPECTS FOR DEVELOPMENT OF A YELLOW FEVER CELL CULTURE VACCINE

Most YF vaccine used at the present time in South America is produced by two national government controlled laboratories, one in Rio de Janeiro, Brazil, and the other in Bogota, Colombia. Although these two laboratories have provided an uninterrupted supply of vaccine, until recently their procedure for producing the vaccine from eggs remained basically the same as when the vaccine was first introduced 40 years ago. Since 1981, however, the Pan American Health Organization (PAHO) has been actively involved in improving the quality of YF vaccine produced in the two laboratories. As a result, significant progress has been achieved in modernizing the production facilities and techniques for vaccine manufacture in both countries.

Despite these improvements, efforts are under way to develop new techniques for the production of YF vaccine. These efforts have resulted, in part, from increased concern over the risk of YF extending to certain cities near jungle YF foci in South America. These cities have been heavily "reinfested" with Aedes aegypti (an urban vector of YF virus). Moreover, other areas in the world, such as North Africa, the Middle East, Southeast Asia, and the Far East, are known to be vulnerable to YF because of the presence of the same mosquito vector in high densities. The reappearance of YF in urban centers of South America, and its importation into susceptible areas elsewhere, would immediately produce a great demand for the vaccine. The demand would be very difficult to meet with currently available vaccine stocks. The reappearance of urban YF transmission at a time when the world's stock of YF vaccine is said to have dropped to a dangerously low level could be catastrophic, not only for the Americas, but also for the rest of the world.

Development of a YF vaccine grown in cell culture by modern techniques is a solution to the problem. Cell culture would greatly improve the speed and economy of vaccine production and provide for rapid expansion in the event of an emergency. In addition, safety would be improved because the amount of potentially allergenic proteins in the vaccine would be reduced. Because of its purity, a YF cell culture vaccine also would be more suitable for combined use with other live viral vaccines, such as measles.

Current experience indicates that efforts to develop a 17D cell culture vaccine will be successful. The 17D vaccine virus has been grown on various cell substrates up to titres comparable to those obtained in embryonated eggs (Pan American Health Organization, 1981). These substrates include primary chick and duck embryo fibroblasts, as well as a diploid cell strain. Many have been used for other vaccines and have met WHO safety requirements. It is expected that the efficacy of a 17D cell culture vaccine will be excellent (90 to 100 percent), with fewer side effects than the currently available embryonated egg vaccine.

It is anticipated that studies required for developing a YF cell culture vaccine will encompass four phases:

1. the development, characterization, production, and certification of a primary seed virus for a cell culture 17D vaccine
2. research, preferably conducted in an existing YF vaccine production facility, leading to the development of production protocols for a cell culture YF vaccine
3. research to improve biological markers and reduce neurovirulence of the 17D vaccine and to define the dose response of the product on the basis of studies in man
4. formulation and evaluation of more satisfactory thermal stabilization agents for the currently available YF vaccine.

If chick embryo cell cultures are used as the substrate, they should be derived from embryonated eggs from a monitored, specific pathogen-free flock of chickens. Diploid cell culture products must meet WHO requirements for freedom from cellular DNA and should be used only if they have been used in the past for a live attenuated virus vaccine. The original seed virus should be a 17D derivative that is free from leucosis virus and that meets WHO requirements for a YF fever vaccine seed.

The thermal instability and relatively short shelf life of the live-attenuated YF vaccine probably could be corrected through inexpensive and straightforward investigations. Such investigations could provide a cheaper, longer lasting, and more abundant YF vaccine.

At present, basic information about the 17D virus strain is lacking. Basic research studies on the biological and biochemical properties of this virus strain should be conducted simultaneously with the investigations described above to provide a better understanding of genetic variation from passage in cell cultures. Particular emphasis should be given to defining genetic markers useful for the characterization of cell culture derived vaccines. The availability of in vitro and in vivo markers for the characterization of the cell-culture adapted YF seed to be used for vaccine production is vitally important, and several marker systems should be developed for this purpose. The markers should be shown to be reliable and reproducible, and each passage of virus should be monitored for changes.

Currently, YF 17D vaccines are not recommended for use in infants under 6 months of age, and some countries do not require the International Certificate of Vaccination under 1 year of age. The incidence of encephalitis following YF 17D vaccination of infants is not known with any certainty and should be studied further. In one analysis, the incidence was estimated to be at least 0.3 percent in infants under 6 months of age (Louis et al., 1981). Because immunization of infants younger than 6 months of age is desirable in many circumstances, reduction of the existing level of neurovirulence of 17D vaccine should be a goal of YF research.

Such a research project could produce a vaccine ready for initial trials in humans in about 2 years, depending to some extent on the amount of vaccine and seed virus testing in monkeys. In any event, vaccine testing in humans is not expected to be a special problem.

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Appendix E

Questionnaire for Assessing Morbidity-Mortality Trade-Offs

The objective of any vaccine development program is to reduce the medical, social, and financial costs resulting from a disease. Unfortunately, time and resource constraints limit the number of vaccine development programs that can be pursued at one time. Priorities must be set in a manner that is consistent with both the needs of the population and the capabilities of current technologies.

The committee has proposed a method that would allow quantitative comparison of the consequences of various diseases. The system combines information on disease-related illnesses (including incidence, severity, complications, durations, and distributions) and deaths into a single numerical score for each disease. It also allows expression of individual value judgments on the undesirability of different types of illness (morbidity). These value judgments are an inevitable part of the ranking process, whether they are clearly stated or assumed: the committee chose to make them explicit.

The first step in the comparison process was to develop a format that would ensure uniform collection of data on the various diseases. The format consists of categories in which to group estimates of the number of cases, complications, and deaths associated with each disease. Three levels of severity were established for both acute and chronic illnesses, and provision was made for recording the durations of acute illnesses. The format was also designed to show the distribution of cases, complications, and deaths among four age groups.

Attachment 1 lists eight categories of clinical consequences that may be associated with the diseases and vaccines under consideration. We are compiling estimates for each disease of the annual number of days of morbidity in categories A through C, and the annual number of cases in categories D through H. Determination of the total health impact of each disease requires, however, that these figures be modified to reflect the relative importance of morbidity and mortality at different ages.

We are requesting that you prepare a personal, subjective assessment of the relative importance to be assigned to each of the eight categories. Because the relative value may depend on the ages of the afflicted populations, we ask that you provide separate scores for each of four age groups: (1) children under 5 years of age; (2) children

from 5 to 14 years of age; (3) adolescents and adults from 15 to 59 years of age; and (4) adults 60 years of age and older. Additionally, we ask that you estimate the relative importance of the death of a child under 5 years of age to a death in the three higher age groups.

The problem of assigning relative importance could be approached in many ways. For the sake of consistency, we ask that you try to work through the exercise as described below. Attachments 2 and 3 are the recording forms for your answers.

INSTRUCTIONS FOR COMPLETING THE RECORDING FORM

To understand how to complete Attachment 2, please read the following examples. First, consider column 1 of the "Age Related Morbidity and Mortality Trade-offs" table, which refers to illness occurring in children under 5 years of age. For each category, we are seeking a value which can be compared the death of a single young child. For categories A through C, estimate the number of days of illness, and for categories D through G, estimate the number of cases of illness which you think to be as bad as one death of a child.

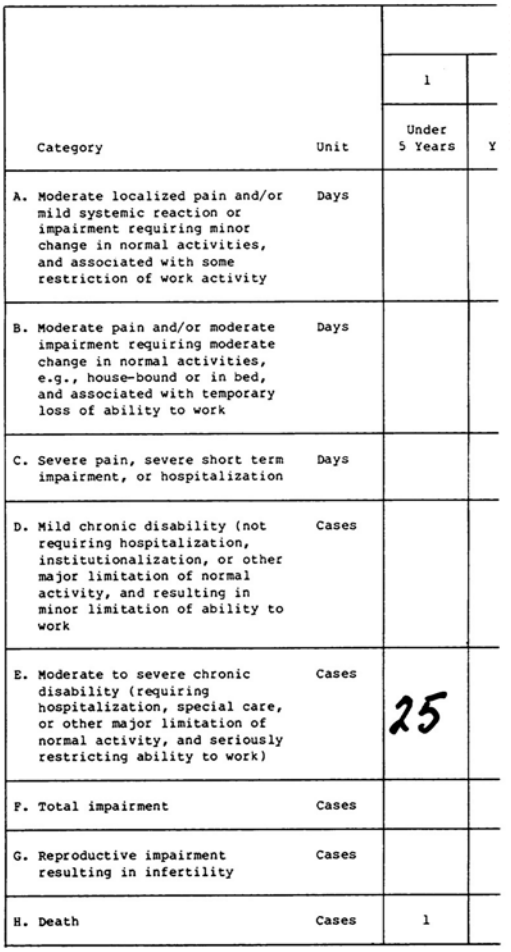
For example, consider category E: moderate to severe chronic (lifelong) disability (see Example 1). You might think that such a

		1	
Category	Unit	Under 5 Years	Y
A. Moderate localized pain and/or mild systemic reaction or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Days		
B. Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., house-bound or in bed, and associated with temporary loss of ability to work	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, and resulting in minor limitation of ability to work	Cases		
E. Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Cases	2	
F. Total impairment	Cases		
G. Reproductive impairment resulting in infertility	Cases		
H. Death	Cases	1	

EXAMPLE 1: This means that 2 cases of moderate to severe chronic disability are as bad as 1 death.

disability would be almost as bad as dying for a young child. Maybe you think that two cases of moderate to severe disability are equal to one death. Then you would write the number **"2"** in the space next to category E in column 1.

Or maybe you think that children can adapt well to severe disability, and therefore, disability is not as bad as death for a child. You would then be willing to accept a larger number of cases (maybe 25 or more) as equal in value to one death. In that case, you would put a "25" or larger number in the space next to category E in column 1 (see Example 2).



Category	Unit	1 Under 5 Years	Y
A. Moderate localized pain and/or mild systemic reaction or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Days		
B. Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., house-bound or in bed, and associated with temporary loss of ability to work	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, and resulting in minor limitation of ability to work	Cases		
E. Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Cases	25	
F. Total impairment	Cases		
G. Reproductive impairment resulting in infertility	Cases		
H. Death	Cases	1	

EXAMPLE 2: This means 25 cases of moderate to severe chronic disability are as bad as 1 death.

In contrast, you might think that severe disability for a young child is worse than death. You might think that 2 deaths are better than 1 case of severe disability. In that case, you consider 0.5 cases of severe disability equal to 1 death (see Example 3).

Categories D through G can be completed in this manner. All refer to different types of chronic illnesses, and therefore you can balance the number of cases for each category with the death of one child.

Category	Unit	1 Under 5 Years	Y
A. Moderate localized pain and/or mild systemic reaction or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Days		
B. Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., house-bound or in bed, and associated with temporary loss of ability to work	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, and resulting in minor limitation of ability to work	Cases		
E. Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Cases	0.5	
F. Total impairment	Cases		
G. Reproductive impairment resulting in infertility	Cases		
H. Death	Cases	1	

EXAMPLE 3: This means that 0.5 cases of severe chronic disability is equal to 1 death; or 2 deaths are equal to 1 severe chronic disability case. This means that death is preferable to severe chronic disability.

Now consider categories A through C. These are categories of acute illness, and therefore are measured in days rather than in cases. For example, category A is "moderate localized pain, minor systemic reaction, or impairment indicating minor change in normal activities." As before, you want to compare this category to the death of one young child. You would probably use a large number for category A because you are measuring relatively mild consequences in terms of days in each category. Perhaps it is helpful to think that a child under 5 years of age may have a life expectancy of 55 more years, which is equal to 20,000 days. You might think that category A would only make a person unable to work or play for a small part of each day. Therefore you would need a very large number of days of mild illness to be as bad as the death of a young child. Perhaps you would say 150,000 days or more. You would then write the number "150,000" in the space next to category A.

Categories A through C can be filled out in this manner. Each category refers to different types of acute illnesses, and therefore you can balance the number of days for each category with the death of a young child.

The examples provided here are to help you understand the information needed for our analysis. There is no right or wrong answer, and your answer may be higher or lower than the examples we have given.

After you have completed column 1 (for children under 5 years of age), do the same for the other age categories (columns 2 through 4). Every number written should represent the number of cases (categories D through G) or days (categories A through C) that you think are equal to the death of one person in that age group.

INSTRUCTIONS FOR ESTIMATING MORTALITY TRADE-OFF ACROSS AGE GROUPS

Attachment 3 asks you to indicate the relative undesirability of deaths in the different age groups. The unit of measure is the death of one child under 5 years of age. The question is how many deaths in each of the other age groups do you believe would balance the death of a young child. You might believe all deaths are equivalent, and mark a "1" in all the spaces; or you might believe a death of an adult (15 to 59 years) is worse than a death of a child and assign a number smaller than 1.0 to such adult deaths (column 3). You might be willing to balance 10 deaths among the elderly (column 4) against one early death. Again, any trade-offs are legitimate as long as they reflect your best personal judgment.

	Column			
	1	2	3	4
Category	Under 5 Years	5–14 Years	15–59 Years	60 Years and Over
Deaths	1	1	1	1

EXAMPLE 4: Here, a death in each age group is equivalent.

	Column			
	1	2	3	4
Category	Under 5 Years	5–14 Years	15–59 Years	60 Years and Over
Deaths	1		0.10	

EXAMPLE 5: Here, adult deaths are worse than infant deaths. Ten infant deaths would be equal to one adult death.

	Column			
	1	2	3	4
Category	Under 5 Years	5-14 Years	15-59 Years	60 Years and Over
Deaths	1			10

EXAMPLE 6: Here, infant deaths are worse than deaths in the elderly. Ten deaths in the elderly are equal to the death of one infant.

Please be sure to fill out the entire tables. All answers will be regarded as strictly confidential.

Attachment 1

A. Moderate localized pain and/or mild systemic reaction or impairment requiring minor change in normal activities, and associated with some restriction of work activity.
B. Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., house-bound or in bed, and associated with temporary loss of ability to work.
C. Severe pain, severe short-term impairment, or hospitalization
D. Mild chronic disability (not requiring hospitalization, institutionalization, or other major limitation of normal activity, and resulting in minor limitation of ability to work).
E. Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work).
F. Total impairment.
G. Reproductive impairment resulting in infertility.
H. Death.

Attachment 2

			Column			
			1	2	3	4
	Category	Unit	Under 5 Years	5–14 Years	15–59 Years	60 Years and Over
A.	Moderate localized pain and/or mild systemic reaction or impairment requiring minor change in normal activities, and associated with some restriction of work activity	Days				
B.	Moderate pain and/or moderate impairment requiring moderate change in normal activities, e.g., house-bound or in bed, and associated with temporary loss of ability to work	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, and resulting in minor limitation of ability to work	Cases				
E.	Moderate to severe chronic disability (requiring hospitalization, special care, or other major limitation of normal activity, and seriously restricting ability to work)	Cases				
F.	Total impairment	Cases				
G.	Reproductive impairment resulting in infertility	Cases				
H.	Death	Cases	1	1	1	1
	Deaths		1			

Attachment 3

Category	Column 1 Under 5 Years	Column 2 5-14 Years	Column 3 15-59 Years	Column 4 60 Years and Over
Deaths	/			

Appendix F

Technical Notes

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 or other error may have escaped detection.

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

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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 G

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 10 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 and Health Education, 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 Branch of the California Department of Health Services and clinical professor of epidemiology, University of California School of Public Health, Berkeley. 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. from the University of Michigan, an M.D. from the State University of New York, Downstate, and an M.P.H. from the University of California, School of Public Health, Berkeley.

PURNELL W.CHOPPIN recently became vice president and chief scientific officer of the Howard Hughes Medical Institute. Previously, he was Leon Hess Professor of Virology and vice president for academic programs at The Rockefeller University. He was 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 he 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 2 years in Taiwan as a postdoctoral 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 was president of the Society for Medical Decision Making for 1984–1985. 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 H

Additional Sources of Advice to the Committee

Robert Austrian, The University of Pennsylvania, Philadelphia
Edwin H.Beachey, The University of Tennessee Center for Health Sciences, Memphis, Tenn.
T. Bektimirov, World Health Organization, Geneva, Switzerland
Alan L.Bisno, The University of Tennessee Center for Health Sciences, Memphis, Tenn.
Robert Black, The Johns Hopkins School of Hygiene and Public Health, Baltimore, Md.
Paul A.Blake, Centers for Disease Control, Atlanta, Ga.
Barry R.Bloom, Albert Einstein College of Medicine, Bronx, N.Y.
Claire V.Broome, Centers for Disease Control, Atlanta, Ga.
Donald S.Burke, Walter Reed Army Medical Center, Washington, D.C.
Charles C.J.Carpenter, Case Western Reserve University, Cleveland, Ohio
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Carl E.Frasch, Food and Drug Administration, Bethesda, Md.
Roger Glass, National Institutes of Health, Bethesda, Md.
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Emil C.Gotschlich, Rockefeller University, New York, N.Y.
Dan M.Granoff, Washington University in St. Louis, Mo.
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Arthur L.Reingold, University of California, Berkeley
John B.Robbins, National Institutes of Health, Bethesda, Md.
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Alexis Shelokov, The Johns Hopkins University, Baltimore, Md.
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Appendix I

Contents of Supplement to Volume II

To be available on a "publication on demand" basis from the National Academy Press.

Appendix J

Preface to Volume I

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

Appendix K

Contents to Volume I

Vaccine candidates for the following pathogens and diseases were evaluated in Volume 1 of the committee's report:

Bordetella pertussis
Coccidioidomycosis
Cytomegalovirus
Hemophilus influenzae type b
Hepatitis A virus
Hepatitis B virus
Herpes simplex viruses 1 and 2
Herpesvirus varicellae
Influenza viruses A and B
Neisseria gonorrhoeae
Parainfluenza viruses
Respiratory syncytial virus
Rotavirus
Streptococcus group B

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