DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

MAY 4 1988

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The Honorable George Bush
President of the Senate
Washington, D.C. 20510

Dear Mr. President:

The enclosed report is submitted to you in accordance with Subtitle 1 of Title XXI of the Public Health Service Act, as amended by Title III of P.L. 99-660, the National Childhood Vaccine Injury Act of 1986.

Although no funds have been appropriated for operation of the National Vaccine Program, the Secretary decided to establish the Program with available resources. This report provides information on the implementation of the National Vaccine Program, and discusses the activities planned for Fiscal Year 1988 that are related to the long-term goals of the National Vaccine Plan.

This first report was prepared without input from the National Vaccine Advisory Committee. The Committee has been chartered and letters soliciting nominees have been sent out, and members are being appointed.

Sincerely,

Robert E. Windom, M.D.
Assistant Secretary for Health,
and Director, National Vaccine
Program

Enclosure

NATIONAL VACCINE PLAN

FIRST REPORT TO THE CONGRESS

APRIL 1988

Prepared by The National Vaccine Program
U.S. Public Health Service
Department of Health and Human Services

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EXECUTIVE SUMMARY

P.L. 99-660 establishes a National Vaccine Program (NVP) and calls for the development of a National Vaccine Plan, which is to be submitted to Congress and subsequently updated annually (see Subtitle 1 of Title XXI, Public Health Service Act). To implement the NVP, an independent staff office was created in the Office of the Assistant Secretary for Health, staff were selected, and a NVP Interagency Group was created. In addition, the National Vaccine Advisory Committee called for by the legislation was chartered and is being formed.

This document represents the first step toward development of a long-term comprehensive National Vaccine Plan. It indicates the eight major areas to be addressed during Fiscal Year 1988 by the National Vaccine Program and describes the major activities planned for Fiscal Year 1988 within each of these areas. Subtitle 2 of Title XXI, which has recently gone into effect, calls for a variety of specific activities relating to patient/parent notification, reporting of adverse events associated with vaccination, and special studies to be carried out. Implementation of Subtitle 2 will substantially alter the sections of this Plan dealing with these three issues. The magnitude of the changes is not yet clear.

Many of these activities are currently underway, and therefore, do not require additional resources. Should additional resources become available, these activities will be expanded as necessary. The report does not attempt to assess the appropriate mix of private and public sector involvement required to achieve National vaccine goals.

This report does not deal specifically with development of a vaccine for AIDS, although a summary of AIDS vaccine development is appended.

OUTLINE OF REPORT

I. IMPROVING COORDINATION OF VACCINE RESEARCH, DEVELOPMENT, USE, AND EVALUATION.

1. Formation and functioning of the National Vaccine Advisory Committee.
2. Develop a comprehensive long-term National Vaccine Plan.
3. Continue functioning of the NVP Interagency Group.
4. Continue liaison with private sector advisory groups.
5. Continue promotion of dialogue on vaccine policies.
6. Meet with individual manufacturers, researchers, public health agencies, etc.
7. Complete a survey to inventory current vaccine research.

II. ASSURING AN ADEQUATE SUPPLY OF VACCINES.

1. Purchase additional vaccines for stockpile.

2. Determine what other vaccines should be included in the stockpile.

3. Develop approaches to ensure supply of vaccines of limited use.

4. Consider longer-term approaches to assuring adequate supplies.

III. ASSESSING BENEFITS AND RISKS OF VACCINES AND ASSURING PUBLIC AND PRACTITIONER AWARENESS OF THE BENEFITS AND RISKS.

1. Continue Assessing the benefits and risks of immunization.

- Maintain and improve national surveillance systems for major vaccine-preventable diseases.
- Maintain, improve, and establish sentinel and/or pilot surveillance systems for other diseases.
- Maintain, improve, and establish surveillance systems for adverse events following immunization.
- Maintain, improve, and establish surveillance systems for specific events following the administration of certain vaccines.
- Identify other data bases which may be useful in estimating the incidence and severity of vaccine-preventable diseases in the U.S. and abroad.
- Conduct basic, applied, and operational research in the U.S. and elsewhere.

2. Improve practitioner awareness.

- Publish information and surveillance summaries in Morbidity and Mortality Weekly Reports and the FDA Drug Bulletin and elsewhere.
- Update manufacturer's package inserts when indicated.
- Present surveillance and other data at scientific meetings.
- Continue to work with various advisory groups.
- Prepare, update, and distribute "Important Information Statements."

- Coordinate with private and public organizations various vaccine-preventable disease-related educational programs.
- Conduct knowledge, attitudes, and practices survey of health care providers and of the public.
- Prepare prototype educational materials for primary-care physicians and other providers.
- Prepare prototype manuals for vaccination programs in hospitals, HMOs, and other outpatient settings.

3. Improve public awareness.
   - Prepare and distribute lay publications.
   - Promote the use of patient education materials and attempt simplification of the "Important Information Statements".
   - Prepare and distribute public information materials such as radio and TV public service announcements.
   - Prepare prototype public educational materials such as videotapes and slide sets.

IV. ASSURING ADEQUATE REGULATORY CAPACITY TO EVALUATE VACCINES.

1. Continue to review existing INDs and license applications, perform control tests, inspect, perform research, prepare regulations, and monitor adverse reactions.
2. Assure prompt evaluation of new vaccines.
3. Assure continuation of the necessary research base.
4. Complete the reorganization of the Center for Biologics Evaluation and Research.
5. Continue discussions through appropriate channels for new laboratory facilities as requested in the President's Fiscal Year 1989 budget request.

V. IMPROVING SURVEILLANCE OF ADVERSE EVENTS.

1. Improve reporting of adverse events.

2. Improve adverse events surveillance systems.

3. Implement the National Childhood Vaccine Injury Act.

4. Investigate additional approaches for adverse event surveillance.

5. Examine specific research questions.

   - CDC/Vanderbilt cooperative studies.
   - Study of Neurologic Illness in Childhood (SONIC)

VI. ESTABLISHING RESEARCH PRIORITIES.

1. Reevaluate or reassess the Institute of Medicine priorities for vaccine research.

2. Continue emphasis on the development of improved, acellular pertussis vaccines.

3. Continue emphasis on the development of improved vaccines to prevent disease caused by Haemophilus influenzae type B.

4. Stimulate basic and clinical research on targeted vaccines.

5. Stimulate basic and clinical research on other important vaccines.

6. Establish liaison with members of the pharmaceutical industry.

7. Complete a survey to inventory current vaccine research.

VII. PROMOTING RAPID DEVELOPMENT AND INTRODUCTION OF IMPROVED PERTUSSIS VACCINES.

1. Analyze and present the clinical results from the Swedish trial.
2. Test blood specimens from Sweden and correlate results with clinical findings.

3. Continue IND reviews and license application evaluations on new candidate vaccines.

4. Carry out clinical studies of candidate vaccines in NIAID Vaccine Evaluation Centers.

5. Assess feasibility of a large scale safety and efficacy trial in the U.S.

6. Standardize serologic tests for pertussis.

7. Complete evaluation of new diagnostic tests for pertussis.

8. Complete pilot Study Of Neurologic Illness in Children.

9. Continue intramural research on pertussis at FDA, NIH, and CDC.

VIII ASSURING OPTIMAL IMMUNIZATION LEVELS IN ALL HIGH RISK AND TARGET GROUPS.

1. Assess appropriate mix of private and public sector involvement to achieve optimal immunization levels in high risk and target groups.

2. Revise adult immunization action plan.

3. Form an ad hoc Committee to promote information and education on the need for adult immunization.

4. Implement cooperative agreement for studying Health Maintenance Organizations.

5. Distribute and promote use of adult immunization materials.

6. Monitor activities outlined in program grant guidelines.

7. Conduct surveys to establish baseline data.

8. Develop and implement appropriate strategies to improve immunization levels in high risk groups.

9. Distribute automated patient recall systems.

10. Review effectiveness of preschool efforts.

11. Convene a National immunization conference.

FIRST NATIONAL VACCINE PLAN

INTRODUCTION

Subtitle 1 of Title XXI of the Public Health Service Act, enacted by P.L. 99-660 (Appendix 1) establishes a National Vaccine Program and calls for the development of a National Vaccine Plan, which is to be submitted to Congress and subsequently updated annually. The Assistant Secretary for Health (ASH) was appointed as the Director of the NVP. To implement the NVP, an independent staff office was created in the Office of the Assistant Secretary for Health, staff were selected, and a NVP Interagency Group was created. In addition, the National Vaccine Advisory Committee called for by the legislation was chartered and is being formed.

This document represents the first step toward development of a long-term comprehensive National Vaccine Plan. It is clear from the legislation as well as statements of congressional staff that wide input was intended in development of the Plan, particularly from the National Vaccine Advisory Committee. Since that Committee had not been appointed by the end of Fiscal Year 1987 it was not possible to develop a definitive Plan. Consequently, this Report should be read as indicating the major items to be addressed during Fiscal Year 1988 by the National Vaccine Program, one of which is to develop a definitive National Vaccine Plan.

It must also be recognized that Subtitle 2 of Title XXI, establishing a National Childhood Vaccine Injury Compensation Program, mandates a variety of specific activities relating to patient/parent notification, reporting of adverse events associated with vaccination, and special studies to be carried out. At the time this document was prepared, Subtitle 2 had just gone into effect. Implementation of Subtitle 2 will alter the sections of this Plan dealing with these three issues. The magnitude of the changes is not yet clear.

During Fiscal Year 1988, activities will be directed towards achieving eight long-term goals: improving coordination of vaccine research, development, use and evaluation; assuring an adequate supply of vaccines; assessing benefits and risks of vaccines and assuring public and practitioner awareness of the benefits and risks; assuring adequate regulatory capacity to evaluate vaccines; improving surveillance of adverse events; establishing research priorities; promoting rapid development and introduction of improved pertussis vaccines; and assuring optimal immunization levels in all target and high risk groups. For each of these areas there will be a brief description of the current situation as well as a discussion of the activities planned for Fiscal Year 1988.

Many of these activities are currently underway, and therefore, do not require additional resources. Should additional resources become available, these activities will be expanded as necessary. The report does not attempt to assess the appropriate mix of private and public sector involvement required to achieve National vaccine goals.

AIDS vaccine development is being coordinated by the AIDS Vaccine Research and Development subgroup of the PHS Executive Task Force on AIDS. The National Vaccine Program collaborates with this subgroup but primarily directs its efforts at non-AIDS vaccines. A brief summary of AIDS vaccine development is included as Appendix 2.

I. IMPROVING COORDINATION OF VACCINE RESEARCH, DEVELOPMENT, USE, AND EVALUATION

A. CURRENT SITUATION

In the last ten years, several different reviews of vaccine-related activities and policies have been carried out. These include a National Conference held in two parts in 1976 and 1977, two reviews by the Government Accounting Office (GAO), two reviews by the Congressional Office of Technology Assessment (OTA), and a series of studies and meetings carried out by the Institute of Medicine (IOM) of the National Academy of Sciences (NAS). The IOM carried out 3 separate studies, 2 of them primarily funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) and the Agency for International Development (AID), addressing the establishment of priorities for vaccine research and development for the United States (1985) and the developing world (1986), respectively (see Section VI of this Report). The third study, on the topic of Vaccine Supply and Innovation, was completed in 1985. Finally, the IOM convened another Workshop on Vaccine Innovation and Supply in 1986.

In general, these reviews concluded that existing advisory bodies (see below), although quite useful, tended to dwell on relatively narrow issues and they recommended formation of an independent Committee or Commission to consider all aspects of vaccine issues, including research, development, production, distribution, supply, utilization, liability, and compensation.

There are currently three Public Health Service (PHS) Advisory Committees dealing directly with vaccines. These are (1) the NIAID Microbiology and Infectious Diseases Research Committee, (2) the Food and Drug Administration (FDA) Vaccine and Related Biologic Products Advisory Committee (VRBPAC), and the Centers for Disease Control (CDC) Immunization Practices Advisory Committee (ACIP). The first of these Committees reviews and makes recommendations on research grants, cooperative agreements, and contracts. In addition, it provides review and recommendation on research directions in infectious diseases (including vaccines) to the NIAID. The second reviews and evaluates data relating to safety and effectiveness of vaccines and related biological products and makes recommendations, including those related to licensure. It also considers the quality and relevance of FDA's research program. The third advises on the most appropriate use of vaccines for disease control in the civilian population, particularly those served by the public sector (approximately 50% of the childhood population); reviews and reports on immunization practices; and recommends improvements in national immunization efforts.

For the Department of Defense (DOD), the Armed Forces Epidemiological Board (AFEB) reviews a variety of issues, including vaccine use, and makes recommendations for the Armed Forces. In addition, the American Public Health Association (APHA) covers many vaccines in its handbook "Control of Communicable Diseases in Man", which is revised every 5 years. Finally, the World Health Organization (WHO) has a Global Advisory Group (GAG) for its Expanded Programme on Immunization (EPI) which also makes recommendations regarding vaccine use.

In addition to these external Advisory Committees, since 1980 the Department has had an Interagency Group to Monitor Vaccine Development, Production, and Usage composed of representatives of NIH, FDA, and CDC, with liaison representation from the military. The purpose of this group is to monitor production and distribution of vaccine and resolve problems relating thereto, monitor development and stimulate research on new vaccines, plan for continuing availability of vaccines of limited use, and consider options as to when the Federal Government should manufacture vaccines. This Group has played an important coordinating role, particularly with regard to the evaluation of new types of pertussis vaccines (see Section VII of this Report). These efforts included sponsoring a visit to Japan by a group of PHS scientists; sponsoring a workshop on acellular pertussis vaccines; and being intimately involved in the design, funding, and monitoring of the Swedish acellular pertussis vaccine field trial.

In the private sector, three groups currently make recommendations on vaccine use. These are the Committee on Infectious Diseases (the "Red Book" Committee) of the American Academy of Pediatrics (AAP), the Committee on Immunization of the American College of Physicians (ACP), and the Scientific Activities Division of the American Academy of Family Physicians (AAFP), each of which publishes its own set of recommendations. PHS agencies have maintained formal liaison with each of these groups, as well as with international advisory bodies such as the GAG of WHO and the National Advisory Committee on Immunizations (NACI) of the Canadian Ministry of Health and Welfare. Because of this liaison, vaccine recommendations in the public and private sectors (and internationally) are generally concordant. However, occasional issues arise that would benefit from even wider input (e.g., the preferred vaccine for prevention of poliomyelitis and the balance between benefits and risks of Haemophilus B polysaccharide vaccine [HBPV] and pertussis vaccines).

During FY 1987, several activities were undertaken to implement the National Vaccine Program and improve coordination. These included designation of the Assistant Secretary for Health as the Director of the NVP (in January) and formation of an Interagency Work Group chaired by the Deputy Assistant Secretary for Health (Planning and Evaluation) to consider the most appropriate means of implementing the Program. This group submitted its report in May. Subsequently, the NVP was formally established (Appendix 3), a coordinator was selected, and further staff were obtained.

In addition, an expanded NVP Interagency Group was formed (Appendix 4), including representatives of the Department of Defense (DOD) and the Agency for International Development (AID).

The National Vaccine Advisory Committee (VAC) was chartered (Appendix 5) and is being formed. This Committee will provide one of the most important mechanisms for coordination between governmental and non-governmental vaccine activities, just as the NVP Interagency Group provides the mechanism for intra-governmental coordination. The VAC also will play a major role in developing the comprehensive National Vaccine Plan.

B. ACTIVITIES FOR FISCAL YEAR 1988

1. Formation and Functioning of the National Vaccine Advisory Committee.

It is anticipated that the appointment of Committee members will be completed early in calendar year 1988 and that the first meeting of the Committee can occur during the second quarter of that year, with quarterly meetings thereafter. Although the Committee will clearly set its own priorities, it is intended that all of the topics mentioned in the law as well as in this Report will be discussed with the Committee. In addition, the Committee will be heavily involved in preparation of the National Vaccine Plan (see below) and consideration of the resource requirements to implement the Plan.

2. Develop a Comprehensive Long-Term National Vaccine Plan.

Following initial discussions with the National Vaccine Advisory Committee, NVP staff and the NVP Interagency Group will draft a comprehensive long-term National Vaccine Plan for review by the Committee. After needed modifications, this Plan will be submitted to Congress and will serve as the basis for development of Government agency budget requests as well as outlining the activities projected by non-governmental organizations.

3. Continue Functioning of the NVP Interagency Group.

As the primary means of implementing the National Vaccine Program, continued functioning of the NVP Interagency Group is critical. It is anticipated that the Group will probably meet at least on a monthly basis during 1988. In addition to working with the VAC to draft the National Vaccine Plan, this Group will be responsible for assuring that the other activities called for in this Report are accomplished as well as dealing with other issues that may arise.

4. Continue Liaison With Other Advisory Groups.

To assure continued concordance between recommendations in the public and private sectors, representatives of the PHS agencies will continue formal liaison with other governmental, private sector, and international advisory bodies.

5. Continue Promotion of Dialogue on Vaccine Policies.

At the request of the PHS, the Institute of Medicine held a workshop to review all aspects of poliomyelitis prevention on January 21-22, 1988. The IOM expert panel will make recommendations for consideration by the Immunization Practices Advisory Committee (ACIP) which will then make its recommendations to the PHS. Public meetings have previously been held on the benefits and risks of pertussis vaccines and HBPV. At this point it is not clear what other topics might merit such an approach but this matter will be brought to the VAC for its consideration.

6. Meet With Individual Manufacturers, Researchers, Public Health Agencies, etc.

To assure the fullest communication with involved parties, individual staff members of the NVP Office and NVP Interagency Group will meet with manufacturers, researchers, public health agencies, etc., for in-depth consideration of a range of vaccine issues.

7. Complete a Survey to Inventory Current Vaccine Research.

This survey is attempting to catalog current vaccine research activities in the private and public sectors.

II. ASSURING AN ADEQUATE SUPPLY OF VACCINES.

A. CURRENT SITUATION

In recent years, the continuity of supply of essential vaccines has been threatened by a number of factors, including the limited number of manufacturers, production problems, strikes of manufacturers' employees, and liability issues. For example, there are currently only one licensed manufacturer in the U.S. of oral poliovirus vaccine (OPV) and one manufacturer of measles, mumps, and rubella vaccines (MMR). Two manufacturers currently distribute diphtheria and tetanus toxoids and pertussis vaccine (DTP) and three distribute Haemophilus B polysaccharide vaccine (HBPV). For some vaccines (e.g., rabies), the sole manufacturer is a foreign firm. On several occasions, production problems have resulted in temporary shortages of vaccines although these have been resolved by redistribution of existing supplies or temporary alteration in immunization schedules. Strikes have posed threats to continuing supply but fortunately have been resolved before actual shortages occurred. Concerns about liability issues have been a major factor in recent dramatic increases in vaccine prices (most notably with DTP) and apparently are also important factors as manufacturers consider whether to enter (or remain in) the marketplace.

To forestall the impact of interruptions of supply, in 1983 CDC began to establish a six month stockpile of childhood vaccines, which were felt to represent the most pressing need. This stockpile is to be continually rotated so vaccines would have adequate shelf life. A six month stockpile was selected as representing the most reasonable compromise between the limited shelf life of vaccines, the likely duration of an interruption, and the likely time required to license an alternative manufacturer. The status of the stockpile as of the end of Fiscal Year 1987 is shown below, expressed as the number of weeks the stockpile could supply the total national demand (both public and private).

Vaccine	Amount
DTP	13.8 weeks
MMR	20.8 weeks
OPV	20.5 weeks
IPV	8.0 weeks
DT	20.8 weeks
Td	20.8 weeks

B. ACTIVITIES FOR FISCAL YEAR 1988

1. Purchase Additional Vaccines for Stockpile.

Insofar as resources are available, additional vaccines will be purchased toward the desired goal of a 6 month supply. In addition, discussions will be held with the VAC regarding the appropriate size of the stockpile.

2. Determine What Other Vaccines Should be Included in the Stockpile.

The stockpile currently includes only vaccines used in childhood or very widely in adults (Td). Other vaccines of quite wide use which might be included are pneumococcal polysaccharide vaccine and hepatitis B vaccine. Although influenza vaccine is also widely used, since its composition changes each year the stockpile approach does not seem appropriate. The NVP Interagency Group will bring this issue to the VAC for consideration.

3. Develop Approaches to Ensure Supply of Vaccines of Limited Use.

Certain licensed vaccines are in limited use but nonetheless quite important for use in either civilian or military populations (e.g., meningococcal polysaccharide vaccine, yellow fever vaccine). In addition, other important vaccines are not currently licensed in this country but have been available under Investigational New Drug (IND) permits (e.g., Japanese B encephalitis [JE] vaccine). The supply of JE vaccine in this country is currently in serious jeopardy. Although these vaccines are in limited use, they may play an essential role in preventing or controlling certain infections. Continued availability of these vaccines must be assured. The NVP Interagency Group will discuss the supply of limited use vaccines with the VAC.

4. Consider Longer-Term Approaches to Assuring Adequate Supplies.

Other approaches to assuring adequate supplies of vaccines will also be brought to the VAC, including the possibilities of stimulating the entry into the marketplace of new manufacturers, increasing competition, changing the liability climate, direct government manufacture, government subsidy of manufacture or guarantee of purchase, etc.

III. ASSESSING BENEFITS AND RISKS OF VACCINES AND ASSURING PUBLIC AND PRACTITIONER AWARENESS OF THE BENEFITS AND RISKS.

A. CURRENT SITUATION

Assessing Benefits and Risks of Immunization

The Food and Drug Administration (FDA), the Centers for Disease Control (CDC), and the National Institutes of Health (NIH) have been the principal Federal agencies involved in evaluating the benefits and risks of immunization for both children and adults. Initially, FDA, often in conjunction with its VRBPAC, reviews preclinical and clinical data prior to licensing a product. Various pre and post marketing studies may be conducted. For example, data collected from a number of sources are analyzed periodically to: 1) obtain current estimates of morbidity, complications, and mortality attributable to various vaccine preventable diseases (VPD) in the U.S.; 2) identify groups at high risk of severe morbidity and/or mortality from each VPD; 3) obtain estimates of the efficacy in field experience of vaccines recommended for use; 4) obtain estimates of the frequency of adverse events associated with each vaccine in field experience; and 5) project the overall benefits and risks for vaccines using techniques such as mathematical modeling and decision analysis. The results of these and other assessments are disseminated to the general public and practitioners in both the public and private sectors. Since the balance of benefits and risks may change over time and varying epidemiological circumstances, the assessment is a continual process.

The Public Health Service established the Immunization Practices Advisory Committee (ACIP) to routinely review critical issues regarding immunization practices and surveillance data. This committee, composed of leading authorities in vaccine-preventable diseases from academia, public health agencies and national medical organizations meets three or four times a year at CDC. The ACIP assesses the risks and benefits of vaccination and makes recommendations for use of vaccines and other selected interventions. These recommendations are published in Morbidity and Mortality Weekly Reports (MMWR).

Practitioner Awareness

The recommendations of the ACIP as well as surveillance summaries reach practitioners through publication in the MMWR, FDA Drug Bulletin, and subsequent reprinting in other medical and scientific journals. Package inserts accompanying each container of product provide relevant information for each manufacturer's product. In addition, articles regarding other aspects of vaccine-preventable diseases are periodically published in the leading medical and scientific journals. Surveillance and epidemiologic data are presented at professional and scientific symposia, conferences, and other appropriate forums. CDC has established formal liaison with other national and international advisory groups including the Committee on Infectious Diseases of the AAP, the Committee on Immunization of the ACP, and the Scientific Activities Division of the AAFP, each of which publishes its own set of recommendations.

Public Awareness

The PHS has created a variety of publications, pamphlets, posters and other educational materials for the general public. The pamphlet "A Parent's Guide to Immunization" was created and distributed (primarily in the public sector) to assist parents in knowing what immunizations were advised for their children and when they should be administered. Disease-specific pamphlets such as "Questions and Answers Regarding Pertussis and Pertussis Vaccine" have been developed and distributed to assist parents in evaluating the risks and benefits of immunization. CDC has developed a complete series of "Important Information Statements" for use with Federally purchased vaccines used in public clinics to aid in informing parents regarding the vaccines their children may need. The "Important Information Statements" (IIS) describe the specific disease, the risk of infection, and the risks of severe complications. In addition, they describe the indications and contraindications to vaccination, the possible side effects associated with the vaccine, and the benefits of vaccination.

B. ACTIVITIES FOR FISCAL YEAR 1988

The activities described below may change as the National Vaccine Injury Compensation Program (Subtitle 2 of Title XXI of the PHS Act) is implemented.

1. Continue Assessing the Benefits and Risks of Immunization.

- Continue the review of preclinical and clinical data submitted as part of investigational new drug (IND) or license applications;

- Maintain and improve national surveillance systems for measles, mumps, rubella (including congenital rubella syndrome), pertussis, tetanus, diphtheria, paralytic poliomyelitis, and influenza;

- Maintain, improve, and establish sentinel and/or pilot surveillance systems at local and/or regional levels for hepatitis B, meningococcal and pneumococcal disease, and Haemophilus influenzae type B disease;

- Develop and use tools which may facilitate diagnosis of illnesses such as pertussis, pneumococcal pneumonia, etc.

- Maintain, improve, and expand surveillance systems for identifying a wide range of adverse events following administration of vaccines (see Section V of this Report);

- Maintain, improve, and expand surveillance systems for specific events following the administration of certain vaccines (e.g., fetal outcome following rubella vaccination in the first trimester of pregnancy; development of residual paralysis following the administration of oral polio vaccine, etc.);

- Identify other data bases which may be useful in estimating the incidence and severity of VPD;

- Investigate outbreaks of VPD in the U.S. and elsewhere;

- Conduct basic, applied, and operational research related to VPD in the U.S. and elsewhere; and

- Examine surveillance and other pertinent data reported from other nations.

2. Improve Practitioner Awareness.

- Publish surveillance summaries in the Morbidity and Mortality Weekly Report (and/or other medical and scientific journals), which are often publicized simultaneously in the lay press;

- Publish information in the FDA Drug Bulletin relevant to vaccine use or adverse events when indicated.

- Update manufacturer's package inserts when indicated.

- Publish and update ancillary documents such as "Health Information for International Travel" and special advisory memoranda;

- Present surveillance data and other relevant epidemiologic data at scientific meetings, symposia, public meetings, seminars, and other forums;

- Continue to work with the ACIP, whose recommendations are published in the MMWR and reprinted in the Journal of the American Medical Association, Annals of Internal Medicine, and other medical journals with a wide circulation;

- Continue formal liaison with other national and international advisory groups, including the Committee on Infectious Diseases of the AAP, the Committee on Immunization of the ACP, and the AFEB to assure timely exchange of information;

- Prepare, update, and distribute "Important Information Statements" for use with federally purchased vaccines given in public health clinics and make available camera-ready copy for use in the private sector;

- Contact private and public sources to identify the type and content of VPD-related educational programs initiated outside the Federal Government; assist in the coordination of these activities as needed to avoid unnecessary duplication of effort (see Section I of this Report);

- Continue to encourage professional organizations to urge their members to become actively involved in immunization activities, through becoming more knowledgeable personally and by developing systems to ensure identification and vaccination of high risk persons;

3. Improve Public Awareness.

- Prepare, update, and distribute lay publications such as "A Parent's Guide to Immunizations" and "Questions and Answers Regarding Pertussis and Pertussis Vaccine" and expand to include other vaccines as necessary;

- Promote the use of patient education materials such as the "Important Information Statements" in the private sector;

- Attempt simplification of the "Important Information Statements". These statements are currently assessed as requiring a reading skills level equivalent to 12-13 years of education;

IV. ASSURING ADEQUATE REGULATORY CAPACITY TO EVALUATE VACCINES

A. CURRENT SITUATION

The FDA has the primary responsibility for the regulation of vaccines through its Center for Biologics Evaluation and Research (CBER). The CBER (formerly the Office of Biologics Research and Review [OBRR] of the National Center for Drugs and Biologics [NCDB]) has been recently formed as a separate entity. It will continue to reflect FDA's commitment to assuring that high quality vaccine regulation and the related research programs continue as well as the agency's increased efforts in its activities related to AIDS.

The research and laboratory activities of the scientists of the Center are an integral part of its regulatory activities as the research is aimed at understanding disease pathogenesis and immunity. The laboratory investigator brings state-of-the-art methods and knowledge to the review and regulatory process. The scientists play a major role in evaluating specific products and use their laboratory skills to develop and evaluate quality control procedures and to evaluate methods of manufacture.

CBER staff reviews Investigational New Drug (IND) applications and the supplements to these applications for vaccines and other biologics; meets with manufacturers for pre-IND and IND discussions; reviews license applications and amendments for biologics and issues licenses for biologics and establishments; reviews and approves labeling (including package inserts); performs selected analytical, potency and other quality control assays; and performs inspections of production establishments before and after licensing. In addition, other parts of CBER address issues of compliance, preparation of regulations (e.g., Notices of Proposed Rule Making and preparation of guidelines and regulations) and address issues related to post-marketing surveillance (e.g., release of product lots submitted by manufacturers, adverse reaction reports, and epidemiologic issues).

The Center works closely with the scientific and industrial communities to identify problems in vaccine development and manufacture. FDA's investigators present their findings at scientific meetings and in the scientific literature. The Center holds workshops to focus on the scientific issues related to product development, as well as frequent meetings of the advisory committee, to involve outside experts in the decision making process.

B. ACTIVITIES FOR FISCAL YEAR 1988

1. <u>Continue to Review Existing INDs and License Applications, Perform Control Tests, Inspect, Perform Research, Prepare Regulations, and Monitor Adverse Reactions</u>.

2. Assure Prompt Evaluation of New Vaccines.

New types of vaccines can be expected in 1988 and ensuing years which will result in many new IND's. The preparation of these products will likely involve many new technological methods. In addition, many new license applications will be submitted for review. FDA will review the allocation of its staffing resources to review these documents, continue review of existing applications, perform control tests, and inspect manufacturers' facilities.

3. Assure Continuation of the Necessary Research Base.

Basic and applied research programs will be continued and expanded in order to meet the increasing number of product applications and differing types of products being developed. Adequate numbers of highly qualified scientific personnel are needed to address specific issues and to evaluate or develop appropriate methods to be used for control of vaccines, including the establishment of vaccine standards, i.e., methods of antibody assay and physicochemical criteria. Appropriate reference reagents will need to be identified, evaluated, and collaborative studies conducted to assure the appropriate standardization and testing of vaccines by manufacturers and other involved parties. Emphasis in recruiting scientists knowledgeable in the new technologies, such as molecular biology, genetics, biochemistry, cell physiology, immunology, and pharmacology will be necessary to enhance CBER's regulatory capabilities.

4. Complete the Reorganization of the Center for Biologics Evaluation and Research.

This reorganization is expected to assist in the provision of resources which will allow an expansion of the regulatory and research programs needed to meet the increasing number of products and to assure that appropriate resources are available to evaluate the currently licensed products.

5. Continue Discussions Through Appropriate Channels for Adequate Laboratory Facilities.

Adequate facilities are required for the activities associated with the regulation of other vaccines and biologics, including the rapidly expanding AIDS program. The Fiscal Year 1989 President's budget includes a request for $25 million to expand FDA laboratory facilities for vaccines and biologics review and research, particularly in the area of AIDS.

V. IMPROVING SURVEILLANCE OF ADVERSE EVENTS

A. CURRENT SITUATION

There are two complementary national systems in the United States for the surveillance of adverse events after immunization: the Spontaneous Reporting System (SRS) of the FDA, and the Monitoring System for Adverse Events Following Immunization (MSAEFI) of the CDC. The SRS is a physician- and manufacturer-based, passive system primarily designed for the detection of new, previously undescribed, serious adverse reactions and for some frequency measurements for serious known reactions. SRS has collected reports of biologics adverse reaction data from the private sector since 1984 when biologics reaction reporting was integrated into a pre-existing drug reaction reporting system. Prior to that time, biologics adverse event information was collected and stored in a computerized catalog not designed for this type of epidemiologic analysis.

MSAEFI is a stimulated passive surveillance system in operation since 1979 for events temporally related to vaccination with public sector vaccines. "Public sector vaccines" are all vaccines purchased with Federal, State, or local government funds, and account for approximately one-half of all childhood immunizations in the United States. Events severe enough to require a health care provider visit which occur within 28 days after immunization are to be reported to MSAEFI.

A major problem with passive reporting systems is underreporting, i.e., lack of sensitivity. Also, a nonrandom sample of all adverse events is reported to FDA and CDC. The actual reporting fraction is unknown and is likely to differ between systems and among States. In addition, although adverse events reported to SRS and MSAEFI are temporally related to vaccination, vaccine causation can not be inferred. Also, adequate data are not available on the expected background rate of occurrence of events such as convulsions or encephalitis, making it difficult to assess risk for these adverse events after immunization.

One additional approach to adverse event surveillance is the use of population-based data bases. A current project funded by CDC in Tennessee involves the linkage of immunization clinic records to Medicaid records. This linkage defines a cohort of children in whom adverse events following immunization can be followed. Such population-based systems offer the potential of universal reporting of serious events whether or not immunizations were received. Comparison of rates of event occurrence with and without vaccination allows determination of whether vaccine causes a particular type of event as well as calculation of the actual risk attributable to vaccination.

FDA has established contracts with five States to explore means of informing health care professionals about FDA's SRS and providing ready access to the system. These contracts have resulted in increased reporting to FDA from these States. In addition, FDA may require a post marketing study for safety of a newly licensed vaccine and may target possible adverse events of particular concern for specific post-marketing surveillance studies as part of requests made of manufacturers prior to licensure of new biological products.

Furthermore, FDA has access to several extramural data bases through cooperative agreements to investigate biologic or drug events. These data bases include the Boston Collaborative Drug Surveillance Program (based on automated data from a large Health Maintenance Organization); Medicaid data from several states through Health Information Design (based on Medicaid billing data); and the Drug Epidemiology Unit (based on various national data bases). Existing databases may be expanded and others initiated to design and perform particular epidemiologic studies on vaccine-associated adverse events.

FDA and CDC share data on at least a quarterly basis, including the provisional numbers of deaths, convulsions and selected other events (encephalopathies or anaphylaxis) reported to each agency after immunization with HBPV, DTP, and MMR vaccine. Informal collaboration is frequent between the two agencies on individual vaccines or specific adverse events being monitored. Dialogue is maintained on specific issues and has included studies on the efficacy of HBPV and on adverse events reported after hepatitis B vaccine.

Subtitle 2, Sec. 2125(b), of the PHS Act mandates reporting from each health care provider and vaccine manufacturer of the occurrence of any event in the Vaccine Injury Table or any event which is a contraindication to further doses of vaccine. When implemented, Subtitle 2 will necessitate significant changes in adverse events surveillance systems of both CDC and FDA which will substantially modify present and future planned activities.

B. ACTIVITIES FOR FISCAL YEAR 1988

1. Improve Reporting of Adverse Events.

Evaluation of methods to stimulate reporting of adverse events will be a priority during Fiscal Year 1988. These methods could include increasing routine availability of surveillance results, increasing access to the system by individual reporters, and mandating reporting by manufacturers and providers. Providing information to health care providers and others involved in monitoring systems is a positive reinforcement to reporting of adverse events. A summary of MSAEFI results for the years 1985-86 will be published and distributed during the year. In addition, feedback letters to MSAEFI coordinators and State Vaccine Program managers will be produced periodically.

FDA will continue to evaluate methods to increase reporting through contracts with individual States to increase health care provider awareness of the SRS and to improve access to the SRS by reporters. CDC will evaluate methods of electronic data transfer from reporting States to CDC. The FDA is developing proposed regulations to require manufacturer reporting of vaccine adverse events similar to that required for drugs under 21 CFR 314.80. Currently, reports received by manufacturers are submitted to FDA voluntarily following this same system.

2. Improve Adverse Events Surveillance Systems.

The quality of surveillance systems can be improved by continuing to coordinate approaches to adverse events monitoring among the FDA, CDC and large vaccine providers, and by focusing on the evaluation of serious adverse events. Dialogue and sharing of data between CDC and FDA will continue.

3. Implement the National Childhood Vaccine Injury Act.

PHS will develop approaches for implementation of the mandatory reporting requirements of Subtitle 2 of Title XXI of the PHS Act.

4. Investigate Additional Approaches for Adverse Event Surveillance.

Population-based data bases, such as Medicaid or Health Maintenance Organizations, may provide an additional method to monitor vaccine safety. In addition to the Tennessee Medicaid study, CDC will establish and evaluate an additional population-based data set in at least one other location. FDA has cooperative agreements with such data bases which may be used depending on the questions to be studied. FDA will continue to include post-marketing surveillance and reporting requirements in new vaccine licensures, and will explore additional types of studies to monitor potential adverse events in prelicensure negotiations with manufacturers.

5. Examine Specific Research Questions.

A. CDC/Vanderbilt cooperative studies

The final report of the Tennessee Medicaid study on the relation of Sudden Infant Death Syndrome (SIDS) and DTP vaccination will be prepared and submitted for publication. Continued progress on a study of neurologic illness after DTP will be monitored. An additional study on the relationship of vaccination to subsequent serious infection after immunization is being planned.

B. Study of Neurologic Illness in Childhood (SONIC)

A pilot study of the risk factors associated with neurologic illness in children was begun in 1987 in Washington and Oregon. This pilot is expected to demonstrate whether or not a full scale study of this question is feasible. An objective for Fiscal Year 1988 is to complete the pilot study and arrive at a decision about undertaking a larger, more definitive project.

VI. ESTABLISHING RESEARCH PRIORITIES

A. CURRENT SITUATION

Five Institutes of the National Institutes of Health and its Division of Research Resources support vaccine research and development. The lead Institute is the National Institute of Allergy and Infectious Diseases (NIAID). Other PHS agencies involved are FDA and CDC. In addition, the Department of Defense (DOD) and the Agency for International Development (AID) provide support for vaccine research and development. In the fall of 1981, NIAID began a program for the "Accelerated Development of New Vaccines." The purpose of the new initiative was to develop within DHHS a clearly-defined and coordinated approach to the further conquest of vaccine-preventable diseases. The incentive for this expanded effort lay in new knowledge and processes emerging from recombinant DNA and hybridoma technology, and in the better understanding of the workings of the immune system. In December 1979 the Secretary of Health and Human Services accepted the recommendation of the HHS Steering Committee for the Development of a Health Research Strategy that the NIAID proposal for the "Accelerated Development of New Vaccines" be added as one of four new initiatives to 11 priority initiatives identified.

The goal of the initiative on Accelerated Development of New Vaccines was to expedite the availability of needed vaccines by selecting a few candidate vaccines for extra research and development efforts. It was anticipated that with the assistance of existing advisory committees and "state-of-the-art" reviews by workshops, and in coordination with the PHS Interagency Group to Monitor Vaccine Development, Production, and Usage, and with enhanced collaboration with industry, selected high priority candidate vaccines could be brought into use several years earlier than otherwise might be the case.

To assist in planning, NIAID and AID commissioned the Institute of Medicine (IOM) of the National Academy of Sciences to develop a model decision process that could be used for establishing priorities among candidate vaccines. The IOM study, which began in September 1982, was divided into two major phases; first, development of a model decision system for the examination of vaccines for domestic use, and second, development of a model decision system for international vaccines. The IOM developed a model based on comparisons of expected health benefits and expected net costs (or savings) calculated for candidate vaccines. This quantitative approach combines elements of decision analysis and cost-effectiveness analysis.

The IOM Committee considered 14 disease pathogens for analysis by the domestic model, the criterion for consideration being whether or not a vaccine was foreseeable within the next decade. The analysis assigned the highest priority to the following five vaccines in the order listed:

Hepatitis B virus (HBV, recombinant DNA-derived)
Respiratory Syncytial virus (RSV, live-attenuated)
Haemophilus influenzae, type b
Influenza (live attenuated)
Varicella (immunocompromised children)

An improved pertussis vaccine had already been assigned high priority by NIAID, so pertussis was not ranked by the IOM. Acquired Immunodeficiency Syndrome (AIDS) had just been recognized and the HIV retrovirus had not yet been isolated when the IOM began its deliberations. A vaccine for AIDS has now been assigned special priority apart from this program.

The IOM Committee considered 19 disease pathogens for analysis by the international model, including six previously reviewed for domestic use, since developing countries have all the infectious diseases of developed countries as well as others peculiar to or magnified in the tropics. The analysis assigned the highest priority to the following five vaccines in the order listed:

Streptococcus pneumoniae (protein-polysaccharide conjugates)
Rotavirus
Plasmodium species (sporozoite)
Salmonella typhi
Shizella species

NIAID and AID had previously assigned priority to ten agents or agent pairs, five for use in the U.S., and five for use in developing countries. Concordance between the NIAID and IOM rankings was excellent. The NIAID and IOM lists have been combined to provide the following list of vaccines targeted for priority development.

U.S.	International
1. Bordetella pertusssis (improved)	1. Streptococcus pneumoniae (conjugate)
2. Hepatitis B virus (rDNA)	2. Rotavirus
3. Haemophilus influenzae type b	3. Plasmodium species (sporozoite)
4. Respiratory syncytial virus	4. Salmonella typhi (typhoid)
5. Influenza viruses A & B (live, attenuated)	5. Shigella species (dysentery)
6. Herpesvirus varicellae	6. Vibrio cholerae
7. Neisseria gonorrhoeae	7. Mycobacterium leprae

The fact that vaccines for other diseases do not appear on the priority lists does not mean that the disease is not important or that no work is being done on development of a vaccine for it. Indeed, considerable progress has been made in fashioning new or improved vaccines for many of the 13 other agents reviewed by the IOM.

Total NIAID expenditures for vaccine research and development in Fiscal Year 1987 are estimated to have been $31.16 million, exclusive of AIDS. Within the NIH, the next largest expenditure, $2.1 million, was by the National Institute of Child Health and Human Development (NICHD). Other estimated Fiscal Year 1987 Federal expenditures for vaccine research and development include $25 million from the Department of Defense, $17.0 million from the Agency for International Development, $9.3 million from FDA, and $3.2 million from CDC.

Considerable progress has been made toward developing and evaluating vaccines for high priority diseases. A synopsis of progress for each is presented in Appendix 6. Much of this effort was supported by NIH as well as other government agencies, including the World Health Organization. Individual vaccine manufacturers have also been quite active.

B. ACTIVITIES FOR FISCAL YEAR 1988 (Excluding AIDS)

1. Reevaluate or Reassess the Institute of Medicine (IOM) Priorities for Vaccine Research.

This activity will determine if the domestic and international priorities established earlier still apply. This is particularly important in view of the significant progress achieved to date in the development of vaccines identified on the IOM list of priorities.

2. Continue Emphasis on the Development of Improved, Acellular Pertussis Vaccines.

The results of the Swedish clinical trial will serve as an important guide to future directions with these vaccines (see Section VII of this Report).

3. Continue Emphasis on the Development of Improved Vaccines to Prevent Disease Caused by Haemophilus Influenzae type B.

The clinical trial of one vaccine in native Alaskan infants continues for at least another winter season of observation. The results of studies in Finnish infants will be evaluated for their applicability to any license applications for this type of product.

4. Stimulate Basic and Clinical Research on Targeted Vaccines.

This effort will be directed particularly to vaccines to prevent disease caused by Respiratory Syncytial Virus, rotavirus, Streptococcus pneumoniae. Plasmodium species, varicella, and vaccines to prevent sexually transmitted diseases.

5. Stimulate Basic and Clinical Research on Other Important Vaccines.

Several diseases of importance in developing countries did not rank high enough to make the targeted vaccines list, in part because of the amount of basic research required (e.g. Chagas' disease, schistosomiasis, filariasis). Other vaccines of interest in the U.S. also to be addressed are parainfluenza viruses and Herpes simplex viruses. Efforts will be made to stimulate needed research in these areas.

6. Establish Liaison With Members of the Pharmaceutical Industry.

This will enable the NVP to keep abreast of individual companies' research activities for vaccines of U.S. and international interest.

7. Complete a Survey to Inventory Current Vaccine Research.

This survey is attempting to catalog current vaccine research activities in the private and public sectors.

VII. PROMOTING RAPID DEVELOPMENT AND INTRODUCTION OF IMPROVED PERTUSSIS VACCINES

A. CURRENT SITUATION

The development of a safer pertussis vaccine has been a longstanding goal. Recently, progress has been made in understanding the pathogenesis of pertussis and in isolating antigens which could be protective in a vaccine. Much of the pioneering work in this area was carried out in the Laboratory of Pertussis, Center for Biologic Evaluation and Research, FDA. Two antigens which have received the most attention in this regard are pertussis toxin (PT) or Lymphocytosis Promoting Factor (LPF) and Filamentous Hemagglutinin (FHA).

Acellular pertussis vaccines containing principally PT and FHA have been developed and used in Japan since 1981. Their use has been almost exclusively in children 2 years of age and older. Available data suggest that these vaccines cause fewer immediate reactions than whole cell vaccines and protect against pertussis.

A clinical trial of two Japanese vaccines containing PT alone and in combination with FHA sponsored in part by the U.S. has been underway in Sweden since 1986. This trial is expected to define the clinical efficacy of these vaccines in 6-10 month old infants and possibly provide a serologic means by which other candidate vaccines could be evaluated without the need for other field efficacy studies. This trial will provide information about the safety of these vaccines with regard to commonly seen reactions but is not large enough to address the incidence of rare adverse events.

Currently, three manufacturers with an interest in marketing in the U.S. have either imported vaccine from Japan or have developed their own acellular pertussis vaccines. All of these products are currently undergoing clinical evaluation in NIAID sponsored Vaccine Evaluation Centers or at clinical sites sponsored by the manufacturers. Lederle is also working in collaboration with investigators in Japan to evaluate their vaccine in infants. In addition, a vaccine containing exclusively PT has been developed at NIH laboratories and has undergone limited clinical evaluation in U.S. adults and children.

Other U.S. researchers, such as those at the Michigan Department of Health are working on the development of acellular pertussis vaccines containing antigens similar to those previously described. Likewise, investigators at the NIAID Rocky Mountain Laboratory are working on the use of recombinant DNA techniques to produce PT, however this research is still in its early stages and is expected to produce second rather than first generation acellular pertussis vaccines.

Investigators in Britain have also developed an acellular pertussis vaccine which they expect to evaluate in young children during the fall of 1987. This vaccine contains PT and FHA as well as agglutinogens which British scientists believe will be important for protection against pertussis. Of interest to the United States is that British researchers may include Lederle and Merieux vaccines in their comparative trial in 1987 and plan to conduct an efficacy trial beginning in 1988 which will furnish a direct comparison of the efficacy of acellular and whole cell vaccines. Other manufacturers currently have or are developing vaccines which may eventually be proposed for licensure in the U.S. There reportedly is some hesitation to seek entry to the U.S. market because of concerns about liability.

In addition to these vaccine development activities, other studies have been underway at the FDA and CDC which are expected to facilitate the eventual licensure of improved pertussis vaccines in the United States. FDA scientists have purified and evaluated several of the virulence factors which have been considered important antigens for inclusion in acellular pertussis vaccines. These scientists have developed methods for evaluating the structure, function, and inactivation of pertussis toxin. These studies served as the basis for the preparation, review, and evaluation of acellular pertussis vaccines described above. In addition, they are evaluating the role of other pertussis antigens in inducing protection (e.g., agglutinogens, adenylate cyclase, etc.). In addition, FDA scientists have developed serologic assays to evaluate antibody responses to pertussis antigens, the preparation of purified reagents, and the establishment of serological reference standards for international use. At CDC, studies have focused on the development of improved diagnostic tests for pertussis, and on a large case-control study to assess the association between whole cell pertussis vaccine and neurological events in children. These data may eventually be useful in assessing the risk of rare neurological illnesses after whole cell compared to acellular pertussis vaccines.

B. ACTIVITIES FOR FISCAL YEAR 1988

The major focus of efforts in the coming year will be to help collect the additional information necessary to support licensure of one or more acellular pertussis vaccines. This priority assumes that the trial in Sweden will demonstrate the efficacy of acellular pertussis vaccines containing PT alone or in combination with FHA, and that an acceptable serologic correlate of protection is derived from the same trial.

1. Analyze and Present the Clinical Results From the Swedish Trial.

Data collection for the trial has been completed and plans for analysis of the results have been made. An objective for Fiscal Year 1988 is to help insure adequate and appropriate analysis of the clinical results of the trial and timely presentation of the findings to the international community.

2. Test Blood Specimens From Sweden and Correlate Results with Clinical Findings.

The blood specimens collected in the Swedish trial are expected to provide data on the relationship between antibody response to vaccination and protection from disease. If a correlation can be established, it may be possible to assess other candidate vaccines in terms of the antibody responses they evoke in lieu of clinical trials to evaluate prevention of disease. Blood specimens from the trial will be analyzed both in Sweden and, if available, at the laboratories of the FDA. An objective for Fiscal Year 1988 is to accomplish this serologic evaluation of the specimens from the trial and to present the results in a timely manner. In addition, sera from trials of other candidate vaccines are expected to be submitted to the FDA laboratories and these will be assessed in light of the findings on the Swedish sera tested in the same labs.

3. Continue IND Reviews and License Application Evaluations on New Candidate Vaccines.

The FDA reviews all new products submitted for Investigational New Drug (IND) applications and examines proposed protocols. Since additional new vaccines are expected to be ready for clinical evaluation in the coming year, an objective for Fiscal Year 1988 is to review IND submissions and evaluate license applications as expeditiously as possible on all products submitted.

FDA laboratories have tested several candidate vaccines to evaluate the characteristics of the vaccines including selected toxic activities and immunogenicity in animals. All new vaccine candidates will be tested expeditiously to ensure that clinical evaluation is not delayed.

4. Carry out Clinical Studies of Candidate Vaccines in NIAID Vaccine Evaluation Centers.

Presently, NIAID supports four Vaccine Evaluation Centers at Marshall, Vanderbilt, Baylor, and Rochester Universities. These Centers are currently evaluating products from Connaught and Merieux. During Fiscal Year 1988, other products from these manufacturers and from different producers are expected to be made available. An objective for the coming year is to accommodate any vaccine producer who obtains an IND and who requests assistance in clinical evaluation. It is anticipated that at least four separate producers will have their products evaluated in NIAID Centers in Fiscal Year 1988.

5. Assess Feasibility of a Large Scale Safety and Efficacy Trial in the U.S.

Preliminary discussions have been held with NIH vaccine developers and Massachusetts investigators about the desirability and feasibility of conducting a safety and efficacy trial in the U.S. using the vaccine developed at NIH or some other equally suitable vaccine. More detailed discussion about this large scale project in the U.S. will be carried out in Fiscal Year 1988 to define the objectives and design of any proposed trial and to assist in obtaining support for it if indicated.

6. Standardize Serologic Tests for Pertussis.

Serologic tests to measure the antibody responses to pertussis and to pertussis vaccines have been developed in different laboratories. These tests have not yet been standardized to permit accurate comparison of the results from different laboratories. An objective for Fiscal Year 1988 is to standardize procedures and prepare and distribute reference sera which will facilitate comparison of results between manufacturer, government, and university laboratories.

7. Complete Evaluation of New Diagnostic Tests for Pertussis.

At present, other than culture of Bordetella pertussis organisms, there is no agreed upon test which can reliably diagnose pertussis. A rapid diagnostic test would facilitate clinical and epidemiologic studies. FDA and CDC have used enzyme-linked immunosorbent assays (ELISA) for an experimental assay which appears very promising in identifying pertussis infection. CDC has funded contracts in the U.S. and abroad which have shown promising results. An objective for Fiscal Year 1988 is to consolidate the information obtained to date, to select the most practical test, and to finalize test evaluation so that it can be made available to a wider group of researchers.

8. Complete Pilot Study Of Neurologic Illness in Children.

A pilot study of the association between risk factors (including pertussis vaccination) and neurologic illness in children was begun in 1987 in Washington and Oregon. This pilot is expected to demonstrate whether or not a full scale study of this question is feasible. An objective for Fiscal Year 1988 is to complete the pilot study and arrive at a decision about undertaking the larger, more definitive, project.

9. Continue Intramural Research on Pertussis at FDA, NIH, and CDC.

The Laboratory of Pertussis of CBER, FDA, has been an international leader in identifying and characterizing pertussis antigens as well as developing techniques for measuring antibodies and assessing virulence factors. Laboratories at NIH and CDC are heavily involved in developing candidate vaccines and diagnostic tests, respectively. These efforts will be continued.

VIII. ASSURING OPTIMAL IMMUNIZATION LEVELS IN ALL HIGH RISK AND TARGET GROUPS

A. CURRENT SITUATION

High immunization levels have been best achieved in school age children. Continued efforts have resulted in the adoption of state laws requiring certain immunizations for attendance in kindergarten through grade 12 in most states, and kindergarten entrants in all states. As a result of this, immunization levels greater than 95% have been achieved in school age children. Continued support will maintain these gains. Activities dealing with infants, preschoolers, and adults are not proceeding as well. For example, immunization levels for 2-year old children are estimated to be approximately 80% nationwide, with levels in some inner cities substantially lower than that.

Age appropriate immunization in preschoolers can be assured in settings such as day care facilities where appropriate monitoring is possible. However, the majority of preschool age children do not enter such programs. Additionally, opportunities for immunization may be missed when children (or adults) seek medical care for another reason and do not receive indicated vaccines or when indicated vaccines are withheld for inappropriate reasons. Such missed opportunities for immunization play an important part in the underimmunization of both preschool and adult populations. Moreover, many persons in need of vaccination fail to interact with the health care system at all. Although vaccines are safe and effective in preventing disease, there is need to increase awareness on the part of the general population about the need to immunize preschoolers at recommended ages and to maintain protection against vaccine preventable diseases throughout their adult life.

Increasingly, vaccine prices in recent years have made it more difficult for public sector agencies to obtain adequate quantities of vaccines and have also raised concerns about possible shifts from private to public sector. Federal immunization grant funds have provided a stable quantity of childhood vaccine but State and local resources have not always been able to purchase other vaccines for public sector use. To date there is no evidence of a significant shift from the private to the public sector.

The occurrence of vaccine-preventable diseases in adult and preschool groups is unacceptably high because of the low vaccine coverage in these groups. Reliable baseline data to measure progress or determine current status are unavailable at this time. Activities to increase the acceptance of vaccine in a timely manner are increasingly necessary. Immunization levels in other high risk groups (e.g., hepatitis B vaccine in health care workers, homosexual males, and injectable drug users) are also quite low and require increased attention.

The Federal government currently provides Medicare reimbursement for pneumococcal polysaccharide vaccine and hepatitis B vaccine. In 1988 a Medicare demonstration project will support influenza vaccination. It is not proposed to use Federal immunization grant funds to purchase adult vaccines. In addition to the Medicare reimbursement mentioned above, Federal efforts will concentrate on making adults aware of the need for immunizations.

B. ACTIVITIES FOR FISCAL YEAR 1988

The major focus will include program activities to increase awareness of the need for vaccines in the adult population and other high risk groups and to continue programs to locate and immunize children outside controlled settings such as schools and day care centers.

1. Assess Appropriate Mix of Private and Public Sector Involvement to Achieve Optimal Immunization Levels in High Risk and Target Groups.

2. Revise Adult Immunization Action Plan.

An adult immunization action plan was developed by CDC in 1985. The plan is in need of revision to reflect current activities and future needs. These revisions will be made and the revised plan will be distributed to immunization projects and other health organizations.

3. Form an Ad hoc Committee to Promote Information and Education on the Need for Adult Immunization.

CDC will provide direction to a campaign aimed at increasing awareness of vaccine needs of the general public and among health professionals by calling on organizations and manufacturers to promote a unified theme for the nation. The Committee would develop a plan directed toward raising immunization awareness among adult populations.

4. Implement Cooperative Agreement for Studying Health Maintenance Organizations (HMOs).

CDC will assist the American Medical Care and Review Association (AMCRA) in assessing policies, procedures and coverage levels among representative types of Health Maintenance Organizations (HMOs) and to design and implement interventions to increase immunization levels in adult populations. The cooperative study will assess the coverage levels for pneumococcal, influenza, adult tetanus and diphtheria toxoids, and other appropriate vaccines.

5. Distribute and Promote Use of Adult Immunization Materials.

CDC has a contract to develop materials and methods appropriate for increasing levels of awareness in the general public and among health professionals about the need for immunizing adults. CDC will distribute the materials and assess their use and effectiveness in promoting adult immunization program activities.

6. Monitor Activities Outlined in Program Grant Guidelines.

A recent change in program guidelines allows immunization project grantees to expand their role to include promotion of adult and additional childhood immunizations through education as a part of grant supported activities. Many areas have approaches that could be used by other immunization programs around the nation to assist in the promotion of adult and childhood immunization.

These new programs and activities will be summarized on a quarterly basis and shared with other state and local projects. The elimination of indigenous rubella in the United States was also added as an overall program goal and efforts to achieve this and monitor progress will be continued.

7. Conduct Surveys to Establish Baseline Data.

Appropriate methods to establish baseline data in certain areas including size of target population, immunization coverage, and vaccine usage in public and private sectors, will be necessary. Studies will be designed that will measure knowledge, attitudes, and practices in nursing homes, hospitals and selected physicians' practices.

The hospital study may include the use of such activities as home health programs to determine levels of coverage for influenza, pneumococcal and other appropriate vaccines. The nursing home survey would be conducted on a nationwide basis and would be designed to determine usage and coverage with influenza, pneumococcal, and Td vaccines in residents. The survey would assist in evaluating the distribution and use of the manual "Managing an Influenza Vaccination Program in the Nursing Home" and provide information regarding vaccine coverage. Preschool baseline data collection techniques will be evaluated in Chicago during 1988.

8. Develop and Implement Appropriate Strategies to Improve Immunization Levels in High Risk Groups.

Based on the results of the studies enumerated above, new approaches will be undertaken to improve immunization coverage in defined high risk groups.

9. Distribute Automated Patient Recall System.

An automated data system has been developed under contract to assist clinics in patient recall and program management. This Immunization Control and Evaluation (ICE) system will be made available to project grantees during 1988. It should allow programs to assess levels of coverage in preschool populations and assist them in tracking and follow-up of those shown to be delinquent in immunizations.

10. Review Effectiveness of Preschool Efforts.

During Fiscal Year 1988, data obtained from studies in St. Louis on immunization education systems directed at mothers of newborns and in Los Angeles on an active recall system in public clinics will be reviewed to evaluate their effectiveness.

PHS will also review a new reporting format for vaccine administered in the public and private sectors. This new format will allow better determination of vaccine coverage and age, appropriate administration of vaccine, and estimates of coverage levels in specific age groups. These evaluations will be shared with State projects.

11. Convene a National Immunization Conference.

CDC will hold a National Immunization Conference in San Antonio, Texas, June 20-24, 1988. This conference will feature programs and activities emphasizing the needs of the preschool and adult populations. Conference proceedings will be published and distributed.

LIST OF ACRONYMS/ABBREVIATIONS

AAFP	- American Academy of Family Physicians
AAP	- American Academy of Pediatrics
ACIP	- Immunization Practices Advisory Committee
ACP	- American College of Physicians
AFEB	- Armed Forces Epidemiological Board
AID	- Agency for International Development
AIDS	- Acquired Immunodeficiency Syndrome
AMCRA	- American Medical Care and Review Association
APHA	- American Public Health Association
ASH	- Assistant Secretary for Health
CBER	- Center for Biologics Evaluation and Research
CDC	- Centers for Disease Control
CMI	- Cell-Mediated Immunity
DHHS	- Department of Health and Human Services
DOD	- Department of Defense
DT	- Diphtheria and tetanus toxoids (pediatric formulation)
DTP	- Diphtheria and tetanus toxoids and pertussis vaccine
EPI	- Expanded Programme on Immunization
FDA	- Food and Drug Administration
FHA	- Filamentous hemagglutinin
GAG	- Global Advisory Group
GAO	- Government Accounting Office
HBPV	- Haemophilus B polysaccharide vaccine
HMO	- Health Maintenance Organization
IIS	- Important Information Statements
IND	- Investigational New Drug
IOM	- Institute of Medicine
IPV	- Inactivated poliovirus vaccine
JE	- Japanese B encephalitis
LPF	- Lymphocytosis promoting factor
MMR	- Measles, mumps, and rubella virus vaccines (combined)
MMWR	- Morbidity and Mortality Weekly Reports
MSAEFI	- Monitoring System for Adverse Events Following Immunization
NACI	- Canadian National Advisory Committee on Immunization
NAS	- National Academy of Sciences
NCDB	- National Center for Drugs and Biologics
NIAID	- National Institute of Allergy and Infectious Diseases
NICHD	- National Institute of Child Health and Human Development
NIH	- National Institutes of Health
NVP	- National Vaccine Program
OBRR	- Office of Biologics Research and Review
OPV	- Oral poliovirus vaccine
OTA	- Office of Technology Assessment
PHS	- Public Health Service
PRP	- Polyribosylphosphate
PT	- Pertussis toxin
PTA	- Parent Teacher Association
rDNA	- Recombinant DNA (desoxyribonucleic acid)
RSV	- Respiratory Syncitial Virus

SIDS	- Sudden Infant Death Syndrome
SONIC	- Study of Neurologic Illness in Childhood
SRS	- Spontaneous Reporting System
Td	- Tetanus and diphtheria toxoids (adult formulation)
VAC	- National Vaccine Advisory Committee
VPD	- Vaccine-preventable diseases
VRBPAC	- Vaccines and Related Biologic Products Advisory Committee
WHO	- World Health Organization

TITLE III—VACCINE COMPENSATION

National Childhood Vaccine Injury Act of 1986.
42 USC 201.

SEC. 301. SHORT TITLE.

This title may be cited as the "National Childhood Vaccine Injury Act of 1986".

PART A—VACCINES

42 USC 300aa *et seq.*, 300cc *et seq.*

SEC. 311. AMENDMENT TO PUBLIC HEALTH SERVICE ACT.

(a) NEW TITLE.—The Public Health Service Act is amended by redesignating title XXI as title XXIII, by redesignating sections 2101 through 2116 as sections 2301 through 2316, respectively, and by inserting after title XX the following new title:

"TITLE XXI—VACCINES

"Subtitle 1—National Vaccine Program

"ESTABLISHMENT

42 USC 300aa-1. "SEC. 2101. The Secretary shall establish in the Department of Health and Human Services a National Vaccine Program to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines. The Program shall be administered by a Director selected by the Secretary.

"PROGRAM RESPONSIBILITIES

42 USC 300aa-2. "SEC. 2102. (a) The Director of the Program shall have the following responsibilities:

"(1) VACCINE RESEARCH.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction for research carried out in or through the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development on means to induce human immunity against naturally occurring infectious diseases and to prevent adverse reactions to vaccines.

"(2) VACCINE DEVELOPMENT.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction for activities carried out in or through the National Institutes of Health, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development to develop the techniques needed to produce safe and effective vaccines.

"(3) SAFETY AND EFFICACY TESTING OF VACCINES.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction for safety and efficacy testing of vaccines carried out in or through the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development.

"(4) LICENSING OF VACCINE MANUFACTURERS AND VACCINES.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction for the allocation of resources in the implementation of the licensing program under section 353.

42 USC 263a.

"(5) PRODUCTION AND PROCUREMENT OF VACCINES.—The Director of the Program shall, through the plan issued under section 2103, ensure that the governmental and non-governmental production and procurement of safe and effective vaccines by the Public Health Service, the Department of Defense, and the Agency for International Development meet the needs of the United States population and fulfill commitments of the United States to prevent human infectious diseases in other countries.

"(6) DISTRIBUTION AND USE OF VACCINES.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction to the Centers for Disease

Control and assistance to States, localities, and health practitioners in the distribution and use of vaccines, including efforts to encourage public acceptance of immunizations and to make health practitioners and the public aware of potential adverse reactions and contraindications to vaccines.

"(7) EVALUATING THE NEED FOR AND THE EFFECTIVENESS AND ADVERSE EFFECTS OF VACCINES AND IMMUNIZATION ACTIVITIES.—The Director of the Program shall, through the plan issued under section 2103, coordinate and provide direction to the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the Food and Drug Administration, the National Center for Health Statistics, the National Center for Health Services Research and Health Care Technology Assessment, and the Health Care Financing Administration in monitoring the need for and the effectiveness and adverse effects of vaccines and immunization activities.

"(8) COORDINATING GOVERNMENTAL AND NON-GOVERNMENTAL ACTIVITIES.—The Director of the Program shall, through the plan issued under section 2103, provide for the exchange of information between Federal agencies involved in the implementation of the Program and non-governmental entities engaged in the development and production of vaccines and in vaccine research and encourage the investment of non-governmental resources complementary to the governmental activities under the Program.

"(9) FUNDING OF FEDERAL AGENCIES.—The Director of the Program shall make available to Federal agencies involved in the implementation of the plan issued under section 2103 funds appropriated under section 2106 to supplement the funds otherwise available to such agencies for activities under the plan.

"(b) In carrying out subsection (a) and in preparing the plan under section 2103, the Director shall consult with all Federal agencies involved in research on and development, testing, licensing, production, procurement, distribution, and use of vaccines.

"PLAN

"SEC. 2103. The Director of the Program shall prepare and issue a plan for the implementation of the responsibilities of the Director under section 2102. The plan shall establish priorities in research and the development, testing, licensing, production, procurement, distribution, and effective use of vaccines, describe an optimal use of resources to carry out such priorities, and describe how each of the various departments and agencies will carry out their vaccine functions in consultation and coordination with the Program and in conformity with such priorities. The first plan under this section shall be prepared not later than January 1, 1987, and shall be revised not later than January 1 of each succeeding year. 42 USC 300aa-3.

"REPORT

"SEC. 2104. The Director shall report to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate not later than January 1, 1988, and annually thereafter on the implementation of the Program and the plan prepared under section 2103. 42 USC 300aa-4.

"NATIONAL VACCINE ADVISORY COMMITTEE

42 USC 300aa-5.

"SEC. 2105. (a) There is established the National Vaccine Advisory Committee. The members of the Committee shall be appointed by the Director of the Program, in consultation with the National Academy of Sciences, from among individuals who are engaged in vaccine research or the manufacture of vaccines or who are physicians, members of parent organizations concerned with immunizations, or representatives of State or local health agencies or public health organizations.

"(b) The Committee shall—

"(1) study and recommend ways to encourage the availability of an adequate supply of safe and effective vaccination products in the States,

"(2) recommend research priorities and other measures the Director of the Program should take to enhance the safety and efficacy of vaccines,

"(3) advise the Director of the Program in the implementation of sections 2102, 2103, and 2104, and

"(4) identify annually for the Director of the Program the most important areas of government and non-government cooperation that should be considered in implementing sections 2102, 2103, and 2104.

"AUTHORIZATIONS

42 USC 300aa-6.

"SEC. 2106. (a) To carry out this subtitle other than section 2102(9) there are authorized to be appropriated $2,000,000 for fiscal year 1987, $2,500,000 for fiscal year 1988, $3,000,000 for fiscal year 1989, $3,500,000 for fiscal year 1990, $4,000,000 for fiscal year 1991.

"(b) To carry out section 2102(9) there are authorized to be appropriated $20,000,000 for fiscal year 1987, $22,500,000 for fiscal year 1988, $25,000,000 for fiscal year 1989, $27,500,000 for fiscal year 1990, $30,000,000 for fiscal year 1991.

NIH PLAN FOR AIDS VACCINE DEVELOPMENT AND EVALUATION

EXECUTIVE SUMMARY

Development of a safe and effective vaccine to prevent human immunodeficiency virus (HIV) infection and AIDS presents a wide range of scientific and public policy challenges. The continual growth of the AIDS pandemic, coupled with epidemiological estimates of the numbers of persons currently infected with HIV and capable of spreading the virus, has placed vaccine development into a prominent role among the strategies for prevention and control of AIDS. The National Institutes of Health (NIH) is the agency of the United States Public Health Service (PHS) with the lead responsibility for AIDS vaccine research and development efforts. Recognizing that AIDS vaccine development will require a coordinated effort and active participation by government, industry, and academia, the NIH has generated a comprehensive plan to assure the expedited preclinical and clinical development of a safe and effective AIDS vaccine.

BACKGROUND

Historically, vaccine research and development has relied on an interactive system between federally funded academic and government laboratories and commercial manufacturers of vaccines. In a broad sense, this process can be divided into three major steps: basic research; preclinical development; and clinical development. In addition, an infrastructure of research resources serves to complement the major steps in vaccine development by providing the resources necessary to expedite the stepwise progression from basic research through clinical testing.

The basic research necessary to define the pathogenesis of the disease, mechanisms of immunity, genetic and immunologic variation, animal models and other factors which precede preclinical development of experimental vaccines can often be time-consuming and expensive. Because of this large investment of time and other economic costs, basic research studies have generally been carried out by government and academic research scientists funded by the federal government.

Preclinical development of vaccines includes all of the steps from immunogen identification through manufacture, scale-up and testing of vaccine lots in suitable animal model systems, to the filing of an Investigational New Drug (IND) application with the Food and Drug Administration (FDA) for permission to conduct safety, immunogenicity and efficacy studies in humans. These preclinical development steps have generally been undertaken by commercial vaccine manufacturers. The manufacture of vaccines requires a long-term commitment in biotechnology, a major capital investment in technologically advanced scale-up production facilities for biological products, and the willingness of the manufacturer to undertake risks and commitments in the face of several economic disincentives such as an uncertain market and

apprehension over liability issues. These risks have led to a decreasing number of commercial manufacturers remaining in the vaccine industry over the past twenty years. As a result, the U.S. has become dependent on single suppliers for many vaccines, and the vaccine industry has become dominated by a few large commercial firms. The urgency of the AIDS problem, coupled with the recent advances in molecular biology and recombinant DNA technology has led to an explosion of interest by small biotechnology companies in AIDS vaccine development. However, many of these companies do not have the resources to undertake several of the preclinical development steps. Thus, these lack of resources may serve as obstacles to the development of a safe an effective AIDS vaccine and novel approaches to public-private sector interactions may be required to accelerate AIDS vaccine development.

The clinical development of vaccines includes the human safety, immunogenicity, and efficacy trials, the license application process, and the mechanisms for distribution of AIDS vaccines to the general public. Clinical testing of candidate vaccines has been carried out by both commercial vaccine manufacturers and by federally sponsored vaccine evaluation efforts. AIDS vaccine testing is associated with complex recruiting, seroconversion, ethical, and liability issues, and highlights the necessity for establishing mechanisms to assure that collaborative efforts at the interagency, public-private sector, and international levels are promoted. The license application process includes a review of the sponsor's vaccine production and clinical trials data by the FDA, often following consultation with the Vaccines and Related Biological Products Advisory Committee. A series of advisory groups from the PHS, American Academy of Pediatrics, and American College of Physicians are involved in recommendation process for vaccine utilization within the United States.

As discussed below, the NIH Plan for AIDS Vaccine Development represents a multidisciplinary framework for a government-industry-academia cooperative effort to expedite AIDS vaccine development. This Plan will utilize a coordinated program of innovative strategies aimed at maximizing the interaction of public and private sector components through resource allocation, reagent distribution, technology transfer, and information exchange.

AIDS VACCINE RESEARCH AND DEVELOPMENT SURVEILLANCE

The advances in understanding the molecular biology of HIV which have occurred since the virus was first isolated have been remarkable. The molecular biology and genome organization of HIV is more clearly delineated than for any other retrovirus. However, the basic information on the pathogenesis of infection and mechanisms of immunity which are necessary to predict whether immunization against HIV is possible and what types of host responses must be induced to elicit resistance against HIV infection and AIDS have not been defined. As a result, the state-of-the-art in basic research related to AIDS vaccine development is constantly being surveyed in order to identify areas of research which require greater emphasis. These surveys are conducted by both formal and informal mechanisms. Major conferences and smaller workshops sponsored by NIH, other agencies of the PHS, professional societies, the World Health Organization (WHO), commercial manufacturers, and other interested parties serve as forums for information

exchange regarding the identification of gaps in research. Within the PHS Executive Task Force on AIDS, NIH chairs the Vaccine Research and Development Subgroup which also focuses on plans for future research initiatives, and coordinates efforts between other PHS agencies and the Department of Defense. Similarly, surveillance of research gaps is provided within the NIH by a series of committees including the NIH AIDS Advisory Committee, the NIH AIDS Executive Committee, and the NIH Scientific AIDS Vaccine Advisory Committee. This continual review of the basic research related to AIDS vaccine development is a critical exercise which facilitates the process of resource allocation on AIDS vaccine studies to scientists within the academic and commercial sectors of the extramural community and within the intramural structure at NIH.

BASIC RESEARCH INITIATIVES

Basic research serves as the seed and soil from which advances toward AIDS vaccine development are cultivated. NIH has dedicated significant resources to the major research disciplines of virology, immunology, structural biology, and molecular biology which continue to yield a wealth of information accelerating the vaccine development process. Several Institutes of the NIH, coordinated by the NIH AIDS Executive Committee, participate in the support of scientists of the extramural community and intramural NIH laboratories to address the major gaps in the knowledge base required for AIDS vaccine development. The basic research challenges remain formidable, yet the current rate of progress coupled with expanded efforts in coordination and information exchange offer promise for future success. Among the major unanswered questions still impeding AIDS vaccine development are: What are the immune mechanisms responsible for protection against HIV infection and development of AIDS? What is the extent of genetic variation in HIV, and how does this variation affect AIDS vaccine development? Can a standardized animal model-challenge system be established to evaluate the efficacy of candidate AIDS vaccines? What approaches can be developed to interfere with cell-free and cell-associated transmission of HIV?

Investigator initiated research grants continue to serve as the major avenue for basic research studies. However, given the urgency of the AIDS problem, NIH has taken active measures to stimulate studies on basic research problems which impact AIDS vaccine development. Programs of Excellence in Basic Research on AIDS (PEBRA) will soon be awarded to encourage multidisciplinary efforts at academic research settings. Similarly, the National Cooperative Vaccine Development Groups are scheduled to be awarded in February, 1988. These groups are composed of government-industry-academic participants interacting in a formalized framework with the capacity to move rapidly from the basic research setting through the preclinical development process for candidate AIDS vaccines. These groups represent the first of what is anticipated to be an expanding network of scientists linking resources, reagents, and technology with the common goal of expediting AIDS vaccine development. In addition, several other grants, cooperative agreements, and contracts serve as a basic research core for future applied research initiatives. They address issues such as pathogenesis of HIV infections, animal models for HIV, sequencing and cloning of HIV strains, correlates and markers of immunity in AIDS, structural biology of HIV proteins, studies on vaccine adjuvants, and

methods to quantitate HIV.

Similarly, the intramural research programs at NIH have established major efforts in basic research studies on AIDS which have resulted in several important research breakthroughs directly related to AIDS vaccine research. NIH intramural scientists, working in the fields of retrovirology, immunology, and structural and molecular biology, have been major players in the progress towards understanding the molecular and cellular mechanisms of HIV infections. Through a series of subcontracts and collaborative agreements, the intramural programs have linked up with commercial firms in efforts to accelerate these basic research efforts.

Information exchange efforts on basic research studies on AIDS related to vaccine development continue to be carried out through workshops and ad-hoc advisory group meetings. In efforts to enhance reagent distribution, NIH is instituting an HIV Reagent Repository where HIV reagents will be deposited and made available to the entire research community. Similarly, contracts to support virus production and viral component production will soon be in place to feed into the repository, thereby expanding the potential volume of reagents available to the research community. In total, these efforts are aimed at establishing an interactive atmosphere for government, industrial, and academic scientists to engage in basic research studies with the goal of closing the gaps in the knowledge base required to expedite the preclinical development of AIDS vaccines.

PRECLINICAL AIDS VACCINE DEVELOPMENT

Commercial manufacturers of vaccines are presently faced with a series of economic disincentives to vaccine innovation and production, which has caused the number of manufacturers to dwindle over recent years. These disincentives include the long term nature of vaccine development, production and quality control; the costs of research and development in relation to anticipated sales; concerns over liability; patent concerns relating to the perception that vaccines have less patent protection than drugs. Recognizing these concerns, the NIH Plan for AIDS Vaccine Development provides for a network of national resources to facilitate all steps in AIDS vaccine development. This network of resources will assist commercial vaccine manufacturers by providing mechanisms to insure that no gaps exist in the AIDS vaccine development process.

The NIH is committed to encouraging active participation by industrial, academic, and government scientists in the preclinical development of AIDS vaccines. As already mentioned, one of the mechanisms to coordinate multidisciplinary approaches to AIDS vaccine development will be through the National Cooperative Vaccine Development Groups. In addition, the NIH will establish biocontainment facilities at institutions involved in AIDS vaccine development thereby allowing for an increased effort in virus production and genetic manipulation studies. Primate breeding and testing facilities will be established. The breeding facilities will expand the numbers of rhesus macaques available for the simian immunodeficiency virus (SIV) model development, and expand the numbers of chimpanzees available for HIV studies. The planned testing facilities will be a national resource for the evaluation of candidate AIDS vaccines in these experimental primate systems.

Reagent distribution will be expanded via the HIV Reagent Repository, and efforts are being developed to establish an AIDS Vaccine Information Network, which will provide rapid dissemination of information to all investigators involved in basic, preclinical, and clinical research on AIDS vaccines. This infrastructure of national research resources serves to complement the steps in preclinical AIDS vaccine development. These approaches, coupled with continued efforts by NIH to address the complex issue of AIDS vaccine liability through public-private sector interaction provides greater incentives to commercial firms to commit resources to AIDS vaccine development.

Preclinical development of AIDS vaccines consists of the following steps: identification of the immunogen; choice of the vaccine type; vaccine stock production for preliminary studies; immunogenicity and safety studies in small animals; immunogenicity studies in primates; manufacture and scale-up of vaccine lot; biological products tests; immunogenicity, safety, and efficacy studies in chimpanzees; filing of the IND application with the FDA.

Based on prevention models in other retrovirus systems, the major emphasis in AIDS vaccine development has been directed towards HIV envelope gene products (gp160; gp120; gp41) and fragments of these gene products which contain neutralizing antibody or cell mediated immune epitopes. However, recognizing that other internal core proteins of the virus may be implicated in the host immune response against infection, NIH has allocated resources to both intramural and extramural scientists to explore the role of all HIV gene products and determine their relationship to the host immune response during natural infection. A series of cooperative agreements on vaccine adjuvant development serve to complement these immunogen identification studies by providing resources to evaluate methods of enhancing the immunogenic responses of HIV proteins.

Similarly, research into several types of vaccine approaches is being supported. These include killed virus, natural viral products, recombinant DNA products, synthetic peptides, recombinant viruses, anti-idiotype vaccines, combination vaccine cocktails, and passive immunization. These studies are complemented by a series of resource contracts on animal models for AIDS. Through the AIDS vaccine research and development surveillance mechanisms outlined above, NIH maintains progress updates on all current AIDS vaccine approaches being undertaken by government-industry-academic scientists.

In order to facilitate vaccine stock production for preliminary testing in small animals, the NIH Plan for AIDS Vaccine Development calls for combined efforts of NIH and industry. Research support contracts which will be established to provide reagents for the HIV Reagent Repository may be supplemented to provide vaccine production facilities. In addition, dependent on volume, a small-scale vaccine production facility may be established to assist small biotechnology firms with limited resources in the vaccine development process. In addition, efforts will be expanded to coordinate with industry, in order to insure that this step in the AIDS vaccine development program does not provide a roadblock to vaccine production.

Once a vaccine candidate is produced in sufficient quantities for

preliminary testing, it is subjected to a series of immunogenicity and safety tests in small animal models. Tests for immunogenicity include neutralizing antibody, cell mediated immune responses, cytotoxic antibody, and antibody dependent cellular cytotoxicity. Safety tests include general safety studies and evaluation of any immunologic dysfunction associated with the experimental vaccine. Similar to efforts to facilitate vaccine stock production, NIH is dedicated to insuring that evaluation of candidate vaccines in small animal models does not impede the AIDS vaccine development process. As such, utilizing the research support contract mechanism, NIH proposes to establish a small animal models testing facility for candidate AIDS vaccines. This could serve to complement efforts currently underway in the commercial vaccine industry.

Establishing the immunogenicity of an experimental AIDS vaccine in primate model systems is an important consideration for vaccine manufacturers prior to their decision for large scale production of a vaccine lot. This step does not ordinarily involve chimpanzees, but is limited to other primates such as rhesus macaques. Access to primates for evaluation of candidate vaccines can be a major concern to vaccine manufacturers, particularly those with limited resources, due to the small number of available primates and testing facilities. As the number of experimental vaccines requiring testing increases, the limited numbers of primates and testing facilities takes on added significance. In order to address this potential impediment in AIDS vaccine development, the NIH proposes a major expansion in the both primate breeding and testing facilities. Rhesus macaque breeding facilities would increase in number and size, allowing for both an expanded effort in SIV studies and for immunogenicity studies of experimental HIV vaccines. In addition, a rhesus macaque testing facility would be established to evaluate experimental AIDS vaccines for immunogenicity. This facility would utilize a standard panel of immune response assays (e.g. neutralizing antibody; T-cell activation; T-cell cytotoxicity; cytotoxic antibody; antibody dependent cellular cytotoxicity) and provides a mechanism for expediting primate immunogenicity studies.

The manufacture and scale-up of vaccines requires a major capital investment in technologically sophisticated production facilities. The FDA issues guidelines on good manufacturing practices (GMP) which address topics such as production and process controls, packaging and labeling controls, laboratory controls and others. Manufacturers of vaccines are required to abide by these GMP guidelines. Historically, the production and scale-up of vaccines has been undertaken by commercial vaccine manufacturers. However, the urgency associated with the AIDS pandemic which continues to drive efforts to expedite the vaccine development process, coupled with the diminishing number of major commercial firms participating in vaccine development suggests a need for the establishment of a national AIDS vaccine large-scale production facility. The NIH Plan for AIDS Vaccine Development proposes that a national AIDS vaccine scale-up facility be established, and that this facility be utilized as a national resource to accelerate the vaccine development process.

Following the production of a vaccine lot, the lot is subjected to a series of biological products tests required by the FDA for all biologicals. These tests include the evaluation of safety, identity, purity, sterility, and potency. While manufacturers of vaccines are usually equipped to undertake

these general biological products tests, a research support contractor equipped to run these assays under quality controlled conditions would facilitate this step in the vaccine development process. Finally, the vaccine lot is evaluated in the chimpanzee model system for safety, toxicology and immunogenicity. While efficacy studies in chimpanzees are not currently required for entrance into Phase 1 clinical testing, it is anticipated that efficacy testing may be required either at the Phase 1-Phase 2 interface, or Phase 2-Phase 3 interface. Current estimates indicate that approximately 600 chimpanzees are available for AIDS research. The cost, small numbers, and lack of access to chimpanzees by vaccine manufacturers is viewed as a major impediment to AIDS vaccine development. The NIH proposes to expand the number of chimpanzee breeding facilities, and to establish a chimpanzee testing facility where candidate AIDS vaccines can be tested utilizing standard protocols for dose, route, strain, and form (free versus cell associated) of the challenge virus pool. This national resource would fill a major need in providing for standardized preclinical testing of experimental AIDS vaccines.

The final step in the preclinical AIDS vaccine development process is the filing of the IND application with the FDA for permission to initiate clinical testing of the candidate AIDS vaccine. The IND provides the preclinical safety data and rationale for clinical testing, reviews the manufacturing methods and quality control procedures of the vaccine manufacturer, and contains a plan for the Phase 1 safety and immunogenicity clinical trial. The sponsor of the vaccine trial is required to have the IND approved by the FDA prior to initiation of clinical testing. In addition, federal regulations require that an institution conducting a trial with human subjects must have the protocol approved by the Institutional Review Board before beginning clinical testing.

Several of the preclinical steps described above are currently being undertaken to some degree by commercial vaccine manufacturers. In order to maximize coordination efforts, efficiently utilize resources, and promote technology transfer, reagent distribution, and information exchange, the NIH Plan for AIDS Vaccine Development proposes to establish a blue-ribbon government-industry-academia AIDS Vaccine Development Advisory Panel. Composed of representatives from PHS, academic institutions, pharmaceutical companies, biotechnology companies, WHO, and other institutions, this Panel would provide for a formalized framework to review and advise NIH on prioritizing resource allocations for AIDS vaccine development.

AIDS VACCINE CLINICAL TRIALS

Clinical trials of candidate AIDS vaccines will be done in three phases. Phase 1 trials will examine safety and immunogenicity in small numbers of volunteers, and will provide preliminary dosage information. Phase 2 trials utilize larger numbers of volunteers, comprehensively examine safety and immunogenicity, and provide refined information on dosage and route of administration. Finally, phase 3 trials examine the efficacy of the candidate vaccines in field trials using very large numbers of volunteers.

AIDS vaccine trials portend to be more complex than any vaccine trials ever undertaken, indicating the necessity for comprehensive coordination efforts.

Issues including identification of target populations, limited availability of test populations, vaccine induced seroconversion, liability, and the decision-making process for proceeding to Phase 2 and Phase 3 highlight the need for interagency, public-private sector and international collaboration. The proposed AIDS Vaccine Development Advisory Panel along with the PHS Vaccine Research and Development Subgroup could serve as forums for these collaborations.

NIH proposes a major expansion in international epidemiological studies in collaboration with other PHS agencies and the WHO to define potential populations for vaccine efficacy trials. NIH precedents for international collaboration in vaccine development include pertussis trials in Sweden, meningococcal trials in Finland, and typhoid trials in Egypt. It is anticipated that AIDS vaccine efficacy trials may be carried out in the following population groups at high risk for HIV infection: homosexual men; I.V. drug abusers; prostitutes; partners/spouses of hemophiliacs; prisoners; military/foreign service personnel in countries with high rates of HIV infection; other high risk populations in countries with high rates of HIV infection.

Based on preliminary evidence from the first Phase 1 AIDS vaccine trial currently underway at the NIH, recruiting of volunteers for these trials will require a comprehensive effort. The NIAID already has in place a series of Vaccine Evaluation Units which serve as an international resource to expedite the testing of candidate AIDS vaccines. These Units have several years of experience in testing other viral vaccines, and have developed recruitment strategies to address AIDS vaccine trials. Several of the Units contain isolation facilities for the testing of recombinant virus vaccines. AIDS vaccine testing will utilize the multicenter approach to facilitate the recruitment of volunteers. As the number of candidate vaccines moving into Phase 2 and Phase 3 increases, the NIH stands ready to expand the number of Vaccine Evaluation Units to accelerate vaccine testing.

Vaccine induced seroconversion is a significant issue relating to both recruitment of volunteers, and the welfare of these volunteers during and following their participation in AIDS vaccine trials. Persons immunized with candidate AIDS vaccines who mount an effective immune response will appear positive by HIV antibody ELISA testing. Although Western blot tests can discriminate between vaccine induced seroconversion and HIV infection for the first generation of candidate AIDS vaccines, future combination AIDS vaccine cocktails may be less easily differentiated by Western Blot. Thus, volunteers in the AIDS vaccine trials may be subjected to the social discrimination of appearing to be positive on HIV antibody tests. This social discrimination may include difficulties in donating blood, obtaining life and health insurance, entering foreign countries, joining the military or foreign service, and other elements. In order to address this issue, NIH has engaged in multiple approaches. An extensive information exchange campaign is currently underway to inform representative organizations about the vaccine induced seroconversion issue. In this regard, letters of understanding have now been obtained from more than 100 of the largest health and life insurance companies in the United States indicating that persons presenting with indeterminate Western Blots due to immunization with an AIDS vaccine should not face difficulty in life, medical, or disability insurance applications. Similarly, NIH will offer an identification card

with a toll-free 800 number linked to NIH for all volunteers in the vaccine trials. Should a volunteer become involved in a situation where social discrimination occurs due to vaccine induced seroconversion, he/she can call the NIH to verify his/her participation in an AIDS vaccine trial. A confidential computer registry of participants in the vaccine trials has been established to assure that the verification process can be handled efficiently.

AIDS vaccine liability remains a complex issue which jeopardizes the development of a safe and effective vaccine. The spectrum of participants concerned about the liability issue include the volunteers, investigators and institutions carrying out clinical trials, vaccine manufacturers, interest groups, and the federal government. Product liability is probably the major disincentive to manufacturers for vaccine innovation and production. Recruitment into the vaccine trials is also impeded by liability concerns regarding compensation in the event of severe adverse reactions. Investigators and institutions where vaccine trials will be undertaken share concerns regarding potential legal battles arising from real/alleged AIDS vaccine induced injury. While tort reform measures primarily address liability regarding administration of licensed vaccines, there has been limited movement addressing liability concerns in the pre-licensing phase of clinical development. NIH has actively participated in meetings and workshops addressing these issues, and will continue to explore potential solutions with all interested parties.

Finally, the decision-making process for moving candidate AIDS vaccines from Phase 1 to Phase 2 trials, and from Phase 2 to Phase 3 trials is a centerpiece regarding resource allocation. Because of the extremely large numbers of high risk volunteers that would be required in a statistically significant evaluation of vaccine efficacy, it is anticipated that Phase 3 AIDS vaccine trials will require enormous resources. Thus, it is imperative that the decision-making process for endpoint criteria and movement of candidate vaccines into Phase 2 and Phase 3 trials be expedited in a coordinated fashion. The NIH Plan for AIDS Vaccine Development proposes that these criteria be delineated with input from the FDA Vaccines and Related Biological Products Advisory Committee, the proposed AIDS Vaccine Development Advisory Panel, and the PHS Vaccine Research and Development Subgroup.

PRODUCT LICENSING AND DISTRIBUTION

When a candidate AIDS vaccine has demonstrated efficacy in a Phase 3 clinical trial, the final step before the vaccine is made available to the general public is known as the Product License Application (PLA) which is prepared by the vaccine sponsor for the FDA. The PLA contains preclinical toxicology data, a summary of Phase 1 safety and immunogenicity studies, Phase 2 dose-ranging studies, Phase 3 efficacy studies, an environmental impact assessment, and an on-site inspection of production facilities.

A number of vaccine advisory groups are involved in making recommendations for vaccine use in the United States including the U.S. PHS Immunization Practices Advisory Committee (ACIP), the Committee on Infectious Diseases of the American Academy of Pediatrics, and the Committee on Immunization of the

Council of Medical Societies, American College of Physicians. However, the decision-making process in vaccine distribution is complex, and estimated market size impacts on vaccine innovation and production. NIH proposes that efforts be initiated to educate health care providers and the lay public into the risk/benefits of AIDS vaccine immunization programs. These educational outreach activities surrounding the lay public participation in AIDS vaccine immunization programs would not only enhance the recruitment potential for vaccine trials, but would serve to remove impediments to vaccine utilization following licensing.

Statement of Organization, Functions and Delegations of Authority; Office of the Assistant Secretary for Health

Part H, Public Health Service (PHS), Chapter HA (Office of the Assistant Secretary for Health), of the Statement of Organization, Functions and Delegations of Authority for the Department of Health and Human Services (DHHS) (42 FR 61318, December 2, 1977, as amended most recently at 52 FR 23502, June 22, 1987), is amended to reflect the establishment of a National Vaccine Program Office in the Office of the Assistant Secretary for Health reporting directly to the Assistant Secretary for Health who also serves as the Director of the National Vaccine Program. The Office will provide support to the activities of the National Vaccine Program as described in subtitle 1 of Title III, Pub. L. 99–660.

Office of the Assistant Secretary for Health

Under Part H, Chapter HA, Office of the Assistant Secretary for Health (OASH), Section HA–10, Organization, add to the list of organizations, item 20, National Vaccine Program Office (HA2).

Under Section HA–20, Functions, after the statement for the *National Aids Program Office (HAA),* add the following title and statement:

National Vaccine Program Office (HA2)

The National Vaccine Coordinator serves as the head of the Office and reports directly to the Director of the National Vaccine Program for activities regarding the National Vaccine Program (NVP). The Office: (1) Serves as PHS focus in coordinating a national vaccine program including governmental and nongovernmental vaccine activities; (2) identifies issues, and makes recommendations to the Director, NVP, concerning vaccine activities; (3) develops the NVP Implementation Plan for approval by the Director; (4) develops and maintains a directory of organizations and calendar of events involved in vaccine activities; (5) coordinates PHS public education activities related to vaccines; (6) monitors Federal spending for vaccine activities; (7) provides executive secretary and administrative support to the National Vaccine Advisory Committee; and (8) prepares the National Vaccine Report for the Director, NVP to submit to Congress.

Date: August 13, 1987.

Robert E. Windom,

Assistant Secretary for Health.

[FR Doc. 87–19252 Filed 8–21–87; 8:45 am]

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

SEP 29 [illegible]

Kenneth J. Bart, M.D.
Agency Director for Health
Agency for International Development
Room 709 - SA 18
Washington, D.C. 20523

Dear Dr. Bart:

The National Vaccine Injury Compensation Act of 1986 (PL 99-660) contains a provision (Subtitle I) establishing a National Vaccine Program (NVP) to coordinate vaccine-related activities of the Public Health Service, the Department of Defense, and the Agency for International Development. The Secretary has asked me to serve as Director of the Program. I have recently established a staff office for the NVP and have asked Dr. Alan Hinman (Director, Division of Immunization, Centers for Disease Control) to head that office and report directly to me on NVP activities. The enclosed Federal Register notice formally establishes the NVP office and describes its functions.

To assure optimal coordination of government vaccine efforts, I intend to establish a National Vaccine Program Interagency Group with representatives from the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control, the Department of Defense, and the Agency for International Development. This Group will be chaired by Dr. Hinman and will replace the existing Interagency Group to Monitor Vaccine Development, Production, and Usage, which has functioned very effectively in the past even though it has not had formal representation from DOD or AID.

The functions of the NVP Interagency Work Group will include (but are not limited to):

- Developing and revising the National Vaccine Program Plan;
- Serving as primary agency liaison with the National Vaccine Advisory Committee;
- Monitoring supply and distribution of currently available vaccines, identifying and attempting to resolve problems affecting vaccine availability;
- Monitoring research and developmental activities with regard to new or improved vaccines and recommending any needed changes in emphasis or levels of support to ensure timely completion of studies and introduction of new products;

- Coordinating public and professional information/education activities with regard to vaccine recommendations, adverse events, and contraindications;
- ensuring continuing availability of vaccines which have limited use; and
- coordinating other vaccine-related issues on an ad hoc basis.

I anticipate the Work Group will need to meet frequently initially but that after the Plan is well underway and the Advisory Committee formed, meetings should be less frequent and many may be able to be accomplished by conference call. Some meetings may only require participation of a single representative from each agency whereas, depending on the issues to be discussed, others may benefit greatly from much wider representation. Although the Work Group will keep abreast of AIDS vaccine development, the lead in this area will come from the AIDS Vaccine Research and Development subgroup of the PHS Executive Task Force on AIDS.

I would appreciate it very much if you could send me, by September 30, the name of your representative for the NVP Interagency Work Group as well as the name of a backup representative. Thank you very much for your continued cooperation.

Sincerely yours,

/s/ Robert E. Windom

Robert E. Windom, M.D.
Director, National Vaccine Program
Assistant Secretary for Health

Enclosure

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

CHARTER

NATIONAL VACCINE ADVISORY COMMITTEE

Purpose

The Secretary of Health and Human Services is mandated under Section 2105 of the Public Health Service Act (42 U.S. Code 300aa-1) to establish a National Vaccine Program to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines. The National Vaccine Advisory Committee shall advise and make recommendations to the Director of the Program on matters related to the Program responsibilities.

Authority

42 U.S. Code 300aa-5, Section 2105 of the Public Health Service Act as amended by Public Law 99-660. The Committee is governed by the provisions of Public Law 92-463 (5 U.S.C. App. 2), which sets forth standards for the formation and use of advisory committees.

Function

The National Vaccine Advisory Committee shall:

(1) study and recommend ways to encourage the availability of an adequate supply of safe and effective vaccination products in the States,

(2) recommend research priorities and other measures the Director of the Program should take to enhance the safety and efficacy of vaccines,

(3) advise the Director of the Program in the implementation of sections 2102, 2103, and 2104, and

(4) identify annually for the Director of the Program the most important areas of government and non-government cooperation that should be considered in implementing sections 2102, 2103, and 2104.

Structure

The Committee shall consist of 13 members including the chair. Members and chair shall be appointed by the Director of the Program, in consultation with the National Academy of Sciences, from among individuals who are engaged in vaccine research or the

manufacture of vaccines or who are physicians, members of parent organizations concerned with immunizations, or representatives of State or local health agencies, or public health organizations; and five nonvoting ex-officio members as follows: Director, National Institutes of Health; Commissioner, Food and Drug Administration; Director, Centers for Disease Control; Agency Director for Health, Agency for International Development; and Deputy Assistant Secretary for Professional Affairs and Quality Assurance, Office of the Assistant Secretary for Health, Department of Defense (or designees of such offices).

Members shall be invited to serve for overlapping four year terms, except that any member appointed to fill a vacancy for an unexpired term shall be appointed for the remainder of such term. A member may serve after the expiration of the member's term until a successor has taken office. Terms of more than two years are contingent upon the renewal of the Committee's charter by appropriate action prior to its expiration.

Subcommittees composed of members of the parent committee may be established. The Department Committee Management Officer will be notified upon establishment of each subcommittee, and will be provided information on its name, membership, function, and estimated frequency of meetings.

Management and support services shall be provided by the Office of the National Vaccine Program, Office of the Assistant Secretary for Health.

Meetings

Meetings shall be held approximately four times a year at the call of the chair with the advance approval of a Government official who shall also approve the agenda. A Government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of the proceedings kept, as required by applicable laws and Departmental regulations.

Compensation

Members who are not full-time Federal employees shall be paid at the rate of $150 per day, plus per diem and travel expenses in accordance with Standard Government Travel Regulations.

Annual Cost Estimate

Estimated annual cost for operating the Committee, including compensation and travel expenses for members but excluding staff support, is approximately $40,640. Estimate of annual person-years of staff support required is .76, at an estimated annual cost of $23,050.

Reports

An annual report shall be submitted to the Secretary and the Director, National Vaccine Program no later than September 30 of each year, which shall contain as a minimum a list of members and their business addresses, the Committee's functions, dates and places of meetings, and a summary of Committee activities and recommendations made during the fiscal year. A copy of the report shall be provided to the Department Committee Management Officer.

Duration

Continuing.

The charter for this Committee shall terminate two years from the date of approval.

APPROVED:

JUL 30 1987
Date

Otis R. Bowen M.D.
Otis R. Bowen, M.D.
Secretary

SELECTED CURRENT VACCINE RESEARCH ACTIVITIES

Targeted Vaccines - U.S.

Pertussis (improved): See Section VII of this Report.

Hepatitis B virus (rDNA). In July, 1986, the FDA licensed a yeast cell-derived recombinant DNA HBV vaccine manufactured by Merck, Sharp & Dohme. While licensing of the first rDNA vaccine heralded a new era for vaccines, public health officials were disappointed since Merck indicated that the cost will be the same as for their plasma-derived vaccine. To enhance the potential for cost reduction, the NIAID is assisting other manufacturers by performing phase I (safety and immunogenicity) clinical trials at its Vaccine Evaluation Units. Two such trials have been completed at the Baylor College of Medicine. Both of the rDNA candidate vaccines will be evaluated further through the U.S.-China Joint Health Protocol administered by CDC. AID has sponsored development of a plasma-derived vaccine in Korea which may cost only 1/100th as much as U.S. manufactured vaccine. Trials are currently underway on alternative routes of administration (intradermal injection) which could potentially reduce the cost even further.

Haemophilus influenzae, type b. A polyribosyl phosphate (PRP) polysaccharide vaccine was licensed by Praxis Biologics in April, 1985, and by Connaught and Lederle in January 1986. This is the first new vaccine recommended for universal pediatric use since the introduction of rubella vaccine in 1969. Children 2-5 years of age have been recommended to receive the vaccine as part of their general health care. Unfortunately, polysaccharide is not effective in preventing illness in infants and children less than 2 years old who are at highest risk. The U.S. efforts directed at developing polysaccharide-protein conjugate vaccines were led by investigators at FDA and subsequently at NIH. These vaccines constitute a new class of vaccine and give promise of being effective in those less than two. An efficacy trial was begun in December 1984 to test a new conjugate vaccine developed by Connaught Laboratories in a high-risk population of native Alaskan infants. The vaccine or a placebo control is being administered in a primary series at 2, 4, and 6 months of age simultaneously with DTP. The study is designed to assess the protective efficacy of the vaccine in reducing the incidence of invasive disease caused by Haemophilus influenzae, type b and other less invasive disease. The current activities in Alaska include education and counseling, recruitment, immunization, and the follow-up of study participants. The total number of subjects needed to fulfill the recruitment requirement is 2,000 and this goal

has been achieved. No significant differences have been observed in the reported rates of local and systemic reactions between the vaccine and placebo groups. In addition, none of the reported illnesses, major reactions, or deaths in the study population are attributable to vaccine administration. Efficacy and serology data will not be available until the code is broken, estimated to be August 1988.

Another efficacy trial of the Connaught conjugate vaccine was undertaken in Finland in January 1986. The study was designed so that 50% of all newborns (randomly selected) in 1986 received three injections at 3, 5, and 7 months of age. The other 50% received nothing and served as controls. Data reported recently indicated that the vaccine was highly effective in preventing disease due to Haemophilus influenzae, type b, in this population. The duration of this protection continues to be monitored. Another similar type of conjugate vaccine made by NIH scientists is being evaluated clinically, with some studies taking place in Sweden.

Two new conjugate vaccines were recently introduced into clinical evaluation by Praxis Biologics and Merck, Sharpe & Dohme. Both vaccines were shown to be safe and highly immunogenic for toddler-aged children and infants. Both of these vaccines appear to be highly immunogenic in infants even after one dose, with levels of antibody comparable to those observed after two or three doses for other conjugate products.

Respiratory Syncytial Virus. Investigators have identified the presence of more than one type of respiratory syncytial virus (RSV), necessitating evaluation of type-specific antibodies. Cloning and expression of genes coding for the F and G surface glycoproteins of RSV in vaccinia virus vectors has been independently accomplished in government and academic laboratories. The cloning and expression of other RSV-specific genes is in progress. The identification of protective immune responses in RSV infections is under investigation. Preliminary results, using either the mouse or cotton rat models of RSV infection, suggest that antibodies induced to the F glycoprotein may confer protection against heterologous challenge. Vaccinia virus vectors containing the G glycoprotein were also demonstrated to confer protective immunity, although not to the same extent as those expressing the F glycoprotein. No significant protection against subsequent virus challenge was observed when a vaccinia virus vector containing an RSV nucleocapsid protein was expressed. Other high efficiency vector systems, such as the baculovirus vector, are currently being tested for their ability to express large quantities of antigenic RSV specific surface proteins.

Influenza. Phase 3 clinical trials are in progress to compare the efficacy of the cold-adapted (ca) live, attenuated influenza A virus vaccines and the contemporaneous inactivated trivalent vaccine for their respective abilities to prevent natural influenza infections. The trial is a five-year, placebo controlled study with a projected enrollment of 3,000 volunteers. To date, greater than 90% of the projected number of participants have been vaccinated. Additional, large field trials are under way to compare the duration of immunity and cross-protective abilities of the ca and inactivated vaccines. Similarly, the ca vaccine is being studied in family settings to determine if the vaccine is effective in limiting the spread of influenza virus. The safety, immunogenicity, and reaction rate of the ca vaccine is also being evaluated in high-risk populations, particularly the elderly and those with congestive heart failure.

Phase 1 trials of a ca influenza B vaccine have shown it to be safe and not associated with reactions. The safety and immunogenicity of a ca trivalent vaccine is being assessed in the ferret animal model system. Although the major emphasis on influenza virus vaccines has been the assessment of ca vaccines, studies continue on the influenza avian-human (ah) reassortants, developed by NIAID intramural scientists. For example, clinical evaluation of the comparative effectiveness of the ca and ah vaccines are in progress. Long-term studies on the effectiveness of annual immunization with trivalent inactivated influenza virus vaccines are continuing at the Influenza Research Unit at Baylor Medical School.

Varicella Virus. The etiologic agent of chickenpox, Herpesvirus varicellae, may cause serious illness and death in immunosuppressed children such as those with acute leukemia on chemotherapy . The NIAID evaluated an attenuated varicella virus vaccine--developed by Japanese scientists and manufactured by Merck, Sharp & Dohme--in leukemic children, and demonstrated safety, immunogenicity and efficacy. However, difficulties were encountered when further trials were undertaken with "consistency lots" of vaccine which are prepared using scaled-up production procedures. In an attempt to determine whether the increased reaction rate was due to variations in the vaccines themselves, or differences reflected in the population under study, the trial returned to the use only of research lot material. Seventy-five children with leukemia in remission received the research material and had identical reaction rates to those observed previously when this material was administered; therefore, the "consistency lot" material was different. The manufacturer has carefully analyzed steps in making the vaccine and has prepared new consistency lots that are practically identical to the original research lots. These consistency lots are now being tested in leukemic children in remission for evaluation. The manufacturer has demonstrated that all of the vaccine lots prepared thus far are safe and effective in normal children but is interested in producing a product equivalent in safety and immunogenicity to the research lots for leukemic or immunosuppressed children.

Gonococcus. Investigation to develop a candidate vaccine for Neissaria gonorrheae infections is continuing. Previous approaches through the use of proteins derived from the pili of the bacteria were unsuccessful in protecting sexually active males from infections by different antigenic types of N. gonorrheae. These studies were supported in part by DOD. Other preparations consist of synthetic peptides that have been obtained from the conserved domain of the pilus protein and from outer membrane protein complexes. The synthetic peptides have elicited antibody responses in animals but these responses waned quickly with time. It is unknown whether these responses were protective because there is no adequate animal model for gonorrhea. The lipooligosaccharide (LOS) family of complex macromolecules that are the principal toxins of N. gonorrheae also have been investigated for vaccine potential but their toxicities have mitigated their use. Studies with the P1 protein, a porin of the outer membrane complex, demonstrated that it can translocate from the gonococcal membranes and insert into the membranes of host cells, changing the transmembrane potential and initiating the endocytotic process. When investigated as a potential vaccine, investigators found the P1 protein unevenly distributed on all gonococci within a population. The P1 protein when administered as a vaccine to male volunteers did not protect against intra-urethral challenge even though it elicited a good antibody response.

The H8 protein is a 22kd protein which appears to be highly conserved among a wide variety of strains of N. gonorrheae. Studies are now underway to determine the antigenic variation of H8 and its role as a target for human lytic antibody. Two other membrane proteins, P2 and P3, appear to be highly conserved among strains of gonococci and are subjects of study for vaccine potential. Two different iron repressing proteins may be crucial to the viability and pathogenicity of gonococci since they are apparently expressed during natural infections and react specifically with convalescent antisera. Interest is now focusing on the potential of such proteins as candidate vaccines.

Targeted Vaccines - International

Streptococcus pneumoniae. Since the licensure of the 14-valent pneumococcal vaccine in 1977 and the completion of trials for the prevention of otitis media, the NIAID pneumococcal vaccine program has gradually decreased in size. The present program consists primarily of collaborative studies of vaccine in various patient populations at high risk of pneumococcal infections which are made possible by support of a reference laboratory for performance of pneumococcal antibody assays located at the State University of New York, Downstate Medical Center. Results indicated that immunosuppression, whether the result of treatment or the underlying disease, is important in determining response to the vaccine.

The licensure of the 23-valent pneumococcal vaccine has provided an opportunity to reassess vaccine efficacy and current recommendations for immunization. This vaccine covers over 90% of the strains causing invasive disease both in the U. S. and elsewhere in the world, but, unfortunately, it has not been found to be effective in young children in industrialized countries because they respond poorly to polysaccharide antigens. By contrast, a study in Papua New Guinea did demonstrate efficacy in young children. Most pneumococcal infections in children occur before two years of age. It is estimated that approximately 71% of children born in the U.S. experience at least one attack of otitis media during the first three years of life. Since coupling of H. influenzae polysaccharide to protein carriers renders it more immunogenic, prototypes of pneumococcal conjugate vaccines were developed by NIH scientists and others. This type of vaccine has been tested in rhesus monkeys and human adults for safety and antigenicity with the objective of developing multivalent conjugate vaccines containing the six or eight most important pediatric serotypes. Such vaccines might also be more effective in those with impaired immune responses.

The World Health Organization has estimated that more than three million children die each year from pneumonia, and that one-fourth to one-third of the mortality of children less than five years of age is due to acute respiratory infections. NIAID, in collaboration with the CDC and AID, proposes to develop pneumococcal conjugate vaccines and to select one or more sites where their efficacy can be tested in young children in the developing world. AID is sponsoring trials of the currently licensed unconjugated vaccine in three developing countries for immunogenicity in children less than 2 years old and is also sponsoring an efficacy field trial in The Gambia.

The role of pneumococcal surface proteins in pathogenicity is now being studied to examine whether these proteins can be used to elicit immunity. Monoclonal antibodies to several pneumococcal surface proteins can protect mice from fatal pneumococcal infection, and have been used as a probe for cloning the genes that code for these proteins. Studies are in progress to express these genes using recombinant DNA techniques for the production of such surface proteins as potential vaccine components.

Rotaviruses. Several approaches to the production of rotavirus vaccines are being pursued. One strategy, developed by NIAID investigators, was to attenuate an otherwise virulent strain of human rotavirus by passing it repeatedly in gnotobiotic piglets and cell culture. This attenuated strain, called WA, represented the first oral rotavirus vaccine candidate. It was fed to volunteers, but when questions about its passage history arose, further trials were suspended. The Japanese have under development temperature-sensitive mutants of human serotypes 1 and 2.

Another strategy involves the use of an animal rotavirus strain that can infect man and evoke cross-protective immunity without inducing illness. An animal strain, designated Smith Kline RIT 4237, derived from the Nebraska calf diarrhea strain of bovine rotavirus, provided 80-90% protection against serious rotarvirus diarrhea in Finnish infants over six months of age for at least two years. It also significantly reduced the severity of rotavirus diarrhea, but not its overall incidence, in Sweden and Peru. Unfortunately, the vaccine failed for unknown reasons in trials conducted in The Gambia and Rwanda, and work on RIT 4237 was stopped by the manufacturer.

Another oral vaccine strain derived from animals and developed by NIAID investigators was isolated from a baby rhesus monkey with diarrhea. This strain (MMU 18006) was considerably more immunogenic than RIT 4237 and thus could be used in lower doses. It causes mild fever and occasional mild diarrhea in children older than 5 months, but not in younger infants. In seven ongoing or recently concluded field trials in the U.S. and overseas sponsored by NIAID and AID, the rhesus vaccine gave highly variable results depending upon the trial; in some it failed to protect altogether, in others it offered protection against severe rotavirus diarrhea only, while in others it seemed to reduce the incidence of rotavirus diarrhea as well as of diarrhea of unknown etiology which may have been due to rotavirus. Additional information is needed on the duration of protection, the extent, if any, of heterologous cross-protection against the four human rotavirus serotypes, optimum dose and schedule, the effect of vaccine formulation and breast feeding on vaccine take, and the extent of reciprocal interference between oral poliovirus and the rhesus vaccines.

A third vaccine strain (WC3), derived by investigators at the Children's Hospital of Philadelphia, from a Pennsylvania calf isolate, was suitably safe and effective in reducing the severity of rotavirus diarrhea in children 3 to 12 months of age in Pennsylvania. The WC3 vaccine, itself serotype 3, seemed to cross-protect against a serotype 1 outbreak even though it induced little serotype 1 humoral antibody in the children. More trials are being planned.

In yet another stratagem, fastidious human rotaviruses have been co-cultivated with less fastidious animal rotavirus strains in tissue culture. In this system, designed to produce reassortant rotaviruses, the segmented genes of the non-cultivatable human rotavirus that restrict growth in vitro are replaced by the animal genes permitting such replication, while the genes coding for the antigenic coat of the human strain are preserved. The resulting progeny viruses not only grow efficiently in cell culture, but also have the neutralizing specificity of the human rotavirus parents. Reassortants have been developed at the NIAID combining wild type bovine or rhesus rotavirus and each of the four human rotavirus serotypes. Human safety and antigenicity trials are under way with the rhesus reassortants, serotypes 1 and 2. Also available are seemingly naturally attenuated strains isolated from asymptomatic infants representing each of the four human serotypes. These so-called "nursery" strains could be tested alone as vaccine candidates or after they have been reassorted with virulent human strains. The strategy of using a mixture of reassortants may provide a broader serotype immunity.

The recent availability of both cloned rotavirus genes and the protein sequences of important rotavirus antigens should permit yet additional approaches to vaccine development. For example, cloned rotavirus genes have been incorporated into a prokaryotic expression vector (E. coli K-12) and into vaccinia virus to produce a vaccinia-rotavirus recombinant strain. If the synthesis of rotavirus antigens can be achieved in such systems, a large amount of antigen could be produced for a subunit synthetic vaccine comprised of two or more major neutralization proteins of the rotavirus. The degree of cross-protection between serotypes and the duration of that protection are particularly critical questions, because it is not yet known whether all four serotypes must be included in a vaccine. Whatever vaccine or vaccines emerge, they must be compatible with breast feeding, oral poliovirus vaccine, and the stability requirements of the cold chain.

Malaria. Malaria kills an estimated five million people each year. In Africa alone, it is estimated that one million child deaths each year are associated with malaria.

Research has focused on anti-sporozoite and anti-red cell stages of the parasite; for the most part, investigators have abandoned antigametocyte work. AID and DOD funded research has developed several prototype synthetic and recombinant (produced in E. coli antigens as vaccine candidates against the circumsporozoite protein of P. falciparum. These prototypes have undergone safety, immunogenicity, and limited efficacy trials in human volunteers in the U.S. The immunogenicity of both vaccines was found to be less than anticipated when compared to the results in animal studies. The challenge studies in humans with the synthetic polypeptide demonstrate limited protection suggesting the potential of these candidate antigens. Testing of these antigens as conjugates is currently underway in hopes of both enhancing immunogenicity and eliciting cell-mediated immunity (CMI).

Prototype recombinant antigen candidates against the circumsporozoite protein of P. vivax grown in yeast and E. coli, respectively, are currently completing primate trials for safety, immunogenicity, and efficacy.

AID is sponsoring clinical testing facilities for Phase I and Phase IIb testing in Thailand and a field trial site in Papua New Guinea has been identified for Phase III trials of candidate antigens.

Salmonella typhi (typhoid). The development in Switzerland and the successful field trial in Egypt of a live, oral S. typhi vaccine is considered a major advance. This vaccine consists of a mutagenized, enzyme deficient strain of S typhi (Ty21a) that is incapable of utilizing galactose after this sugar enters the bacterium. Ty21a successfully proliferates in sufficient numbers to immunize the bowel before galactose accumulates and kills the bacterial cell. In Chile, ongoing field trials of Ty21a, using a more practical vaccine formulation and dosage schedule than used in Egyptian studies, has shown an efficacy rate of 75% in the first trial year, but only 56% and 65% after the second and third trial years. This is less than the three-year, 95% efficacy rate reported in Egypt. The reason why the Ty21a vaccine has shown lower efficacy in Chile than in Egypt is not clear, although the different attack rates of typhoid fever may affect efficacy. Differences in the vaccine formulation used may also be a factor. The vaccine caused few reactions in both trials. Efforts are now being made to test a more practical liquid formulation in Chile and Indonesia to see if it will confer greater and more sustained protection.

Investigators at Stanford University have attenuated two strains of S. typhi by inducing auxotrophic mutations in them (Aro^-, Pur^-). That is, each has a deletion mutation (therefore incapable of reversion) in a gene such that, in order to replicate, the mutation causes a requirement for one or more metabolites which are not available in mammalian tissues. In consequence, the strains cannot maintain growth and persist in mammalian tissues. One strain (541Ty) contains Vi antigen while the second strain (543Ty) does not. In calves, a similar auxotrophic oral vaccine against S. typhimurium was shown to be safe, genetically stable, and capable of penetrating the intestinal mucosa to attain intracellular sites within the reticuloendothelial system but not capable of persisting long-term therein. The vaccine confers protection against virulent S. typhimurium, and offers hope that an analogous auxotrophic mutant may serve as an improved typhoid vaccine in man. Trials in volunteers show the two Stocker auxotrophic S. typhi vaccines to be safe, infective and immunogenic in terms of stimulating cell-mediated immunity, but less so in stimulating S. typhi antibody. Volunteer trials will proceed with strain 541Ty to evaluate immune response following variations in dosage, immunization schedules and formulations. An alternative auxotrophic mutant strain (Aro^-) is available for volunteers in the event that the Aro^- Pur^- 541Ty strain proves to be overattenuated.

The Vi polysaccharide is a linear homopolymer of galacturonic acid that forms a capsule on the surface of S. typhi; it represents a virulence antigen. A purified Vi polysaccharide antigen preparation developed by an NIH scientist has been tested in volunteers as an alternative killed vaccine that might provide protection after one dose. A purified Vi polysaccharide vaccine prepared in collaboration with the Merieux Institute caused few reactions and produced Vi antibody in $\geq$ 85% of volunteers. A field trial to test the efficacy of this vaccine was performed in Nepal under AID auspices. It has also been given to 6,000 school children by investigators at the South African Institute for Medical Research. The preliminary results of both trials have been reported and are quite encouraging.

Shigella (dysentery). Parenteral, killed, whole-cell Shigella vaccines have failed to provide significant protection. Live, oral Shigella vaccines proved to be safe, but too many doses were required for efficacy, and occasional genetic revertants arose. Currently, genetic engineering techniques are being used to develop several types of Shigella vaccines, the most promising of which are noted below.

Genes coding for the protective O-antigen on Shigella sonnei, and contained within a 140 Mdal plasmid of that species, have been inserted into the genome of the Ty21a vaccine strain of Salmonella typhi by U.S. Army scientists. The resultant transconjugant strain (5076-IC) manifests both S. sonnei and S. typhi antigens; it appeared safe, stable, and protected volunteers effectively against challenge with S. sonnei. However, the variability in the efficacy of different vaccine lots has delayed the initiation of field trials; further studies to determine the reasons for the variability are in progress.

More recently, the 140 Mdal plasmid of S. flexneri 2a that encodes proteins necessary for epithelial cell invasion has been transferred into E. coli K-12, together with the chromosomal genes encoding the group and type-specific O-antigens of S. flexneri 2a. The resultant hybrid E. coli expresses smooth S. flexneri 2a O-antigen and invades epithelial cells, but does not cause fluid secretion in ligated segments of rabbit intestine. This vaccine is both safe and protective in monkeys. In volunteers, the vaccine causes reactions in doses of 10^9 CFU, but not in lower doses of 5×10^6-10^7. Efficacy studies of the lower dose given twice are under way. If successful, analogous E. coli K-12 strains expressing O antigens of S. flexneri 1a and 3a, S. sonnei, and S. dysenteriae 1 have been prepared for studies in volunteers. Such vaccines, when combined into one multivalent preparation, protect monkeys as well as does a monovalent preparation.

As noted above, it is likely that only one, or at most a few Shigella antigens, such as the O-antigen, specific outer membrane proteins, and perhaps a Shiga toxoid, may be required to evoke protection. It may be feasible to construct a series of hybrid plasmids encoding these antigens which could be inserted into selective antigen delivery systems, such as E. coli K-12, attenuated Vibrio cholerae, or auxotrophic mutants of Salmonella typhi. Further research will be required, however, to define the requirements for efficient expression of these antigens in an optimally immunogenic form.

Romanian investigators have developed an attenuated oral vaccine, named strain T32-Istrati, by serially passing Shigella flexneri 2a 32 times on 2% nutrient agar. This vaccine was genetically stable, avirulent in animals and man, and was 87% effective in protecting over 36,000 Romanian children and adults housed in institutional settings against bacteriologically confirmed dysentery. Its efficacy in the field has also been proven in China. The immunoprophylactic effect was equally good against homologous and heterologous species, such as S. sonnei and others. The vaccine was given 5 times over 2 weeks for full effect, but even one dose afforded 37% protection lasting 6 months. Biannual revaccinations were necessary to maintain full immunity. Attempts are underway to obtain this vaccine and confirm these excellent results in the West.

Vibrio cholerae. The search for a better cholera vaccine has been stimulated by studies in volunteers demonstrating that natural infection is followed by solid long-lasting immunity. The goal is to design safe oral vaccines, either killed or attenuated, that can provide 90-100% protection for several years after one dose, or after a closely spaced series of doses. Oral immunization, rather than parenteral immunization, is more likely to stimulate the protective intestinal immune response of secretory IgA antibodies, and live organisms are likely to stimulate a more effective mucosal memory response.

The oral vaccines currently under development are of two classes: 1) inactivated V. cholerae strains combined with altered toxin or purified toxin subunits which do not cause reactions, and 2) attenuated V. cholerae strains, genetically engineered to be deletion mutants or auxotrophic mutants, and hybrid vaccine strains such as E. coli K-12, S. typhi Ty21a, or auxotrophic Salmonella, genetically engineered to carry and express selected virulence genes of V. cholerae. Studies of inactivated vaccines have focused on products combining whole vibrios with either glutaraldehyde-treated toxin, heat-aggregated toxin (procholeragenoid) or the purified B-subunit pentamer of the toxin that binds to the intestine. In a small number of volunteers the protective efficacy of these vaccines was disappointing, ranging from 27% to 67%. Nevertheless, AID sponsored a field trial in Bangladesh of a combined oral B subunit plus killed whole cell vaccine. Preliminary results indicated that the combined vaccine gave 85% protection against cholera for at least 4-6 months, while the whole cell vaccine gave 58% protection. The trial is designed to determine the duration of protection. Other formulations that may be more practical are also under study.

The first live vaccine strain of V. cholerae to be tested in volunteers was prepared by nitrosoguanidine mutagenesis. This strain, Texas Star-SR, produced ample amounts of the nontoxic, antigenic B subunit portion of the toxin molecule, but only very small quantities of the toxic A subunit portion that was activated. Although Texas Star-SR colonized the small bowel and induced antitoxin or vibriocidal antibody responses in 85% of volunteers, it provided only 61% efficacy against diarrhea caused by V. cholerae challenge

and caused mild diarrhea in 24% of vaccinees. Encouraged by these results, investigators attenuated pathogenic V. cholerae by specifically removing genes encoding all other antigens, such as lipopolysaccharide, outer membrane proteins and colonization factors likely to be involved in immunity. This method is free of the disadvantages of nitrosoguanidine mutagenesis, which involves the induction of uncontrolled and unwanted mutations and the theoretical risk of reversion to toxigenicity.

Several strains of V. cholerae with precise genetic lesions have been constructed by DNA recombinant techniques and tested in volunteers. The JBK 70 strain has no cholera toxin genes (A minus, B minus). In the CVD 101 strain, the toxic A subunit gene was deleted while the immunogenic, but nontoxic, B subunit gene was retained and expressed (A minus, B plus). Of a small number of volunteers fed strain JBK 70, 90% were protected against severe illness. Some volunteers, however, developed low-grade diarrhea after vaccination, an occurrence which led to the discovery that strains JBK 70 and CVD 101 each produce one or more toxins different from cholera toxin. The existence of these other toxins in V. cholerae was not previously known. One is a Shiga-like toxin. Attempts are underway to characterize, clone and then remove the gene or genes for these new toxin(s) from these attenuated vaccines in hopes of rendering them less virulent but still protective.

A promising vaccine candidate, CVD 103, an A minus, B plus derivative of a V. cholerae classical Inaba strain, does not produce the Shiga-like toxin found in other cholera vaccine strains. CVD 103 induced mild diarrhea in only 12% of volunteers, significantly less than that produced by other attenuated vaccine strains. A single oral dose of CVD 103 induced vibriocidal and antitoxin antibodies in 95% of volunteers, and afforded 87% protective efficacy against the virulent parent strain and 67-78% efficacy against virulent El Tor and Ogawa strains. It protected against severe, purging diarrhea for as long as 11 months after vaccination. This live, oral vaccine candidate is being developed for field trials overseas.

New auxotrophic mutants of V. cholerae are also being developed. CVD 102, a thymine-dependent derivative of CVD 101, was fed to volunteers; but it colonized poorly and failed to stimulate potent vibriocidal antibody responses. Observations to date in volunteers challenged with attenuated V. cholerae vaccine strains suggest that retaining the ability to colonize the small intestine leaves the strain inherently capable of inducing reactions, while impeding the strain's ability to colonize reduces its immunogenicity. In response to this dilemma, hybrid strains of harmless, non-vibrio enteric bacterial vectors are being engineered to carry genes encoding for the antigens responsible for V. cholerae colonization and other outer membrane virulence antigens in an attempt to attain immunogenicity without unacceptable reaction rates.

Leprosy. A number of Mycobacterium leprae-specific antigens have been identified and purified by NIAID-supported investigators. These natural and semi-synthetic antigens have been shown to be useful for the serodiagnosis of both symptomatic and asymptomatic leprosy.

NIAID-supported investigators have purified a complicated lipoarabinomannan (LAM-B), a major cell wall immunogen from M. leprae. These investigators have also stripped the leprosy bacillus of mycolic acids, lipids, carbohydrates, etc., leaving the cell wall skeleton (CWS). Preliminary information indicates that LAM-B and CWS are powerful immunogens and may be an ultimate source of protective immunity against M. leprae infection.

The World Health Organization (WHO), along with AID, is presently funding the testing of two M. leprae vaccines. A vaccine composed of heat-killed M. leprae and live BCG cells has been tested for activity and safety in Venezuela. The second vaccine is composed of heat-killed M. leprae cells only. It has been tested in the U.S. for adverse reactions, dosage level and activity (skin test reaction). These preliminary tests are now completed, and a trial of the vaccines will be carried out in India. It will be a number of years before their effectiveness can be determined.